# INSECTICIDES

## 1. Introduction

There are nearly one million described species of insects, constituting approximately 72% of all animal species (1). About 1% of them are considered significant pests. This article summarizes the chemistry, properties, uses, and advantages and disadvantages of many chemicals used for insect control. Some products mentioned are of largely historical interest, and others are not registered for use in the United States but used elsewhere in the world.

Approximately 70% of all insecticide use is in agriculture, and applications are generally made directly to raw agricultural commodities to protect plants and animals from insect attacks. With the exception of microbial insecticides, nearly all of the uses of insecticides result in residues of the various chemicals and their degradation products.

Basic guidelines for the limitations of pesticide residues in raw agricultural commodities are established by national and international agencies. For example, the U.S. Environmental Protection Agency (USEPA) establishes the maximum amount of a particular pesticide that is legally permitted on a particular crop, i.e., the tolerance. This includes both the parent pesticide and any toxicologically significant degradation products (http://www.epa.gov). International standardization is highly desirable for trade in foodstuffs, and values of maximum residue levels or MRLs (synonymous with tolerances) have been determined for many pesticides by the JMPR/Codex Alimentarius committee of the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) (http://www.fao.org). The proceedings of these meetings have been published in a series of 171 volumes.

Insects attack humans or domestic animals, transmit human, animal, and plant diseases, destroy structures, and compete for available supplies of food and fiber. In the United States, there are more than 10,000 species of insects, mites, and ticks that cause losses to agriculture, but only about 600–700 species require annual applied control measures. About 40% of these (235 species of 600) are exotic importations, illustrating the vulnerability of U.S. agriculture to infestations resulting from global travel. Estimates suggest that the total losses to agricultural crops from insect attacks in the United States average about 10% of production and amount to more than $14 billion annually. Worldwide agricultural losses from insect attacks have been estimated as about 14% of production (2). Termites may cause more direct monetary damage than any other group of insect pests. It has been estimated that termites damage human made structures annually to the extent of 1% of their value in the United States and to 10% in the tropics.

Losses resulting from the depredations by insect vectors of human and animal diseases are almost beyond monetary estimation (1–3). Malaria transmitted by the bites of some 60 species of Anopheles mosquitoes results from the infection of human erythrocytes by four species of protozoa, *Plasmodium falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. Despite a global program of eradication and control, begun in 1955, the WHO estimated in 1990 that there were annually about 270 million cases of malaria with about one million deaths. It has been estimated that there are currently (year 2000 figures) close to three million human deaths annually from malaria. The number of persons suffering from lymphatic filariasis transmitted largely by the common house mosquito *Culex pipiens* and caused by the nematode parasites *Wüchereria bancrofti* and *Brugia malayi* is estimated at 100 to 250 million annually. The number of persons at risk from this predominantly urban disease has doubled over the past several decades. Trachoma, a viral disease causing blindness, is widespread in India and North Africa. It is transmitted by the housefly *Musca domestica*; and an estimated 80 million persons are infected. African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma gambiense* and *T. rhodesiense* and is transmitted by the biting of several species of tsetse flies, *Glossina* spp. This disease and the related cattle disease (nagana), caused by *T. brucei*, have retarded the economic development of some 11 million $km^2$ of equatorial Africa.

A number of species of biting black flies, *Simulium* spp., transmit the filarian *Onchocerca volvulus* to humans. This disease afflicts an estimated 20 million humans in the Volta River basin of Africa and in Central America. It is the cause of river blindness, which has greatly retarded agricultural and economic development in the infested areas. American trypanosomiasis is caused by *Trypanosoma cruzi*, which is transmitted by a number of species of the genera *Triatoma* (kissing bugs), *Panstrongylus*, and *Rhodnius*. Approximately 10 to 12 million humans in South and Central America are afflicted with this disease, known as Chagas' disease. It may result in fever as well as inflammation of the brain and may be fatal. Like many of the diseases mentioned above, Chagas' disease does not have a cure. Other human diseases transmitted by insects include plague, *Yersina pestis*, caused by the bites of the oriental rat flea *Xenopsylla cheopis* and other fleas, and epidemic typhus, *Rickettsia prowazeckii*, transmitted by the bite of the human body louse, *Pediculus humanus*. Insects are the vectors of more than 250 viruses (arborviruses) that are pathogens of humans and higher animals. These include yellow fever and dengue hemorrhagic fever for which the mosquitoes *Aedes aegypti* and *A. albopictus* are the important vectors. Human encephalitides, such as the California, St. Louis, eastern, western, and Venezuelan types, are transmitted by the biting of a variety of Aedes and Culex mosquitoes. West Nile encephalitis is caused by a virus, transmitted predominantly by Culex mosquitoes; it has recently become endemic in parts of the eastern and central United States, with over 3000 cases and in excess of 200 human fatalities in 2002 (http://www.cdc.gov).

## 2. Role of Chemicals in Insect Control

The role of chemicals in the control of insect pests constantly undergoes searching reevaluation in terms of benefits versus adverse effects. Benefits and the long-term and short-term implications for ecological systems, human health, and the environment are constantly reassessed as each new insecticide discovery is factored into the balance.

Plant-derived insecticides, e.g., nicotine, rotenone, veratrine, and pyrethrum, have been used to kill insect pests since antiquity. A tea of nicotine from tobacco leaves was recommended to control aphids in 1793, but the principal development of insecticides for crop protection began about 1865 with the use of paris green, an arsenical stomach poison, for the control of the Colorado potato beetle, *Leptinotarsa decimlineata*. An improved compound, lead arsenate, was introduced in 1892 and calcium arsenate in 1907; their combined production in the United States, approximately 40 million kg annually, was applied predominately for the control of cotton insects. Cryolite (sodium aluminium fluoride, $AlF_6Na_3$) was introduced as a stomach poison insecticide in 1928, to avoid objectionable arsenical residues on fruits and vegetables. These stomach poison insecticides were effective only against chewing insects and had little or no contact action. The arsenicals had the grave disadvantages of high toxicity to humans and domestic animals, considerable phytotoxicity, and extreme environmental persistence. These disadvantages have been largely eliminated in agrochemicals developed over the past 10–20 years.

The first practical synthetic organic insecticide was the potassium salt of 4,6-dinitro-2-methylphenol or DNOC [534-51-1] developed in Germany in 1892 as a dormant spray for orchard pests. However, it was the discovery of the insecticidal properties of DDT [50-29-3] in 1939 that began an era of chemical pest control, resulting in the synthesis and evaluation of hundreds of thousands of synthetic organic chemicals as insecticides (4). Dichlorodiphenyltrichloroethane (DDT), with its efficient contact insecticidal action together with long residual persistence and relative safety to humans and domestic animals, largely replaced the arsenicals. Hundreds of new uses were developed, and DDT production in the United States attained a maximum of 77,800 t in 1961. Massive use of other organochlorines, such as benzene hexachloride, chlorinated camphenes, chlordane, heptachlor, aldrin, dieldrin, and endrin followed, and by 1964, these chemicals represented 70% of the total (53,000 t) use of insecticides in agriculture together with organophosphates at 20% (10,600 t). However, as insecticide resistance supervened and concern over environmental pollution increased, the use of the organophosphates (introduced in 1948) and the carbamates (introduced in 1957) increased rapidly. By 1976, more than 200 chemical compounds were marketed as insecticides and the total application to primary crops was 58,000 t. The organochlorines represented 29%, the organophosphates 49%, and the carbamates 19%. Cotton was the most heavily treated crop (49% of the total) followed by corn, 25%, and soybean, 6%. Increasing use of integrated pest management (IPM) practices and the introduction of the pyrethroids, which are effective at about one-tenth the application rate of the older insecticides, resulted in decreased insecticide use, and by 1982, the farm use on primary crops was estimated at 32,000 t, comprising organochlorines, 6%; organophosphates, 67%; carbamates, 18%; and pyrethroids, 4%. Corn became the most heavily treated crop with 42% of the total, followed by cotton, 24%, and soybean, 16%. Over the past 10–15 years, the use of organophosphates and carbamates has declined further, whereas several new classes of chemistry affecting several "new" target sites have been developed (8).

Since the early 1940s, insecticides have been of immeasurable value in curbing the ravages of insect pests. In the words of the National Academy of Sciences, "when their use is approached from sound ecological principles, chemical pesticides provide dependable and valuable tools for the biologist. Their use is indispensable in modern society. There are many problems of insect pest control for which the use of chemicals provides the only acceptable solution. Chemical pesticides will continue to be one of the most dependable weapons for the entomologist for the foreseeable future" (4).

In agriculture, the average benefit/cost ratio from insecticide use ranges from \$3 to \$5 return for every \$1 invested by the farmer(s). There are many examples where the return is much greater. In California, treatment of sugarbeets with granular phorate systemic insecticide to control the aphid and leafhopper vectors of virus yellows increased sugar yields up to 1685 kg/ha (1500 lb/acre), for a ratio of \$18 to \$1 invested. The use of DDT in Wisconsin to control the Colorado potato beetle and the potato leafhopper, *Empoasca fabae*, increased yields by as much as $5.7\,m^3$/ha (65 bushel/acre) for a ratio of \$29 to \$1. It is scarcely possible to produce apples, sweet corn, lettuce, or broccoli of modern marketable quality without the use of insecticides.

The value of insecticides in controlling human and animal diseases spread by insects has been dramatic. It has been shown that between 1942 and 1952, the use of DDT in public health measures to control the mosquito vectors of malaria and the human body louse vector of typhus saved 5 million lives and prevented 100 million illnesses. Insecticides have provided the means to control such important human diseases as filariasis transmitted by *Culex* mosquitoes and onchocerciasis transmitted by *Simulium* blackflies.

The EPA estimated that 975 million pounds of active ingredients of all types of pesticides were used in 1997 compared with 1009 million pounds in 1996. This represents an expenditure of \$8.3 billion or 4.5% of total farm production expenses. A majority of the pesticides produced in the United States is used in agriculture to produce food and fiber (77% or 944 million pounds of active ingredient in 1997), with the remainder used in industry/government applications and by homeowners. With usage of 1.23 billion pounds (for conventional pesticides plus other pesticide chemicals), the United States accounts for about one-fourth of such usage worldwide.

Between 1979 and 1997, annual farm expenditure on insecticides increased in the United States from \$1783 million to \$3553 million. Over the same period of time, the amount of active ingredient used fell from 188 to 90 million pounds. In addition to a reduction in the amounts of insecticide used, fewer new chemical active ingredients are being registered over time (5,6).

## 3. Classes of Insecticides and Their Modes of Action

Although the economic benefits of insecticide use became rapidly apparent to the farmer, it was observed that after several years of repeated applications of an insecticide, the onset of resistance in a pest species could rapidly nullify its beneficial effects. Insecticide resistance may originate in a variety of ways (see article), but identification of biological target sites and the metabolic pathways involved in detoxification of the active ingredient revealed that many insecticidal classes possessed similar modes of action. Replacement of a member of one class by another that had a similar mode of action was ultimately fruitless as a resistance management technique.

Pest management systems in which chemicals could be used more effectively were developed as were alternative practices to control insects. Amounts applied per acre were reduced by the introduction of chemicals that were effective at low rates. Table 1 shows the amounts of insecticides used in 1995. The top ten have been categorized in order of weight of active ingredient used, but if the number of acres treated by a particular pesticide was used as a basis, it is likely that several pyrethroids and perhaps avermectins would now be included in the top ten. To illustrate this point, imidacloprid, a nicotinic acetylcholine receptor agonist, described as a neonicotinoid is now the top-selling insecticide worldwide in terms of revenue. Neonicotinoids now represent a major class of insecticides (8).

Compounds irreversibly inhibiting acetylcholinesterase (AChE) still dominate the world market (9). However, the market share of these AChE inhibitors, i.e., organophosphates and carbamates, decreased from 71% in 1987 to 51% in 1999. The AChE inhibitors and those insecticides acting on the voltage-gated sodium channel (VSC), in particular, the pyrethroids, account for about 70% of the world market.

It should also be noted that inhibitors of AChE also have applications in the treatment of various human diseases e.g. myasthenia gravis, schistosomiasis and Alzheimer's disease (10). However, in the latter case it is now thought that the initial inhibition of AChE may not be the primary mechanism for the improvements in cognition that have been observed following the administration of certain organophosphates. Instead, acylpeptide hydrolase, a brain enzyme that may function in regulating neuropeptide turnover, appears to be much more sensitive to inhibition by these organophosphate insecticides than does AChE. For example, chlorpyrifosmethyl oxon, dichlorvos and diisopropylfluorophosphate were six to ten times more potent at inhibiting acylpeptide hydrolase, than they were at inhibiting rat brain AchE (10).

Oils occupy an important place and have long been in use for control of a variety of insects and plant diseases, and they have the advantage that, unlike chemical pesticides, rapidly breeding insects have not become resistant to oil treatments.

Organochlorine insecticides were heavily used initially until the disadvantages of using compounds that were not readily degraded under environmental conditions became clear. The implementation of national environmental policies became, from 1970, a major driving force in the selection of pesticides. Research on mode of action not only guided the design of molecules, but also served as an indicator of potential resistance problems that might occur particularly when compounds were used injudiciously. If an insect species showed resistance to a particular class of insecticides, resistance to insecticides of other classes possessing the same mode of action was a likelihood. Resistance ascribed to the same mechanism is termed "cross resistance" in a strain of insects, whereas the term "multiple resistance" is used to describe the resistance of the strain to different compounds that arises from different mechanisms.

The organochlorine insecticides affect neural transmission. Although carbamate and organophosphate insecticides were much more susceptible to environmental degradation than were the majority of organochlorine pesticides, they are both inhibitors of acetylcholinesterase. Consequently, the potential for resistance was a major concern, and it was important to exploit other modes of action in designing new insecticides. The introduction of the pyrethroids and imidacloprid, which acted at different sites of the nervous system, represented major advances. Higher biological activity and greater environmental and applicator safety became major goals in the search for new insect pest management tools.

Many promising new leads for compounds possessing pesticidal activity were discovered by random screening. However, there are many constraints affecting the selection of a candidate for development, such as patent status, ease of manufacture, environmental implications, and toxicology. This approach had long been pursued by most manufacturers and proved fruitful. Initial success rates of 1 in 12,000 were encouraging. Nevertheless, success rates fell yearly. Although in 1970–1973, the number of chemicals screened per new compound was 8500, it rose to about 21,600 during 1986 and 1987 (11). As a consequence, higher throughput rates became the goal of industry, and in recent years, it has become more practicable to generate large libraries of compounds for screening and accelerate the rate of submission.

The basis of this approach to the discovery of new active moieties was to make fundamental changes in the screening programs and increase the rate at which compounds are screened. The models adopted by the pharmaceutical industry provided a basis for an approach to discovery of new molecules, and the discovery and development of new compounds may be facilitated by sharing techniques used for discovery of new pharmaceuticals, particularly techniques for genetic manipulation, combinatorial chemistry, and screening processes. Routes to drug discovery, including the generation of libraries for screening, identification of biochemical target sites, molecular modeling, and new rapid high throughput screening techniques parallel those used for the discovery of new leads for pesticidal activity. For example, the former practice of screening *ca.* 5000–10,000 new chemical compounds yearly is giving way to much higher rates of screening. These allow over 100,000 compounds a year to be examined in major industrial laboratories. This common industrial goal has been achieved by customized high throughput screens in which extremely small amounts of compound are tested *in vitro* in enzyme/protein assays based on 96-well microtitre plates (12). The ingenuity of the synthesis chemists led to the production of many new classes of molecules. However, chemists were criticized for their preoccupation with older modes of action. It has been suggested that the preoccupation with older sites of action should be abandoned and that research should move into unknown areas of chemistry. In recent years, the success of products derived from plants and fermentation products of microorganisms continues to draw attention to natural products and the varieties of biological potential and resources available as lead materials for synthetic analogues (eg, pyrethroids), as starting materials for semisynthetic derivatives (eg, emamectin, dihydroazadirachtin), and, in their own right, for direct use in agriculture (eg, Bt-endotoxins, spinosyns, and essential oils) (13).

A parallel approach to the discovery of new active compounds was based on more rational approaches to synthesis. Molecules would be designed to attack more specific biological targets. This was a reasonable approach in view of the historical over-reliance on the selection and use of insecticides that targeted the central nervous system. The so-called "biorational approaches" yielded many biologically active molecules. The relationship of molecular structure and biological activity and the interaction of molecules with biological targets were investigated intensively to provide rational bases for designing molecules, which would compete with normal substrates at specific receptor sites or inhibit essential processes. New approaches, such as quantitative structure activity relationships and computer-aided molecular design, became components of the discovery process. Much information on modes of action and metabolic pathways emerged from these studies. One drawback was that the approach relied on known target sites. Another drawback was that in the whole organism, predictability was often limited by the failure of an active molecule to overcome physical and physiological barriers, which are not readily apparent in isolated *in vitro* tests.

The focus on newer modes of action and environmental acceptability led to the exploration of vulnerable biological target sites. This included the investigation of compounds that influenced insect development or behavior. Juvenile hormones and their analogs achieved some commercial success, and attractants and pheromones of several species are widely used in pest management programs. Behavioral compounds have no lethal effects and must be used in traps or programs to suppress populations by, for example, mass trapping or the disruption of mating.

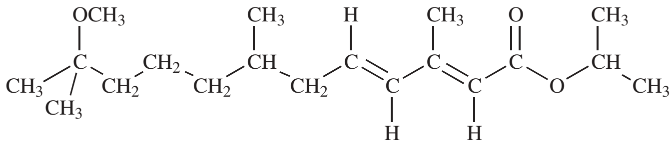
## 4. Insect Growth Regulators, Juvenile Hormones, and Analogs

The development of chemicals for insect control based on insect juvenile hormone models followed extensive research in insect physiology. This revealed that molting and metamorphosis were controlled by hormones circulating in the hemolymph. Many compounds may interfere with insect development. These include compounds that affect larval ecdysis (cuticle shedding process when larvae molt from one instar to the next), subsequent chitin deposition (or tanning), and metamorphosis (transition from larvae to pupae and adults in holometabolous insects).

The identification of the juvenile hormone from the male, silk moth, *Hyalophora cecropia*, as methyl (*E,E*)-cis-10,11-epoxy-7-ethyl-3,11-dimethyltridecadi-2,6-enoate (JH I, [13804-51-8]) was followed by the synthesis of thousands of analogs that were evaluated, and several were developed as practical insecticides (14). JH mimics or agonists act at the receptor sites for JH and affect embryogenesis, metamorphosis, reproduction, diapause, and other critical developmental processes. They tend to maintain an insect in a juvenile stage.

JH is insecticidal when applied exogenously to insect eggs and last instar larvae, and it prevents the development of physiologically competent adults. The structurally optimized analogs are more lipophilic and environmentally stable than are the natural compounds and are often highly specific in their insecticidal action. Generally, they possess low oral toxicity to mammals and are readily degraded in the environment to simpler molecules. The drawbacks for agricultural pest control lie in their very slow toxic action and general lack of persistence.

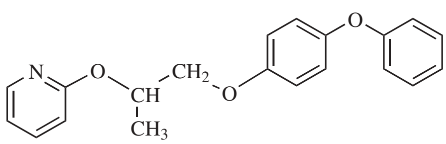
The first structural modifications of naturally occurring hormones developed commercially were methoprene and hydroprene. These were sufficiently stable in the environment for practical application as pest control agents. They were very effective against household pests but were not highly active against agricultural pests and had low residual activity under field conditions. JH agonists tend to be impractical for the control of insect pests where the immature forms cause the crop damage e.g., *Lepidoptera*. Methoprene (isopropyl *(E,E)-(R,S)*-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate, [40596-69-8]) acts as an insect juvenile hormone and prevents metamorphosis of larvae to viable adult stages. It is readily degraded in the soil environment. It is readily biodegraded by hydrolysis of the ester group, *O*-demethylation, and oxidative cleavage of the bond at the 4-position. Methoprene is highly specific to insects, and its oral toxicity to mammals is extremely low (rat oral $LD_{50}$ is >34,000 mg/kg).




Methoprene

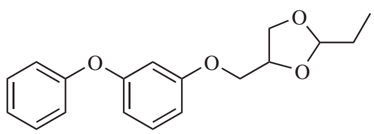
Hydroprene (ethyl *(E,E)-(R,S)*-3,7,11-trimethyldodeca-2,4-dienoate) is closely related structurally to methoprene. It is known as Gen Trol* [40196-46-2]. It also is an insect juvenile hormone mimic and, when applied to larvae, prevents metamorphosis to viable adult stages. The *(E,E)-(S)*-isomer is more effective against insects than is the *(E,E)-(R)*-isomer.

Other synthetic mimics have been developed commercially, including pyriproxifen (4-phenoxyphenyl *(R,S)*-2-(2-pyridyloxy) propyl ether, [95737-68-1]), which suppresses embryogenesis and adult formation (15).




Pyriproxyfen

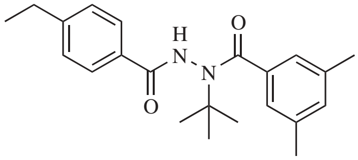
A juvenile hormone analog, diofenolan, a dioxalane derivative, is active against scales and *Lepidoptera*.



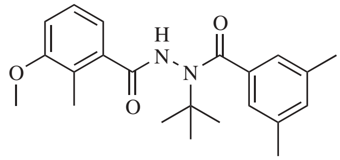

Diofenolan

Ecdysone receptor agonists or molting accelerating compounds (MACs) are non-steroidal ecdysone analogs and mimic the natural function of the endogenous molting hormone 20-hydroxy-ecdysone. Compounds currently marketed are tebufenozide [112410-23-8], methoxyfenozide, halofenozide, and chromafenozide.

All except halofenozide are more or less specific to *Lepidoptera*.




Tebufenozide

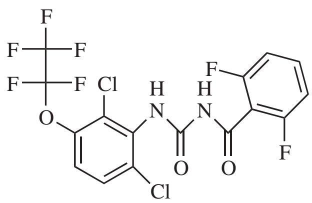



Methoxyfenozide

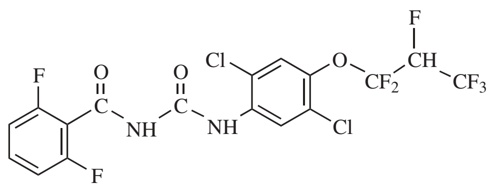
Methoxyfenozide induces a precocious moult in lepidopteran larvae. This is followed by cessation of feeding and, ultimately, death.

## 5. Compounds Affecting Other Metabolic Pathways

A metabolic pathway peculiar to insects (and *Crustacea*) is the synthesis of chitin, a glucosamine polysaccharide, which is an important component of the insect integument. Inhibitors of this pathway have been synthesized, and diflubenzuron (1-(4-chlorophenyl)-3-(2,6-difluorobenzyl)urea, [35367-38-5] effectively controls a wide range of insects. Hexaflumuron [86479-06-3], an insect growth regulator of the benzoylphenylurea class, was registered for subterranean termite control in 1994, and lufenuron [103055-07-8] was registered for flea control.




Hexaflumuron



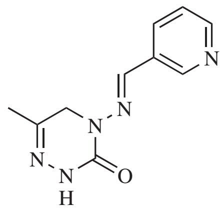

Lufenuron

## 6. Compounds Affecting Insect Behavior

A variety of compounds affect insect behavior. Repellents, such as Deet (*N,N*-diethyltoluamide, [134-62-3]) are applied directly to human skin. Many different synthetic compounds, extracts, and baits are used in insect traps as baits to monitor and detect the presence of a pest species or to reduce its population. Pheromones may elicit a variety of behavioral responses in insects and are used as components of pest management systems.

Insect pheromones are released into the atmosphere by insects to affect the behavior of other insects. They are termed "semiochemicals," a class that includes pheromones, kairomones, feeding stimulants, synthetic attractants, and repellents. The compounds most frequently used in pest management are the sex attractant pheromones released by female *Lepidoptera* to attract the male for mating purposes. They are ideal for situations in which only a single major pest species must be controlled or detected, and they can be used to reduce insect populations by permeating the air during infestations to disrupt mating.

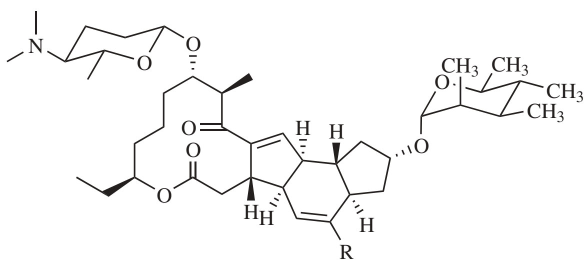
Pymetrozine [123312-89-0], a pyridine azomethine, has been introduced as an antifeedant and is active against homopterous pests.




Pymetrozine

## 7. Compounds Acting on the Nicotinic Acetylcholine Receptor

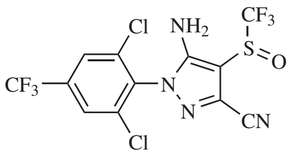
Neonicotinoid insecticides act as agonists of the insect nicotinic acetylcholine receptor (nAChR) located in the central nervous system. There is evidence that they may also have an antagonistic site of action at another site in the nAChR complex. The nitromethylenes as a class appear to have a much higher affinity for the insect nicotinic receptor than for its mammalian equivalent. This confers great selectivity toward insects. Another agonist at this insect receptor is the macrocyclic natural product spinosad, a mixture of two naturally occurring macrolides spinosyn A (85%) and spinosyn D (15%), which were isolated from the soil microorganism *Saccharopolyspora spinosa*. Spinosad appears to have a different binding site at the nicotinic acetylcholine receptor than do the nitromethylenes.



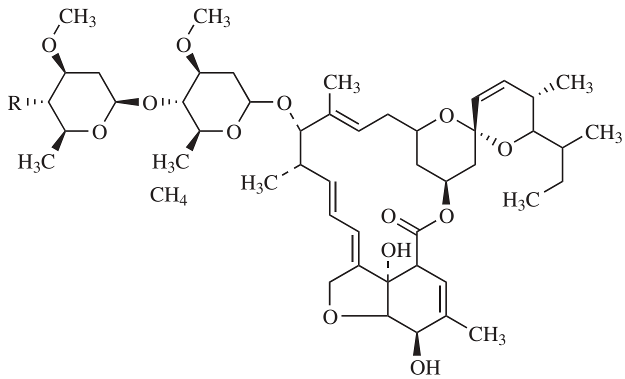

Spinosyn A (R=H) & D(R=Me)
Spinosad

## 8. γ-Aminobutyric Acid (GABA) Receptor/Chloride Ionophore Complex

In insects, GABA-gated chloride channels are found in both the CNS (central nervous system) and at the skeletal neuromuscular junction. GABA antagonists with insecticidal properties include the chlorinated cyclodienes (e.g., dieldrin) and a new class of compounds, the aryl-amino-pyrazoles, e.g., fipronil [120068-37-3]. Although appearing to act at the same target site as the chlorinated cyclodienes, i.e., the chloride ionophore, there is little or no evidence of cross-resistance; ie, cyclodiene-resistant insects are not resistant to fipronil.



Fipronil



Avermectin $B_{1a}$ (R1=OH)
Emamectin $B_{1a}$ (R=NHMe)

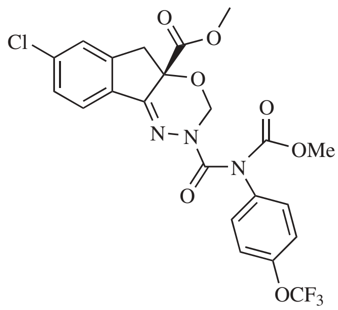
The avermectins are natural products (macrocyclic lactones) or semi-synthetic derivatives. They are potent agonists at the glutamate-gated chloride channel in the insect nervous system. They may also interact with the GABA receptor complex, which was originally thought to be their primary target site.

Recently, a new semi-synthetic avermectin derivative, emamectin benzoate, was introduced (MK 244; [137512-74-4]). The hydroxy-group in the terminal sugar ring (R) is replaced by a methylamino group.

## 9. Voltage-Gated Sodium Channel Effectors

The voltage-gated sodium channel (VSC) in nerve axon membrane of insects has many pharmacologically characterized toxin binding sites. These are the targets for several synthetic insecticides; natural toxins, e.g., tetrodotoxin; and polypeptide neurotoxins, e.g., from snails and scorpions. The propagation of action potentials in insect nerve axons is due to a rapid increase in membrane sodium conductance via VSC. Among common synthetic insecticides, DDT, pyrethroids, and dihydropyrazoles are known to interact with VSC.

A new compound from DuPont, indoxacarb [144171-61-9], also interacts with the VSC at the binding site of local anaesthetics. This is an oxadiazine insecticide that is especially active on lepidopteran larvae (16).



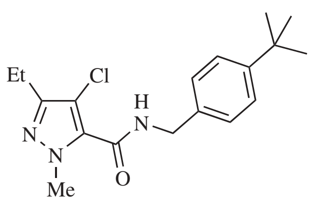
Indoxacarb

Indoxacarb is a pro-insecticide with only weak activity on VSC. It is metabolically activated by cleavage of the *N*-methoxycarbonyl group. The resulting *NH*-derivative is a potent sodium channel blocker. Because indoxacarb acts on a binding site different from that of pyrethroids, no cross-resistance between these classes has been found.

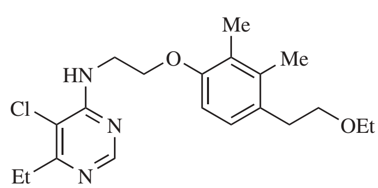
## 10. Insecticides and Acaricides Acting on Mitochondrial Respiration

Mitochondrial electron transport coupled with oxidative phosphorylation is vital for energy production in insects as well as in other organisms. Electrons from reduced cofactors such as NADH (nicotinamide adenine dinucleotide) are transferred via several intermediates (complexes) to reduce oxygen to water, producing ATP as an energy source.

**10.1. Complex I Inhibitors.** Several inhibitors of complex I (NADH dehydrogenase) are known, eg, rotenone and the piericidins. Several newer synthetic acaricides that have this mode of action have been introduced, e.g., fenpyroximate, [134098-61-6] (Nihon Nohyaku 1991); pyridaben, [96489-71-3] (Nissan 1991); fenazaquin (Dow 1993); tebufenpyrad, [119168-77-3] (Mitsubishi 1993); and pyrimidifen, [105779-78-0] (Sankyo, Ube 1995).

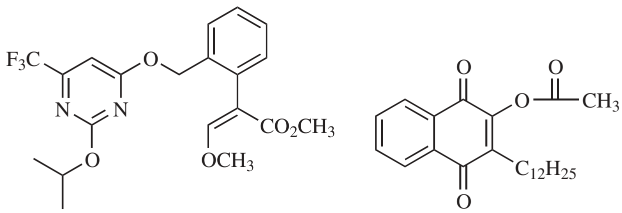


Tebufenpyrad (M K 239)



Pyrimidifen

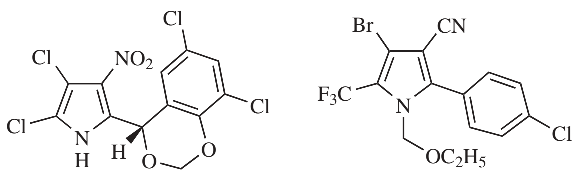
**10.2. Complex III Inhibitors.** The methoxyacrylate (MOA) group is the toxophore of many commercially successful strobilurin-based fungicides, which act as inhibitors of complex III (cytochrome c reductase). Fluacrypyrim is the first acaricide from this group (Nippon Soda/BASF), with the same mode of action. Methoxyacrylates with excellent insecticidal activity have been found, but unfortunately, high mammalian toxicity has precluded their development. Acequinocyl, [57960-19-7] (AKD-2023) is an acaricide under development by Agro-Kanesho. It has great lipophilicity and shows activity against all stages of spider mites (17).




Fluacrypyrim Acequinocyl

Acequinocyl is a pro-acaricide, and the de-acylated metabolite with its free hydroxy group is a potent inhibitor of complex III of the mitochondrial electron transfer (ubiquinol oxidation site, $Q_0$ center).

**10.3. Uncouplers.** Uncouplers are generally weakly acidic compounds that destroy the proton gradient of mitochondrial cell membranes by transporting protons through the membrane, but without linking this to ATP production. One of the early synthetic organic pesticides, DNOC, acts through an uncoupling mechanism. Because nitrophenols uncouple oxidative phosphorylation from electron transport, this leads to the depletion of energy reserves and, eventually, to cell death. Nontarget organism toxicity must be considered due to this nonspecific mode of action. Synthesis of analogs of the natural product dioxapyrrolomycin, which has moderate insecticidal activity, led to the insecticidal 2-arylpyrroles. Chlorfenapyr, [122453-73-0] (AC-303630) was introduced to the market in 1995 as an insecticide with a broad spectrum of activity against lepidopteran and sucking pests. The compound is a pro-pesticide, the active compound being generated by oxidative *N*-dealkoxylation to the *NH* derivative.




Dioxapyrrolomycin Chlorfenapyr

## 11. Integrated Pest Management

Although employment of chemicals for insect pest control is essential to modern society, the extensive and injudicious use of chemical insecticides since 1946 has resulted in many problems, including (i) widespread insect resistance, (ii) emergence of resurgent and secondary pests whose regulating natural enemies have been adversely affected, (iii) hazards to human health, (iv) environmental pollution, and (v) exponentially increasing costs of new insecticides (18–21).

Many of these unintended consequences of chemical pest control arose from the pervasive eradication philosophy that resulted from the euphoria about the effectiveness of successive generations of organochlorine, organophosphorus, carbamate, and pyrethroid insecticides.

The WHO initiated a global eradication program for malaria based on annual residual house spraying directed at the Anopheles mosquito vectors. In the United States, eradication programs by insecticide applications were undertaken against such pests as the gypsy moth *Lymantria dispar*, the Japanese beetle *Popillia japonica*, the red imported fire ant *Solenopsis invicta*, and the yellow fever mosquito *Aedes aegypti*.

Initial reaction was to exploit yet another group of insecticides with different chemistry as each program faltered because of insecticide resistance, destruction of wildlife, and environmental pollution. Thus, humans are confronted by the anomaly that since the 1940s, despite a 10-fold increase in the use of insecticides and a 20-fold proliferation of the chemicals available for insect control, there has been little change in the benefit/cost ratio to the farmer. Repeated estimates by the U.S. Department of Agriculture have not indicated any appreciable decrease in the extent of insect damage to the crops most heavily treated with insecticides, i.e., alfalfa, apple, corn, cabbage, cotton, and potato. Average losses due to insect and mite pests in these crops were estimated as follows: 1900–1904, 11.3%; 1910–1935, 14.0%; 1942–1951, 11.0%; and 1951–1960, 13.3% (22).

Management systems have been proposed that will direct insect pest control away from exclusive reliance on insecticides and toward the optimization of pest control tactics in an ecologically and economically sound way. Integrated pest management (IPM has been variously defined as (i) "a system in which all available techniques are evaluated and consolidated into a unified program to regulate pest populations so that economic damage is avoided and environmental disturbances are minimized," (ii) as "the intelligent selection of and use of pest control actions that will ensure favorable economic, ecological, and sociological consequences," or (iii) as "the selection, integration, and implementation of pest control based on predicted economic, ecological, and sociological consequences"). IPM is similar to or synonymous with the term integrated crop management (ICM) in Europe. This has been defined as follows: "An approach to farming which aims to balance production with economic and environmental considerations by means of a combination of measures including crop rotation, cultivations, appropriate crop varieties and careful use of inputs" (http://glossary.eea.eu.int/).

The primary goals of IPM are (i) to determine how the life system of the pest needs to be modified to reduce the numbers to tolerable levels, i.e., below the economic threshold; (ii) to apply biological knowledge and current technology to achieve the desired modification, i.e., applied ecology; and (iii) to devise procedures for pest control compatible with economic and environmental control aspects, i.e., economic and social acceptance.

IPM practices rely heavily on protection and conservation of natural enemies, parasites, predators, and diseases that regulate or balance populations of insect pests. IPM programs are based on two important parameters: the economic injury level defined as that population density of a pest that causes enough injury to justify the cost of remedial treatment, and the economic threshold, defined as that pest density at which control measures should be applied to prevent an increasing insect population from reaching the economic injury level. Thus, IPM is a dynamic concept akin to game, fisheries, and forest management.

Whenever applied, IPM practices have consistently resulted in decreases in insecticide applications of 50% to 90% over conventional spray programs. By encouraging natural enemies, IPM practices markedly decrease the process of natural selection by pesticides that is responsible for resistance. Natural enemy preservation also prevents the great fluctuations and surges in insect pest populations observed after the injudicious use of broad-spectrum insecticides. Under the IPM concept, insecticides are generally used when other practices are inadequate and the pest population reaches the economic threshold. In order to make the IPM concept effective, insecticides must be used as selectively as possible, with minimal disturbance to all other elements of the ecosystem. Thus, IPM practices are essentially blueprints for the proper use of insecticides in insect pest control.

Insecticide management is concerned with the safe, efficient, and economical handling of insecticides during manufacture, utilization, and disposal. The essential components are selection of the proper insecticide for the IPM program; selection of the mode, timing, and dosage of application; consideration of the problems of resistance and resurgence, the possible effects of insecticide residues on food crops, and in the environment; and the impact of these on humans, domestic animals, and wildlife.

## BIBLIOGRAPHY

"Insecticides" in *ECT* 1st ed., Vol. 7, pp. 881–908, by D. E. H. Frear, The Pennsylvania State College, and M. A. Coler and M. H. Peskin, Markite Co.; in *ECT* 2nd ed., Vol. 11, pp. 677–738; "Insect Control Technology" in *ECT* 3rd ed., Vol. 13, pp. 413–485, by R. L. Metcalf, University of Illinois; in *ECT* 4th ed., Vol. 14, pp. 524–602, by Robert L. Metcalf, University of Illinois, Urbana-Champaign; "Insect Control Technology" in *ECT* (online), posting date: December 4, 2000, by Robert L. Metcalf, University of Illinois, Urbana-Champaign.

## CITED PUBLICATIONS

1. R. L. Metcalf and R. A. Metcalf, *Destructive and Useful Insects*, 5th ed., McGraw-Hill, New York, 1993.
2. E-C Oerke et al., *Crop Production and Crop Protection*, Elsevier PO Box 211,1000 AE Amsterdam, The Netherlands, (1994), 808 pp.
3. R. L. Metcalf, *J. Agr. Food Chem.* **21**, 511 (1973).

4. Insect–Pest Management Control, *Principles of Plant and Animal Pest Control*. Volume 3. National Academy of Sciences, Publication 1695, Printing and Publishing Office, Washington, D.C.(1969).
5. A. L. Aspelin, *Pesticide Industry Sales and Usage, 1992 and 1993 Market Estimates and Pesticide Industry Sales and Usage, 1994 and 1995 Market Estimates*, Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C., 1997.
6. A. L. Aspelin and A. H. Grube, *Pesticides Industry Sales and Usage: 1996 and 1997 Market Estimates*, Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C., 1999.
7. J. R. Plimmer in R. Krieger, ed., *Handbook of Pesticide Technology*, 2nd ed., Vol. 1, Academic Press, San Diego, 2001, pp. 95–107.
8. R. Nauen and co-workers, in I. Ishaaya, ed., *Biochemical Sites Important in Insecticide Action and Resistance*, Springer, Berlin, 2001, pp. 77–105.
9. R. Nauen and T. Bretschneider, *Pesticide Outlook*, **13**, 241–245(2002).
10. P. G. Richards, M. K. Johnson, and D. E. Ray, *Mol. Pharmacol.* **58**, 577–583(2000).
11. M. Ollinger and J. Fernandez-Cornejo, *Regulation, Innovation and Market Structure in the U.S. Pesticide Industry*, ERS Economic Report No. 719, USDA, Washington, D.C., 1995.
12. V. Salgado, in G. T. Brooks and T. R. Roberts, eds., *Pesticide Chemistry and Bioscience: The Food Environment Challenge*, Royal Society of Chemistry, Cambrige, U.K., 1999, pp. 236–246.
13. I. Ujvary, *Phytoparasitica*, **30**, 5(2002).
14. J. Edwards and J. J. Menn in R. Wegler, ed., *Chemie der Pflanzenschutz und Schädlingbekämpfungsmittel*, Vol. 6, Springer-Verlag, Berlin, 1981, pp. 185–214.
15. J. Miyamoto et al., in S. O. Duke, J. J. Menn and J. R. Plimmer, eds., *Pest Control with Enhanced Environmental Safety*, ACS Symposium Series 524, American Chemical Society, Washington D.C., 1993, pp. 144–168.
16. K. D. Wing and co-workers, *Arch. Insect Biochem. Physiol.* **37**, 91–103(1998).
17. S. Kinoshita and co-workers, *Pesticide Science* **55**, 633–675(1999).
18. R. L. Metcalf, *Annu Rev. Entomol.***25**, 219(1980).
19. C. B. Huffaker, ed., *New Technology of Pest Control*, Wiley, New York, 1980.
20. R. L. Metcalf and W. H. Luckmann, eds., *Introduction to Insect Pest Management*, 3rd ed., Wiley, New York, 1994.
21. L. Pedigo, *Entomology and Pest Management*, Macmillan Publishing Co., New York, 1989.
22. C. B. Huffaker, ed., *New Technology of Pest Control*, Wiley, New York, 1980.

## GENERAL REFERENCES

The following articles are from J. R. Plimmer, ed., *The Encyclopedia of Agrochemicals*, Wiley, New York, 2003.

J. R. Plimmer "Insecticidal Carbamates," Vol. 2, pp. 924–932; J. R. Plimmer and D. W. Gammon, "Insecticides, Organochlorines," Vol. 2, pp. 946–977.

I. Ishaaya and D. Degheele, *Insecticides with Novel Modes of Action*, Springer, Berlin, 1998.

A. S. Perry, I. Yamamoto, I. Ishaaya, and R. Y. Perry, *Insecticides in Agriculture and Environment*, Springer, Berlin, 1998.

I. Ishaaya, ed., *Biochemical Sites Important in Insecticide Action and Resistance*, Springer, Berlin, 2001.

JACK R. PLIMMER
Tampa

DEREK W. GAMMON
Sacramento

Table 1. **Insecticides Used by American Farmers in 1995 t**[a]

| Name | | Class |
|---|---|---|
| Oil | 23,181 | petroleum oils |
| Chlorpyrifos | 6,697 | organophosphate |
| Terbufos | 3,942 | organophosphate |
| Methyl parathion | 2,704 | organophosphate |
| Carbofuran | 2,314 | carbamate |
| Carbaryl | 2,073 | carbamate |
| Phorate | 2,020 | organophosphate |
| Cryolite | 1,839 | inorganic |
| Aldicarb | 1,825 | carbamate |
| Propargite | 1,646 | propynyl sulfite (acaricide) |
| *Total* | *67,594* | |

[a] Ref. 7.