8949

sprays. The active ingredient is dissolved in some type of oil or organic solvent. Oils may be further diluted in kerosene or diesel fuel. Oil solutions are applied as liquid sprays.

Flowables (F) . This formulation was created for insecticides that were not soluble in water or oil. Therefore, the technical material is wet-milled with a clay diluent and water, leaving the pesticide-diluent mixture finely-ground but wet. This thick and creamy "pudding" mixes well with water and can be sprayed. However, constant agitation is required as with the WPs. Flowables are applied as liquid sprays.

Ultralow-volume (ULV). Technical material dissolved in a very low volume of solvent. Applied without dilution by special aerial or ground equipment that limits the volume applied (0.5 pints to 0.5 gallons gallons per acre). ULVs are applied as a liquid spray.

Dusts (D). An active ingredient with an inert clay diluent (such as pyrophyllite). Dusts are distinguished from granulars by size. Dusts will pass through a 60 mesh screen. Drift is a major disadvantage of using dusts. Dusts are applied as a dry formulation.

Granular (G). Small pellets formed from inert clays sprayed with a toxicant-containing solution to give the desired content. Granulars range from 2 to 25% active ingredient. Granulars are applied as a dry formulation.

Aerosols. A common formulation used by homeowners. Aerosols are comprised of technical material solubilized in a volatile, petroleum solvent which has been pressurized (by a propellant gas). When the petroleum solvent is atomized, it evaporates quickly, leaving micro droplets of toxicant suspended in the air. Little to no residual activity is provided by aerosols. Aerosols are a liquid formulation.

Fumigants. The active ingredient of a fumigant either sublimates or boils at standard temperature and pressure. For example, moth balls and moth crystals, naphthalene and paradichlorobenzene, respectively, are solids that sublimate slowly at room temperature. Other fumigants have extremely low boiling points and are kept as liquids under high pressure. Pressurized fumigants are primarily used for drywood termite control, nematode control, and stored product insect control. Fumigants are applied as a gas.

Baits. This formulation has seen renewed interest in recent years because they use a very small quantity of insecticide and specifically target the pest of interest. Baits are comprised of an active ingredient incorporated into a food matrix that is palatable to the target insect pest.

Controlled-release (CR). This formulation is based on the incorporation of a volatile insecticide into a (usually) polymer matrix. By several mechanisms, including degradation or diffusion, a steady release of insecticide occurs. Controlled release formulations may be liquids or solids that are released as a gas.
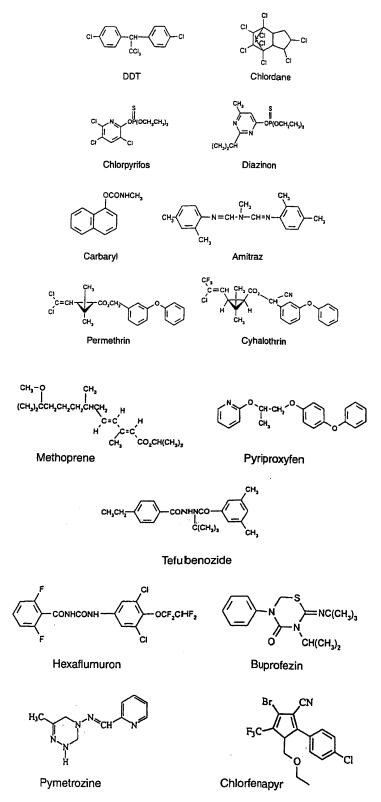
Insecticides

Insecticides can be classified or grouped by their chemical structure, mode of entry into the insect, toxicity, or mode of action. The most common method of classification employed by insecticide toxicologists is chemical structure. By this method, insecticides with a similar chemical framework or motif are grouped together. As this is the most widely accepted method of discussing insecticides, it will be employed here. Pesticides have been used since at least 1200 BC; however, the following discussion will focus on modern synthetic organic insecticides debuting after World War II. Some mention of botanical insecticides will also be included as these plant-derived chemicals often serve as models for synthetic organic insecticides. The characteristics, mode of action, toxicity, uses, examples and peculiarities of each insecticide chemical class will be described.

Organochlorines

Dichlorodiphenyltrichloroethane (DDT) group. Examples of this group include DDT, DDD, TDE, Dicofol, and Methoxychlor. These insecticides are effective against a wide range of insect pests, most notably the mosquito. In fact, Paul Müller won the Nobel prize in 1948 for discovering the insecticidal properties of DDT. These insecticides are environmentally persistent (DDT has a half life of 10 years), have a low vapor pressure, low water solubility, moderate stability to sunlight and low mammalian toxicity (toxicity category II to III). They are also lipophilic and metabolically stable which results in bioaccumulation.

Interestingly, these insecticides exhibit a negative temperature coefficient of toxicity. In other words, they become more toxic at lower temperatures.

Fig. 539 Representative molecular structures of each insecticide class.

Imidacloprid

$F_3C-CF_2-CF_2-CF_2-CF_2-CF_2-CF_2-CF_2-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-NH-CH_2-CH_3$

Sulfuramid

Avermectin (base structure)   Hydramethylnon

Fipronil

Fig. 539 (Continued).

DDT was banned from use in the United States in 1973. The target site for this group is the voltage-gated sodium channel, a neuron protein involved in the propagation of nerve impulses. It is believed that these chemicals act as a wedge that hold the channels in the open position thus preventing repolarization and resulting in constant stimulation of the nerve.

Chlorinated cyclics. Examples of this group include Lindane, Aldrin, Dieldrin, Endrin, Isodrin, Chlordane, Mirex, Heptachlor, Chlordecone, and Endosulfan. These insecticides were used widely in urban settings, most notably for termite (Chlordane, Aldrin, Heptachlor) and imported fire ant (Mirex) control. Also, because they were stable in soil and against ultraviolet light, they were used against soil inhabiting insects in agriculture. Most of these insecticides were banned from agricultural use in the USA between 1975 and 1980. Mirex was banned for use in the USA in 1977 and chlordane in 1988. This group is persistent, lipophilic and has a low vapor pressure (10^{-6}–10^{-7} mmHg). Lindane is still available for use in the USA on avocados, pecans, Christmas trees, commercial ornamentals, structural treatments, and dog dusts. Many of these insecticides

are metabolically activated (i.e., are made more toxic *in vivo*) by an epoxidation reaction catalyzed by cytochromes P450. The mode of action of cyclodienes was only recently elucidated. These insecticides are gamma-aminobutyric acid (GABA) receptor antagonists. Although environmentally persistent, acute toxicity of organochlorines is generally low to moderate (toxicity category II to III).

Organophosphates. Derived from phosphoric acid, this is the most toxic group of insecticides (toxicity category I to II). This large group of insecticides replaced the organochlorines and includes Malathion, Parathion, Dimethoate, Dicrotophos, Disulfoton, Monocrotophos, Trichlorfon, TEPP, Acephate, Methamidophos, Diazinon, Azinphosmethyl, and Chlorpyrifos among others. Organophosphates are unstable, susceptible to hydrolytic and oxidative detoxification, moderately to considerably water soluble and have a vapor pressure in the range of 10^{-3} to 10^{-5} mmHg. The insecticidal activity of organophosphates was discovered in Germany during World War II while studying the nerve gases Sarin, Soman, and Tabun, which are also phosphoric acid derivatives. Organophosphate insecticides are

anticholinesterases. They bind, with tenacious affinity, to acetylcholinesterase (AChE), a crucial enzyme found in the synaptic cleft between neurons or neuromuscular junctions. AChE normally hydrolyses the neurotransmitter acetylcholine released from the presynaptic neuron. However, organophosphate insecticides inhibit this enzyme preventing normal hydrolysis of acetylcholine and resulting in constant post-synaptic depolarization (stimulation). Many organophosphate insecticides are activated (made more toxic) *in vivo*. Phosphorothioate (P = S) is oxidized to an oxon (P = O) form by cytochromes P450 making the insecticide bind even more tightly to acetylcholinesterase.

Although organophosphorus insecticides are all derived from phosphoric acid, there are 6 different subclasses depending on the molecular composition about the phosphate nucleus. These subclasses include phosphate, phosphonate, phosphorothioate, phosphorothiolate, phosphorodithioate, and phosphoramidate. Organophosphate insecticides have seen wide use in agricultural, silvicultural, and urban insect control. However, because of their acute toxicity, much of this insecticide class is being banned from use, especially in the urban environment.

Carbamates. Introduced by the Geigy Chemical Company in 1951, carbamates are derivatives of carbamic acid (CO_2NH_3). As with the organophosphates, these insecticides are also anticholinesterases. They are biodegradable, moderately volatile (vapor pressure between 10^{-4} and 10^{-6} mmHg), moderately soluble in water, and susceptible to hydrolysis. Some of the more common carbamates include Propoxur, Bendiocarb, Carbaryl, Methomyl, Carbofuran, Aldicarb, and Thiodicarb. These insecticides exhibit toxicities that range from class I (e.g., Methomyl) to III. Carbaryl, introduced in 1956, has been used more than any other carbamate because of its low mammalian toxicity (Oral LD_{50} 307 mg/kg) and broad spectrum of insect control.

Formamidines. This is a small group of pesticides with insecticidal, acaracidal and ovacidal activities. The only formamidine currently in use in the USA is Amitraz. Chlordimeform was found to be carcinogenic and banned from use in the USA in 1988. Formamidine insecticides are octopaminergic agonists, so they interfere the normal activity of biogenic amines. Because octopamine is an important neurotransmitter, formamadine interference results in behavior

modification. For example, it causes loss of appetite and feeding, alters mating behavior, and detachment of ticks from the host. They also have been shown to synergize pyrethroid insecticide toxicity by modifying binding cooperativity in neural proteins. Toxicity category ranges from II to III.

Pyrethroids. Pyrethroids are synthetic chemicals modeled after the botanical insecticide pyrethrum, an organic extract of *Chrysanthemum cinerariaefolium* (Compositae) flower heads. The active principle of pyrethrum is pyrethrins, esters formed by the combination of acid (mono- and di-chrysanthemic acids) and alcohol (pyrethrelone, cinerolone, and jasmolone) components. Although pyrethrins exhibit good insecticidal activity, they were very labile. Therefore, synthetic versions were produced to improve their stability. Pyrethroids may be further categorized based into Type I and Type II groups. These refer to the types of neurological tremors produced and is loosely associated with the presence of a cyano (-CN) moiety at the alpha carbon position. Pyrethroids are widely used broad spectrum insecticides including Permethrin, Resmethrin, Tetramethrin, Allethrin, Bifenthrin, Cypermethrin, Fenvalerate, Deltamethrin, Tralomethrin, Fluvalinate, Fenpropathrin, Cyhalothrin, and Esfenvalerate. Pyrethroids exhibit stereoisomerism (geometric, enantiomeric), low water solubility and vapor pressure (10^{-6} to 10^{-7} mmHg), negative temperature coefficient of toxicity (the alpha-cyano pyrethroids may exhibit a slightly negative or positive temperature coefficient of toxicity) and stability without persistence (bioaccumulation). They are susceptible to hydrolysis. Pyrethroids represent one of the first steps toward a precision targeting approach to pest control because they are more toxic to insects than mammals. This moderate level of specificity has resulted in extensive use of pyethroid insecticides. Unfortunately, pyrethroids are extremely toxic to fish, so care must be exercised when applications take place near water. Pyrethroids target the voltage-gated sodium channel of the nervous system and result in uncontrolled nerve excitation, as do the DDT insecticides. However, the specific binding site on the voltage-gated sodium channel is different from the DDT group.

Insect growth regulators. This group is comprised of a diverse group of chemical compounds with varying molecular structures. However, they are grouped together here because they all affect insect growth in

some manner. Note that these chemicals are comparatively new tools used in insect control. Interestingly, these chemicals illustrate the evolution of insect control methods which are becoming more specific for the target species which reduces environmental impact and improves efficacy.

Juvenoids. Compounds that mimic the juvenile hormone of insects include Methoprene and Hydroprene. These juvenoids keep the insect in its immature form which prevents the production of future generations and often results in death from conflicting hormonal messages during ecdysis to the adult stage. Fenoxycarb (a carbamic acid derivative without anticholinesterase activity) and Pyriproxyfen also are juvenoids, however, unlike Methoprene and Hydroprene do not resemble the structure of juvenile hormone. All of these compounds act as juvenile hormone agonists (mimics).

Ecdysone agonists. These chemicals mimic the action of the insect hormone ecdysone and thus induce premature molting. Rohm and Haas have developed several ecdysone agonists including Tebufenozide and RH-5849. These are substituted dibenzoyl hydrazine compounds.

Chitin synthesis inhibitors (CSI). The final group of insect growth regulators include the chitin synthesis inhibitors. These include benzoylphenyl ureas (Diflubenzuron, Chlorflurazuron, Teflubenzuron, Hexaflumuron, and Novaluron) and buprofezin. These CSIs inhibit chitin formation thereby causing abnormal cuticular formation and abortive molting. Benzoylphenyl ureas have become important components of subterranean termite control in the US. They also have found utility in veterinary and agricultural areas.

Pyridine azomethines. The only example of this new insecticide group is Pymetrozine (GCA 215,994). Pymetrozine is anticipated to be an important component of IPM programs against sucking insect pests because it exhibits a high degree of selectivity, low mammalian toxicity, and safety to birds, fish and nontarget arthropods. The target site for this insecticide is not currently known; however, it causes an immediate and irreversible cessation of feeding after exposure. The mode of action is due to a blockage of stylet penetration.

Chloronicotinyls. This group was initially developed during the 1970s (heterocyclic nitromethylenes), but recent chemical optimizations have resulted in the highly active insecticide, Imidacloprid. Other modifications resulting in insecticidal chloronicotinyls include Nitenpyram and Acetamiprid. The group has broad applicability as many insect species are susceptible. Imidicloprid is translocated making it ideal for use against sucking insects. It has also been shown to be quite effective as a termiticide. Imidicloprid has been shown to displace alpha-bungarotoxin, a specific ligand of the nicotinic acetylcholine receptor (nAChR) which demonstrates that it acts directly on this receptor. Indeed, electrophysiological experiments have shown that Imidacloprid depolarizes the cell membranes of insect cholinergic motor neurons. Furthermore, Imidacloprid does activate vertebrate nAChRs, however, the effect is more than 1,000-fold weaker than the action on insects. Therefore, it appears as if Imidacloprid is insect selective.

Inhibitors of cellular respiration. A number of relatively new insecticide classes that target cellular respiration are available. These insecticides exhibit a novel mode of action by inhibiting oxidative phosphorylation through several mechanisms. Many are proinsecticides (i.e., they require metabolic activation for toxicity).

Pyrroles. The inspiration for development of this group originated in dioxapyrrolomycin, a fermentation product of *Streptomyces fumanus* isolated in 1985 by American Cyanamid's Medical Research Division. Unfortunately, the mammalian toxicity of this compound was quite high which precluded its use in the insecticide market. However, after extensive chemical manipulation based on a fundamental understanding of oxidative phosphorylation, an insecticidal chemical was produced with acceptable vertebrate toxicity. CL 303,630 (Chlorfenapyr) was the result. This insecticide uncouples oxidative phosphorylation by disrupting the proton gradient across the inner mitochrondrial membrane impairing ATP production. Interestingly, Chlorfenapyr is a proinsecticide requiring oxidative *N*-dealkylation for toxicity. Chlorfenapyr is active against a wide array of insects and is being marketed for use in agricultural and urban environments.

Amidinohydrazones. This insecticide class is represented by Hydramethylnon. Hydramethylnon is primarily used in baits (e.g., against fire ants, pest ants, and cockroaches). It is an extremely effective

insecticide with low mammalian toxicity (toxicity category III). This insecticide is a potent inhibitor of electron transport, specifically ubiquinone cytochrome c reductase (complex III). Interestingly, Hydramethylnon has been used against the German cockroach, *Blattella germanica*, for nearly two decades, however, no resistance has been observed to date.

Halogenated alkyl sulphonamides. Represented by a single insecticide, Sulfluramid, this compound acts as a protonophore disrupting the proton gradient generated by the electron transport system, thus inhibiting ATP production via oxidative phosphorylation. As is Chlorfenapyr, Sulfluramid is a proinsecticide that requires oxidative *N*-dealkylation for toxicity. It is primarily used in ant and cockroach baits.

Sulfluryl fluoride. Sulfluryl fluoride is a fumigant used primarily for the treatment of drywood termites. This is not an organic insecticide, however, it is included here because of its importance in termite control. Known by the trade name Vikane, sulfluryl fluoride disrupts substrate level and oxidative phosphorylation by inhibiting aconitase in the tricarboxylic acid cycle and enolase in the glycolytic cycle.

Additional inhibitors of cellular respiration. Several additional insecticidal compounds that inhibit cellular respiration have been identified and investigated. However, they are in varying stages of development and not currently available for use in the US. These include: 1) Diafenthiuron, a thiourea that is activated *in vivo* to its carbodiimide product which blocks the coupling site and mitochondrial F_0/F_1 ATPase activity; and 2) Fenazaquin, a quinazoline that uncouples oxidative phosphorylation by inhibiting complex I of the electron transport chain. The only other insecticide known to inhibit complex I is Rotenone, a botanical insecticide.

Avermectins. Avermectins are a series of homologous macrocyclic lactone natural products (termed A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a}, and B_{2b}) derived from the soil microorganism *Streptomyces avermitilis*. The B_{1a} and B_{1b} homologues are very potent against mites and certain insect species. These compounds act as chloride channel agonists (GABAergic channels) as do the cyclodienes. Primarily used as an acaracide, avermectins have also been used in fire ant baits and against several leafminers.

Phenylpyrazoles. Represented by Fipronil, the phenylpyrazoles are also GABA-gated chloride channel antagonists. Other phenylpyrazoles exhibit herbicidal activity. Based on synergist data from some insect species (e.g., German cockroach), fipronil may be activated *in vivo*. This insecticide is effective against a wide array of insects and appears to be an extremely effective termiticide.

Miscellaneous/botanicals. Insecticidal chemicals derived from plants (botanicals) also serve as an important source of insecticides. Numerous botanicals are available with diverse modes of action which are discussed elsewhere in this reference. Although botanical insecticides are "natural," often they are extremely toxic and should be handled with great care.

Other insecticides used currently include *Bacillus thuringiensis* (Bt), the active component of which (delta-endotoxin) is now heterologously expressed in numerous crop plants, inorganic insecticides (e.g., boric acid, cryolite [Na_3AlF_6]), fumigants (e.g., para-dichlorobenzene, methyl bromide), and soaps. Many of these additional insecticides are described elsewhere in this reference or can be found in the following references.

Toxicity

Insecticide toxicity is dependent upon the class, formulation, mode of action and mode of entry of a chemical into an organism, and may be assessed or quantified in many different ways. For example, an insecticide's toxicity can be measured based on its carcinogenicity, dermal effects, inhalation effects, reproductive effects, acute toxicity, subchronic and chronic effects and genetic effects. Each group of insecticides will exhibit unique characteristics, and although the toxicity will vary considerably among and between insecticide groups, they must all be handled with great care.

See also, ACARICIDES OR MITICIDES, DETOXIFICATION MECHANISMS IN INSECTS, INSECTICIDE APPLICATION: THE DOSE TRANSFER PROCESS, INSECTICIDE BIOASSAY, INSECTICIDE RESISTANCE, INSECTICIDE TOXICITY, SYNERGISM, PESTICIDE HORMOLIGOSIS, BOTANICAL INSECTICIDES, FOOD-BASED POISONED BAITS FOR INSECT CONTROL.

Comparative toxicity ratings of some common insecticides by insecticide class

Active ingredient	Insecticide class	Toxicity category	LD_{50} (mg/kg, oral rat)
DDT	Organochlorine	II	113
Methoxychlor	Organochlorine	IV	6,000
Parathion	Organophosphate	I	2
Malathion	Organophosphate	IV	5,500
Chlorpyrifos	Organophosphate	II	96–270
Methomyl	Carbamate	I	17
Carbaryl	Carbamate	II	246
Amitraz	Formamidine	III	650
Permethrin	Pyrethroid	II–III	430–4,000
Cypermethrin	Pyrethroid	II	250
Fenvalerate	Pyrethroid	II	451
Pyriproxyfen	IGR (Juvenoid)	IV	>5,000
Methoprene	IGR (Juvenoid)	IV	>34,600
Tebufenozide	IGR (Ecdysone Agonist)	IV	>5,000
Diflubenzuron	IGR (Chitin Synthesis Inhibitor)	III	>4,640
Buprofezin	IGR (Chitin Synthesis Inhibitor)	III	2,198
Pymetrozine	Pyridine Azomethine	IV	5,820
Imidacloprid	Chloronicotinyl	II	450
Hydramethylnon	Amidinohydrazone	IV	>5,000

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INSECTIVORE. An animal that feeds on insects. An entomophage.

INSIGHT LEARNING. This form of learning requires reasoning, which involves analyzing past experiences from which deductions are made. This level of learning is unknown in insects, although some have suggested that tool use displayed by some insects may be indicative of insight learning.

See also, HABITUATION, ASSOCIATIVE LEARNING, LATENT LEARNING, LEARNING IN INSECTS.

INSTAR. The insect (larva or nymph) between molts. Instars are referred to by number: the first instar is the stage between after hatching and before the first molt, the second instar occurs after the first larval (nymphal) molt but before the second, etc. Technically, the pupal stage (if present) is an instar, though it is not numbered like the others, and is simply referred to as the pupa. This term often is confused with 'stadium,' a term restricted to the time interval of an instar.

See also, STADIUM, METAMORPHOSIS.

INSTINCT. Behavior performed without the benefit of previous experience or learning from other members of the species. Unlearned stereotypic behavior.

INTEGRATED PEST MANAGEMENT (IPM). Integrated pest management (IPM) refers to coordinated systems for managing pest populations that use preventive and suppressive control tactics, which are unified by surveillance to assess hazard for injury and to determine whether curative action