INTRODUCTION AND REVIEW

Insecticides are defined as chemicals which are used to control damage or annoyance from insects by poisoning them through oral ingestion of stomach poisons, by contact with the cuticle or by fumigant action through the air. Insects may also be controlled by chemicals such as attractants and repellents which adversely influence their behaviour, and by chemosterilants which prevent their reproduction.

The term "insecticides" has been now replaced by "pesticides" which includes toxic chemicals, whether used against insects, fungi, weeds or rodents, etc. Agricultural disinfectants and animal health products are, in many instances, also included under the term "pesticides".

The use of insecticides has not only permitted the control of diseases transmitted by insects but also has led to increased food production and better health.

Classification of insecticides :

Insecticides have been classified into the following classes according to their mode of action:

1. Stomach or internal insecticides : Insecticides which are eaten by insects are known as stomach insecticides. These insecticides are generally applied against insects with chewing mouthparts but under certain conditions they are also effective against insects with sponging, syphoning, lapping or sucking mouthparts.

2. Contact or external insecticides : The insecticides which kill the insects by means of external contact are known as contact insecticides. These may penetrate into the blood directly through the insect cuticle or by entrance through the spiracles of the respiratory system into the tracheae.

Contact insecticides may be applied directly to the insect or as residues to plant surfaces, animals, habitations or other places frequented by insects.

3. Fumigants : Insecticides which exert their action in the gaseous state are known as fumigants. Their application is generally limited to plants or products in tight enclosures or those which can be enclosed in gas-tight tents or wrappings or to soil.

4. Attractants : These are the insecticides which lure insects through olfactory stimulation. They may be food lures, sex lures or oviposition lures.

5. Repellents : These are mildly poisonous or only offensive insecticides which make food or living conditions unattractive for insects.

Insecticides may be classified by their chemical nature and source of supply into the following types:
1. Inorganic insecticides; (2) Organic compounds of plant origin; (3) Synthetic organic insecticides.

1. Inorganic insecticides : They generally act only as stomach poisons.
2. Organic Compounds of plant origin: They largely act as contact poisons.
3. Synthetic Organic insecticides : They have contact and stomach poison action and are sometimes used as fumigants. However, the contact action predominates.

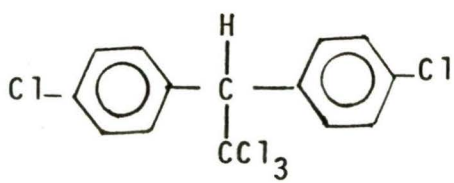
Though in countries with advanced agricultural technology synthetic organic insecticides dominate the market, the inorganic insecticides and organic compounds of plant origin still find useful application in several areas. Some important insecticides are listed in a tabular form below :

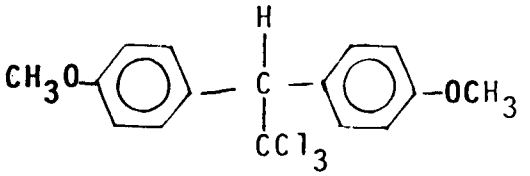
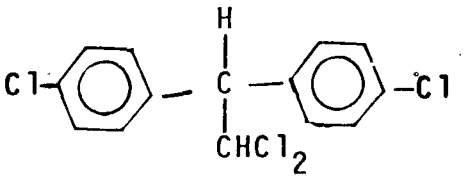
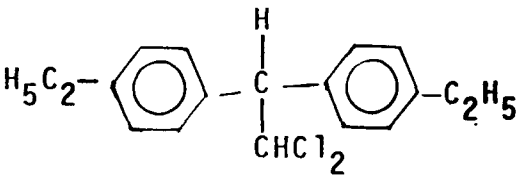
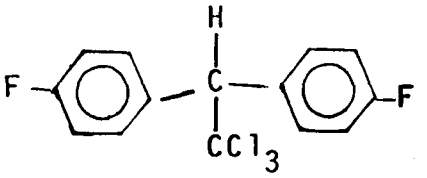
INORGANIC INSECTICIDES :

Compound	Formula	Uses
1. Lead arsenate	$PbHAsO_4$	Control of the gypsy moth, Porthetria dispar, control of the coddling moth, chewing insects, cotton insects and coddling moth controls in apples as well as for other insect-control purposes.
2. Calcium arsenate	$[Ca_3(AsO_4)_2]_3Ca(OH)_2$	Certain cotton insects and coddling moth controls in apples as well as for other insect-control purposes.
3. Fluorides :		
a. Sodium fluoride	NaF	a. Cockroaches, chewing lice, toxicant in poison baits.
b. Sodium fluosilicate	Na_2SiF_6	b. Moth proofing
c. Barium fluosilicate	$BaSiF_6$	c. Chewing insects on plants.
d. Sodium fluoaluminate	Na_3AlF_6	d. General stomach poison, spray and dust.
4. Sulphur and its compounds.		Sulphur and its compounds are among the oldest and most widely used pesticides.
a. Sulphur	S	a. Sulphur is used as a wettable powder or dust, alone or in combination with other pesticides for fungal control of mildews and other organisms.
b. Calcium polysulphide	CaS_x, x=4.5	b. Soil conditioning and fungal, mite and insect control.

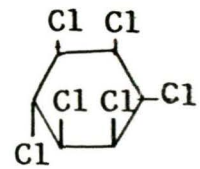
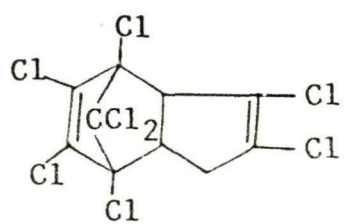
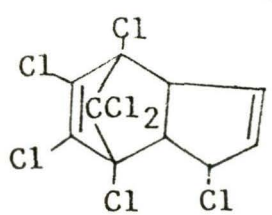
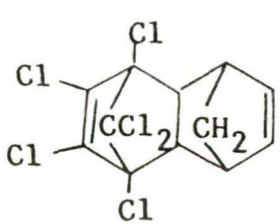
Compound	Formula	Uses
5. Miscellaneous compounds		
a. Cuprous cyanide and Zinc phosphide	CuCN Zn_3P_2	a. Stomach poisons for mosquito larvae and agricultural pests.
b. Borax	$Na_2B_4O_7.10H_2O$	b. To kill house fly maggots in manure or refuse.
c. Boric acid	H_3BO_3	c. Stomach poison for cockroaches.
d. Sodium selenate	Na_2SeO_4	d. Greenhouse soil for the control of red spider mites and aphids.
e. Thallium sulphate	Tl_2SO_4	e. Poison bait for ants.

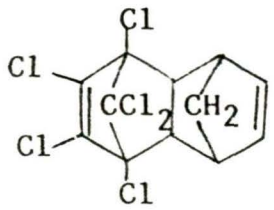
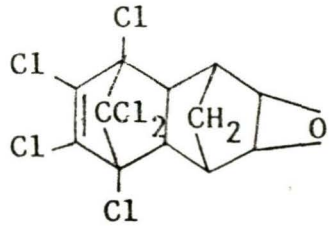
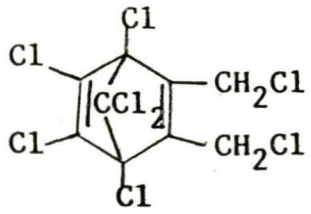
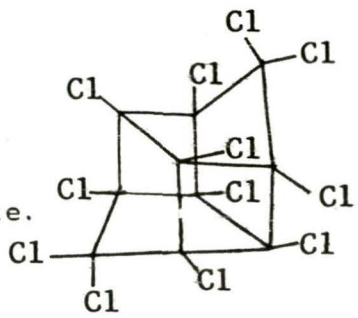
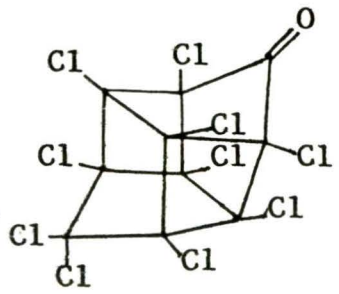
Halogen Derivatives of Aromatic Hydrocarbons

Compound	Formula	Uses
1. DDT [1,1,1-Trichloro-2, 2-bis(p-chlorophenyl ethane)].		Used as a herbicide, fungicide and rodenticide in agriculture.

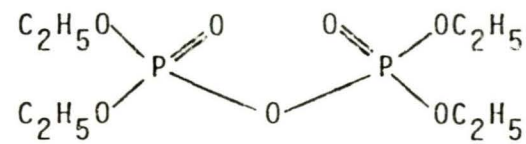
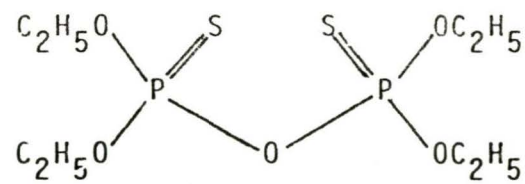
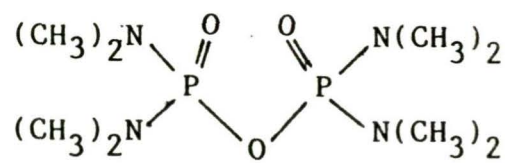
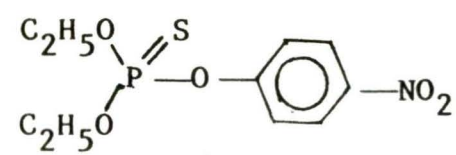
Compound	Formula	Uses
2. DDT analogues.		
a.Methoxy chlor. (1,1,1-trichloro-2,2-bis(p-methoxyl phenyl) ethane].		a.Used on vegetables, crops, cattles and against pests in the household animals and animals forage.
b.DDD (1,1-dichloro-2,2-bis(p-chlorophenyl) ethane].		b.Control of mosquito larvae, tomatohorn worms, and the red-bonded leaf roller.
c.Perthane [1,1-dichloro-2,2-bis(p-ethyl phenyl) ethane].		c.Used in the form of emulsions and suspensions, and also in aerosols.
d.DFDT [1,1,1-trichloro-2,2-bis(p-fluoro-phenyl) ethane].		d.Herbicide, fungicide and rodenticide in agriculture.

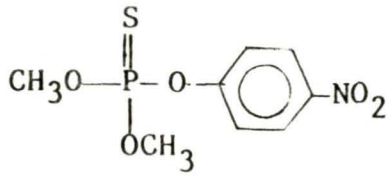
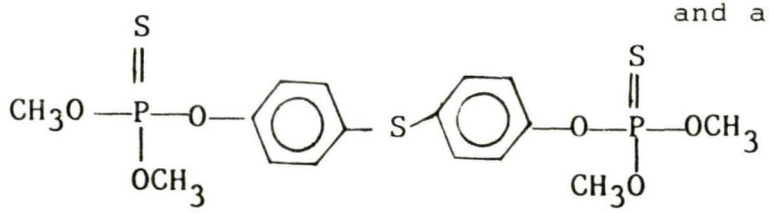
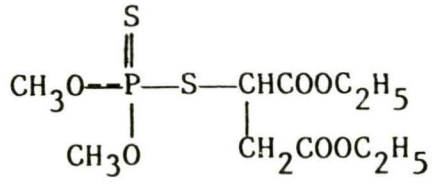
Halogen Derivatives of Alicyclic Hydrocarbons.

Compound	Formula	Uses
1. Benzen hexachloride, Gamma-HCH.		Control various harmful insects, plant pests and animal parasites. The Gamma isomer is the most active compound.
2. Polychloroterpenes.		
a. Strobane.	$C_{10}H_{10}Cl_8$	a. Control of insect pests of cotton, field crops and animals.
3. Polychlorocyclodienes		
a. Chlordane.		a. Control of cockroaches, ants, termites and household pests, soil insects and certain pests of vegetable and field crops.
b. Heptachlor.		b. Control of pests of balfaea, corn and for grasshopper control, insecticidal additive to seed disinfectants.
c. Aldrin.		c. Control of insect pests of fruits vegetables, cotton and as a soil insecticide.

Compound	Formula	Uses
d.Isodrin.		d.Preparation of another insecticide, endrin.
e.Endrin.		e.Control of lepidopterous larvae attacking cotton, field and vegetable crop.
f:Alodan.		f.Control of ectoparasites of animals because of its low mammalian toxicity.
g.Mirex and Kepone.	 Mirex  Kepone	g.Control of ants, soil insects, and against chewing pests of ornamental.

Organophosphorus Insecticides

Compound	Formula	Uses
1. TEPP.(Tetraethyl pyrophosphate).		Control of aphides and red spider mites on agriculture and ornamental crops and in greenhouses.
2. Bladafum.(O,O,O',O' tetraethyl-pyrophosphorodithionate).		This compound has insecticidal, acaricidal activity and an oral LD_{50} of 5 mg/kg for the rat. Greenhouse as a fumigant.
3. Schradan.(OMPA, Octamethyl pyrophosphoroamidate).		OMPA was introduced by pest control. It is well known for its systematic insecticidal properties.
4. Parathion.(O,O-diethyl-O,p-nirophenyl-phosphorothionate).		Acts both as a contact and a stomach poison. It has proved effective against a wider variety of insects than any other insecticide and is generally applied at concentrations of 0.01-0.1%.

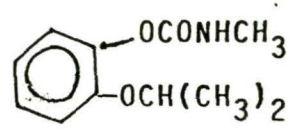
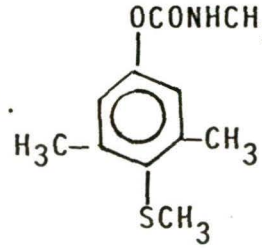
Compound	Formula	Uses
5. Methyl Parathion. (O,O-dimethyl O-p-nitro phenyl-phosphorothionate)		More effective than parathion against aphids and beetles. It acts as a stomach as well as a contact poison. Less toxic to mammals than Parathion.
6. Abate.[4,4'-bis-(O,O-dimethylthiono-phosphoryloxy) diphenylsulphide].		It is used to control mosquitoes and agriculture pests.
7. Malathion. [O,O-dimethyl S-(1,2-dicarbethoxyethyl) phosphorodithioate]		It is a persistent general purpose insecticide, especially suited for household, home garden vegetable and fruit insect control and of public health importance for the control of mosquitoes, flies and lice.

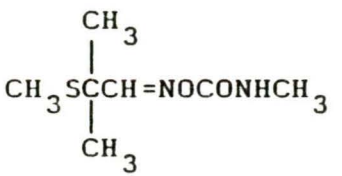
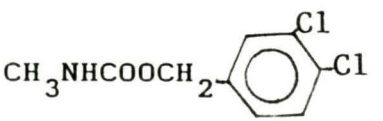
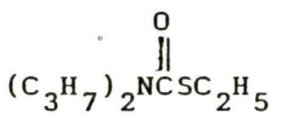
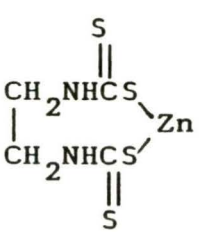
Systemic Insecticides for plants

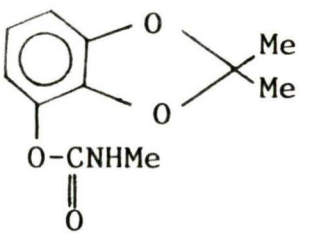
1. Dimefox.[(Dimethyl-amino) phosphoryl-fluoride]	$[(CH_3)_2N]_2\overset{O}{\overset{\|}{P}}F$	Controlling sucking pests of hops and vectors of a virus disease of cacao trees.
2. Dimethoate.[O,O-dimethyl-S-(N-methyl-carbamoyl)methyl-phosphorodithioate.	$(CH_3O)_2\overset{S}{\overset{\|}{P}}-S-CH_2-\overset{O}{\overset{\|}{C}}-NH-CH_3$	Persistent systemic for fruit larvae and for side-dressing of soil about plants.

Compound	Formula	Uses
3. Demeton or Systox. It is a mixture of two parts of O,O-diethyl O-2-(ethylthio)ethyl phosphorothionate(I) and one part of O,O-diethyl S-2(ethylthio)ethylphosphorothionate (II).	$(C_2H_5O)_2$-P(=S)-O-$CH_2CH_2SC_2H_5$ (I) $(C_2H_5O)_2$-P(=O)-$SCH_2CH_2SC_2H_5$ (II)	demeton provides a long-lasting systemic insecticide rapidly absorbed by roots, stems or foliage.
4. Mevinphos or Phosdrin. (Dimethyl 2-carbomethoxy 1-methylvinyl phosphate).	$(CH_3O)_2$P(=O)-O-C(CH_3)=CHCOOCH_3	Treatment of edible produce close to harvest since it is rapidly dissipated by volatilisation and enzymatic decomposition in the plant.

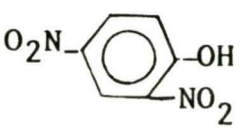
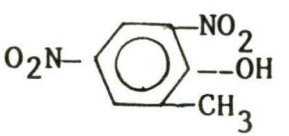
Derivatives of Carbamic Acid.

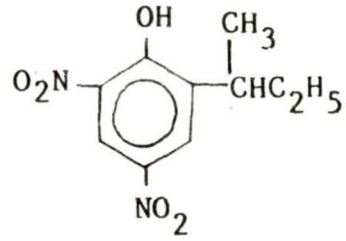
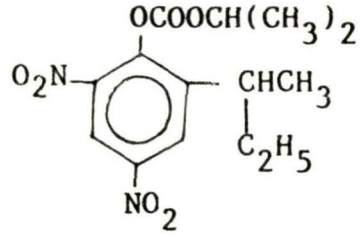
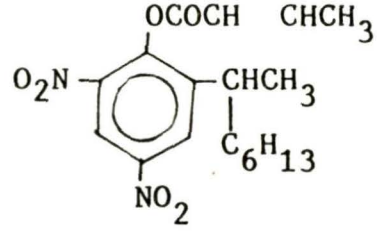
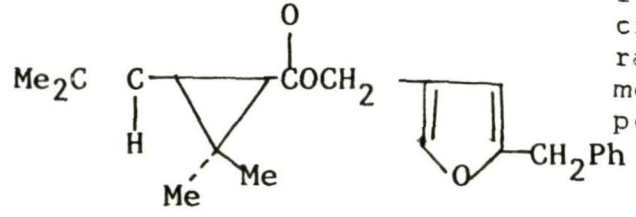
Compound	Formula	Uses
1. Baygon.[2-isopropoxyphenyl N-methyl-Carbamate] .		Control of agricultural pests, household insects, and insects that would menance public health.
2. Mesurol.[4-methyl-mercapto-3,5-dimethyl phenyl-N-methylcarbamate].		It is a broad-spectrum insecticide for the control of pests of fruits and vegetables.

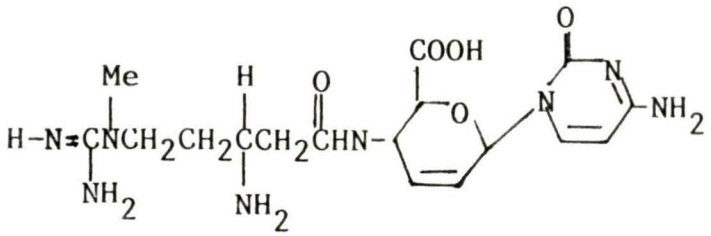
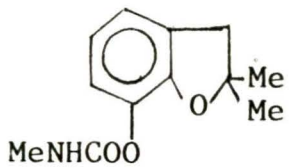
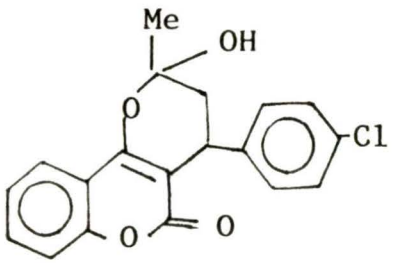
Compound	Formula	Uses
3. Temik.[2-methyl-2-methylthiopropional-doxime O-N-methyl carbamate].		Systemic nematicide for introduction into the soil in the form of special granules.
4. Romate.[3,4-dichlorobenzyl N-methyl-carbamate].		It is a herbicide for the control of weeds in plantings of cotton, potatoes, tobacco and some other crops.
5. Eptam or EPTC. [S-ethyl N,N-di-n-propyl thiocarbamate].		Used as a pre-emergence herbicide to control weeds in plantings of alfalfa, beans, beets, carrots, cabbage, flax, potatoes and many other crops.
6. Di-allate or Avadex. [S-2,3-dichloroallyl N,N-di-isopropylthiocarbamate].		Control of wild oats in such crops as flax, barley, corn, peas lentils, sugar beets, beans, etc.
7. Zineb.[Zinc ethylene-bis(dithiocarbamate)].		It is one of the most important fungicides used in agriculture.

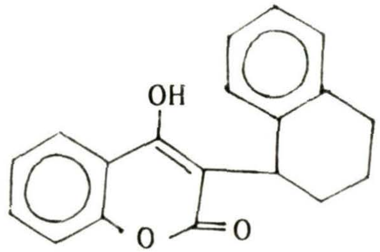
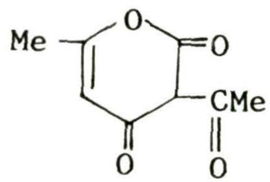
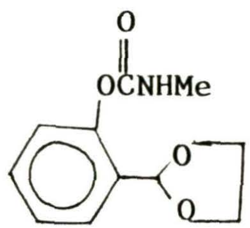
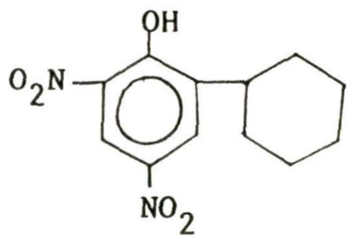
Compound	Formula	Uses
8. Bendiocarb,(2,3-isopropylidene dioxyphenyl methyl carbamate).		Bendiocarb is an insecticide acting by cholinesterase inhibition, effective as a contact and stomach poison. It is active against mosquitoes, flies, wasps, ants, fleas, cockroaches and many other industrial and storage pests.

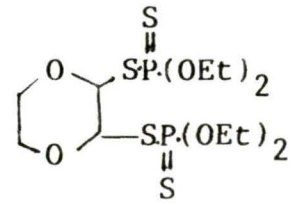
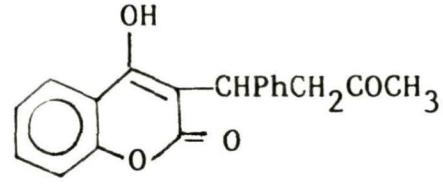
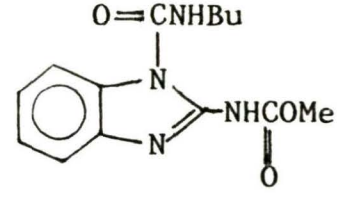
Synthetic organic Insecticides: These were proposed for the control of harmful insects in the last century.

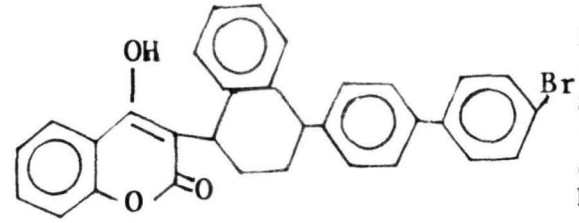
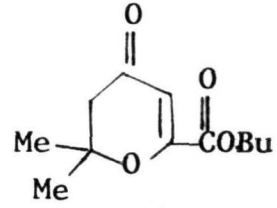
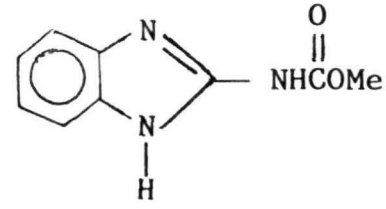
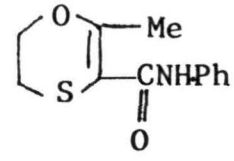
Compound	Formula	Uses
1. p-Nitrophenol.		Preserving natural rubber and some other non-metallic materials from destruction by micro organisms.
2. 2,4-Dinitrophenol.		Scarcely used for the control of plant pests and weeds, but is employed in disinfectant compositions.
3. 2,4-Dinitro-6-methyl phenol. (Dinitro-o-cresol)		Controlling plant pests and diseases, and for treatment of fruit trees before opening of the buds either in the form of oil spray or in the form of solutions of its salts.

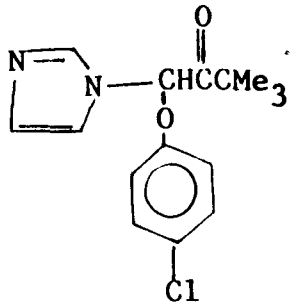
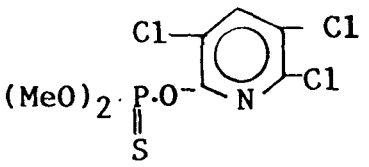
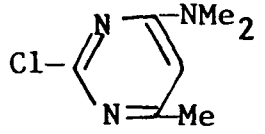
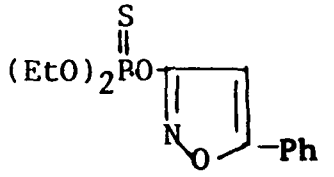
Compound	Formula	Uses
4. 2,4-Dinitro-6-(2'-butyl) phenol.		Used to control plant pests and weeds in the form of aqueous solutions of the phenoates of ammonia and organic amines.
5. 2,4-Dinitro-6-(2'-butyl) phenyl isopropyl carbonate.		It is a nonsystemic acaricide and fungicide.
6. 2,4-dinitro-6(2'-octyl)phenylcrotonate.		Used as an acaricide and fungicide.
7. Bioresmethrin, (5-benzyl-3-furyl methyl(IR) —trans-chrysanthemate).		It is a powerful contact insecticide effective against a wide range of insects including flies, mosquitoes, cockroaches and plant pests and as a grain protectant.

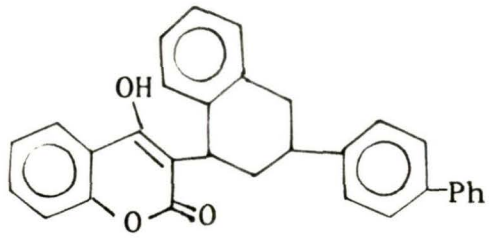
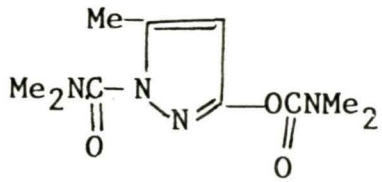
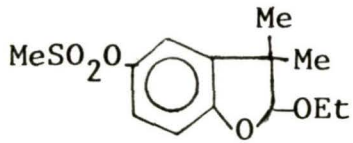
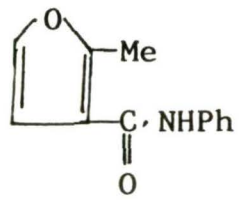
Compound	Formula	Uses
8. Blasticidin-S.		It is a contact fungicide used mainly for the control of piricularia oryzae on rice at C 10 gm. a.i. in 1001 water/ha. Its range of use is limited by phytotoxicity
9. Carbofuran.(2,3-dihydro-2,2-dimethyl-benzofuran-7-yl methyl carbamate).		Carbofuran is a systemic insecticide and nematicide, applied to foliage at 0.25-1.0 kg a.i./ha for the control of insects and mites.
10. Coumachlor.(3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxy coumarin).		Coumachlor is an anticoagulant rodenticide. The acute oral LD_{50} for rats is 900-1200 mg/kg. The LD_{50} with repeated administration for 14-21d to rats is 0.1-1.0 mg/kg daily.

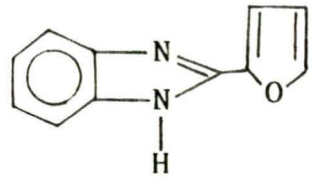
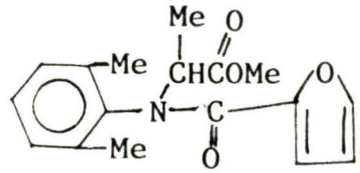
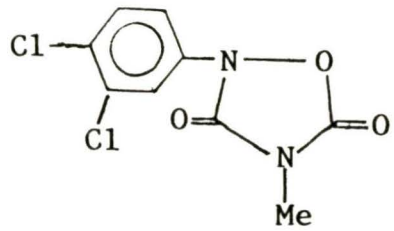
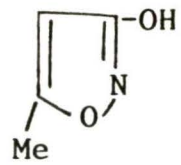
Compound	Formula	Uses
11. Coumatetralyl. (4-hydroxy-3-(1,2,3,4-tetrahydro-1-napthyl) coumarin.		Coumatetralyl is an anticoagulant rodenticide which does not induce bait shyness. The sub-chronic LD$_{50}$(5d) for rats is 0.3 mg/kg daily.
12. Dehydroacetic acid. (3-acetyl-6-methyl-pyran-2,4-dione).		Used as a fungicide for the prevention of mould growth on fresh and dried fruit and vegetables and for the impregnation of food wraps.
13. Dioxacarb. [2-(1,3-dioxolan-2-yl)-phenyl methyl-carbamate]		It is a contact and stomach insecticide used against cockroaches and against a wide range of household and stored products pests, for wall application at 0.5-2.0 gm a.i/m^2.
14. 2,4-Dinitro-6-cyclo-hexyl phenol.		Used for the treatment of fruit and ornamental trees in the dormant state.

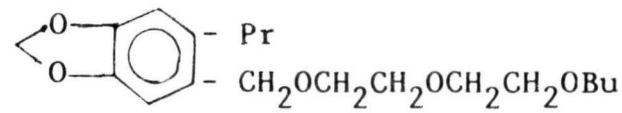
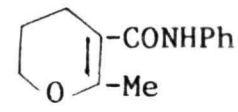
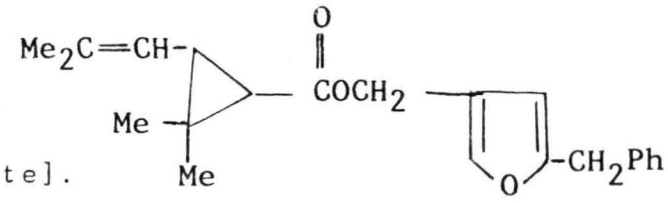
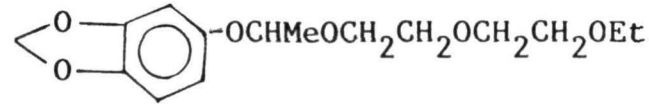
Compound	Formula	Uses
15. Dioxathion. [S,S'-(1,4-dioxane-2,3-diyl) O,O,O',O'-tetraethyl di(phosphorodithioate)].		Dioxathion is a non-systematic insecticide and acaricide especially useful for the treatment of livestock to control external pests including ticks. The cis-isomer is somewhat more toxic to flies and rats than the trans-isomer.
16. Warfarin. [4-hydroxy-3-(3-oxo-1-phenylbutyl) coumarin].		It is an anticoagulant rodenticide to which rats do not develop 'bait shyness'. Rats are killed by 5 daily doses of 1 mg/kg.
17. Benomyl. [methyl-1-(butyl-carbamoyl)benximida-zol-2-yl carbamate].		Benomyl is a protective and eradicant fungicide with systemic activity, effective against a wide range of fungi affecting fruits, nuts, vegetables, field crops; turf and ornamentals. It is also effective against mites, primarily as an ovicide.

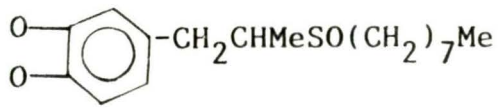
Compound	Formula	Uses
18. Brodifacoum. (3-[3-(4'-bromobiphenyl-4-yl)-1,2,3,4-tetrahydro-1-napthyl]-4-hydroxycoumarin).		Brodifacoum is an indirect anticoagulant active against rats and mice including strains resistant to other anticoagulants, and against rodent species, such as hamsters, that are difficult to control with other anticoagulants.
19. Butopyronoxyl. (butyl dihydro-6,6-dimethyl-4-oxopyran-2-carboxylate).		Butopyronoxyl is an insect repellent with little insecticidal activity.
20. Carbendazim. (methyl benzimidazol--2-yl carbamate).		Carbendazim is a systemic fungicide controlling a wide range of pathogens of fruit, vegetables, cereals, ornamentals and grapes. It is absorbed by the roots and green tissues of plants.
21. Carboxin. (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide)		Carboxin is a systemic fungicide used for seed treatments of cereals against smuts and bunts and with co-fungicides for the control of most other soil borne seedling diseases.

Compound	Formula	Uses
22. 1-(4-chlorophenoxy)-1-(imidazol-1-yl)-3, 3-dimethyl butanone.		It is a fungicide, effective against Aspergillus, Penicillium, Candida and Paecilomyces spp. on various household material, utensils and parts of buildings.
23. Chlorpyrifosmethyl [O,O-dimethyl-O-(3,5,6-trichloro-2-pyridyl)phosphorothioate].		It is an insecticide with a broad range of activity; effective by contact, ingestion and by vapour action but it is not systemic. It is used to control pests of stored grain, mosquitoes, flies, aquatic-larvae and various foliar crop pests.
24. Crimidine (2-chloro-4-dimethyl-amino-6-methyl pyrimidine).		Crimidine is used as a rodenticide the poisoned rats are non-toxic to predators.
25. O,O-Diethyl-O-5-phenylisoxazol-3-yl phosphorothioate		It is a contact insecticide with a wide range of action, controlling aphids and scale insects at 33-50g a.i/1001; also effective against borers, hoppers and gall midges of paddy rice and against caterpillars, beetles and mites on many crops.

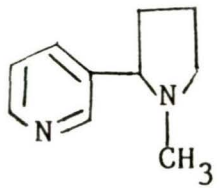
Compound	Formula	Uses
26. Difenacoum. [3-(3-biphenyl-4-yl-1,2,3,4-tetra-hydro -1-napthyl)-4-hydroxy coumarin].		It is an indirect anticoagulant rodenticide, more potent than earlier compounds and effective against rats and most mice resistant to other anticoagulants.
27. Dimetilan. [1-dimethyl-carbamoyl-5-methyl pyrazol-3-yl dimethyl carbamate].		Dimetilan is a stomach poison used for the control of flies. The acute oral LD_{50} is: for rats 64 mg/kg; for mice 60-65 mg/kg.
28. Ethofumesate. [(±)-2-ethoxy-2,3-dihydro-3,3-dimethyl benzofuran-5-yl methane sulphonate].		It is a selective herbicide. Sugar beet shows a very high tolerance, presowing incorporated or pre-em at 1.0-3.0 kg a.i/ha. It controls many important grass and broad-leaved weeds with a good persistence of activity in the soil, high tolerance is shown by other beet crops, onions, sunflowers and tobacco.
29. Fenfuram. [2-methyl-3-furanilide].		Fenfuram is a fungicide highly active as a seed dressing for use against the smuts and bunts of temperate cereals.

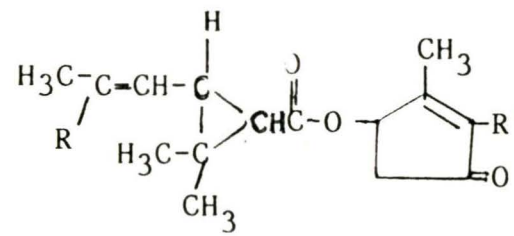
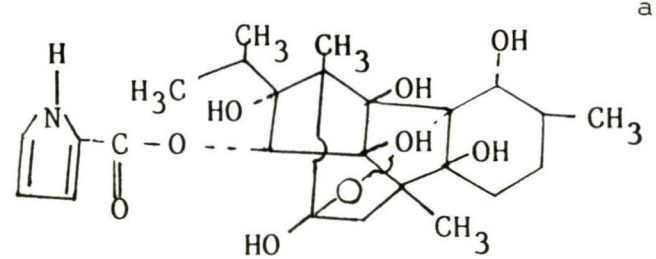
Compound	Formula	Uses
30. Fuberidazole. [2-(2-furyl) benzimidazole].		Fuberidazole is a fungicide used for the treatment of seed against diseases caused by Fusarium spp., particularly F. nivale on rye and F.culmorum on peas.
31. Furalaxyl. [methyl N-(2-furoyl)-N-(2,6-Xylyl)-DL-alaninate).		It is mainly used against Pythium spp. and Phytophthora spp. attacking ornamentals.
32. Methazole. [2-(3,4-dichlorophenyl)-4-methyl-1, 2,4-oxadiazolidine-2,5-dione).		Methazole is a selective herbicide for the control of certain grasses and many broad-leaved weeds when applied pre-em in cotton, garlic and potatoes at ≤6 kg a.i/ha. It is also used for weed control in onions.
33. 5-methylis-oxazol-3-ol.		It is a soil fungicide and a plant growth promoter. It is effective against soil-borne diseases caused by Fusarium, Aphanomyces, pythium and corticium spp.

Compound	Formula	Uses
34. Piperonyl butoxide. (5-[2-(2-butoxy-ethoxy)ethoxy-methyl]-6-propyl-1,3-benzodioxole).		Piperonyl butoxide is a synergist for the Pyrethrins and related insecticides.
35. Pyracarbolid. [3,4-dihydro-6-methyl-2H-pyran-5-carboxanilide].		It is a systemic fungicide, effective against Basidiomycetes. It controls rust, smut, and damping off disease. It is used in cereal, coffee, tea and bean crops.
36. Resmethrin. [5-benzyl-3-furyl-methyl(IRS)-cis, trans-chrysanthemate].		Resmethrin is a powerful contact insecticide effective against a wide range of insects.
37. Sesamex. (5-{1-[2-(2-ethoxyethoxy)-ethoxy]ethoxy}-1,3-benzodioxole).		Sesamex is a synergist for the pyrethrins and allethrin and is used in experimental studies.

Compound	formula	Uses
38. Sulfoxide. [1-methyl-2-(3,4-methylenedioxyphenyl) ethyl octyl sulphoxide].		Sulfoxide is a synergist for the pyrethrins and allethrin.

Natural(plant) Insecticides: Some plant materials have been most widely used as insecticides.

Compound	Formula	Uses
1. Nicotinoids a. Nicotine		a. Destruction of aphids.
b. Nicotine sulphate		b. Contact insecticide for aphids attacking fruits, vegetables, and ornamentals, and as a fumigant for greenhouse plants and poultry mites.

Compound	Formula	Uses
2. Pyrethroids.		
a.Pyrethrum.		a.Used for killing insects and worms.
3. Ryania.		
a.Ryanodine.		a.Highly toxic to some insects, particularly caterpillars. This compound is effective both as a contact and a stomach poison.

Fumigants

The various fumigants often exhibit considerable specificity towards insect pests. The fumigants may be used individually or in combination. For example, carbon tetrachloride is often used in combination with carbon disulphide to decrease flammability.

Citrus and deciduous fruit trees have been fumigated for the control of scale insects for many years by hydrogen cyanide introduced under relatively gaslight tents. Buildings have been fumigated by methyl bromide for the control of termites or power post beetles.

Ethylene bromide is uded for controlling stored food pests.

Ethylene dichloride is used for stored grain pests.

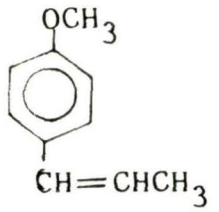
Repellents

N,N-diethyl-m-toluamide is a very good mosquito repellent. It can be applied in alcoholic solution directly on the skin and gives a pleasant lotion feeling.

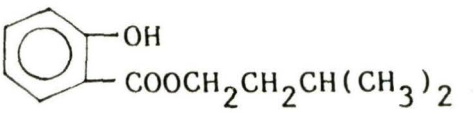
Attractants

Attractants have been used to attract live insect into traps or to poison baits for control as well as for the determination of population densities.

Fermenting sugars and syrups have been used as attractants for moth and butterflies. Anethole is used for the codlling moth and isoamyl salicylate for the tomato and tobacco hornware moths.

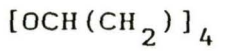


Anethole



Isoamyl salicylate

Metaldehyde is used as an attractant in poison baits for snails and slugs.



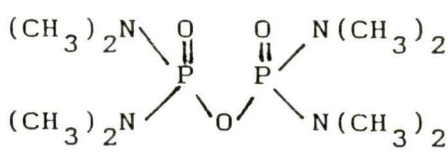
Metaldehyde

During recent years the intense public controversy over the use of pesticides, revolving largely around preoccupation with the quality of environment, has frequently generated the suggestion that more narrowly selective pesticides should be developed.

This view carries the implicit concept that the closer one approaches a one pest-one chemical pesticide balance, the greater the degree of safety to all other organisms. Minimum persistency is frequently coupled to this recipe for an environmentally acceptable pesticide, since the compound which self-destructs in the shortest period of time and is target-selective should be even more environmentally desirable.

The concept of insecticide selectivity was introduced to the scene by W.E. Ripper in 1944 as a "chemical that kills the uneconomic arthropod species and spares the economic species, namely, the pest's natural enemies"[1]. Nicotine offered the earliest known example of such selectivity. Progress in developing such chemicals was not outstanding, however, so that by 1956 Ripper, in a classic review, could indicate only a few synthetic chemicals meeting his definition for selectivity[2].

Schradan was the one found effective at that time.



Ripper emphasized that ecosystem stability depended on selective and partial control of the pest population by chemicals allowing the natural enemy population to stabilize on the reduced food supply represented by the pest numbers maintained near the economic threshold.

The developing physiological and biochemical understanding of insecticide toxicology soon provided an outline of the essential principles for selective insecticide action in relation to chemical properties of the compounds[3]. By the early sixties, therefore, it appeared that a rational search for development of selective insecticides should be possible. The desirability of such a search was then clearly in the public mind because of the forceful disclosures of problems with some broad-spectrum persistent insecticides as presented by Rachel Carson and other popular writers.

A clear statement of this philosophy became part of the U.S. federal research policy following the report in 1963 of the President's Science Advisory Committee on "Use of Pesticides"[4]. That PSAC report stated, among others, the following recommendation: "In order to develop safer, more specific control of pests, it is recommended that government-sponsored programmes continue to shift their emphasis from research on broad-spectrum chemicals to provide more support for research on (a) selectively toxic chemicals, (b) non persistent chemicals, (c) selective methods of application, and (d) non-chemical control methods such as attractants and the prevention of reproduction". The PSAC Committee felt that production of safer, more specific, and less persistent pesticide chemicals did not represent an unreasonable goal and in this way encouraged the U.S. Dept. of Agriculture(USDA) and others to shift research programmes toward development of increasingly specific controls, including selective chemicals.

After that date the rate of progress toward such goals was far from rapid with the result that the Mrak Commission[5] report to the Secretary of Health, Education and Welfare in late 1969 recommended that "incentives should be provided to industry to encourage the development of safer chemicals with high target specificity, minimal environmental persistence, and few, if any, side effects on nontarget species". By that time it was more clearly appreciated that the developmental costs of specific

chemicals to be used selectively would be disproportionately high in relation to profits from the correspondingly low volume of sales for selective use. The Mrak Committee thus perceived that high development costs would discourage research and development of selective pesticides without some form of incentive being provided.

Along the way it had been pointed out by E.F.Knipling, as well as others, that the development of selective systems for controlling pests cannot be accomplished without great effort and research[6]. "One of the chief advantages of a broad-spectrum pesticide is that a good one may lead to practical ways of controlling hundreds of pest species. In contrast, research on highly selective ways to control specific pests necessitates intensive research on every major pest. In many instances, the use of selective pest control measures will also mean higher cost to the grower or to the public".

Recently, economists have turned their attention to the costs of environmental pollution and related modern maladies. As a result, the term "externalities" is becoming familiar. Externalities may be defined as those losses or rewards inherent in production or consumption for which no adequate compensation is made in the market. The economics of pest control presents a number of interesting examples of externalities foremost of which are the hidden costs of pesticide usage[7,8]. In other words, such unwanted side effects as acute or chronic toxicity to wildlife and man, and damaging effects on natural biological control agents, even where recognized, have not been charged directly to the cost of chemical pest control. Until recently, little economic advantage has accrued to any insecticide because it happened to be free of such spillover effects and , consequently, these properties have played a relatively minor role in decisions to seek, develop, market, and apply new compounds. Quite logically under these conditions the ideal control agent has been regarded as being potent, broad-spectrum, cheap, and reasonably persistent[9-11].

At the same time many materials with interesting and potentially useful patterns of selective toxicity must have been relegated to the archives for economic reasons of cost, limited spectrum of activity, or marginally reduced potency.

The results of these priorities become immediately obvious if we consider the properties of the insecticides most widely used today.

In Table-1 are listed the 18 insecticides produced in the United States at 2 million pounds or more in 1971, as listed in a recent compendium[12]. Alongside are given the acute oral and dermal LD_{50} values for the rat as indices of hazard to mammals, including man, and the Pest Management Index, devised by Metcalf[13] to cover toxicity to other non target organisms (fish, birds, and the honeybee) and environmental persistence (half-life) as well as mammalian toxicity. This Index has a scale from 3(most desirable) to 15 (least desirable) for general pest management purposes. Any attempt to classify what is or is not hazardous in these respects will be arbitrary, since hazard varies with the nature of usage, but a reasonable attempt is made in Table 2. The four numerical degrees of toxic hazard are based on provisional levels suggested by the U.S.Environmental Protection Agency in the administration of the new Federal Environmental Pesticide Control Act[14].

Applying this classification to the insecticides in Table-1 reveals that of these most common compounds, fully 39 percent, would be classified as highly or relatively hazardous by the oral route and only 28 percent as very safe. By dermal contact again 34 percent are hazardous and only some 22 percent are classified as very safe. As least 40 percent have properties which may make them poorly compatible with pest management practices. Unfortunately, but significantly, data are generally lacking on the toxicity of these compounds to beneficial insects. However, several have been criticized on this account also, which is in keeping with their broad-spectrum properties.

TABLE 1

Toxicological properties of the Insecticides produced in largest quantity in the United States in 1971.

Compound	Acute LD_{50} (mg/kg; rat) Oral[12]	Dermal[121]	Pest management index 13
1. Aldrin	55	98	13.0
2. Azinphos-methyl	10-18	220	10.0
3. Azodrin	21	112	- -
4. Bux	1050	400[d]	- -
5. Carbaryl	540	>4000	7.0
6. Carbofuran	8-14	885[d]	12.0
7. Chlordane	570	530	7.3
8. Dasanit	2-10	4.1	-
9. DDT	113	2510	10.7
10. Diazinon	350	455	9.7
11. Disulfoton	12.5	6.0	11.3
12. Dursban	135	202	9.7
13. Heptachlor	130	250	12.7
14. Malathion	1375	>4444	5.3
15. Methoxychlor	6000	>6000	5.3
16. Methyl Parathion	9-42	67	9.7
17. Parathion	6-15	6.8	11.0
18. Toxaphene	60	780	10.0

Rating Scale: 3 = most desirable; 15 = least desirable. [d]=rabbit, not rat.

TABLE 2

Classification of the Hazard of the Insecticides produced in the largest quantity in the United States in 1971.

	Oral LD_{50} (rat) (mg/kg)		Dermal LD_{50} (rat) (mg/kg)		Pest management index	
	Range	Percent	Range	Percent	Range	Percent
Very hazardous	<10	17	<40	17	>12	13
Relatively hazardous	10-50	22	40-200	17	10-12	27
Relatively safe	50-500	33	200-2000	44	8-10	33
Very safe	>500	28	>2000	22	<8	27

One could argue that these materials are older ones, marketed before the necessity for avoiding toxicity to non-target organisms was fully appreciated, and soon to be replaced by more sophisticated tools. Unfortunately, this view may be only partly correct. For example, if we group the 94 insecticides listed by Johnson[12] by the date of their U.S. patent as shown in Table 3 and again consider their oral LD_{50} values to the rat, there is no discernible trend towards development of safer compounds over the last 20 to 25 years. A fairly constant 30 percent are hazardous in each period. Furthermore, since a higher percentage (40 percent) of the most successful of these insecticides fall in this class (Table 2), it appears that a hazardous compound has a better chance of being widely used than a safer one.

This does not leave much ground for complacency and it is clear that in practice, despite their undoubted benefits, insecticides, particularly the dangerous few, have led to death and injury to man and to a variety of toxic effects in the environment, just as the data in the previous tables would predict. Although the extent is not fully known, such accidental poisoning remains a serious problem on a world scale and, it seems, is unlikely to change dramatically in the near future.

Another indicator that there are lessons still to be learnt concerning the externalities of pesticide use is the frequent substitution of the parathions for DDT after its removal from general use. Here we have replaced a compound suspected to be environmentally damaging through excessive persistence by compounds harmful in terms of acute toxicity to vertebrates and poor compatibility with beneficial insects. Since safer, if more expensive, replacements do exist for many, this decision seems shortsighted and is liable to cause further erosion of public confidence in pesticides as well as more repressive regulation.

TABLE 3

Long-term Trends in the level of Acute Toxicity of Insecticides to Mammals

	Oral LD_{50} (rat) (mg/kg)	Date of U.S.Patent		
		Before 1957	1957-1966	1967-1971
		Percent	Percent	Percent
Very hazardous	<10	14	10	13
Relatively hazardous	10-50	16	20	19
Relatively safe	50-500	41	43	44
Very safe	>500	29	28	25
Range of toxicities (mg/kg)		1.2 to 8,170	0.9 to >20,000	5 to >34,000
Number of compounds		38	40	16

Fortunately, it is clear that over the last few years the need for improved selectivity has at last been acknowledged and that, like limited environmental persistence, reasonable selectivity is a basic aim in current development programmes. However, the lead time from research bench to field is long and getting longer, and change, if any, will come only slowly.

If there is a real desire to discover and develop compounds with improved selectivity, two questions must be answered: what type of selectivity is realistic to aim for and what strategies will lead us to it ?

It is not uncommon to read of the necessity for insecticides active against a single pest species. This, in most cases, is quite unrealistic. Very few pests alone are economically important enough to justify the immense costs of new compound development, particularly since there is the very real risk that the total market is lost if control conditions change (e.g., the onset of resistance in the target species, development of alternative controls).

Additionally, most crops are attacked by a complex of pests, although one or two may be key ones, and the prospect of applying different species-specific agents against each one is not attractive either economically or practically. Finally, and decisively, such monotoxic compounds are very rare and are unlikely to be found in general screening programmes using a limited number of test species[15].

A more realistic target, recognizing the economic imperatives and limits to our technical abilities, would be to seek biodegradable compounds active at the phylar or even class levels, i.e., compounds with toxicity limited to arthropods or insects. Barring unforeseen secondary effects, this would provide materials of high safety for man and other vertebrates, plants, and microorganisms. This compromise leaves a substantial group of beneficial or neutral arthropods at risk. However, past experience suggests that if such novel groups of selective toxicants can be found, individual compounds will have

differing ranges of specificity. Those with appropriate properties will then be available to fit a given pest management situation or can be used in a way to enhance selective effects. Although this overall goal of devising toxicants of limited selectivity may seem modest enough, a historical perspective suggests that in the past it has not proved easy to accomplish.

Over 40 years ago Ripper[16] outlined two separate roads to achieving selective action in insecticides. This familiar division remains appropriate.

1. Ecological Selectivity in which an intrinsically non-selective agent is applied in such a circumscribed way that the exposure of non-target organisms is minimized. Examples include specificity of time or place of application, or of formulation (e.g., combination with attractants or baits, microencapsulation), or special chemical properties (e.g., systemic action). Understanding of the ecological basis of insect control should increase rapidly in the future and will present increasing opportunities for this type of selectivity.

2. Physiological Selectivity in which non-target organisms are able to tolerate exposure to the agent while target organisms succumb. This distinction depends on innate physiological or biochemical differences between the two organisms and will be the major topic addressed here. At this point, we again have two broad and critical choices concerning the most efficient division of resources in the search for new compounds with physiological selectivity:

    1. Should we seek completely novel structures based on new modes of action? In this case the role of design is broad-scale and based logically on the known differences between vital sites in the metabolism of target and non-target groups, or

    2. Should we seek to modify existing general groups of insecticides for improved selectivity? In this case the role of design is fine-scale involving molecular manipulations of current compounds, often of a rather minor nature.

There are obviously many facets to this choice. Some major factors favouring the first option are the promise of very high selectivity if the metabolic target is chosen judiciously, better patentability of novel groups, the potential in some cases for rapid onset of resistance to new analogues of currently used structures, together with the discouraging fact that highly selective alternatives to current compounds are already known in many instances, but for various reasons have not been successful in replacing their more hazardous analogues. Finally, there may be the feeling that the potential of older classes of insecticides is close to being worked out. On the other side of the balance favouring the second option are the proven potency and economic viability of known families of insecticides which is difficult to duplicate along with the substantial background of knowledge about their toxicity, metabolism, structure-activity relationships, terminal residues, and environmental compatibility. The low investment requirement in production facilities for similar compounds is a consideration. Also, perhaps, there is a reluctance to commit effort to the speculative, long-term exploration and basic research needed for entirely new materials in the current climate of uncertainty and rising costs of pesticide development. In this light it is reasonable to conclude that both approaches have merit and both are considered below. In general, fine-scale design is more promising in the short term and broad-scale design in the longer term.

Compounds with useful selectivity might be obtained by random screening, partial design, or complete design, depending on the degree to which knowledge of the toxicological systems being attacked is used for predictive purposes. It must be admitted that most of our present selective insecticides have arisen largely by the first route, and that for most purposes complete design of compounds is still beyond our abilities. The major contribution of design lies between these extremes as an aid to directing and improving the efficiency of screening programmes towards a defined goal.

STRATEGIES IN DISCOVERING :

Intrinsically Selective Insect Toxicants

Many processes, physical and biochemical, govern the dynamics of toxicity of an insecticide and its variation between species which leads to selective toxicity. These include penetration of external and internal barriers, distribution within the body, sites of loss including metabolism, excretion, and interference with the operations of some vital receptors leading to a physiological lesion. These factors have been reviewed thoroughly[17-19] and need little general elaboration. The clear conclusion that emerges out of these events are of overwhelming importance in governing selective toxicity, namely metabolism and action at the target receptor, with penetration barriers also playing a role in selectivity on occasion. In fine-scale modification of existing compounds an understanding of these processes and the likely effect of molecular modifications is a prerequisite. However, in the broad-scale design of new types of toxicants discussed here first, we are concerned initially only with identifying a biological receptor system and attempting to produce chemicals to influence it adversely.

Again there exists a choice of two general classes of effect depending on the type of receptor system influenced; behavioural toxicants and metabolic toxicants. There is no absolute dividing line between behavioural and metabolic toxicants. By metabolic toxicants are meant those compounds which attack interior receptors causing a biochemical lesion which then fatally disrupts internal physiology. Behavioural toxicants are compounds that act on exterior-receptors causing a "behavioural lesion" in such a way as to reduce the ability of the insect to survive, adapt, or reproduce.

BROAD-SCALE DESIGN :

Behavioural Toxicants

Many possibilities for inducing behavioural toxicity,

varying in practicality, have been suggested, the most promising now being, techniques employing insect pheromones. In theory such ideas are very promising and could lead us closer to the ideal of mono-selectivity (toxicity against a single species) than any other approach except sterile male techniques. However, not unexpectedly, considerable problems have been met under field conditions in using pheromones either as mass trapping agents or to confuse orientation of the two sexes for mating, and the extent of the future usefulness in these roles is not yet well defined[20,21]. Frequently there may be a need for a precision in timing, placement, or concentration in using a pheromone, which makes it hard to achieve the requisite high degree of behavioural control over a wide area, something which is not required with many conventional pesticides.

In addition to mating behaviour, behaviours essential for oviposition, sociality, dispersal, aggregation, and feeding offer attractive targets. As an illustration of this general approach and its manifold challenges one example, with unfulfilled potential, is worth further exploration here.

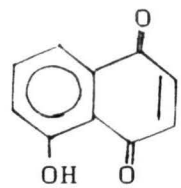
Much of insect behaviour is comparatively stereotyped, reflecting a nervous system of limited size and complexity. The choice of a suitable food plant is one such behavioural pattern. Acceptability of a host plant involves a complex balance of positive and negative stimuli, many of which are chemical, and is based to a considerable extent on the presence or absence of secondary plant substances among others[22a,b,c,d]. This has stressed the importance of the absence of feeding deterrents rather than the presence of specific attractants as a major factor influencing host acceptability. This is reasonable if we accept that such deterrents have very commonly evolved in plants as a defence against predators[23].

This effect plays an important role in the development of insect resistance in plant breeding by producing strains which are unacceptable to the insect (non-preference). A second type of resistance, based on the presence of metabolic toxicants in the plant (antibiosis), already has a man-made analogue through the use of systemic insecticides which render susceptible strains toxic. There is a distinct possibility that we can also mimic the non-preference mechanism by the development of synthetic antifeeding compounds.

Antifeeding compounds (feeding deterrents, in the terminology[24] are chemicals which prevent the initiation or continuance of feeding on an otherwise suitable host. They are not necessarily repellants or toxicants. Typically an insect feeding on a treated substrate will make an exploratory probing of the surface, find it unacceptable, repeat this abortive process a number of times at different sites, and then either cease feeding or leave the plant to try elsewhere. This response is no inflexible that the insect may starve to death while sitting on an unrecognized banquet. Antifeeding agents already have some practical application since many moth-proofing agents act, at least in part, this way[25].

Some examples of known antifeeding compounds are shown in Fig.1. Obviously a wide range of structures are capable of acting in this manner. The first two are naturally occurring agents isolated from insect-resistant plants. Beck and his co-workers[26,27] identified 6-methoxybenzoxazolinone (I) (MBOA) as an antifeeding principle for the first brood of the European corn borer in resistant strains of corn. It is present as the glucoside of a precursor, 2,4-dihydroxy-7-methoxy-1, 4-(benzoxazin-3-one) (DIMBOA), which is released enzymatically on injury to the plant by feeding. Slow conversion of DIMBOA to MBOA then occurs. In fact Klun[27] has claimed that the major antifeeding effect in the plant is due to DIMBOA and possibly its glucoside rather than to MBOA.

More recently Juglone (2) has been extensively studied by Norris and his associates[28,29] as an antifeeding compound for scolytid bark beetles. It has a potential, as yet

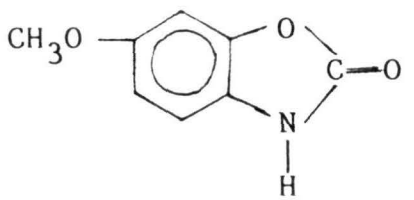


unrealized, in treating elms to prevent attack by the beetle vector of Dutch elm disease. Since it is also effective against the American Cockroach[30] its spectrum of action may be quite broad.

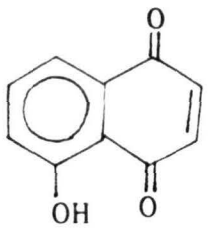
Other examples of such natural compounds are easily found and very many must await discovery. Thus coumarins and their precursors act as antifeedants for blister beetles in sweet clover[31]. Two complex triterpenoids, meliantril[32] and the more potent azadirachtin[33], present in the fruit, leaves, and seeds of Meliaceae(e.g. Indian neem tree, chinaberry tree) are effective as locust antifeedants. Earlier studies of the "neem" principle are reviewed by Ascher[34]. Azadirachtin is particularly impressive since it gave 100 percent antifeeding effect against desert locust nymphs at a concentration of 1 ng per cm^2 of substrate. Its action is claimed to be limited to the Acrididae and it is ineffective against termites, but recent studies have shown it to be active at higher concentrations against some but not all lepidopterous larvae[35].

A variety of other natural antifeeding agents have been investigated, in some cases with chemical identification of the active principle[36,36a].

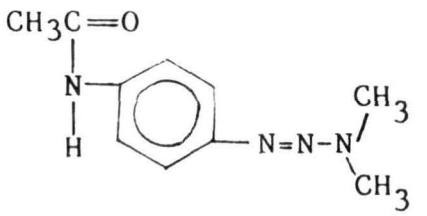
The best known synthetic feeding deterrent is American Cyanamid AC-24055(3). The properties and field testing of this compound have been presented in detail by Wright[25,25a]. In the laboratory it proved to be highly active in deterring attack by many surface feeders but was less effective against those insects that feed only on the deeper tissues, presumably



6-Methoxy benzoxazolinone (1)

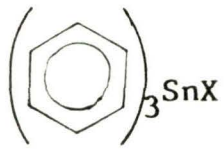


(Juglone), 5-Hydroxy-1,4-naphthoquinone (2)



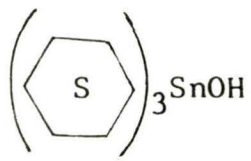
American cyanamid AC-24, 055

4'-(3,3-Dimethyl-1-triazeno) acetanilide (3)



X = OH DU-Ter (4)

X = $OOCCH_3$ Brestan (5)

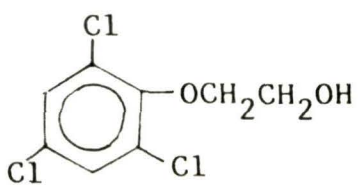


Plictran (6)

$(CH_3)_3Sn-Sn(CH_3)_3$

Pennwalt TD-3052 (7)

Hexamethylditin



2,4,6-Trichlorophenoxyethanol (8)

Fig.1. Natural and synthetic antifeeding compounds.

contacting the surface deposit only fleetingly. Success in the field was encouraging in view of the pioneering position of this compound and established that the antifeeding concept is effective and acceptable under some practical conditions. However, for several reasons discussed by Wright[25], the compound has never been placed on the market. Basically the major drawbacks are the lack of coverage of new growth occurring after the antifeedant is applied, its limitation to surface feeding pests and the marginal cost-effectiveness of the compound. Also, triazenes of this general type have been shown to cause tumors of the nervous system and to be teratogenic in mammals[37]. The practicability of this antifeedant for field use is still reexamined from time to time[38,38a].

A second group of compounds, used in agriculture chiefly as fungicides and acaricides, but with marked antifeeding properties are the organotins, e.g., the fentins DU-Ter(4) and Brestan(5), plictran(6) and pennwalt TD-3052(7). Their properties have been investigated and reviewed by Ascher[34] and Jumar[39]. Briefly, a number of organotins are effective feeding deterrents against a range of surface feeders, in some cases under field conditions. But this has not been sufficient to encourage their commercialization on this basis, though it is conceivable that antifeeding may contribute to their overall effectiveness in some field situations.

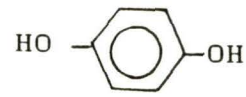
The general conclusion from these studies is that the antifeedant approach has much to recommend it. Not least are its high degree of selectivity and compatibility with pest management principles, since natural control agents are not killed directly and hosts are left available to support such parasites and predators. Jermy[22d] has presented the argument that host range is such a strongly fixed character in insects that resistance to antifeedants is unlikely to occur readily, but this remains to be demonstrated. Most antifeedants tested

show an encouraging broad range of specificity against phytophagous species and in general seem to be of limited acute toxicity to vertebrates. It has been recognized that, of their major disadvantages, the two most telling, i.e., the need for perfect coverage including new growth after application and the lack of effect on deep-feeding insects, e.g., aphids, could potentially be solved by finding systemic feeding deterrents.

An encouraging factor is that several groups of feeding deterrents contain members with marked systemic action. These include hexamethylditin(7)[40], the carbamate insecticide Baygon[41], effective at 30 ppm against the boll weevil, and the natural antifeedant azadirachtin, which is active when applied to the soil in 1-10 ppm solution[42]. The formamidine insecticide -acaracide, chlordimeform has systemic properties and a significant part of its effect in the field may be due to its antifeeding-repellant actions[43]. A particularly interesting series of Polyhalophenoxyethanols and acetic acids (e.g. compound(8), Fig.1 have been synthesized and field-tested by Jermy and his colleagues[44], Matolcsy et. al.[117]. Although these are close relatives of the herbicides 2,4-D and 2,4,5-T they are not phytotoxic but have strong systemic antifeeding action against such diverse groups as beetles, leafhoppers, and mites. Considerable species specificity was found within the individual compounds of this series. According to Jermy[22d], field tests with these materials have not been conclusive, but the future success of the antifeeding concept probably depends on further developments of this kind.

A crucial element in any attempts to find feeding deterrents by more rational means is an understanding of their mechanism of action. In a few cases we are starting to gain this knowledge and the necessary techniques for studying such processes as ligand-receptor interactions and the electrophysiological background of receptor coding are developing. Norris and his associates[30] have made a comprehensive and fascinating investigation of the antifeeding

actions of the naphthoquinone, Juglone(2). Studies have been made of structure-activity relationships of analogues[29] and binding of napthoquinones and catechol to a sulphydryl-containing receptor molecule in the insect antenna in vitro[30] and in vivo[45]. The ultimate outcome of this work may be an understanding of the chemical basis of the receptor-Juglone interaction based on a reversible oxidation of the sulphydryl groups in the receptor by the quinone, leading to change in membrane permeability and potential. Significantly in this redox system the corresponding reduction products, quinols, are feeding stimulants rather than deterrents[29]. Finally, progress has been reported in the isolation of the antennal receptor macromolecule[46,47].



An entirely different mechanism of deterrence has been suggested by Ascher and Ishaaya[47a] to explain the antifeeding action of the organotin, fentin acetate(5), on larvae of Spodoptera littoralis. It was concluded after extirpation experiments that this compound did not act directly on sensory receptors of the mouth area but it was effective on direct injection in the hemocoel. Antifeeding was considered not to be a consequence of the overall toxic action of organotins. A clear decrease in amylase and protease activity in the gut was observed although the organotins are not direct inhibitors of these digestive enzymes. The basis for the decreased activity and its relationship to antifeeding action remains to be established. The antifeeding compound AC-24055(3) was also reported to inhibit protease and amylase activity[48]. However, this mode of action does not seem to be consonant with the observations of Wright[25] who states that AC-24,055 is almost immediate in its effects on insects and is ineffective unless the compound contacts the mouthparts, e.g., no effect is

seen after injection. Furthermore, untreated surfaces are fed on at once by larvae that reject treated ones and there appears to be no residual effect on insects exposed to the compound. Thus, there are clear differences in the mode of action of these two compounds. Azadirachtin also has a direct action on gustatory receptors of the desert locust as shown by electrophysiological and extirpation studies[49,50]. A key group of receptors sensitive to Azadirachtin were located on the inner surface of the clypeolabrum, but receptors at other sites were also effective so that a high degree of redundancy and plasticity is built into the sensory system.

In conclusion, if there is still much room for debate about any final role for antifeedants in the control of phytophagous pests (or even those that feed on animals), there is enough past success to encourage further vigorous investigation of this concept as a long-range possibility for highly selective control. This role could be either as general agricultural agents or more specialized ones, e.g., in crops where no feeding damage is tolerable or where continuous coverage of the substrate can be guaranteed such as in moth-proofing, termite proofing, or the protection of stored food products, progress has not been rapid but, judging from the open literature, the antifeedant concept has hardly received the concentrated attention devoted to other alternatives such as pheromones and sterilants. Whether it is profitable for industry to energetically pursue the speculative and closely defined goal of finding an antifeedant, especially a systemic one, is doubtful and the past productivity of any such programmes has clearly been low, but such a compound should be given the opportunity to show up in general screening programmes. Meanwhile, further additions to our rudimentary knowledge of the structure-activity relations and mode of action of feeding deterrents, continuing study of the sensory processes governing feeding, and the isolation and identification of further natural antifeedants will provide an expanding basis for the development of this concept in selective control.

BROAD-SCALE DESIGN :

Metabolic Toxicants

Numerous metabolic targets have been discussed in the context of selective toxicity of insecticides, but only a few have been investigated to any depth for their potential in this regard. In fact, there are many cases where sufficient difference exists between analogous receptors present in both insects and non-target organisms to allow excellent selectivity Furthermore, some potential targets of this type are still poorly understood and exploited, e.g., the noncholinergic central and peripheral nervous systems of insects, and these too may offer much scope for selectivity. However, there is an imposing logic to the view that in the long run the most fruitful search for selective toxicants will be directed towards metabolic systems unique or peculiarly important to the target group only.

The biochemistry of arthropods and insects shows many such specializations[51,52,17]. Several aspects of the nervous system are promising targets, particularly the neuromuscular apparatus, where the excitatory junctions are probably mediated by glutamate rather than acetylcholine and where inhibitory junctions, perhaps mediated by γ-aminobutyrate, also exist in contrast to the vertebrate condition[53,54]. Other well-defined possibilities include trehalose as the hemolymph sugar and its associated biochemistry, the insect's inability to synthesize sterols and the attendant necessity to modify dietary sterols[55,56], and the α-glycerophosphate shuttle operating in some flight muscle[57]. Insect hormones also differ greatly in structure and function from those of vertebrates. In the case of the juvenile hormone analogues (JHA) a considerable degree of success has been achieved in exploiting these differences and large-scale field trials are proceeding with these novel, highly selective toxicants. The JHA story is well documented already[58,59,60] and need not be discussed here. They are full of promise for the control of a number of damaging insects but

have yet to be proved widely effective in the field. However, the concept of attacking a physiological system limited to certain invertebrates has proved amply correct since so far the JHA have proved virtually innocuous to Vertebrates and, in many cases, highly selective between different groups of insects[61,62]. Much of the success of the JHA depends on the fact that the natural juvenile hormones are relatively simple and lipophilic. Thus structural analogues (JHA) are toxic as contact insecticides and can be produced economically. Unfortunately, niether of these advantages extends to other insect hormones of known structure (e.g. steroids or polypeptides). This leaves the option of devising selective inhibitors for their synthesis, degradation, or other means to prevent their normal utilization by the insect, but this may be several degrees of magnitude more difficult than making simple structural analogues. Along these lines, Maddrell[63] has suggested that since a common feature of the action of neurotoxic insecticides is to cause the release of hormones(e.g., the diuretic hormone) which leads to lethal physiological imbalances, these hormones provide a route to selective toxicants. How this can be achieved is not yet clear. In the same vein, various other neurotoxic agents are released in the stressed or poisoned insect[64,53]. However, these compounds have, with few exceptions so far, resisted identification and any development of selective agents based on this observation still lies in the future.

After the JHA, a good candidate for the physiological system most likely to yield selective insecticides is the insect integument. This is a complex, highly organized structure, radically different from that of vertebrates, with functions immediately vital to the survival of the insect. It has at least two major weaknesses;

1. To allow growth it must be shed and resynthesized repeatedly.

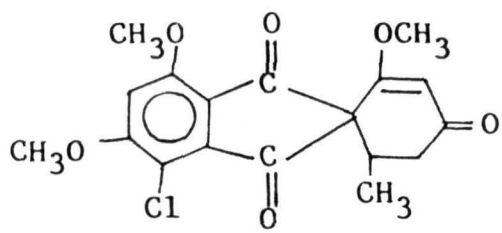
2. To prevent rapid desiccation of the terrestrial insect with its large surface-to-volume ratio, it must be effectively waterproofed.

The intricate biochemistry and endocrinology of the integument clearly involves major synthetic activity, storage, and transport mechanisms for carbohydrates to form the polysaccharide chitin, for proteins and orthoquinones derived from tyrosine for sclerotization, and for a range of lipids for water proofing, specialized products, such as the rubbery protein resilin, and antioxidants for cuticular lipids must be produced in some cases. The old cuticle must be digested by specific enzymic secretions, reabsorbed, and the unrecoverable residue shed at ecdysis. During all these events adequate waterproofing must be maintained. The whole process must be initiated and controlled in time and space by precise regulatory mechanisms. At least four hormones are involved, ecdysiotropin and ecdysone which initiate molting, juvenile hormone to control the form of the new cuticle, and bursicon to initiate tanning.

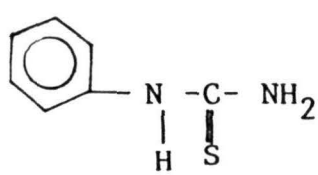
Such a complex of pathways and controls presents a multitude of targets for lethal disruption, and, of course, the JHA and, to a lesser extent, ecdysones are exciting testimonials to the possibilities of success by the hormonal route. However, many other targets are immediately obvious. For instance, can we devise inhibitors for chitinase? If so, the developing insect would be locked in an irremovable armour with no further prospect of growth and maturation. Chitin synthesis is another worthy target. Griseofulvin(9) (Fig.2) is an antibiotic with uses as an agricultural fungicide. Speculation that its fungicidal action was based on interference with the synthesis of fungal chitin (a hypothesis now in doubt) led Anderson[65] to study its effects on insects. He found that at less than 20 ppm it caused gross deformation of the cuticle of mosquito larvae in the subsequent instar, including failure of muscles to attach to the cuticle. Chambers and love[118] also

have reported morphological effects in mites treated with griseofulvin, such as lack of pigmentation and malformation of the abdominal cuticle.

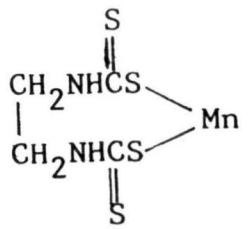
An analogous situation may exist with the polyoxin complex of nucleoside fungicides which bear a structural relationship to UDP-N-acetylglucosamine[66]. Polyoxin D has been shown to be a potent competitive inhibitor of fungal chitin synthetase, which explains its inhibitory effect on the synthesis of cell wall chitin[67]. Polyoxin A has marked insecticidal activity with cuticular involvement e.g. LD_{50} after injection into grasshoppers is 5 µg per insect.



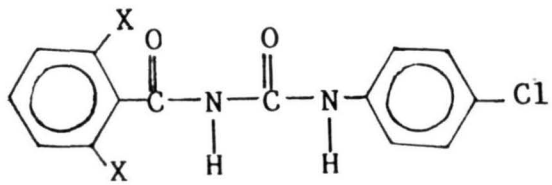
Griseofulvin(9)



1-phenyl-2-thiourea (10)



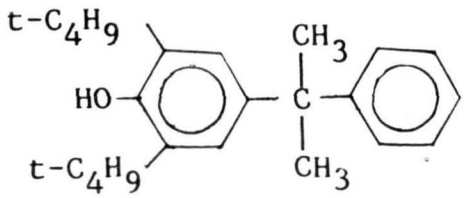
Maneb (11)



X = Cl ; TH - 6038 (12)

X = F ; TH - 6040 (13)

1-Benzoyl-3-Phenylureas



MON - 0585 (14)

Fig.2. Some compounds active against the insect cuticle and molting.

The phenol oxidases of the hemolymph and cuticle necessary for the production of tanning quinones from aromatic amino acids are another interesting prospect. Inhibition of these enzymes should lead to failure to harden and darken the cuticle. There is considerable evidence that this is the case. Thioureas and related compounds(dithiocarbamates, 2-thiouracils) have long been known to be phenoloxidase inhibitors in vitro[68] presumably by virtue of their ability to complex the copper in these metalloenzymes. Corresponding inhibition of cuticular development and pigmentation has often been seen in treated insects, and phenylthiourea (PTU,10 ; Fig.2) has been evaluated as an insecticides e.g., for control of clothes moths and mosquito and housefly larvae [69,70] showed that mosquito larvae lacked melanin and had a much prolonged larval period when exposed to PTU at high concentration (1 mM). McFarlane[71] observed the action of several thioureas and sodiumdiethyl dithiocarbamate on cricket eggs and concluded that the toxic action was related to a decreased level of phenoloxidase, which prevented normal tanning of the chorion and subsequent water uptake. Two further studies have related reduced phenoloxidase activity in vivo with toxicity due to cuticular maldevelopment. Edelman and Posnova[72] studied the effect of feeding 6-methyl thiouracil and 1-methyl-2-mercaptoimidazole to a range of insects. No toxic effects were seen until the subsequent molt when there was a failure to shed the old cuticle and, in some species, the new cuticle was poorly pigmented and sclerotized. A 30-60 percent decrease in total phenoloxidase activity was found in the treated insects. Very similar effects on molting and cuticular synthesis were reported by Chmurzynska and Wojtczak[73] on injecting thiourea into silkworm larvae and again a strong reduction in phenoloxidase activity was considered to be the cause.

Various dithiocarbamate fungicides have been shown to have significant potency in preventing molting in insects, although the mechanism has not been defined, e.g., ziram (zinc dimethyl dithiocarbamate) at 5-10 ppm strongly delayed pupation

of mosquito larvae[74] and Maneb (11, Fig.2) and zineb (manganese and zinc ethylenebisdithiocarbamates) had the strange effect of completely preventing molting of green house white flies without other untoward effects until the insects became bloated and died[75]. Maneb in this case had comparable potency to the positive control compound, Perthane. The basis of the toxicity of Maneb was investigated further by McMullen[76] and is clearly complex with a variety of cellular injuries through effects on sulphydryl enzymes and perhaps metal chelation.

The phenoloxidases represent only one target which can be successfully attacked. A host of other possibilities remain. For example, DOPA decarboxylase converts DOPA to dopamine in the production of tanning quinones. Inhibitors of this enzyme are known e.g., 3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methyl-propionic acid completely blocked sclerotization of the puparium of sarcophagabullata at 5 μg per pupa with lethal results[77]. Different genera of Diptera have unique forms for sequestering the large amounts of aromatic amino acids needed for tanning e.g. β-alanyl-tyrosine (sarcophaga), α-glutamyl-phenylalanine (Musca) and tyrosine-o-phosphate (Drosophila)[78]. Specific enzymes for the synthesis and cleavage of these storage forms are present. Clearly targets of this type may present an opportunity for highly specific insecticides if such are desired. A number of investigators have described examples of the precocious onset of tanning of the new cuticle before the insect has completed ecdysis and expansion to its new form. This has the laudable consequence of locking the insect into an inappropriate shape. Actions of this type have been observed with JHA[79] with ecdysones[80] and with sasturated fatty acids[81]. Presumably, disruption of a variety of targets at different stages of the molting cycle could have the same result, e.g., induction of premature synthesis of tanning agents, premature release of bursicon, or interference with cellular permeability for diphenols[82].

Compounds which interfere with the biochemistry of molting have the limitation of acting only on immature insects. However, an agent which would disrupt water-proofing of the cuticle would not be limited in this respect. A well-known example is the use of inert abrasive or wax-adsorbent dusts, e.g. silica aerogels for control of household and grain insects[83]. The hazards of desiccation which faces many insects is clearly shown by the observation of Turpin and Peters[84] that corn rootworms prefer clay over sandy soil because the latter rapidly abrades the cuticular lipids, leading to death. Knowledge of the biochemistry and control of waterproofing and the nature of repair processes after injury is scanty[85] although there are indications that distinct classes of cuticular hydrocarbons are secreted in adult insects which may be associated with cuticular repair[86]. The continuing production of cuticular lipids appears to be under direct hormonal control[87]. Additional physiological mechanisms may be crucial in controlling water movement through the integument, e.g., Winston and Beament[88] have cited evidence for an energy-requiring cuticular "waterpump" located in the epidermis which lowers the water tension in the cuticle in comparison to the hemolymph.

Examples of interference with waterproofing in insects other than lipid removal by abrasion, sorption, or by surfactants are not plentiful, but Cline[89] has reported that certain fatty amines have an unusual potency in destroying permeability barriers in the cuticle of mosquito eggs, which can lead to lethal desiccation. Another provocative observation was made by sun and Johnson[119], who found that several neurotoxicants led to rapid water loss in treated insects before any other symptoms of toxicity appeared. They suggested that these compounds may be interfering with neurally controlled mechanisms normally responsible for limiting water loss through the integument.

Although they do indicate that the insect cuticle is a valid site of attack for novel insecticides, many of these examples of interference with cuticular processes may be classed as laboratory curiosities, sometimes of dubious etiology, and initiated by compounds of limited potency. At best they might be the starting points in a long and uncertain road to a commercially useful product. However, there are recent examples of success in finding effective insecticides to interfere with cuticular biochemistry which should encourage further efforts in this area.

A series of 1-benzoyl-3-phenylureas having drastic effect on insect molting have been described by Van Daalen[91]. These compounds are neither toxic to adult insects nor to immatures by topical application, and their toxicity to vertebrates and, fortunately, to plants is also low. However, after ingesting the compound, immatures from several orders fail to emerge successfully from the exuvia at the subsequent molt and die. This has been attributed to interference with the process of cuticular deposition and particularly with a failure to lay down a normal endocuticle[92]. It is claimed [93] that these compounds do not interfere with hormonal regulation of molting, and they are clearly unlike JHA in affecting larval-larval molts. It has recently been suggested that they inhibit chitin synthesis in lepidopterous larvae[94] and that they stimulate activity of chitinase and cuticular polyphenoloxidase in larval houseflies[48]. Either, or both, of these actions would lead to a thin, weakened cuticle. Considerable detail of the structure-activity relations of this group has been published[95], and it reveals interesting variations in sensitivity between different species. Two compounds shown in Fig.2, TH-6038(DU-19111),(12) and particularly TH-6040(13) have been chosen for evaluation in the United States.

A second commercially interesting compound with high selectivity and a clear action on insect cuticle is 2,6-di-t-butyl-4-(α,α -dimethylbenzyl) phenol (MON-0585)

(14, Fig.2) developed as a mosquito larvicide[96]. This compound has little activity on insects other than mosquitoes and appears to carry minimal risk for beneficial insects and vertebrates. As with the previous compounds, treated insects show no immediate ill effects. However, when they reach the early stages of pupation the pupae die in an intermediate, unmelanized form. Adults are not affected directly. The timing of the effect is quite different from many known JHA, which block adult emergence rather than pupation[97]. It has been suggested that MON-0585 may be acting as a phenoloxidase inhibitor[98] but its activity in this regard is only modest and the mode of action which remains unknown could occur equally as well at the hormonal level.

In conclusion, there are a variety of vulnerable targets in the biochemistry of insects, many of which are of unique importance to insects or to arthropods in general. Selective toxicants based on such targets are now showing promise of commercial feasibility and there is reason to hope many future successes lie in this direction. It is no hard task to suggest useful targets of this kind in insects and more will become apparent in time. There is every reason to believe that by appropriate, though time-consuming, study we can understand them well enough to make intelligent assessments about how to exploit them.

However, there remains one major obstacle which has severely limited success in achieving this goal, our ability to rationally design agents with requisite properties of selectivity, lipophilicity, potency, and reasonable cost to interfere with known targets has been distressingly limited. It is significant that although the AJH's are compounds designed to perform a specific function, both the benzoylureas and MON-0585 were the children of chance and not intellect. Creative bioorganic chemistry is the weak link which must be strengthened if we are to understand the molecular operations of promising receptors and design effective agents for their disruption.

FINE-SCALE DESIGN

The Modification of Existing Insecticides :

The literature of selectivity is sprinkled with such terms as "tailor-made" insecticides or "precisely-designed" toxicants in reference to agents intended to exactly fit a particular niche in insect control. Interesting though this idea may be, it is far from realization. The reason is abundantly clear. The nature and interaction of events during poisoning and the environmental influences on the activity of pesticides are usually too complex, too poorly understood and quantitated to allow any highly precise relationship of structure to selectivity to be predicted over a range of compounds and organisms. For instance, there are few helpful generalizations as yet possible about the distribution and properties of the enzymes which metabolize insecticides in vertebrates and insect species[99]. Despite many years of study of acetylcholinesterase(AChE) as a target for organophosphorus and carbamate insecticides, no easy rules have emerged to indicate how one can design an inhibitor selective against the insect on versions of this enzyme, although some helpful leads are available. It is perhaps, then, not surprising that we often do not anticipate either the appearance of selectivity when it does arise or, equally, the failure of selectivity when it does arise or, equally, the failure of selectivity in an apparently favourable situation. The power of structure-activity studies has increased considerably in the past few years, notably by the successes of the Hansch approach, but they have not yet been widely used in studying selectivity. At the same time knowledge of comparative toxicology has accumulated rapidly and there are increasing opportunities to develop improved selectivity on a rational basis. Generally this takes the form of "design by analogy", in which known selective agents act as a pattern on which new derivatives can be based, often by the inclusion of a selectophoric group present in the parent molecule, but sometimes, as with the

promising new synthetic pyrethroids, by molecular modification within a class whose members are almost invariably of low mammalian toxicity.

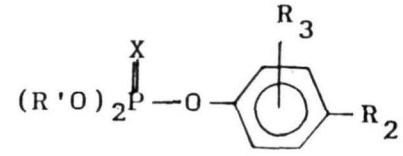
It was earlier suggested that of the manifold events influencing toxicity, differences in rates of metabolism and in properties of the receptor site between organisms are likely to have the greatest influence on selectivity. One brief example from each of the two areas will serve to illustrate how fine-scale design based on observed differences between insect and vertebrate response to known compounds can lead to promising results.

The effect whimsically termed the "magic meta methyl"(17) has been discussed on several occasions[100-102,19]. It refers to the enhancement of selectivity between mammals and insects when a methyl (or chlorine or trifluoromethyl) group is inserted in the meta position of the phenyl ring of some organophosphates. A striking and familiar example is the modification of the inadequately selective methyl Parathion (O, O-dimethyl-O-p-nitrophenyl phosphorothioate) to fenitrothion O,O -dimethyl O-3-methyl-4-nitrophenyl phosphorothioate) which is excellently selective (Table 4). The reason for this startling enhancement in selectivity by such a modest structural change is a mystery which has been widely investigated[103-105,90], incidentally without providing any wholly convincing explanation. The toxicities of methyl parathion and fenitrothion to the mouse and the housefly are shown in table 4, together with the anticholinesterase activity of their oxons.

The ratio of anticholinesterase activities against insect and vertebrate is also shown (Selective Inhibitory Ratio, SIR). The metamethyl group clearly enhances reactivity with the housefly enzyme and decreases it with the two mammalian enzymes. This leads to an improvement in the SIR of 15 to 20-fold. The Selective Toxicity Ratio(STR) is also

Table 4

The selective effect on Anticholinesterase Activity and Toxicity of the presence of a Methyl group in the Ring of some substituted-phenyl organophosphates



Structural modifications			Anticholinesterase activity[a]					Acute Toxicity[b]		
R^1	R^2	R^3	A	B	C	SIR[c] A/B	SIR[c] A/C	D	E	STR[d] E/D
			Fly	Bovine erythrocyte	Mouse brain			Fly	Mouse	
Me[104]	4-NO_2	3-H	2.9	5.2	1.1	0.56	2.6	1.2	23	19
		3-Me	7.6	0.73	0.18	10.4	42.0	3.1	1250	403
			Locust	Sparrow	Rat				Rat	
Me[106]	4-NO_2	3-H	8.0	144.0	15.0	0.06	0.53	-	19	-
		3-Me	4.0	6.0	3.0	0.67	1.33	-	250	-

Contd...

Table-4 (Contd...)

			Fly	Human erythrocyte		Fly	Mouse	
Et[107]	4-$COCH_3$	3-H	27	0.45	60	25-50	200	4-8
		3-Me	77	0.05	1540	16	> 200	>8
		2-Me	0.12	0.02	6.0	>500	> 200	-
Me[107]	4-$COCH_3$	3-H	-	-	-	25-50	> 200	>4-8
		3-Me	-	-	-	8.5	1500	176

---

[a]Activity expressed as $K_i \times 10^{-5}$ ($M^{-1}min^{-1}$) with X = 0, [b]Toxicity expressed as LD_{50} in mg/kg with X=S., [c]SIR = Selective Inhibitory Ratio, Insect/Vertebrate, [d]STR=Selective Toxicity Ratio, Vertebrate/Insect. K_i calculated from I_{50}: LD_{50} based on 50 flies/g.

improved about 20-fold from 19 for methyl parathion to 403 for fenitrothion. This general observation has been confirmed and extended to include avian AChE by Mehrotra and Phokela[106]. Their data for the locust, sparrow, and rat in Table 4 again show that the introduction of the meta methyl group enhances the SIR in favour of vertebrates, especially in the case of the sparrow.

Recently Eto[107] examined the properties of p-acetyl-phenyl phosphate esters as insecticides. o.o-diethyl o-p-acetyl phenyl-phosphorothioate was found to be a reasonably effective toxicant. In keeping with the fenitrothion precedent, the effect of inserting a meta methyl group was examined. As shown in Table 4, this again had the effect of favouring attack on the insect AChE as shown by a 25-fold improvement in SIR.

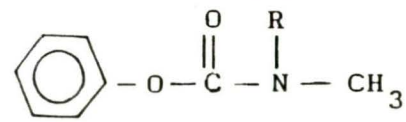
Unfortunately the authors do not present complete details of the mammalian toxicity of these compounds but the meta methyl analogue is shown as less toxic to rats and of increased toxicity to flies, so that the STR has again moved in the direction indicated by the change in SIR. By comparison with the Parathions, one would expect an even greater effect on selectivity with the dimethyl esters in this series (R'=Me in Table 4). o, o-Dimethyl o-3-methyl-4-acetylphenyl phosphorothioate was the least toxic compound to the mouse (LD_{50}=1500mg/kg) and was more toxic than the diethyl derivative to the fly (LD_{50}=8.5 mg/kg) to given an overall STR of 176. This molecular modification has again produced a highly selective compound. Interestingly, moving the methyl group from the 3-position to the 2-position of the ring in these compounds decreases the SIR by 10-fold, primarily by strongly decreasing the reaction with the fly enzyme. Reasonably this also leads to much reduced insecticidal activity. To close this circle of analogy, we see a similar effect with the p-nitrophenyl series[102] where the 2-methyl analogue is 5-to 10-fold less active as an inhibitor of fly AChE than the unsubstituted methyl paraoxon and correspondingly is markedly inferior as a

fly toxicant compared to either methyl parathion or its 3-methyl analogue, fenitrothion. It is hard to imagine a more impressive example of the immense potential for the improvement of selectivity by fine-scale design than the effect of these simple manipulations with a humble methyl group.

The second example, this time based on metabolism as the selective force, is concerned with N-methyl carbamate insecticides. These provide examples of some of the most mammalitoxic (e.g., aldicarb, carbofuran) and some of the most selective (e.g., carbaryl, butacarb) insecticides. A significant improvement in general selectivity between insects and mammals in many members of this class was reported by Fraser[108] through synthesis of the corresponding N-acetyl N-methyl analogues. This effect is shown in Table 5 for m-isopropylphenyl N-methyl carbamate. A 15-to 30-fold decrease in toxicity to the mouse is obtained while the effect on toxicity to insects ranges from a strong decrease to enhanced activity in the case of the mosquito larvae. Changes in anticholinesterase activity do not explain this effect since N-acylation leads to a considerable and general decrease in anticholinesterase activity. A plausible explanation has been provided by Miskus[109] who studied the metabolism of the N-acetyl derivative of Zectran in the mouse and spruce budworm. Previous studies[120] had shown that compared to Zectran, the N-acetyl derivative was much less toxic to the mouse, but only slightly less toxic to budworm larvae. In the budworm, deacetylation occurred to produce significant levels of the potent parent, Zectran. Mice, on the other hand, produced little free Zectran but degraded the N-acetyl derivative largely to innocuous phenolic products. Thus, the improved selectivity appears to depend on a more efficient lethal synthesis of Zectran from its N-acetyl derivative in the insect than the mammal.

Table 5

Selective Effects on Anticholinesterase Activity and Toxicity by N-derivatization of m-isopropylphenyl N-methyl carbamate.



i - C_3H_7

		R=H	R=CH_3CO-	R=$(CH_3O)_2P(S)$-	R=C_6H_5S-	Biscarbamoyl sulphide
Anticholinesterase activity in vitro	Housefly[a]	6.5[116]	4.4[122]	4.2[116]	-	-
	Honey bee[a]	7.7[123]	4.7[123]	-	-	-
	Bovine erythrocyte[b]	7.5[112]	-	-	1.2[112]	0.27[113]
	Housefly[b]	7.7[112]	-	-	0.37[112]	0.23[113]
Toxicity(LD_{50})	Mouse (mg/kg)	16.0[116]	250-500[124]	760[116]	150-200[112]	200[113]
	Fly(sus.) (mg/kg)	41.0[116]	235[122]	32.5[116]	75[112]	85[113]
	Fly(Res.) (mg/kg)	125.0[116]	-	33.5[116]	-	-

Contd...

Table 5 (Contd..)

Culex larva (ppb)	38[122]	28[122]	-	6[112]	5.6[113]
Blowfly larva (ppb)	<30[124]	200[124]	-	-	-
Aedes aegypti (ng/adult)	3.6[125]	4.2[125]	-	-	-
Anopheles stephensi (ng/adult)	2.0[125]	2.8[125]	-	-	-
Mexican bean beetle(ppm)	10[126]	>100[126]	-	-	-
Bean aphid (ppm)	30[126]	>1000[126]	-	-	-

[a] $PI_{50}(M)$; [b] $K_i \times 10^{-5}(M^{-1}min^{-1})$.

Following on these studies a range of analogously N-substituted derivatives of familiar carbamates have been prepared(Table 5). These include a series of N-phosphorylated carbamates[110], alkyl- and arylsulphenylated carbamates[111,112] and a series of biscarbamylsulphides in which two carbamates were linked by a sulphide bridge between the carbamyl nitrogen atoms[113]. As the data in Table 5 reveal, these varied derivatives show a remarkable similarity in their toxicological properties. Like the N-acetyl analogue, in each case mammalian toxicity is significantly decreased while in many cases insecticidal activity is maintained or enhanced. In particular, toxicity to mosquito larvae is improved, perhaps as a result of the enhanced lipophilicity of the derivatives[112]. In each instance, anticholinesterase activity of the derivatives is diminished compared to the parent compound. Metabolic investigations in the case of an N-arylsulphenyl derivative of carbofuran in the housefly and mouse[114] led to the same conclusion obtained with N-acetyl zectran since large amounts of free carbofuran were found in the insect but not in the mouse. A similar explanation may be forthcoming in the case of the N-phosphorylated carbamates[115]. The fact that metabolic activation is a key to toxicity may also explain why the derivatized carbamates also show, in some cases, favourable toxicity against resistant insects in which insecticide metabolism is enhanced, e.g., houseflies (Table 5), mosquitoes[111] and Egyptian cotton leafworms[116]. From these studies emerges a coherent picture ofsuccessful manipulation of toxicity to enhance selectivity, with no indication that the potential of N-derivatization of the carbamates has been exhausted.

CONCLUSION

These examples illustrate that there is still much scope for rational modification of our present families of insecticides and that the potential for devising new types to attack well chosen target receptors remains largely untapped. The central question must then be, if such compounds are found, will they be used? It is unfortunate that frequently an increase in selectivity is accompanied by a contraction of the spectrum of activity and some decrease in potency against important pests. Since the more selective compounds are also often more expensive to synthesize, they have not, under past economic and regulatory incentives, been very successful in displacing established less selective agents. The materials discussed in the final section are a perfect illustration of this most critical problem. However, its use in the United States has been very limited although its much more dangerous sibling, methyl parathion, has seen a rapid growth in importance in the past. The derivatized carbamates are more recent, but have not yet been used commercially.

The foremost strategy in devising selective insecticides is therefore not one of sophisticated biochemistry but simply to find ways to put a high value and reward on selectivity and to penalize those dangerous, broad-spectrum agents with the highest external costs. Unfortunately, although through burgeoning pesticide regulation the latter may be accomplished, the same process tends to so increase the costs and uncertainties of pesticide development that selective and narrower-spectrum compounds become unattractive and long-term innovation is discouraged. This is a paradox which urgently needs resolution. Otherwise many promising advances in selectivity will remain laboratory exercises without practical application.

Three natural products known to be insect juvenile hormones have been examined in detail and modified structurally to provide an insecticide and a plant protectant. After the discovery and modification of these hormones it would seem appropriate to try to look ahead into some areas of insect chemistry which remain to be explored. It is necessary to re-examine continually whether such areas of research on chemical pest control will lead to selectivity on the insect families and to higher animals. Because the hormonal regulation of insect development is so fundamentally different from that of higher animals, the latter kind of selectivity has been inherent in chemical pesticides which interfere with this regulation and it would seem wise to continue the research for class selective pesticides of this type.

William[127,128] reported that 3 μg juvenile hormone can be deposited in 10g tissue in the abdomens of male silk moths. According to Shirk and his co-workers[129] the accessory sex glands of the male secropia moths have the exclusive ability to sequester JH.

In connection with the future isolation of the rare neurohormones of the insects, one may usefully recall this localization of the JH. No doubt the surgical isolation of accessory sex glands would have been much simpler as a purification scheme than the numerous column and gas chromatographic procedures employed. H.Roller and his associates[130] observed that closely related to these events in its implications was the discovery that JH could be isolated, albeit in minute quantities, from in vitro cultures of the endocrine organs. Extraction method may give more pure compound through organ culture. For e.g. Judy[131] isolated JH III from the culture of organs from Manduca Sexta. Schooley et al[132] have proposed biosynthetic pathways of hormones from propionate, acetate and mevalonate. It seems likely therefore, that the techniques of organ and tissue culture will play a major role in the

isolation of workable quantities of insect neurohormones. It is reported[133,134] that the organ culture of prothoracic glands supported the original hypothesis that ∝-ecdysone is secreted by prothroracic glands. In 1965, W.S.Bowers et al[135] predicted accurately all the structural features of the now known JH's. These chemical compounds with hormonal activity undoubtedly open the door to numerous chemists whose skills lay in synthesis and structure optimization for maximum biological activity. The isolation of new hormones and physiologically active substances means the skilful application of new techniques to control the pests.

According to Ito[136], the corpora allata of Bombyx mori might be an endocrine gland, and Weed Pfieffer[137] reported that the removing of the corpora allata from adult grasshoppers inhibits the ovary growth. It means that the corpora allata were necessary for the development of the ovaries. Wiggleworth[138] showed that decapitation of immature Rhodnius resulted in premature metamorphosis and when corpora allata of young nymphs were transplanted into these nymphs giant supernumerary nymphs resulted at the next molt instead of adults. The corpora allata of immature insects produce a hormone which maintains the mature status, and accordingly this hormone is called the juvenile hormone. The main functions of these hormones are -

i. control through the regulation of cellular differentiation (morphosis),

ii. serve as gonadotrophic hormones in females (reproduction).

iii. regulation by the presence of JH and in certain species by a specific titre. (diapause),

iv. regulation of production of sex and aggregation pheromones (behaviour),

v. determination of morphogenetic and behavioural divisions in many social insects(caste formation)

William[127] found that the topical application or injection of ethereal solution of the male cecropia moth abdomen would prevent the metamorphosis of a variety of insects. Derivatives of farnesol[139], especially its methyl ether and diethyl amine were found more active than Schmialek's[140] isolated juvenile hormones. Although the natural juvenile hormones could be demonstrated to interfere with normal morphogenesis during the ultimate stages of metamorphosis, their instability would prevent their application to insect control. The synthetic synergists, piperonyl butoxide and sesamex could be imagined to resemble portions of the juvenile hormone molecule. Several hormone analogues with biological activity and chemical stability much higher than the natural hormones themselves have been synthesised[141-144].

Some stabilised JH analogues have been extensively tested against agricultural insects. The juvenile hormone analogues could be shown to exhibit normal development of insects and eventually result in their death, but the lethan action of excess juvenile hormone affects only the ultimate stages of development when the insects are undergoing metamorphosis.

MODE OF ACTION OF THE PRECOCENES

Bowers and Maritines-Pardo[146] reported that the precocene treated allata of insects became very shrunken and small as a result the secretion of juvenile hormone from the corpora allata had somehow been turned off. Precocene might be acting upon the brain to turn-off the corporus allatum. The surgical denervation of the corpora allata did not prevent the effects of precocene. This result ruled out the brain as the primary side of precocene. It is reported that the double bond of the chromene ring was absolutely necessary to show the activity. Metabolism studies with radiolabled precocene gave

several significant metabolites, especially the 3,4-dihydrodiol. The abundance of the dihydrodiol suggested an epoxide intermediate. Extreme lability of precocene I epoxide suggested[147] that the precocene epoxides were highly reactive with nucleophilic substrates. Brooks and his workers[148] discovered that the methylenedioxy analogues of precocene II inhibited the anti-juvenile activity of precocene II. Precocenes were oxidised within the insect corpus allatum and the resulting epoxides reacted with cellular elements bringing about destruction of the allata cells. Pratt et al[148] have studied the incorporation of radio-labled precocene I into micromolecular components of corpora allata of Locusts. The oxidative bio-transformation of the precocenes into Cytotoxic agents reveals a very subtle plant defensive strategy against insect attack. The discovery of compounds in plants with the unique ability to damage the endocrine system may provide the molecular models for the developments of useful strategies for insect control based upon selective perturbation of insect specific physiological process.

BIOLOGICAL EFFECTS OF PRECOCENES BESIDES PRECOCIOUS METAMORPHOSIS.

Precocenes either interfere with the biosynthesis of juvenile hormone of bring cytotoxic effect on the Corpora allata cells. Besides precocious metamorphosis, precocene has different biological activities on different stages.

1. ON DEVELOPMENT AND MORPHOGENESIS:

a. On embryogenesis:

According to Penner et al[149] embryos of insects are able to produce juvenile hormone 10 days after oviposition in Locusta and gradually haemolymph titre reaches to the peck before hatching. Precocenes induce permanent juvenile hormone deficiency in susceptible insects eggs and may lead to the altered embryonic development. Aboulafia-Baginsky et al[150]

have studied the action of precocene-III on the fully grown embryos (about 64 ± 4% of the egg development) in Locusta migratoria. In some cases treatment leads to the death of the embryo.

b. On early larval instars :

Precocenes induce symptoms of juvenile hormone deficiency in certain insects of young larval instars, especially in Hemiptera, orthoptera and lepidoptera which may result into precocious metamorphosis. In 1976 Bowers[151] first observed the nature of precocious metamorphosis in the milk-weed bug. Topical application of 800 µg precocene I to young fourth instar nymph of schistocerca gregarania showed prothetelic permanent fifth instar adult form. But Unnithan et al[152] observed that the action of Pr-II to second, third and fourth instar nymphs leads to precocious metamorphosis and also the Paranchyma cells of corpora-allata deteriorate.

c. On late larval instars :

Santha and Nair[153] reported that the application of anti juvenile hormone to the larva of different instars shows a number of variable results in a dose dependent manner. Last larval instar of spodoptera mauritia treated on day 0,1 or 2 with 80 µg Precocene-II showed a diminishing tendency for mortality, but the treatment with 160 µg Precocene-II of 0, 1, 2 or 3 day-old larvae was found to be highly toxic. From pupal treatment Deb and Chakraborty[154,155] suggested that precocene-II has no effect on corcyra cephalonica's pupal life. But adult emergence was moderately inhibited. The resultant moths were either externally normal or pupal imaginal.

d. On Rhythmic Activity :

JH has a number of effects on the behaviour of insects. Woodward and Rankin experimentally showed the role of

Pr-II on carcadian rhythm of feeding and mating behaviour of the milk-weed bug oncopeltus fasciatus. Ghosh et al[156] and Roy Choudhury et al[157] observed that rhythmic heart beat rate of insects profoundly slows down by precocene treatment in intermediate form of lepidopteran insects. This may be due to decreased metabolic rate.

On Reproduction :

The gonadotropic role of JH in adult female has been well established by experiments demonstrating the inhibition of ovarian development following surgical ablation of Corpora-allata. All atectomized insects are permanently sterile. Judson et al[158] reported that the adult Dysdercus similies sterile and fail to receive by courting males following Pr-II treatment. In the rice moth corcya cephalonica Pr-II application to the larval and pupae induces damage of spermatocytes. When the hydroprene treated early pupae were applied with Pr-II, the two developmental testes failed to fuse and the differentiation of different testicular compounds found to be inhibited[154,155].

W.S.Bowers first observed that precocenes induce precocious metamorphosis in insects. Precocenes II and III have higher activity than Precocene I. After Bower's, it is also found that there are many other compounds which show anti juvenile hormone activity. These are fluoromevalonate, compatin, imidazol compounds, etc.

Qaistad et al[159] reported that fluoromevalonate (FMev) has anti juvenile activity. Topical treatment of fluoromevalonate on moth showed changes in colouration, patches of pupal cuticle and pre-pupal behaviour. Edward[160] showed that FMev declined the oothee growth of periplaneta americana. Farag and Varjas[161] reported that in Hyphantria cunea FMev evokes three types of responses - precocious metamorphosis, inhibition of ecdysis and prolongation of

larval life. The critical sensitivity depends on the age of the instar. It is also seen that freshly moulted larva are the most sensitive.

Compactin is a fungal metabolite. In 1982 Monger et al[162] reported the anti-juvenile activity of compactin after treatment on Manduca sexta. Edward et al[163] suggested the compactin inhibits the biosynthesis of JH-III of Periplaneta - Americana.

Imidazole compounds when applied to the insects cause JH deficiency in different groups of insects. Among the different types of imidazole KK-42 is the most potent. According to Kuwano et al[164] compounds KK-22, KK-110, etc are effective as growth regulators. Asano et al[165] reported that imidazole compounds also induce precocious metamorphosis in different doses on different instars of Bombyxmori. among the imidazoles, 1-citronyl-5-(2-chlorophenol) imidazole and 2-methyl, phenyl analogues showed 100% precocious pupation without any lethal effect. Derivatives of imidazole having the Anti-JH properties actually inhibit the function of methyl farnesoate epoxidase. Yamashita et al[166] reported that KK-42 temporarily inhibited ecdisteroid synthesis in prothoracic gland of Bombyxmori in vitro and in vivo. So, they suggested the inhibition of ecdysteroid secration induced precocious metamorphosis. Roussel et al[167] also found that KK-42 depressed the total amount of ecdysteroid release by prothoracic gland of Locusta migratoria in vitro.

Staal et al[168] suggest that piperonyl butoxide acts as an anti-JH compound. It evokes JH deficiency syndromes, such as black pigmentation in Manduca sexta.

It is apparent that the action of precocenes on rodents and other pests has not been evaluated. It is therefore planned to synthesise a few precocene like compounds

and study their effect, both short term and long term, on rats. With this in view of the following compounds have synthesised. The structures are consistent with their spectral properties. The action of these compounds on Chrysocoris Stolli will also be studied in view of some of the results from our laboratory.