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Introduction

species will permit low rates of application and thus diminish the risk of contaminating the environment, and at the same time exert the lowest adverse influence on benevolent insect species, on mammals and on men (*table II*). A simple indication of a favourable compound is one with a small median lethal dose (LD_{50}) for the pest species combined with a large LD_{50} for all non-target organisations, producing a high safety ratio (M/I).

Insects : *Smallest* LD₅₀ (I) - highest potency
Mammals and non-target insects : *Biggest* LD₅₀ (M) = lowest potency
Safety ratio = M/I > 1 000 good
 < 10 poor
LD₅₀ = median lethal dose

1. Of 700,000 insect species, 10,000 can be regarded as pests.
2. 30 % of food grown feeds insects, not people.
3. Protection of crops is expensive, ca. \$ 6,000,000,000 annually.
4. Diptera are vectors of malaria, filariasis, schistosomiasis, trypanosomiasis and onchocerciasis, which debilitate and kill humans and cattle on an enormous scale.
5. Insects (e.g. the Spruce budworm) seriously attack seedling and mature forests.
6. Adverse effects of human and animal lice, fleas, bugs and ticks.
7. Migrant insect pests (e.g. locusts, armyworms) cause enormous crop losses.

Such selective properties were certainly not characteristics of some of the early insecticides (*figure 1*). Inorganic compounds of arsenic, lead, calcium, zinc and sodium, etc., were as toxic to mammals as to insects, but could be used as insecticides because insect pests consumed the freshly treated crop, which man washed and ate only after a suitable safety period.

Lead arsenate remains very effective against the codling moth but is prohibited under current practice. Other commonly used insecticides were DNOC and related compounds and chloropirrin, both highly toxic and unpleasant to handle.

A number of naturally occurring compounds have been used to

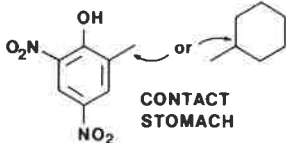

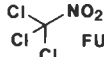
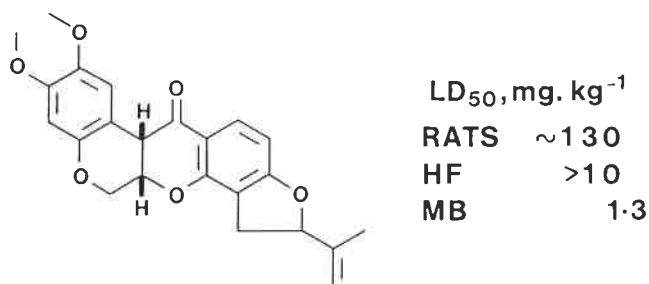
ARSENIC COMPOUNDS	As_2O_3 ; SALTS WITH: Pb (1894), Ca (1906) Cu, Zn, Na, etc.	$LD_{50}, mg. kg^{-1}$	
		INSECTS	RAT
CRYOLITE	$Na_3 Al F_6$ (1929)	300	200
DNOC 1892	 or  CONTACT STOMACH	2-10	25-40
CHLOROPICRIN 1908	 FUMIGANT	UNPLEASANT	

FIGURE 1. - Some early insecticides.

	$LD_{50}, mg. kg^{-1}$
NICOTINE	RAT 50-60 HOUSEFLY 650 (typical of other insects)

ROTENONE & RELATED COMPOUNDS



THE NATURAL PYRETHRINS

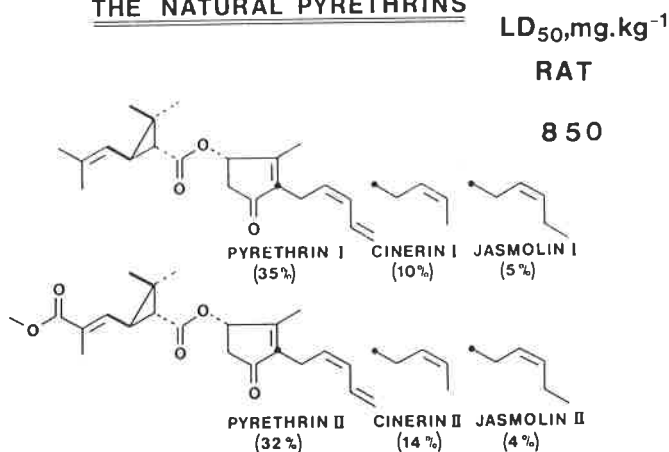


FIGURE 2. - Nicotine and most active related compounds.

control insects for many years [3]. Rotenone and related compounds (figure 2) from dried and powdered species of Derris and

Lonchocarpus were established as insecticides in China long ago and were also used as fish poisons in the East Indies and South America. Nicotine was adopted as an insecticide after tobacco smoking became an accepted habit despite the fact that for man it is one of the most rapid acting and deadly poisons known. Of the important botanical insecticides the natural pyrethrins have the lowest toxicity to mammals (see LD_{50} values in figure 2) but like rotenone and nicotine are restricted in their range of applications particularly for agriculture by supply problems and instability in the field.

Synthetic Insecticides

The limitations for insect control associated with the products, natural and synthetic, reviewed above, stimulated the search for alternative synthetic compounds and led to the introduction of the first useful group, the alkyl thiocyanates (table III) in the 1930's. These were incorporated as knockdown agents in livestock insect sprays and were used to control aphids and white flies. Although they were irritant and by recent standards relatively poor insecticides, they were readily accessible by synthesis and improved variants might have been exploited if the outstanding properties of DDT had not been discovered in 1939.

TABLE III. - Thiocyanate insecticides.

	$LD_{50}, mg. kg^{-1}$	
	RAT	INSECT
LORO		
LETHANE 384	250	100-500
LETHANE 60		
LETHANE A70		
THANITE	1000+	4800
KETONES ALSO ACTIVE		

DDT

In a recent review to place in perspective the discovery of the insecticidal properties of DDT 50 years ago, Mellanby [4] concludes that this was "probably the most important development in the history of pest control"; moreover, "this finding was not the result of a lucky chance but the climax of a carefully planned scientific campaign". DDT is the substance which should "probably take first place among all chemicals for its contribution to saving human life".

Apart from significant activity towards a very broad range of insect pests, DDT and some related compounds had relatively low toxicity to mammals (figure 3). A particularly important property was stability adequate to form active residual films on a range of crops and surfaces so that direct spraying of pests was no longer necessary. DDT could be synthesized in simple plants; perhaps 30,000 tonnes was made in 1945 and over 100,000 tonnes per annum in the late 50's. DDT was thus established as sufficiently powerful and inexpensive for application in both developed and undeveloped countries; its efficacy was confirmed when

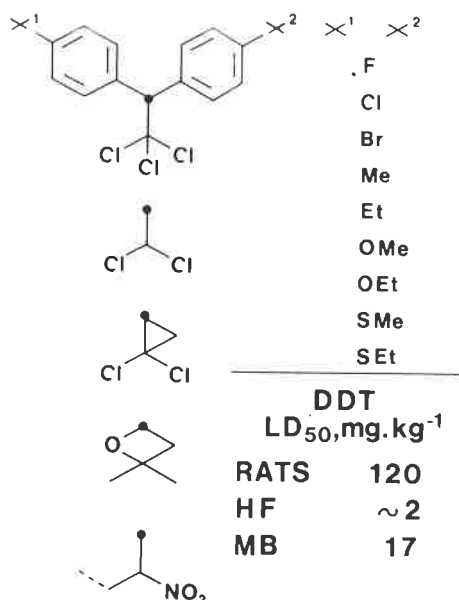


FIGURE 3. – DDT and related compounds.

it arrested a potential epidemic of typhus in Naples in 1943. Despite intensive research no closely related compounds seriously challenged its position.

Chlorinated Insecticides

Following the precedent set by DDT other effective chlorinated insecticides (figure 4) such as lindane, aldrin, dieldrin, endosul-

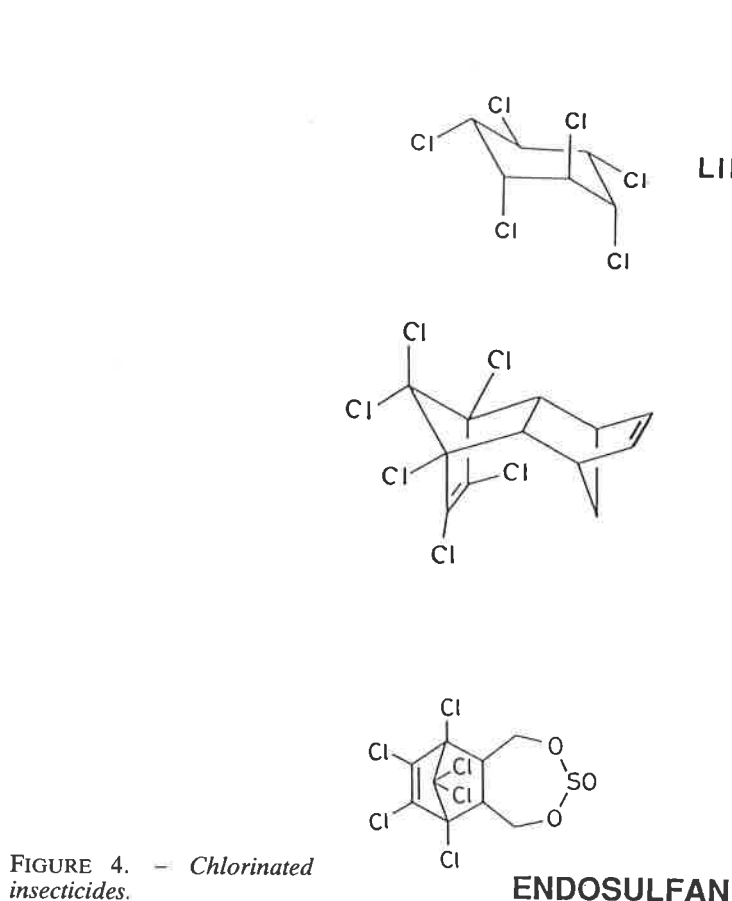


FIGURE 4. – Chlorinated insecticides.

fan and toxaphene were discovered. Some of these were more active than DDT but they were also more expensive and had higher mammalian toxicities. The undue persistence of unchanged or degraded residues of the organochlorine insecticides became progressively apparent ; when it was realised that their long term influence on the environment might be adverse, their use was severely restricted.

Organophosphates and Carbamates

Another group of insecticides, the organophosphates (table IV) was discovered in the course of wartime development of chemical warfare agents. Despite high mammalian toxicity (e.g., parathion) these compounds had good activity against many agricultural and veterinary pests. Some compounds e.g., dimethoate, possessed systemic activity and therefore controlled sap sucking pests such as aphids effectively.

Carbamates (figure 5) were a third large group of insecticides discovered and developed since the second world war. These compounds were readily synthesized and had valuable activity against soil pests as well as showing some systemic properties (aldicarb) ; however mammalian toxicity of some members of the group was high.

Applications of Insecticides

Unlike the organochlorine compounds, the organophosphates and carbamates did not persist unduly in the environment and so were more acceptable. As the world economy expanded, with the need for more food and the increasing tendency to cultivate

LD ₅₀ , mg. kg ⁻¹		
	RAT	SEVERAL INSECTS
LINDANE	90	0.4 - 7.5
LD ₅₀ , mg. kg ⁻¹		
	HF	RAT
ALDRIN	1.5	67
LD ₅₀ , mg. kg ⁻¹		
CAMPHECHLOR COMPONENT	60 - 120	
TOXAPHENE	100	

TABLE IV. - Organophosphate insecticides.

		LD ₅₀ , mg.kg ⁻¹ Rat
$\begin{array}{c} \text{S} \\ \parallel \\ (\text{EtO})_2\text{P}-\text{O}-\text{C}_6\text{H}_4-\text{NO}_2(p) \\ \text{Parathion 1944} \end{array}$	contact, stomach	13
$\begin{array}{c} \text{S} \\ \parallel \\ (\text{EtO})_2\text{P}-\text{S}-\text{CH}_2-\text{SEt} \\ \text{Phorate 1954} \end{array}$	systemic, contact, soil	4
$\begin{array}{c} \text{S} \\ \parallel \\ (\text{MeO})_2\text{P}-\text{S}-\text{CH}-\text{CO}-\text{NH}-\text{Me} \\ \text{Dimethoate 1956} \end{array}$	systemic, contact	550
$\begin{array}{c} \text{S} \\ \parallel \\ \text{EtO} \text{---} \text{P} \text{---} \text{O}-\text{C}_6\text{H}_4\text{SMe}(p) \\ \text{PrS} \\ \text{Sulprofos 1976} \end{array}$	cotton	300

TABLE V. - World use of insecticides (approximate values in £ millions).

Class	1974
Carbamates	220
Organophosphates	500
Organochlorines	160
Pyrethroids, nicotine, rotenone, etc.	18
ca.	900

rous pests of cotton such as the bollworm, *Heliothis zea*, and the tobacco budworm, *Heliothis virescens*, where control was lost or was only possible with repeated levels of organophosphates (e.g., parathion) so high that they endangered the health of operators. In some cotton growing areas of Mexico and Texas, for example the crisis was acute*.

Photostable Synthetic Pyrethroids

The lessen the adverse economic impact of such pest control failures emergency registration was granted to two insecticides of a new class, photostable pyrethroids. The compounds in question had each been developed about 1973. They were, respectively, Fenvalerate, a product from the research efforts of the Sumitomo Chemical Company in Japan and Permethrin, developed in the course of a fundamental study of the relationship between chemical structures and insecticidal activity initiated by Charles Potter in 1948 in the Department of Insecticides and Fungicides, Rothamsted Experimental Station.

Both new compounds controlled the resistant cotton pests very successfully at effective field rates much below those which had become necessary with the longer established insecticides (table VI). These results were typical of those which stimulated the rapid commercial development of the photostable synthetic pyrethroids, a class which included compounds with outstanding properties such as deltamethrin.

Pyrethrum at Rothamsted Experimental Station

Insecticides derived from plants and the relationship between insecticidal activity and chemical structure had been studied in the Insecticides and Fungicides Department at Rothamsted since the time of Frederick Tattersfield (table VII).

For a significant period, pyrethrum plants had been grown in the garden of the Ministry of Agriculture, Milton Road, Harpenden [5] and seeds were supplied to Kenya to help establish the growing industry there. Before he became Head of Department of Insecticides and Fungicides in 1948, Charles Potter had shown that films of the natural pyrethrum in heavy white oil persisted

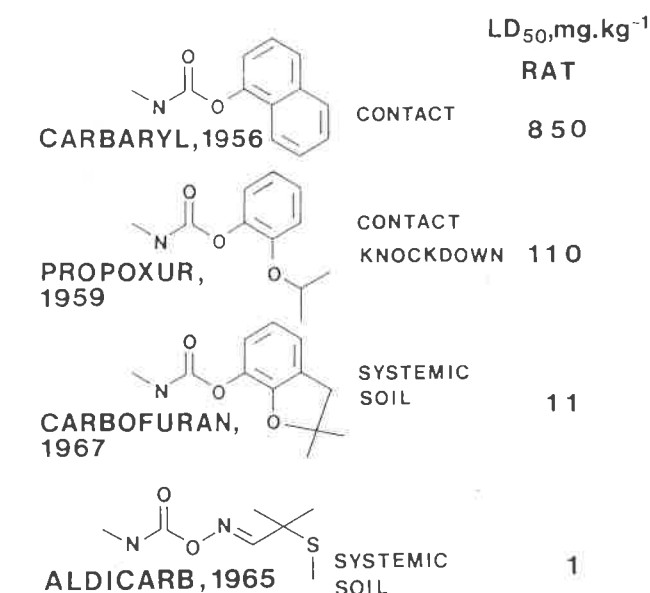


FIGURE 5. - Carbamate insecticides.

crops in monoculture, dependence upon synthetic chemical insecticides expanded so that by 1974 their total value was nearly £900 million. In contrast, the value of the natural insecticides used was only about 2 % of this total (table V).

Organophosphates, carbamates and organochlorine compounds were used on agricultural and horticultural crops on a very big scale ; of all the applications, protection of cotton, very important economically, consumed more synthetic insecticides than any other (figure 6). Organochlorine compounds (DDT, toxaphene and endosulfan), carbamates (carbaryl) or organophosphates (parathion, fenitrothion) were used alone or in combination according to availability and to judgement of the pest control operators. With such continued unregulated application insects infesting many crops worldwide began to develop high levels of resistance. Particularly serious situations arose with lepidopte-

* *Insect Resistance, Mexico and Texas, 1977* : "Without alternative insecticides to control outbreaks of tobacco budworms resistant to organochlorines, carbamates and organophosphates, many farmers saw their cotton yields, destroyed... Cotton farms were abandoned, gins, compresses and cotton seed oil mills were closed ; farm workers were forced to migrate from the area ; the entire economic and sociological structure of the area's small villages and rural communities was affected".
D.G. Bottrell and P.L. Adkisson, 1977.

Consequence : emergency registration of permethrin and fenvalerate.

TABLE VI. - Comparison of some insecticides.

	Effective field rate	LD ₅₀ (rats)	Acceptable daily intake (man)
	g.a.i. ha ⁻¹	mg.kg ⁻¹	mg.kg ⁻¹
Permethrin	100-150*	430-4000*	0.05 *
Fenvalerate	25-250*	450*	0.02 *
Deltamethrin	10-25	140-5000*	0.01 *
Parathion	> 500	3.6-13*	0.005*
Endosulfan	> 500	76-240*	0.008*
DDT	> 750	120*	0.02 *
Carbaryl	250-2000*	850*	0.01 *

* Source : The Pesticide Manual, ed. C.R. Worthing, 1987.

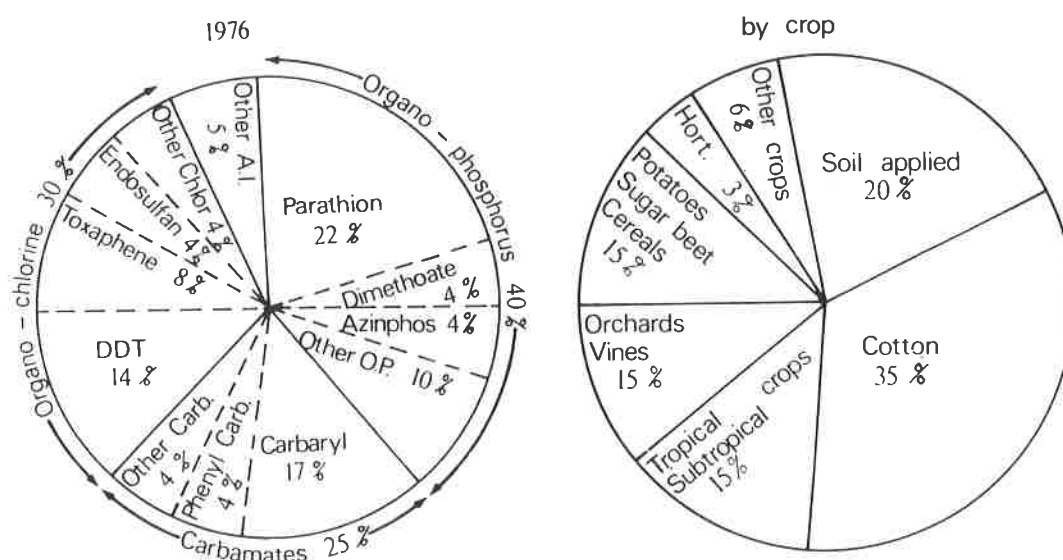


FIGURE 6. - Agricultural insecticides.

TABLE VII. - Rothamsted and insecticides.

1918 : F. Tattersfield heads Department of Insecticides and Fungicides. Systematic studies of structures and insecticidal activities. Chemistry, cultivation and analysis of pyrethrum.

1927 : Harpenden pyrethrum seeds to Kenya.

1935 : C. Potter sprays pyrethrum in warehouses.

1948 : Potter starts multi-disciplinary investigations of insecticides. Structure and activity of pyrethrum and allethrin.

adequately in the dark to control insect infestations of grain in warehouses [6]. Recognising from this work, and other experience, the value of the natural compounds (table VIII), he decided that a detailed examination of the relationship between their biological properties and their chemical constitution would be a rewarding investigation. From the beginning of the work scientific curiosity to explain why plant-derived compounds should affect insects so powerfully and rapidly, yet barely influence mammals was a strong incentive.

The Natural Pyrethrins

The natural pyrethrins occur in the flowers of *Tanacetum* (*Chrysanthemum*) *cinerariaefolium* which grow particularly well on the

TABLE VIII. - Natural pyrethroids.

The natural pyrethrins, from the flowers of *Chrysanthemum cinerariaefolium*, have :

- High toxicity to insects.
- Rapide action against insects.
- Low toxicity to mammals.
- Low stability, especially in sunlight.

They are therefore extremely effective and safe insecticides which do not persist in the environment, are ideal for use indoors and to protect foodstuffs, but too unstable to control agricultural pests.

Equator at altitudes above 5000 ft., but also flourish at other locations. Harvesting in Kenya, a primary source, is by hand picking up of to 3 flushes a year. The product is therefore relatively expensive and the supply depends on the available labour and climatic conditions ; to obtain the optimum yield of insecticide, the flowers must be picked when they are just completely open.

In comparison with other classes of insecticides, the natural pyrethrins have a most favourable combination of properties, very suitable for a fundamental study to discover the structural basis for their activity. Moreover at the start of the work at Rothamsted there appeared little danger that it would overlap or duplicate commercial interest.

Most features of the constitution of the natural esters (figure 7) were established in 1910-1916 by the Swiss chemists Staudinger and Ruzicka who published their work in 1924. Their structures were refined in detail, with syntheses by LaForge, Schechter and their co-workers in the U.S.A.. (1935-1952), and by Crombie and Harper in the U.K. (1942 onwards). Essentially they are chiral esters of isobutenyl substituted dimethyl cyclopropane carboxylic acids with methyl cyclopentenolones having Z-pentadienyl or related side chains [7]. Pyrethrin I is principally associated with the killing action of the pyrethrum mixture and pyrethrin II, which has the more polar methoxycarbonyl side chain, with the rapid knockdown action. Very few of the structural features of the natural esters can be changed or eliminated without significant loss of insecticidal activity. Optical conformation and various sites of unsaturation are especially important (figure 8).

Although Staudinger and Ruzicka's structure for pyrethrin I (figure 9) was wrong in detail, it suggested to them in a remarkable way some compounds to synthesize that contained the essence of a number of future practical advances. For example, their cyclopentenolone chrysanthemate with an allyl side chain representing the natural diene had some insecticidal activity (in a mixture

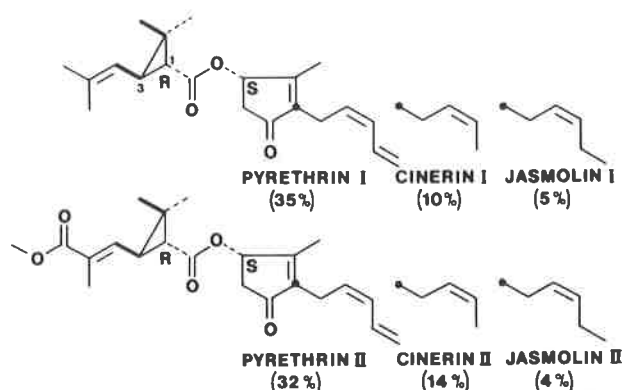


FIGURE 7. - The natural pyrethrins (Staudinger and Ruzicka, Laforge et al. Harper et al., Crombie et al.).

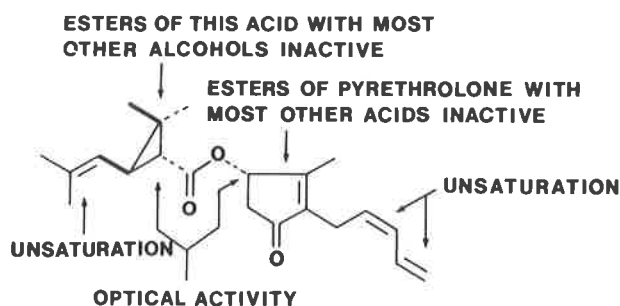


FIGURE 8. - Structure and insecticidal activity.

TABLE IX. - Variation of relative potency of natural pyrethrins and allethrin with insect species.

	Mustard beetle	Saw-toothed grain-beetle	Diamond back moth (larvae)	Potato aphid	Housefly
Natural pyrethrins (six esters mixed)	100	100	100	100	100
(±)-Allethronyl (+)-trans-chrysanthemate	40	48	400	12	150
(±)-Allethronyl (±)-cis, trans-chrysanthemate	20	41	180	6	300

(after Elliott, Needham & Potter, 1950).

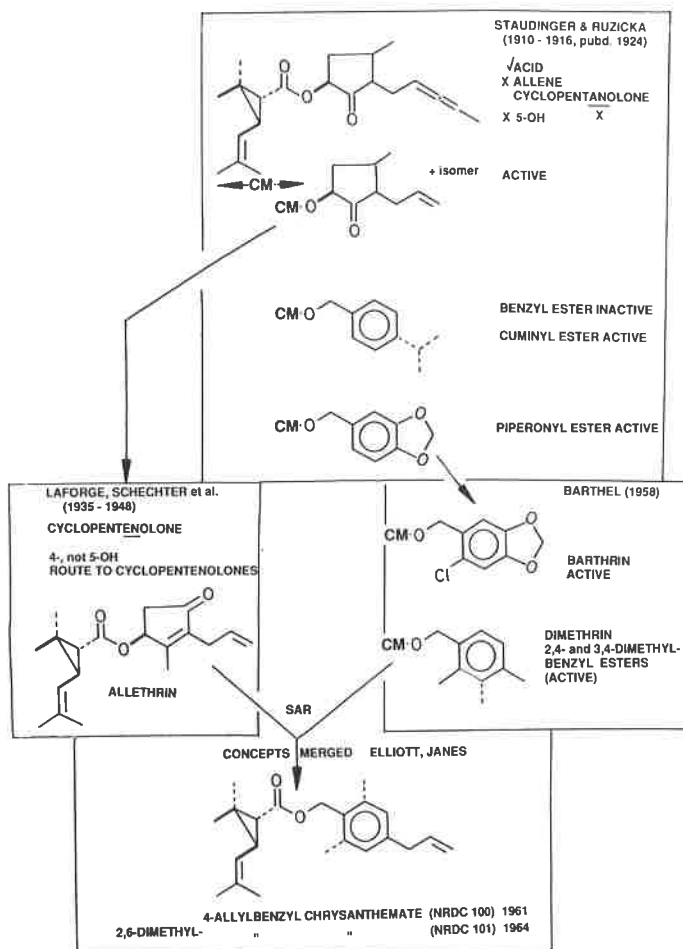


FIGURE 9. - Pyrethroid alcohols : 1.

with an isomer) foreshadowing the first commercial synthetic pyrethroid allethrin ; this was prepared in 1946 by Schechter when he had amended the alcohol structure and developed his new cyclopentenolone synthesis.

Staudinger and Ruzicka also found activity in cuminyll and piperonyl chrysanthemates, but none in benzyl chrysanthemate. Even then, therefore, their results indicated the need for a substituent on the alcohol nucleus, on the side remote from the acid. Examination of benzyl chrysanthemates was pursued by Barthel who made the 6-chloropiperonyl ester and more important, 3,4- and 2,4-dimethylbenzyl chrysanthemates, called dimethrin.

An early stage in our development of active pyrethroid esters at Rothamsted was when we combined the concepts implicit in the structures of allethrin and dimethrin to produce the significantly active esters 4-allyl- and 4 allyl-2,6-dimethylbenzyl chrysanthemates.

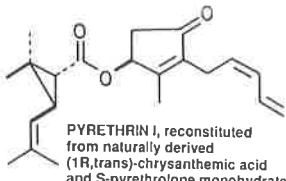
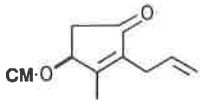
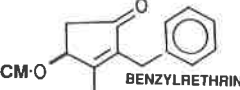

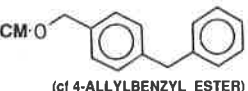
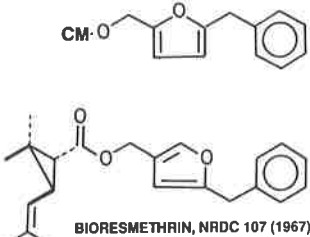
	LD ₅₀ , mg.kg ⁻¹		
	Housefly	Mustard beetle	Rat
 PYRETHRIN I, reconstituted from naturally derived (1R,trans)-chrysanthemic acid and S-pyrethrolone monohydrate	30	0.3	420
 S-BIOALLETHRIN (from LAForge)	6	12	800
 BENZYLRETHRIN		5	
 BENZYLNORTHIN		1.5	
 (cf 4-ALLYLBENZYL ESTER)		2.5	
 BIORESMETHRIN, NRDC 107 (1967)	0.6	0.5	8000

FIGURE 10. – Pyrethroid alcohols : 2.

Another phase in our progress at Rothamsted was based on the finding that pyrethrin I, with its diene side chain, was 40 times more active than the corresponding allethrin isomer, kindly given to us by LaForge, to one of our test species, the mustard beetle (*Phaedon cochleariae* Fab.) ; as had been widely established, allethrin was more active than the natural compound (5 times in our test) to houseflies (*Musca domestica* L.). (For simplicity, the results in figure 10 refer to single isomers tested at a later date ; the initial comparisons were of the mixed natural pyrethrins with partly resolved or fully racemic compounds as shown in table IX).

The result with mustard beetles stimulated us to examine benzyl substituted esters with the naïve, but in practice perhaps justified concept, that a phenyl group could simulate the natural Z-pentadienyl function *in vivo*. Since this compound was active and one without a methyl group on the cyclopentenone ring was even more so, we changed the central nucleus to furan (another five-membered) and investigated many variations (not shown) which maintained the cyclopropane and benzyl groups in roughly similar relative dispositions. Eventually this path of investigation led to bioresmethrin, the first synthetic pyrethroid with activity comparable to that of pyrethrin I against a range of insect species and the very valuable, but unanticipated bonus of considerably diminished mammalian toxicity. (LD₅₀Rat 8000 mg.kg⁻¹ instead of 420 or 800 ; figure 10).

Despite its favourable insecticidal activity and low mammalian toxicity, bioresmethrin and its racemic relative resmethrin were little if at all more photostable under practical conditions than

the natural pyrethrins and allethrin, so that the accepted and limited range of applications of these insecticides was not much extended.

Photostable Pyrethroids

In earlier work, 4-allylbenzyl chrysanthemates had been shown to be more active than the corresponding 3- and 2-allyl isomers. For a period we assumed that a similar relationship would hold for 4- and 3-benzylbenzyl chrysanthemates. However, in 1969, the decision to test this in practice was taken, and unexpectedly, the 3- isomers were found to be more active than the 4-benzyl compounds synthesized earlier (figure 11). The potency of the 3-benzyl compounds also provided a convenient opportunity to dismiss an earlier speculation [8] that a methylene group in the alcohol side chain might be a feature important for activity because the equivalent phenoxy compound was of similar activity.

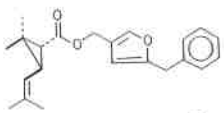
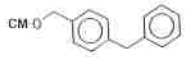

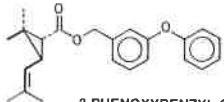
	LD ₅₀ , mg.kg ⁻¹	
	Housefly	Mustard beetle
	0.6	0.5
	15	25
	4	1
	2	0.7

FIGURE 11. – Pyrethroid alcohols : 3 (1969).

The new, achiral furan alcohol, or the equivalent 3-phenoxybenzyl alcohol provided a more convenient and effective component for examining the influence of changes in acid structure on ester activity than allethrolone, used previously in a number of studies. The relative effectiveness of the optical and geometrical isomers of chrysanthemic acid could be assessed without complication from an alcoholic asymmetric centre e.g. cimethrin (figure 12). The enhanced insecticidal activity of the ethano chrysanthemate, RU 11679, discovered by Velluz, Martel and Nominé stimulated our examination of a large number of other variations at that site, including, in succession monochlorovinyl (en route to ethynyl) and then dichlorovinyl. The enhanced activity of the ester of the latter variation, an isostere of chrysanthemic acid, suggested a survey of related compounds. In particular, not only was the combination with 3-phenoxybenzyl alcohol more active than might have been predicted from previous structure-activity studies but it was also much more stable in light than other synthetic pyrethroids examined (figure 13). The photolabile sites (trans-methyl and furan ring) which Casida *et al.* (figure 14) identified in resmethrin were not present in the new esters. The racemic compound permethrin was quickly brought into commercial production and was one of the insecticides first given emergency clearance for use on cotton (see above, p. 60).

Deltamethrin

The effectiveness of permethrin stimulated examination of accessible related compounds, among them those derived by substitution at the α-benzylic position (figure 15). Chen and Barthel had not obtained more active variants of piperonyl chrysanthemate

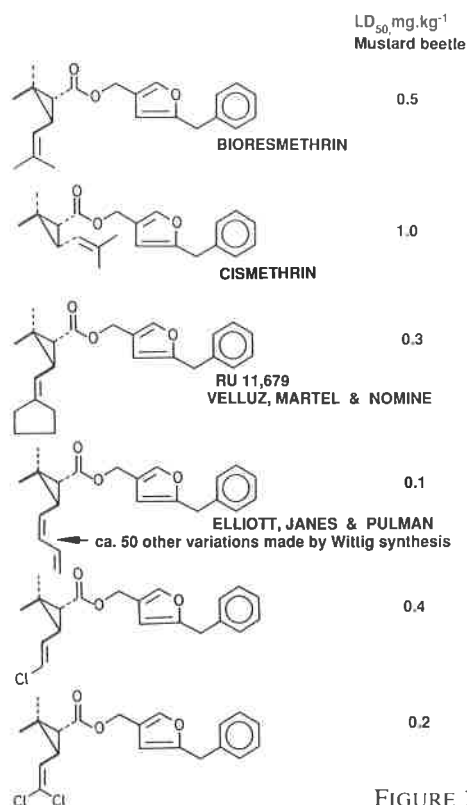


FIGURE 12. – Pyrethroid acids.

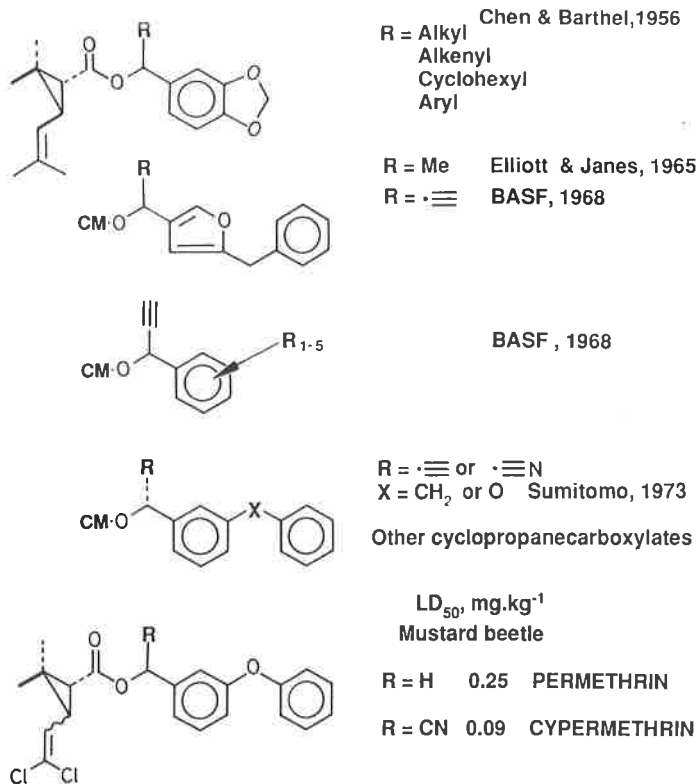


FIGURE 15. – Origin of α -cyanobenzyl esters.

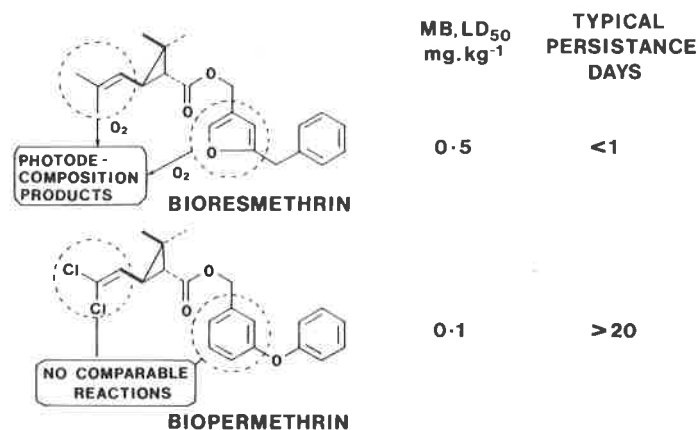
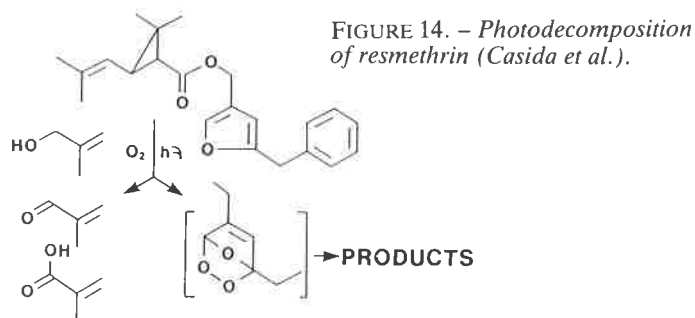


FIGURE 13. – Development of first photostable pyrethroid.



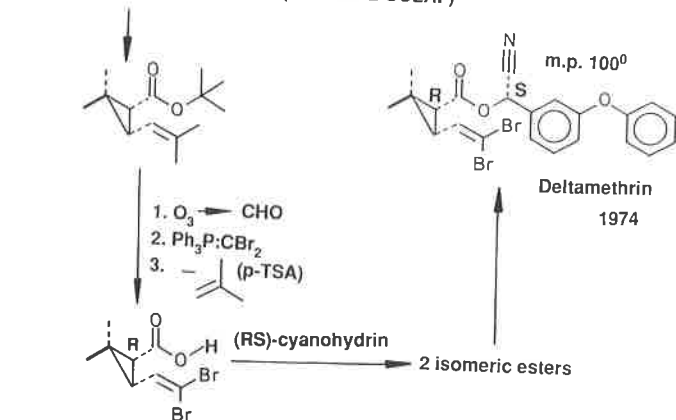
by introducing alkyl, alkenyl, cyclohexyl or aryl substituents there. α -Methyl- and α -ethynyl substituents did not improve the activity of furylmethyl or benzyl chrysanthemates. The Sumitomo chemists made the key discovery that α -ethynyl and particularly α -cyano-benzylbenzyl and 3-phenoxybenzyl chrysanth-

mates had activity equal to or greater than the parent compounds. We found that an α -cyano group approximately trebled the activity of permethrin, which was already greater than that of most known insecticides.

Introduction of the α -cyano group into permethrin created a new chiral centre and raised the possibility that the two optical isomers might differ in potency. Optical resolution of easily racemised alcohols such as cyanohydrins is not readily achieved and we failed in initial attempts to regenerate optically active alcohols from esters with conventional resolving acids. We therefore decided to esterify the racemic cyanohydrin with an optically active acid known to give insecticidal esters. Based on experience that in the pyrethroid field *cis* substituted cyclopropane acids tended to crystallize more readily than *trans* and general knowledge of the relatively high melting points of brominated compounds, we chose to make a [1*R*,*cis*] dibromovinyl acid for later esterification (figure 16). The required acid was obtained from [1*R*,*cis*] chrysanthemic acid (generously given to us by Dr Martel of Roussel Uclaf), by a Wittig reaction on the chiral aldehyde generated by ozonolysis, as indicated. When the mixture of two isomeric cyanohydrin esters from the racemic alcohol was cooled in hexane, one isomer, later designated NRDC 161 or deltamethrin, crystallized. After recrystallization this was found to be much more active than the liquid isomer which remained in the mother liquor; this less active isomer was also accessible from the product of the action of D-oxynitrilase on the aldehyde and hydrogen cyanide. The isomer, m.p. 100°, was much more active as an insecticide than any previous compound examined (see figure 16) and was later found to persist long enough on foliar surfaces to control pest infestations efficiently, but to be degraded to innocuous residues after a suitable period.

The absolute configuration of deltamethrin was determined by Dr John Owen of the Molecular Structures Department of Rothamsted by X-ray crystallographic evidence (figure 17) and confirmed a deduction made by indirect argument based on NMR evidence [9]. Extended tests showed that deltamethrin was considerably more active (figure 18) and more photostable, as predicted, than pyrethrin I; the sample of pyrethrin I used in this

1R,CIS CHRYSANTHEMIC ACID (ROUSSEL-UCLAF)



S (Confirmed X-Ray) Cyanohydrin Ester (Crystalline)
R Cyanohydrin Ester (Liquid) from aldehyde + HCN with D-Oxynitrilase

	Relative Potency*	Life in Soil** (months)
DELTAMETHRIN	400	1
DDT	1	48

* Mean for 10
insect species

** Depending
on conditions

FIGURE 16. – Optical resolution of cyanohydrin esters ; synthesis of deltamethrin (NRDC 161).

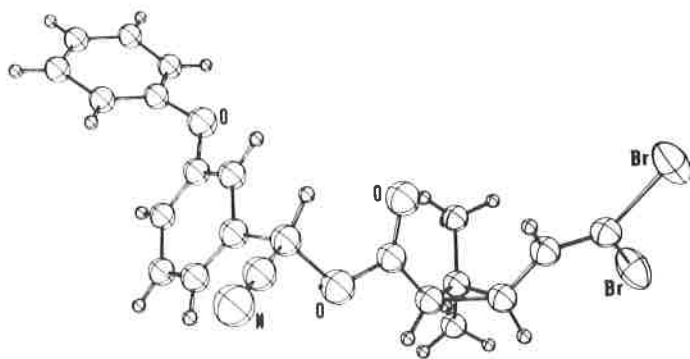


FIGURE 17. – NRCD 161 (1974).

comparison was obtained by reconstitution from purified, naturally derived constituents (figure 7).

The chemists of Roussel Uclaf had developed elegant, unique and efficient routes to [1R,trans]- and [1R,cis]-chrysanthemic

and related acids and so were in a special position to manufacture deltamethrin*. By conducting the final crystallization of deltamethrin in the presence of triethylamine or a suitable alternative base, the less active liquid isomer in the mother liquor was continuously isomerized to give eventually 100 % of the desired crystalline product. Deltamethrin or "Decis" was thus brought rapidly and efficiently to commercial availability, to occupy a unique place in the armoury of insecticides. Figure 19 indicates the range of potent, photostable, cyclopropane pyrethroids now available following the introduction of permethrin, cypermethrin and deltamethrin (NRDC 143, 149 and 161, respectively).

Fenvalerate

Another important range of photostable pyrethroids includes fenvalerate, discovered by the Sumitomo Chemical Company, and with permethrin, first given emergency registration for use on cotton (figure 20). In screening a range of esters of accessible acids with the furan alcohol or the related 3-phenoxybenzyl alcohol, the Sumitomo chemists detected activity in that derived from α -ethylphenyl acetic acid. Optimization of this lead gave the α -cyano-3-phenoxybenzyl ester of α -isopropyl-4-chlorophenyl acetic acid (fenvalerate) now also available in the resolved SS form as asana.

Selectively Potent Insecticides

At the beginning of the discussion, the desirability of insecticides with selective potency between insects and mammals was indicated (table II). An important characteristic of natural and synthetic pyrethroids is their different behaviour in insects and in mammals (table X). Their favourable toxicological properties include their ability to penetrate rapidly to and interact with their sites of action in insects, probably sodium channels of nerve membranes, where a compounds such as deltamethrin is active at concentrations as low as 10^{-12} M. In contrast, following external or oral administration to mammals, the pyrethroids are largely converted by hydrolytic and oxidative mechanisms to polar metabolites (figure 21). These are eliminated in the faeces or urine unchanged or as conjugates before sensitive sites are reached. The importance of the route of administration is indicated by the contrasting toxicities of pyrethroids to birds (very low) and to fish

* Voir L'Actualité Chimique, décembre 1986, p. 5.

MEDIAN LETHAL DOSES (mg. kg⁻¹)

	PHAEDON COCHLEARIAE	PERIPLANETA AMERICANA	MUSCA DOMESTICA	ANOPHELES STEPHENSII	GLOSSINA AUSTENI
 PYRETHRIN I UNSTABLE, VISCOUS LIQUID	0.25	0.33	16	2.4	0.37
 DELTAMETHRIN STABLE, CRYSTALLINE (M.P. 100°)	0.032	0.056	0.03	0.02	0.004

FIGURE 18. – Pyrethrin I and deltamethrin compared.

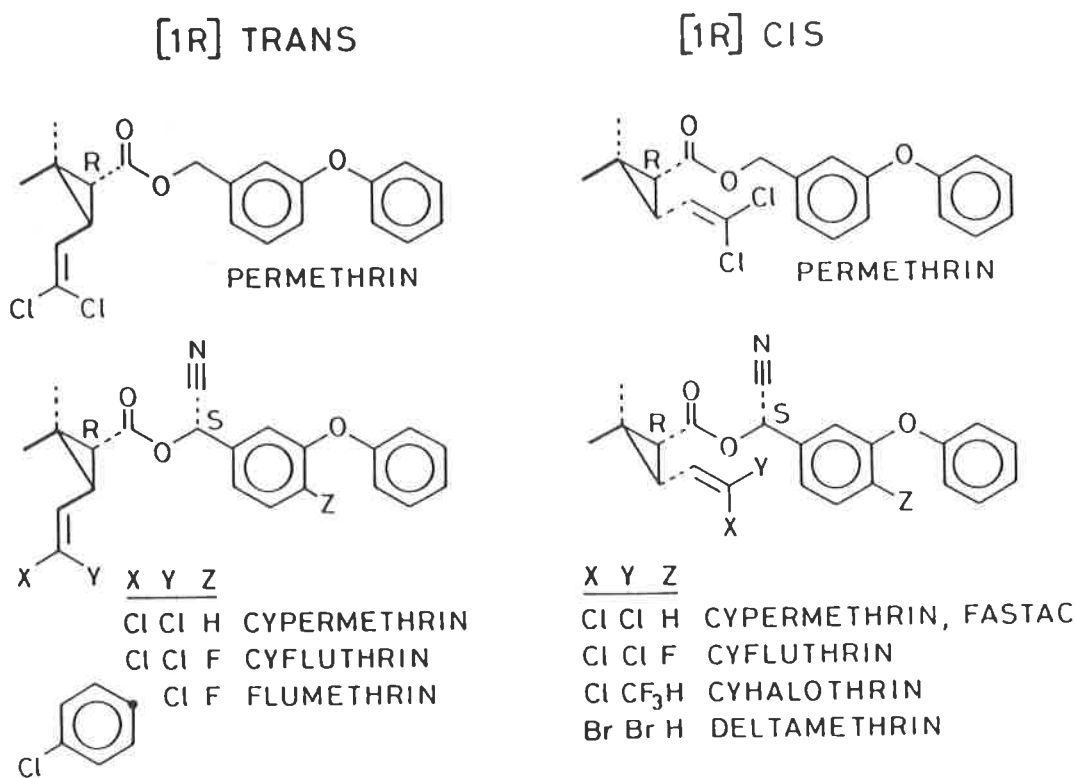


FIGURE 19. – Active isomers in some photostable pyrethroids.

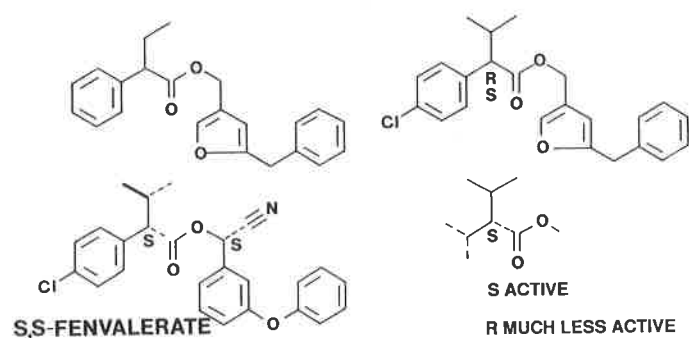


TABLE X. - Selective potency of pyrethroids between insects and mammals.

In insects : Pyrethroids penetrate rapidly to action sites (voltage sensitive sodium channels) without detoxification
in mammals : Pyrethroids are converted to polar metabolites which are excreted before or after conjugation ; sensitive centres not accessible ;

Deltamethrin, LD ₅₀ , mg.kg. ⁻¹	
Housefly (topical)	0.01
Rat (oral)	130
	} x 13,000

FIGURE 20. – Development of fenvalerate (Ohno et al. ; Sumitomo Chemical Co., 1973).

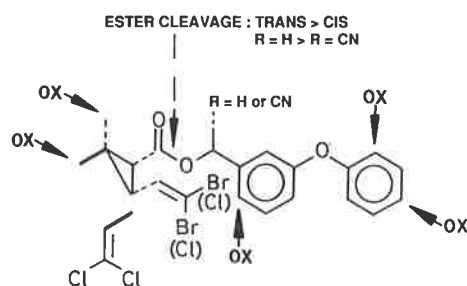


FIGURE 21. – Metabolism of pyrethroids. Nature and extent of metabolism reactions depend on media and environment. Glycine, glucuronide, sulphate, etc. conjugates of polar metabolites (after Casida).

(generally high) to which pyrethroids in water gain access into the bloodstream via the gills. Measurements under idealized laboratory conditions indicate that the more stable pyrethroids are indeed toxic to fish, but in practice the impact of the pyrethroids is less serious than might have been predicted because their concentration in aqueous media is much dimi-

nished by adsorption onto competing lipophilic material on river banks, in ponds and onto organic matter suspended in the aqueous medium.

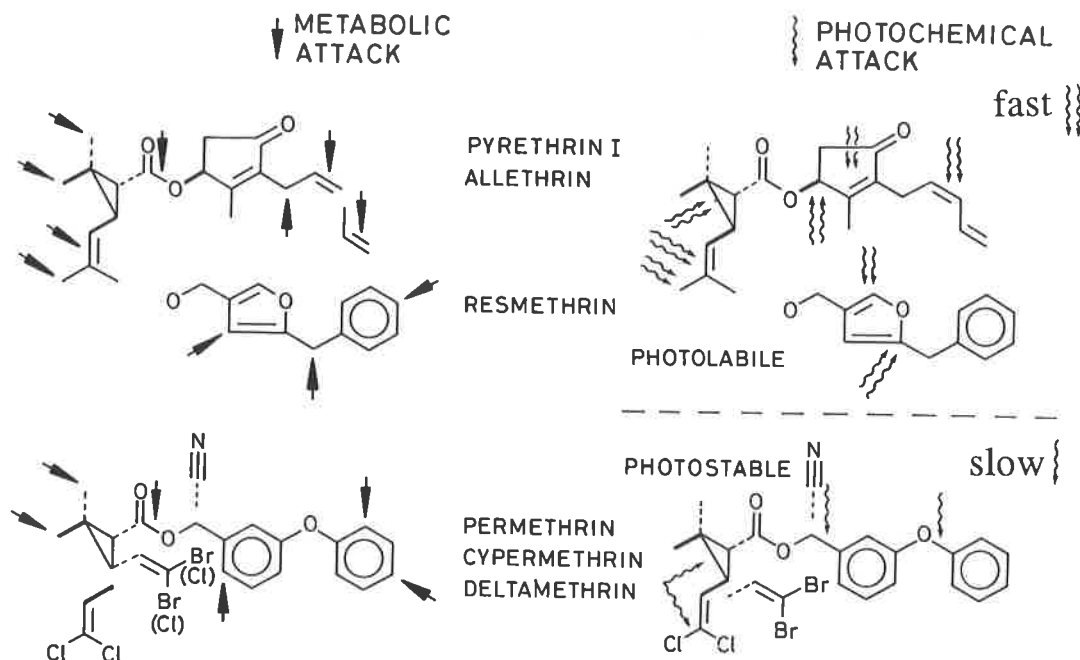
Pyrethroids in the Environment

Pyrethrin I (and the other natural esters), allethrin and resmethrin are powerful insecticides with low mammalian toxicities associated with their efficient metabolism at one or more sites (figures 22). These compounds are also degraded photochemically, so they are not suitable for applications (e.g., protection of field crops) needing stability in light.

Similarly the hazard to mammals in using permethrin, cypermethrin and deltamethrin is low because they retain multiple sites at which they are metabolized in biotic systems. Although they are still susceptible to some photochemical degradation, the reactions by which the proceeds are much slower, because these more stable compounds absorb light and transfer the energy intramolecularly relatively less efficiently.

The synthetic pyrethroids are effective at lower rates of application (table II) in the field than are required for other insecticide

FIGURE 22. - *Metabolism and photochemistry of pyrethroids (after Casida).*



groups because they are in general more active, as indicated by median lethal doses for five species (figure 23). They are sufficiently stable to persist on crops for 7-30 days whilst insect infestations are controlled. Residues reaching the soil are then metabolized by routes comparable to those in other biotic systems and give polar products which are bound to soil particles, where they are further degraded. Residues of non-polar products do not persist and accumulate to contaminate the environment (figure 24).

In contrast, with chlorinated hydrocarbon insecticides (e.g., DDT) products of aerobic or non-aerobic decomposition are non-polar and may persist for years under some circumstances.

Further, nearly all the pyrethroid insecticides have low vapour pressures and are not transmitted throughout the environment by air currents close to land and water surfaces : DDT and some related compounds are known to be translocated in this way.

Pyrethroids are lipophilic compounds like the chlorinated hydrocarbon insecticides, as indicated by their high octanol-water partition coefficients (figure 25) and differ in the respect from carba-

mates and some organophosphates. Pyrethroids therefore are unlikely to show systemic properties, but can be expected to perform in some respects similar to chlorinated hydrocarbon compounds, which they may replace for some applications, but at much lower rates (figure 23).

Table XI compares the toxicities to mammals and to insects of a number of insecticides and other established toxic agents such as strychnine, cyanide and some toxins. Deltamethrin, for example shows a similar level of potency to insects as does tetrodotoxin to mammals, but deltamethrin in much less toxic to mammals. Bioresmethrin is remarkable in its selectivity indicated by the relative levels of its potencies to insects and to mammals.

Resistance

If insects did not develop tolerance to insecticides, the present

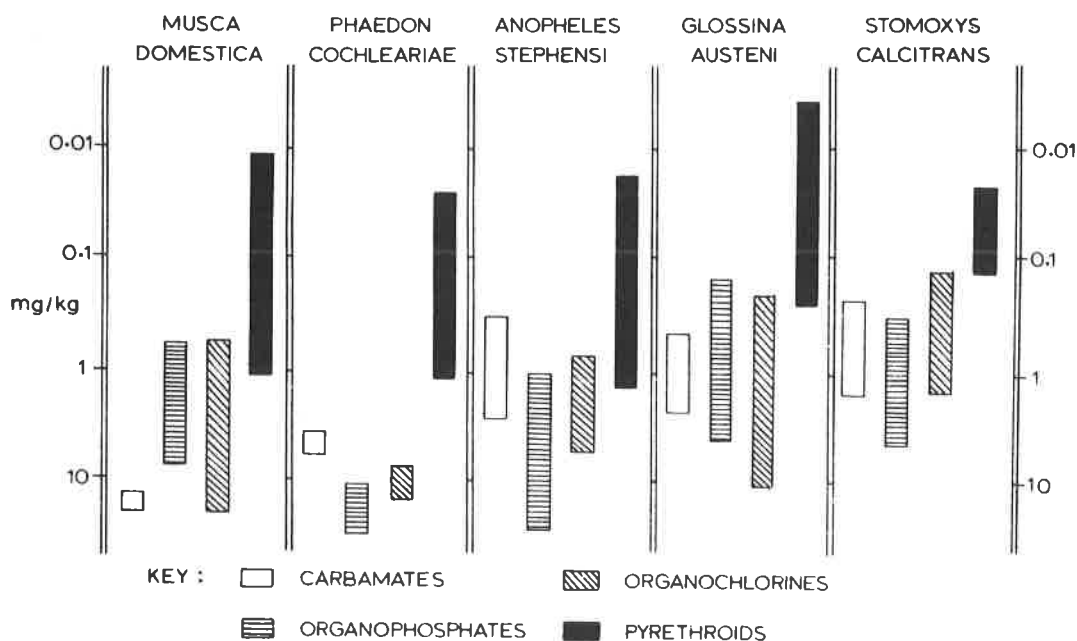


FIGURE 23. - LD_{50} values of insecticides in mg/kg.

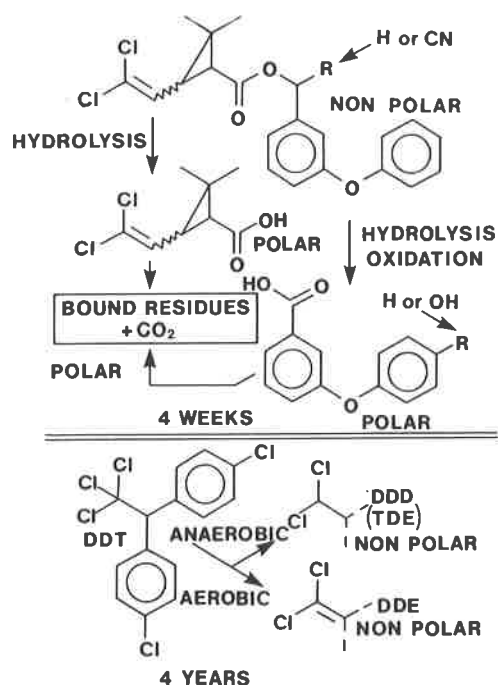
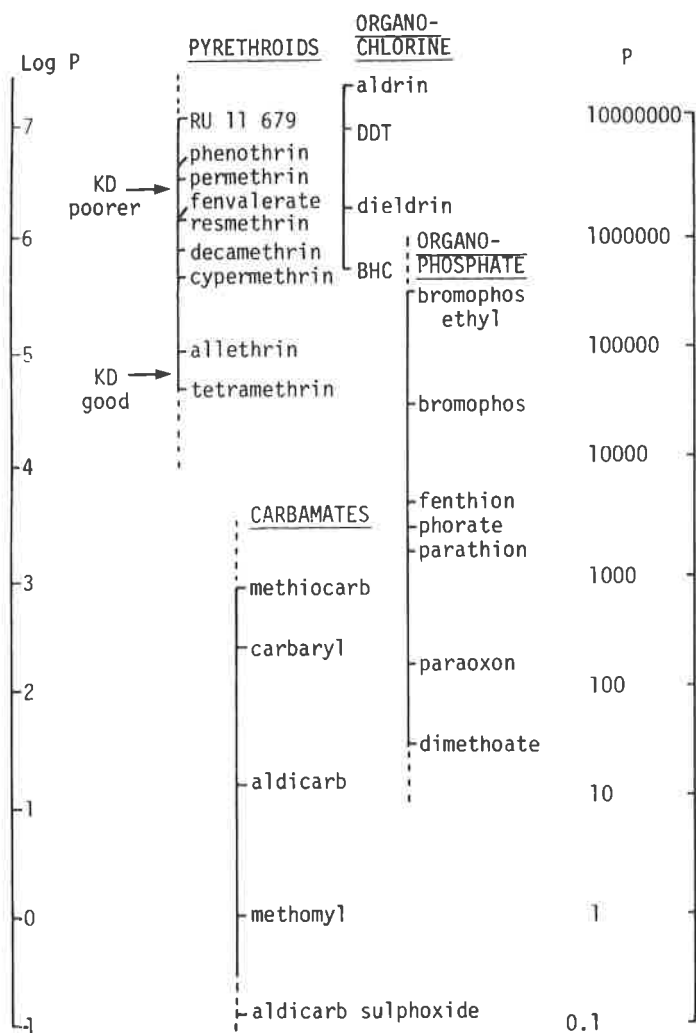


FIGURE 24. TABLE XI.

Pesticide	Toxic dose (mg/kg)	
	to mammals	to insects
Biosmethrin	10 000	
Malathion		
Pirimiphos-methyl		
Permethrin		
Carbaryl	1 000	Nicotine
Rotenone		
Fenvalerate, Pyrethrin I		
Dimethoate		
Diazinon, DDT	100	
Deltamethrin		
Nicotine		
Dieldrine		
Dinitro-orthocresol		
Strychnine	10	Carbaryl
Cyanide		Malathion
Parathion		DDT, Aldicarb
Aldicarb	1	Dinitro-orthocresol
		Diazinon, Rotenone
		Primitphos-methyl
		Parathion
		Permethrin
		Dimethoate
		Dieldrin
		Fenvalerate
		Pyrethrin I
		Biosmethrin
Curare		
Sodium fluoro-acetate		
Dimethyl mercury	0.1	
	0.01	
Tetrodotoxin		
Sarin, Tabun, Soman...		
Botulinium toxin	0.00002	Deltamethrin



P = octanol-water partition coefficient

FIGURE 25. - Polarities of insecticides.

Insect resistance 1950-present

1950-1970 : Successive use of different insecticide groups gave broad cross-resistance.

1988 : 400 species resist insecticides of one or more groups. For 60-70 species, chemical control difficult now or soon.

Improvements on pyrethroids will henceforth be rare or expensive.

Therefore, *Insecticide Resistance Management* - R.M. Sawicki, Rothamsted :

- Fewer treatments minimize resistance development.
- Biological methods and alternative agricultural practices decrease pest populations.

In : Zimbabwe, Egypt, Australia, U.S.A. (cotton belt).

Procedure with pyrethroids :

- Restricted sprays lower selection pressure and permit dilution with genes from non-resistant pests.
- Long-term efficacy retained by application only during maximum flowering and fruiting - otherwise use non-pyrethroids.

Where tested, such strategies have been effective so far however continued vigilance and co-operation between all.

range of insecticides of the various classes would probably be adequate to deal with the majority of control problems. However, the extensive use of successive groups of insecticides has induced broad cross resistance in the important insect pest species. This is especially significant with the widely dispersed resi-

TABLE XII. - Increased global insecticide costs if pyrethroid resistance became established (US \$ mm).

Crop outlet	Current insecticide costs	Costs if resistance occurred	Increase in costs	
			\$MM	%
Fruit/nuts	1,000	1,295	295	29
Vegetables	625	860	235	38
Corn	490	555	65	11
Rice	1,040	1,105	65	6
Others	1,405	1,715	310	22
	4,560	5,530	970	21
Cotton	1,540	2,930	1,390	90
	6,100	8,460	2,360	39

(Ian A. Watkinson, 1989).

dues of DDT which have induced resistance to other lipophilic insecticides.

Carefully managed applications of insecticides of all classes are essential to maintain effectiveness at the highest possible level. However continued vigilance and co-operation between all concerned with production of crops and their protection from pests is essential.

Dr Ian Watkinson [12] has estimated the cost of protecting various crops from insect attack and how much more expensive treatments would be if pests became considerably more resistant to pyrethroids (table XII). A possible 90 % increase in the cost of producing cotton worldwide is particularly striking.

TABLE XIII. - Applications of pyrethroids (1987).

	%
Cotton	46
Fruit and vegetables	22
Other crops	17
Animals	9
Non-agricultural	6
Value : \$ 1 345 millions	
BTG-licensed compounds : \$ 820 millions	

(Source : County NatWest Wood Mac).

Contribution of Pyrethroid Insecticides to Human Welfare

The figures assembled by Dr Watkinson serve to quantify in some respects the worldwide influence of the pyrethroid insecticides on Man's affairs. Synthetic pyrethroids are estimated to have been used to treat 70 millions ha of agricultural crops in 1987 (table XIII). In financial terms their contribution by controlling pests infesting food and fibre crops and transmitting disease rose over little more than a decade at least 40 fold to above \$ 1300 millions per annum, with more than \$ 800 millions associated with the long term research project initiated by Charles Potter at Rothamsted in 1948.

Conclusion

In this review I am conscious that I have given a necessarily simplified and highly condensed description of the development of some of the photostable pyrethroids, emphasizing work at Rothamsted. I have paid less than adequate tribute to much distinguished work by other research groups in both non-industrial and industrial laboratories which directly or indirectly influenced our progress.

I acknowledge my deep and sincere gratitude to a succession of mentors and colleagues without whose help and guidance this work would not have progressed. Amongst these I wish to mention first, the late Stanley H. Harper who started the most important chemical investigations of pyrethrum in the United Kingdom in 1942 and introduced both Leslie Crombie and myself to the subject, and next, Charles Potter who initiated and continually stimulated the work on pyrethroids at Rothamsted. Norman Janes has been my close collaborator and colleague since 1962

and all the significant advances were made with him, and with David Pulman (1970). A number of colleagues performed essential bioassays for us with expert ability and devotion and we benefited greatly by collaboration with the staff of the Medical Research Council Laboratories in Carshalton and the members of the Pesticide Chemistry and Toxicology Laboratory in the University of California, at Berkeley, U.S.A. We are most grateful to the National Research Development Corporation (now the British Technology Group) for almost continuous support since 1961. A number of important agrochemical firms, particularly Roussel Uclaf in France, have contributed most effectively to the practical realization and exploitation of Rothamsted research.

Acknowledgments :

S.H. Harper (1942), L. Crombie (1946), C. Potter (1948), P.H. Needham (1948), R.M. Sawicki (1956), N.F. Janes (1962), A.W. Farham (1963), J.E. Casida (1969), D.A. Pulman (1970), I.J. Graham-Bryce (1972).

The National Research Development Corporation (British Technology Group) (1961), The Medical Research Council (1965), Michel-Cotts, Welcome, I.C.I. (U.K. and U.S.A.), Shell, Roussel Uclaf/Procida, Sumitomo, F.M.C., Penick.

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