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RECENT DEVELOPMENTS IN THE FIELD OF PESTICIDES AND THEIR APPLICATION TO PEST CONTROL

PROCEEDINGS OF THE

INTERNATIONAL SEMINAR

Held at

Shenyang, The People's Republic of China, 8-12 October 1990

Editors

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The photograph on the front cover shows a computergraphic model of binding of a systemic ergosterol bio-synthesis inhibitor fungicide, diclobutrazol with cytochrome P-450 enzyme system (by the courtesy of Imperial Chemical Industries PLC, Agro-chemicals Division United Kingdom).

FOREWORD

"There are no toxic chemicals, just toxic uses of them. Even table salt could kill you, if you use too much of it. We should expect to continue using more potentially harmful compounds because their benefits far outweigh their detrimental effects"

Lindsay, U.S. Food and Drug Administration

The International Seminar on "Recent Developments in the Field of Pesticides and their Application to Pest Control in China and other Developing Countries of the Region" held at Shenyang, China from October 8-12, 1990, commemorated the formal inauguration of the Bio-assay Laboratories at Shenyang Research Institute. Established with the generous financial assistance of UNDP, the Government of the United Kingdom of Great Britain and Northern Ireland through a contribution to the Industrial Development Fund maintained by UNIDO, and the Government of China, the laboratories bear testimony to the effectiveness of multilateral co-operation. Multilateral endeavours of this kind in the field of agrochemicals are of paramount importance to China, and the Pacific region where more than half the world's population depends on agriculture for their livelihood.

With the annual rate of population growth in the developing countries approaching 2.5 per cent, agrochemicals offer an effective means of increasing agricultural production to meet the growing demand for food. A vital component in the food production chain, they should be judiciously applied. International agencies such as UNIDO should thus devote particular attention to promoting technologies related to pesticides that are safe to produce and use, pose no threat to human health and do not disrupt the environment.

The Seminar has given an ideal opportunity to countries from North and South alike to discuss recent developments in pesticide technology, exchange experience and pave the way to further collaboration in making pesticides environmentally safe.

We had the honour to welcome to the Seminar participants from companies and institutions of renown that have contributed directly or indirectly to major changes in pesticide technology. We are confident that the Seminar will contribute appreciably to closing the gap between the developed and developing countries in this crucial area, yielding benefits to both the host country and the other developing countries in the region.

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INTRODUCTION

There is great concern about the use of pesticides, but without them mankind would continue to lose a third of its food production due to pests and most of this loss would continue to take place in the developing countries where food is needed most. During the last 25 years, pesticide technology has gone through a revolutionary change and is moving from bulk chemicals to speciality or fine chemicals. These changes include the invention of highly active pesticides, newer and safer formulations and novel application techniques. Complex data are required for the registration of pesticides and to recognize problems related to pest resistance and damage to the environment owing to misuse of pesticides.

The Seminar marked the inauguration of new facilities for pesticide research at the Shenyang Research Institute of Chemical Industry. This Institute was founded in 1949 and was one of the earliest chemical research organizations for industry in China, covering many needs. Research and development of pesticides began there in 1952. Many activities have since devolved to other centres and today the research concentrates on pesticides, dyestuffs and other fine chemicals.

A programme of assistance by UNIDO/UNDP and the Government of the United Kingdom was evolved and included help through technical visits, training fellowships and provision of equipment. The Chinese Government committed large resources to buildings, services and staffing. The first phase provided modern facilities for toxicology and safety evaluation of pesticides. The second phase, now completed, provides facilities for the biological evaluation of new pesticides in laboratory and glasshouse experimentations. In the Institute, as a whole, the research spans the spectrum of discovery and synthesis of novel pesticides together with investigation of performance, safety, formulation and analysis.

China has lived continuously with a pressing need to increase farm production by controlling pest, disease and weed problems in agriculture and to control insect problems in public health. This has provided the stimulus through the last four decades to increase pesticide production and use. In recent years a particular influence has been the desire to phase out use of chlorinated hydrocarbon insecticides and replace them with efficient alternatives. Thus the Seminar provided a most timely opportunity to bring together this Chinese experience with that of the wider region and to interact with other experts from around the world. The Seminar was attended by delegates from China and 17 other countries.

The proceedings include all the papers and posters presented at the Seminar. Many facets of pesticide research and development and their inclusion in integrated pest management systems are covered. In addition the whole spectrum of the pesticide scenario is dealt with, including likely future developments in the 21st century, and should prove a valuable publication for the benefit of college, universities, R & D institutions, industries, national and international organizations dealing with pesticides.

Participants of the seminar.

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ACKNOWLEDGEMENT

The organizers of the Seminar wish to acknowledge the generous financial support provided by the UNDP, the Government of the United Kingdom of Great Britain and Northern Ireland and the Government of China and the excellent services provided by the staff of the host institute, The Shenyang Research Institute of Chemical Industry. These services contributed greatly to the smooth running and success of the seminar.

The organizers would also like to express their sincere gratitude to the International Experts who not only contributed scientific papers but also provided generously to the various discussions.

AN OVERVIEW OF STATUS OF PESTICIDE RESEARCH IN CHINA

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ABSTRACT

An overview of the need for pesticides, the status of pesticide research and the production of pesticides in China is given. During the past 40 years production of pesticides has grown from nothing to over 200,000 tons of technical products. Statistics presented show that insecticides comprise 70-80% of pesticides used, with fungicides and herbicides each at about 10%. Initially BHC was the principal insecticide. Research during the 1960s concentrated on organophosphorus and carbamate compounds, with attention given more recently to pyrethroid insecticides. Antibiotics and natural products have been included in the research. Pesticide research is organized through institutes administered by the Ministries of Chemical Industry, Agriculture, Health and Education, and the Academy of Science. Local pesticide research institutes also participate. The stages of research and development are presented. In conclusion recent research achievements are described briefly.

GENERAL

China covers an area of 9.6 million square kilometers and has a population of 1.1 billion. It is an agricultural country and it is estimated that more than 80% of the population lives on the land. China is also a developing country, so although many people work on the farmland, farm production, which every Chinese shares, is very low. The population is too great and the cultivated area is very limited. Furthermore, development of agriculture varies in different parts of China.

The data in Table 1 summarise the situation of agriculture in china [1, 2]. Thus, use of less than 7% of the farmland provides food and clothing for 22% of the world population. This is obviously a serious challenge.

There are two ways to increase total production in agriculture. One is to increase the cultivated area, which is very difficult as the land available for farming is limited, and the other is to increase the yield per unit area.

TABLE 1

	China	Total World	China/World (%)
Farmland area (million hectare)	120	1,750	7
Population (million)	1,100	5,000	22
Area (ha) per person	0.1	0.35	30

In the southwest, Tibet and the northwest, Xinjiang, Qinghai, Ningxia provinces and Inner Mongolia, most of the land is impossible to farm because of mountain ranges, deserts and bad climate. Along the coast, a few areas are not cultivated, for example, the original bed of the Yellow River where without irrigation system these salty soil and floods ensure that the land produces no harvest.

Our attempts to increase the area farmed have not been successful. During the 'so-called' cultural revolution period, many forests were cut down and grassland was converted into farmland. The results of deforestation were disastrous, flood and drought increased, soil was eroded and the ecological environment was destroyed. More recently ever-increasing demands were made for farmland to accommodate the industries, including enterprises in towns and villages, and also housing owing to the rapid development of China's economy. Thus, the farmland area was reduced. At the same time the population increased rapidly [3].

In the last ten years we achieved good results in increasing productivity but living standards still remain low. Table 2 compares production rates of grain and cotton in China with that of the Unites States of America. In the chosen 1979 to 1984 period agriculture developed rapidly. China had its best harvest in 1984.

TABLE 2

	1979		1984	
	China	USA	China	USA
Population (million)	975	220	1,035	237
Output of grain (million ton)	332.1	365.2	412.3	370
Production rate (kg/ha)	2,775	3,735	3,600	3,670
Capitation (kg/person)	340	1,618	393	1,584
Output of Cotton (million ton)	2,200	3,100	6,200	7,700
Production rate (kg/ha)	487.5	603.2	707.5	682.5
Capitation (kg/person)	2.26	14.36	6.10	32.80

From the data given in Table 2, we conclude that:

1. Agricultural productivity, for example grain and cotton, was good but per capita share remained 4-5 fold lower than in the United States.

2. To improve Chinese living standards we must increase productivity of the farmland which should be possible with pesticide application. For example, herbicide usage was introduced to China later than in developed countries, as shown by year and area in Table 3 [4]. Even in 1988, the area treated with herbicide was only 11.3% of the total farmland in China.

TABLE 3

Year	Herbicide treated area (M ha)
1956-1967	0.33
1967-1977	1.67
1977-1982	4.00
1983	4.60
1984	6.67
1985	8.54
1986	10.7
1987	12.7
1988	13.6

TABLE 4 [4]

	Crop Area (M ha)	Weed area (M ha)	Serious weeds (M ha)	Reduction (M kg)	Reduction rate (%)
Rice	33.7	15.5	3.8	10,400	13.4
Wheat	31.1	10.0	2.7	4,000	15.0
Cotton	7.1	2.2	0.13	250	14.8
Soybean	8.0	2.0	0.67	500	19.4
Corn and Sorghum	43.1	6.7	1.34	5,000	10.4
Oilseed rape	3.4	1.2	0.34	200	7.1
Peanut	2.4	0.7	0.13	200	9.0

Table 4 indicates that weeds are a serious problem in agriculture. Increasing application of herbicides is necessary. Table 5 compares Chinese and world use of pesticides.

TABLE 5
Area of crop planting (M ha)

Crop Planting		Rice	Wheat	Corn (Maize)	Cotton	Peanut	Soybean
China		33.7	31.1	26.7	7.1	2.4	8.0
World		147	231	133	35	52	18
Cost of pesticide (US $/ha)							
China	high	3.3	3.1	6.0	33.4	23.0	11.8
	low	2.8	3.0	4.6	18.1	11.3	9.6
World		9.8	4.6	15.0	36.0	9.1	28.7

PESTICIDE PRODUCTION IN CHINA

There was no pesticide industry before the founding of the People's Republic of China. During the past forty years, the pesticide industry has developed a production capacity for 400,000 tons of technical products and output of 200,000 tons (Table 6); more than 70% of pesticide applied was of domestic products.

TABLE 6
Production of technical product

Year	1950	1960	1970	1980	1990
Ton	500	16,200	92,000	193,000	220,000

Insecticides comprise 70-80% of pesticides used; fungicides and herbicides are each 10 ± 4% respectively (Table 7). Even so, according to recent statistics, insecticides are in short supply, whereas supplies of fungicides and herbicides are in excess.

TABLE 7

Year	No. of products	Insecticide (%)	Fungicide (%)	Herbicide (%)	Plant growth regulator (%)
1984	93	82.26	13.58	3.70	0.46
1985	84	76.20	13.66	9.30	0.84
1986	75	77.40	7.90	7.62	6.62
1987	132	80.90	9.08	9.41	0.60
1988	139	71.53	14.09	13.73	0.65

BRIEF HISTORY OF PESTICIDE RESEARCH IN CHINA

China began pesticide research in the early 1950s. At that time no organic (synthetic) pesticides were applied in agriculture. Small amounts of BHC and DDT produced by China were used in the public health system for controlling mosquitoes and flies, especially BHC, because of the simple manufacturing process, cheap raw materials, effective and broad spectrum to control pests, and low acute-toxicity to mammals. BHC became the most important insecticide for thirty years. At the end of the 1970s the total production of technical BHC was more than 100,000 tons yearly. On April 1, 1984 the Chinese Government ordered manufacturing, selling and applying BHC and DDT to stop. Since then, these well known insecticides have disappeared from the Chinese pesticide market. Since BHC and DDT are not easily metabolised and decomposed, the simple way to solve accumulation and the residue problem was to stop their use.

At the end of the 1950s and during the 1960s, organophosphorus insecticides and dithiocarbamate fungicides were the main targets of pesticide research. In the 1970s aromatic carbamate insecticides and systemic fungicides were the main subject of pesticide research. Since 1980, pesticide research institutes and universities have paid more attention to pyrethroid insecticides and some herbicides. At the same time, there have been good results with antibiotics and natural products as pesticides.

Generally speaking, pesticide research in China has concentrated on insecticides. There has been some research on fungicides and herbicides. Plant growth regulators and rodenticides are minor parts of pesticide research.

ORGANIZATION OF PESTICIDE RESEARCH IN CHINA

Pesticide research in China is organised differently from that in developed and many developing countries. In advanced regions or countries, such as North America, Western Europe and Japan, pesticide research forms part of chemical company operations. In China, pesticide research is organized in two parts; part I is controlled by central government, part II by local government. There are many pesticide plants in China, but few undertake research on new pesticides; they buy manufacturing technology for new pesticides from research institutes or cooperate with them by providing pilot plant and capital. Sometimes pesticide plants entrust institutes to research and develop certain pesticides or new formulations.

Table 8 illustrates the organization of pesticide research in China, including both central and local institutes. Central research institutions are administered by five bodies as shown in Part A of the Table.

TABLE 8

Pesticide research institutes in China

A. Bodies administering central institutes

Ministry of Chemical Industry	Ministry of Agriculture	National Education Committee	Ministry of Health	Academy of Science
Shenyang Research Institute of Chemical Industry	Chinese Academy of Agriculture Sciences Research Institute of Plant Protection	Nankai University The Institute of Elemento-organic Chemistry	Institute of Prevention Science	Shanghai Institute of Organic Chemistry
(comprehensive research institute)	(Biology)	(Chemistry Biology)	(Toxicology)	(Chemistry)

B. Ministry of Chemical Industry

Research	Production*	Academic Activities	Industry Association
Shenyang Research Institute of Chemical Industry - synthesis,	Tianjin Pesticide Plant Shandong Pesticide Plant	National Pesticide Society - seminar, national and	Pesticide Industry Association - quality

formulation, bioassay, safety evaluation, effluent treatment, physical and chemical analysis, information, quality monitoring	Shanghai Pesticide Plant Shashi Pesticide Plant Hangzhou Pesticide Plant Yangzhou Pesticide Plant Chongqing Pesticide Plant Suzhou Chemical Plant Kuanshan Chemical Plant	international academic exchange	competition, experience exchange, production arrangement

*There are many pesticide factories in China. These nine plants are the most important.

C. Ministry of Agriculture

Chemistry, Mechanics	Biology*	Application	Registration
1. Chinese Academy of Agricultural Sciences Research Institute of Plant Protection Department of Pesticide 2. Beijing Agriculture University Institute of Applied Chemistry	1. Chinese Academy of Agricultural Sciences Research Institute of Plant Protection 2. Cotton Research Institute 3. Rice Research Institute 4. Wheat Research Institute 5. Peanut Research Institute 6. Tobacco Research Institute 7. Orange Research Institute 8. Orchard Research Institute 9. Tea Research Institute 10. Tropical Crop Research Institute	1. National Protection Station 2. Field Trial Net	Institute for Control of Agri-chemicals Ministry of Agriculture (ICAMA)

*In many Institutes, one part is a Plant Protection Department.

D. Ministry of Education (National Education Committee)

The Institute of Elemento-organic Chemistry, Nankai University

This is a well known organic research institute, founded by Professor Yang Shixian.

E. Local Pesticide Research Institutes

The following are important local pesticide research institutions in China:
Liaoning Research Institute of Chemical Industry (Rodenticides)
Tianjin Pesticide Research Institute (Insecticides)
Anhwei Research Institute of Chemical Industry (Formulation of Pesticides)
Jiangsu Pesticide Research Institute (Pyrethroids)
Hunan Research Institute of Chemical Industry (Carbamate Insecticides)
Shanghai Pesticide Research Institute (Antibiotics)
Zhejiang Research Institute of Chemical Industry (Intermediates of Pesticides)

RESEARCH PROGRESS ON PESTICIDES IN CHINA

China has a long way to go in setting up a modern pesticide research system. In this area, we lag 15-20 years behind developed countries. When China began production, inventor's patents had already expired on most technical products. For example, organophosphorus insecticides were commercialized after World War II in developed countries. In China, it was the 1960s. In carbamate insecticides, China was 15 years late; dithiocarbamate fungicides started in the 1940s but China produced dithiocarbamate fungicides only from 1964.

Ten years before the pesticide research system of China was completed registration of new pesticides was not conducted. Since 1980, any pesticide, domestic or imported, must be registered. Therefore research in pesticides was strengthened and integrated.

Procedures are established as follows:

1. Inputs to selection of research

Research Institute of Plant Protection,
Plant Protection Stations,
Agriculture Colleges,
Ministry Agriculture,
Ministry of Chemical Industry

Pesticide Society Activities,
Academic Exchange,
Symposium on Pesticide

Market

→ Pesticide Research Institute (Central or Local) ←

2. Procedure of Research and Development of Product

   (1) Determination of research target
   (2) Investigation of literature
   (3) Selection of synthetic routes
   (4) Process study
   (5) Pilot-scale experiment
   (6) Production (product, formulation, packing, storage)

3. Procedure from Candidate to New Pesticide

Sample	Synthesised, collected, isolated
Biology	Laboratory test Greenhouse experiment Field plot trial Field experiment Demonstration
Chemistry	Synthesis of new compounds Determination of structure analysis Process studies Manufacture Formulation
Safety evaluation	Acute toxicity (oral, dermal, inhalation, irritation to eye and skin) Accumulation toxicity (accumulation toxicity, mutation, metabolism) Sub-chronic toxicity (90 day feeding for reproduction and metabolism) Chronic toxicity (carcinogenic, teratogenic, reproduction, delayed neurotoxicity) Residue experiment Effect on environment

ACHIEVEMENTS OF PESTICIDE RESEARCH

Since China started pesticide research in 1950, many research projects have developed into large scale pesticide production. About 70% of the pesticide produced is insecticide.

Insecticides

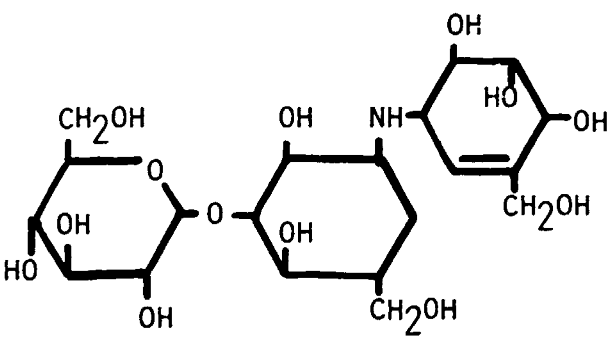
Organophosphates are the most important insecticides, with products such as methamidophos, parathion, trichlorfon, dichlorvos, omethoate, and monocrotophos. The total production for each was more than ten thousand tons. Research institutes now pay attention to new organophosphorus compounds, especially heterocyclic phosphates, for control of underground pests which cause very severe damage to crops such as peanut, sweet potato, and wheat. Aromatic carbamate insecticides are investigated for control of rice pests like rice borer, leafhopper and planthopper, the latter two insects especially being a serious problem in rice.

Most pyrethroid research is at the laboratory or pilot-plant stage, with little commercialized.

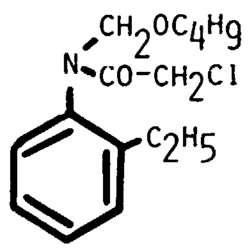
Fungicides

Dithiocarbamate fungicides were commercialized in the 1960s, but the recent debate on the toxicity of ETU (ethylenethiourea) casts doubt on their use. To control some special plant diseases in China, Pesticide Research Institutes must seek more active compounds. For example Fusarium blight of wheat (caused by *Gibberella* spp. and *Fusarium* spp.) is a very serious disease of wheat and infected grains are poisonous. MBC (carbendazim) (methyl 2-benzimidazolecarbamate) was synthesized in 1969 and commercialized in 1972. It has an excellent effect in controlling Fusarium blight of wheat and many other plant diseases. Now it is the most commonly used organic fungicide in China.

Antifungal 402, $C_2H_5SO_2SC_2H_5$ has been applied to control seed and soil diseases of rice, cotton and sweet potato. It was invented by the Shanghai Institute of Organic Chemistry in the 1960s. Another important antibiotic fungicide (Structure I) was isolated from the soil of Jinggang Mountain of Jiangxi province (China), and is an important product controlling sheath blight of rice (caused by *Pellicularia sasakii*). This fungicide is very cheap, effective and of low toxicity, and there is no resistance to it. It was commercialized in the 1970s.



(I)



(II)

Herbicides

In the last ten years, herbicide use has developed rapidly, but remains only 10 ± 4% of the applied pesticide in China. Herbicide research started 15 years later than insecticide and fungicide research [4]. Phenoxyacetic acids and their esters, diphenyl ethers, ureas, organophosphorus compounds and carbamates are the herbicide products used in China. Some new products are on the way to the pesticide market. For example, the compound shown (Structure II) is effective for controlling monocotyledonous and broad-leaved weeds in rice, cotton, corn, soybean, peanut, rape seed and potato.

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ASPECTS OF PESTICIDE DISCOVERY

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ABSTRACT

The discovery and development of new crop protection agents is becoming increasingly expensive. In addition, agriculture is becoming less profitable with the removal of crop subsidies whilst the general public are becoming increasingly concerned about the use of chemicals in crop production. In the light of these facts it is essential that a successful discovery group identifies its research targets to ensure a fair return for investment, establishes reliable screens to guarantee that no potentially useful lead is lost and then runs a synthesis programme which maximises the resources available towards a new pesticide discovery.

Approaches to this vary from group to group but the principles remain the same. The paper is a brief description of the opportunities in discovery research and highlights the various approaches and principles used.

IDENTIFYING TARGETS

The cost of discovery, development, registration and commercialisation of a new pesticide is around $50 million. A new herbicide will usually have a long life expectancy but new fungicides and insecticides/acaricides often encounter resistance problems within a few years of being launched. In order to remain in business, a crop protection group must recoup its investment in a product and also make enough profit to ensure investment in the next generation of products. This situation means that all discovery groups are targeted towards large markets where there exist opportunities for significant sales.

All major agrochemical companies are seeking products to control weeds in corn, soybean, small grains and rice, to control diseases in cereals, vines and rice and to control the insect and mite pests of cotton, corn and rice.

Having established a major market for a compound the opportunities in smaller markets can be exploited. No one would develop a herbicide for use in kale, but having established a market in cereals and then oil seed rape, sales in kale may well add to the product's potential sales. This is the case with a product such as clopyralid. Regrettably, there will always exist some crops for which crop protection agents will never be registered because of the small area grown or the low value of the crop.

ESTABLISHING SCREENS

Once the major uses of a crop protection product have been established the problem of setting up cost-effective and target oriented screens must be addressed. The primary screen should be directed towards rejecting inactive compounds rather than selecting active ones. Rather than showing a compound to possess useful biological activity, it is a means of eliminating quickly and at as low a cost as possible, compounds which have no activity and on which no further work should be done. Hence the usual system employed is a high volume, high dose application of technical material formulated in a solvent, such as acetone, dispersed in a surfactant/water mixture. This "formulation" is applied to a preferably small but diverse range of "indicator species". These target organisms are, wherever possible, primary marketing species but for reasons of country or regional restrictions in some cases alternatives have to be used. For example, culture of the Colorado potato beetle (Leptinotarsa decimlineata) is not permitted in the United Kingdom and so often the mustard beetle (Phaedon cochliariae) is used in its place. Other species are hard or time consuming to cultivate and "easier" species may replace them.

Hence, a standard herbicide primary screen will include annual grasses and annual broad-leaved weeds of both cereal and soybean/corn/rice crops with a secondary screen that confirms and expands the weed/crop spectrum in comparison to a relevant commercial standard. Fungicide screening will include pathogens of the major crops (cereals, vines, rice, top fruit), but also covering wherever possible, the major fungal taxonomic classes. Insecticide evaluation will always concentrate on insect types and will include a caterpillar (noctuid usually), a beetle, especially corn root worm larvae, a sucking insect such as aphid and a hopper, a mite and often a nematode.

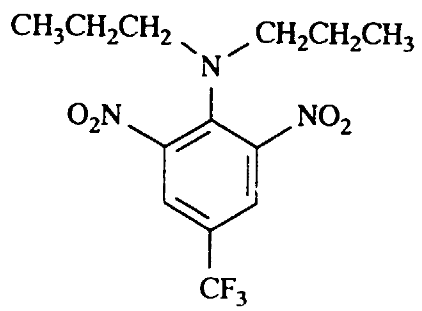
Assessment at the primary level can be on a straight active/inactive basis, as the aim is to reject inactives. Some organisations rate on a percentage scale or on a numerical in-house devised system but always there is a score which has to be exceeded to count as active. Such a system is designed to ensure that as little effort as possible (and hence as little resource as possible) is devoted to compounds with little chance of success. Secondary testing introduces the concepts of dose response, effects on related organisms, crop selectivity, mobility in crop, formulation and comparisons with standards. The objective is to develop tests which allow compounds to be selected for field screening and subsequent progress to field development.

THE SEARCH FOR ACTIVE COMPOUNDS

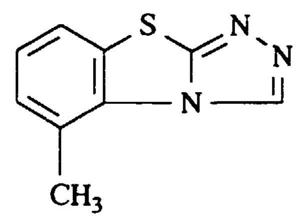
All companies involved in the search for new crop protection chemicals are actively seeking new chemical leads which they can claim and protect as their own discovery. There are several ways in which the lead can be found, but it must always be remembered that once a useful level of biological activity has been identified in a new chemical compound, the optimisation strategy is always the same and could be termed analogue synthesis, albeit, an in-house compound optimisation programme.

Empirical Screening

Traditionally companies which excelled at the discovery of crop protection agents were those which were involved in the chemical industry in all its guises. The evaluation of petrochemical waste materials led to early insecticides and many dye stuffs and their intermediates showed good herbicidal effects. It was the evaluation of as many chemicals as possible in screens which led to products such as trifluralin and tricyclazole (Fig.1).



Trifluralin



Tricyclazole

Figure 1. Two compounds discovered via an empirical approach

As more is learned of the modes of action of existing compounds and the physicochemical properties required of today's pesticides many companies have turned away from the empirical evaluation of many thousands of compounds with different structures for a more "rational" approach. Whilst the value of a targeted programme is clear and will be discussed in more detail later, the success of a random approach is irrefutable and it is a valuable complementary strategy in the quest for new biologically active compounds.

Analogue Synthesis

Once an active compound has been discovered and the decision taken to develop it, a patent is always filed. The patent filing attempts to cover all chemical modifications possible to ensure that the patent for the compound and its analogues is exclusive. The problems encountered in filing a broad based patent are many but key amongst them are the timing of the filing, essential to ensure that the claim is not pre-dated, and the scope of the general formula, to ensure that all compounds which are covered are active as described. It is a necessary consequence of patent law that gaps are left which can be exploited by astute companies often using their own special chemical expertise.

Good examples of analogue synthesis are many. In the herbicide area there are the urea herbicides (Fig.2) and more recently, sulphonylureas (Fig.3). Azole chemistry has been frequently exploited in the fungicide area (Fig.4). Pyrethroid chemistry has been copied in the insecticide area and examples are given in the paper by Elliott in this volume.

Natural Products

The pharmaceutical industry has been exploiting biologically active natural products for many years but it is only recently that agrochemical companies have begun to look for new products from natural sources.

In Japan, a large number of fungicidal products have been discovered and developed particularly for use in rice but their application in other countries and crop systems has been very restricted (Table 1).

TABLE 1
Natural Fungicides discovered and used in Japan

COMPOUND	CROP
Blasticidins	Rice
Kasugamycin	Rice
Polyoxin	Rice/vegetables
Validamycin	Rice

Recently the introduction of avermectin and bilanafos have increased interest by industry in natural products as potential new insecticides and herbicides. There are three reasons for searching for new natural products. Firstly, it is possible that a new product can be used iself as the toxiphore. This is the case with many of the fungicides which are manufactured by fermentation. Secondly, the natural product may represent a new class of chemistry which by either minor (as in the case of avermectin) or major (as

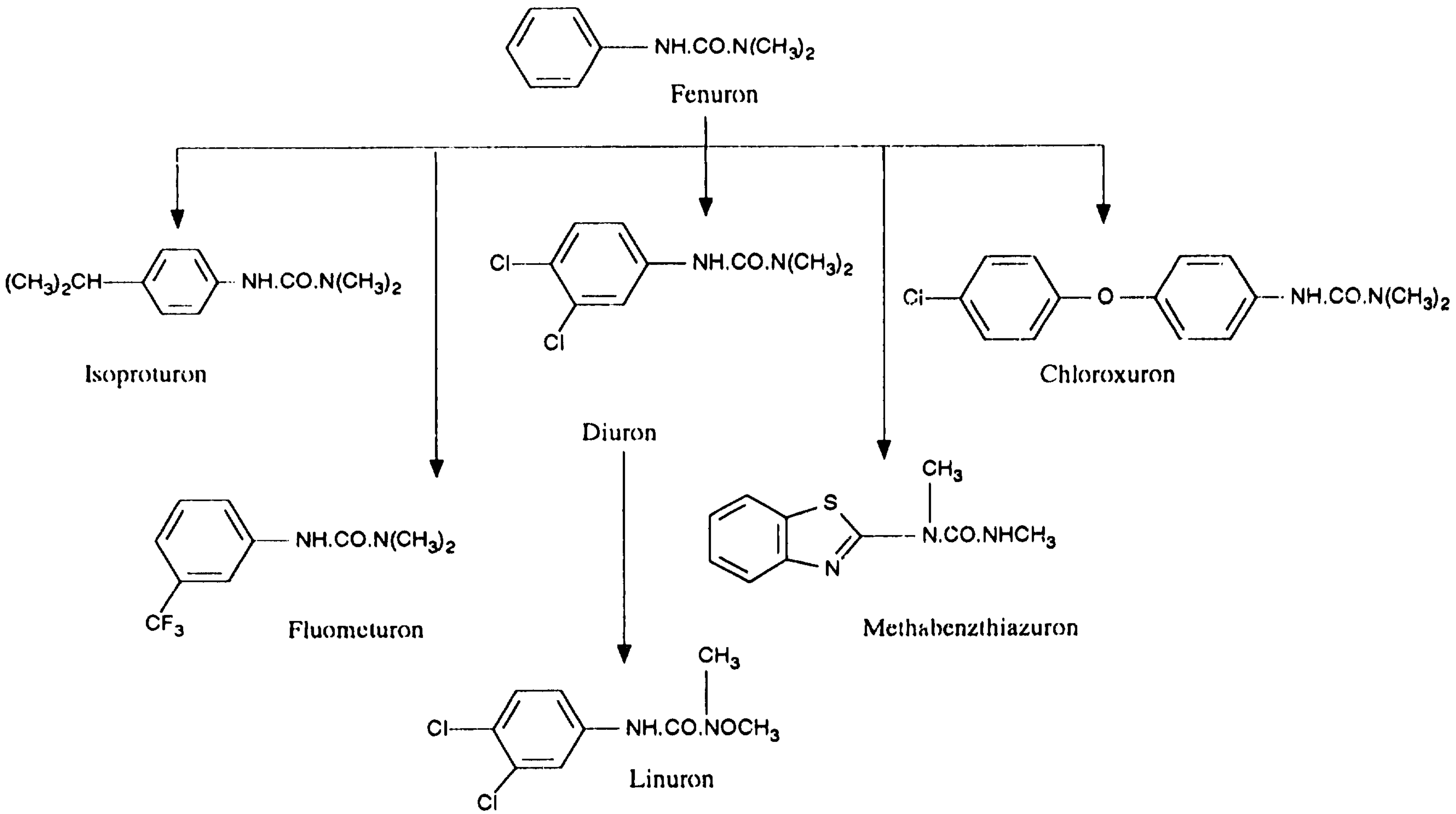


Figure 2. Analogues derived from fenuron (from Weed Control Handbook: Principles 8th Edition 1990, Blackwell Scientific Publications

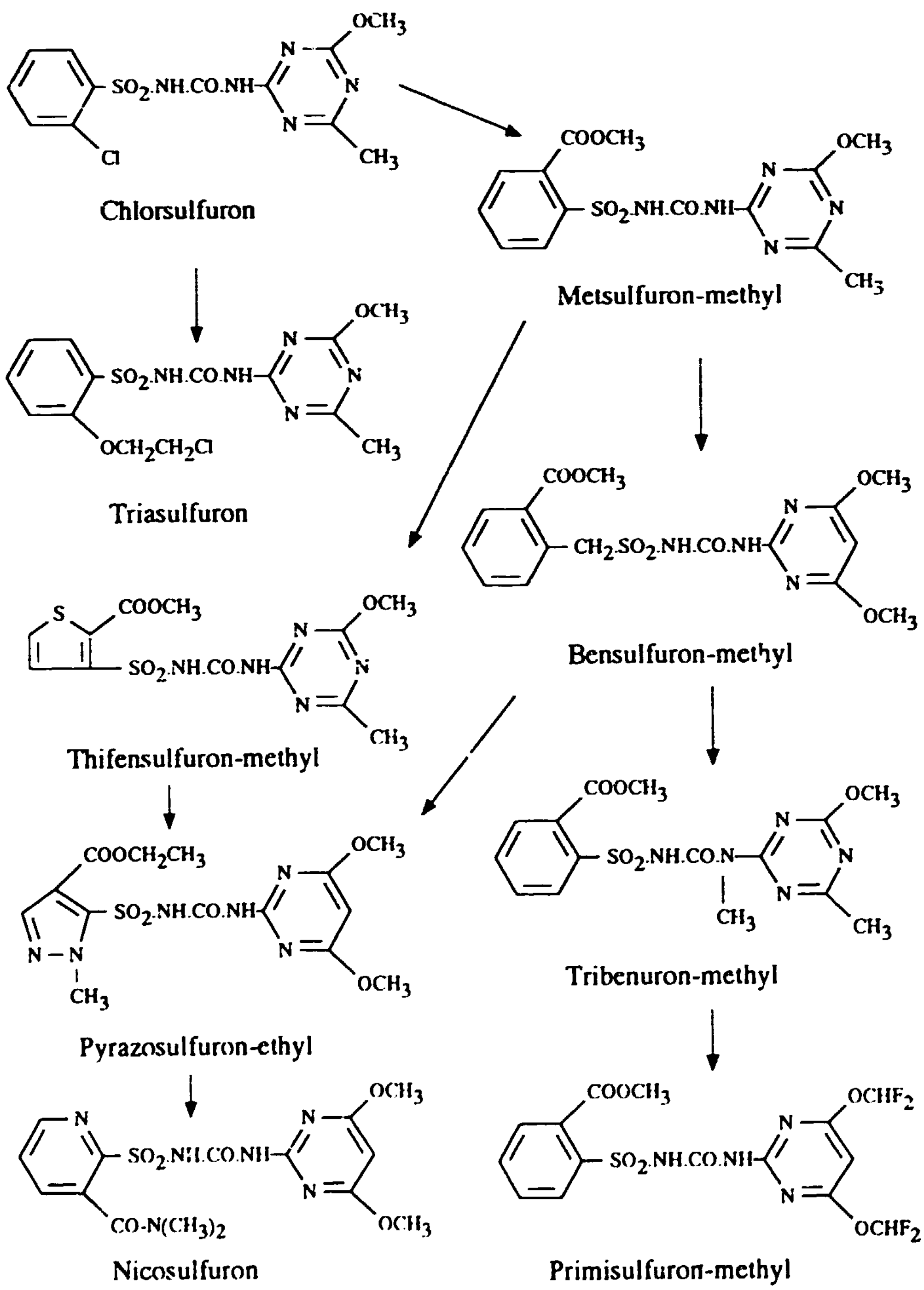


Figure 3. Development of sulphonylurea analogues (from Weed Control Handbook: Principles 8th Edition 1990, Blackwell Scientific Publications)

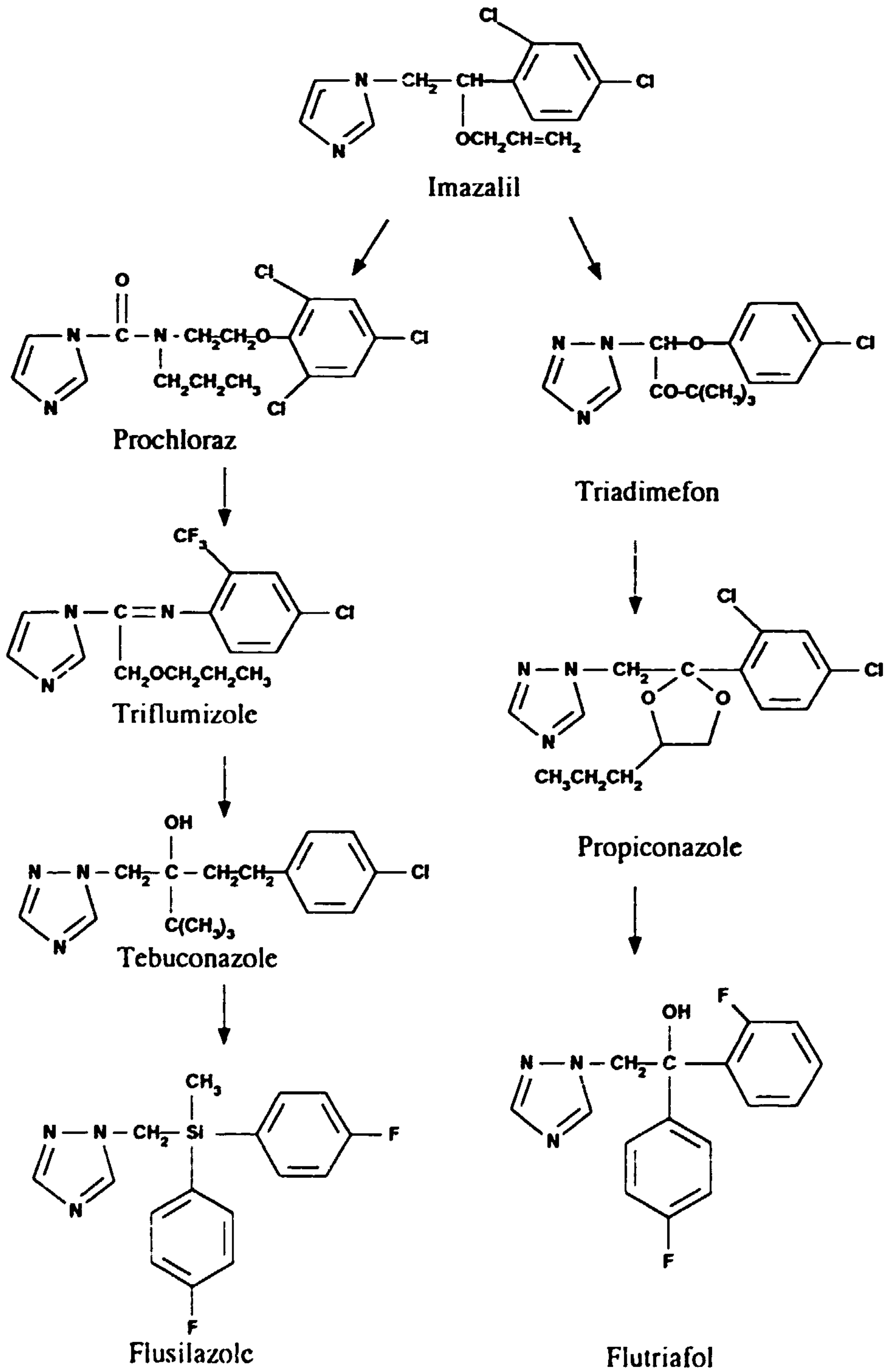


Figure 4. Examples of fungicidally active azoles

in the case of synthetic pyrethroids) chemical modification can lead to a commercially viable product.

Finally, the mode of action of the natural product may be novel and this may lead to a search for new synthetic compounds with a similar mode of action.

Biorational Design

Many terms are used to describe the targeted search for new biologically active compounds. In essence it involves the application of sound biochemical principles in the search for a new product. This can follow a number of pathways.

Firstly, a biochemical pathway in the target pest can be identified which produces an end product which is essential for the survival of the organism. Hence, if this pathway is interrupted, the pest (weed, insect or pathogen) will die. If the mechanism of reaction of one enzyme in this pathway is known it is possible to design compounds which will inhibit that particular process and thereby stop the reaction.

A second application of knowledge of biochemistry is to utilise differences in the rate of metabolic detoxification such that a target crop is able to inactivate a herbicide whilst a weed is not able to do so. Good examples are afforded by the rapid conjugation of atrazine and alachlor in corn by glutathione and the ring hydroxylation of diclofop by wheat.

Knowledge of metabolic activity can also be used to design propesticides. These are compounds which themselves are not biocidal but which are metabolised to the toxic form by the target. Examples include esters and amides of alkanoic acids, sulphenyl analogues of carbamate insecticides (carbosulfan versus carbofuran) and thiophanate-methyl.

Finally, biochemistry may be used to determine the mode of action of novel compounds discovered in an empirical screening process. Once this is determined the level of inhibition shown by the compound can be measured and a decision taken on whether the new target is good or bad as a mode of action. If good control is achieved at low concentrations the biochemical assay can be used in conjunction with _in vivo_ biological screening results to direct and optimise a new chemical series.

However when a new compound is found, it must meet the high standards of specificity to target organism and lack of persistence and mobility in the environment that are shown by today's pesticides. A great deal of information about the physicochemical characteristics needed for a compound to be effective is currently available and care must be taken to ensure that a compound does not persist in certain situations or become water/soil mobile at different pH levels. Much of this can be predicted and compounds where stability or solubility indicates the possibility of environmental problems should be evaluated with care before entering commercialisation.

CONCLUSIONS

A well balanced screen uses all of these approaches in the discovery of a new active molecule. Whilst copying other peoples successes has traditionally been the most successful way of identifying a new product it is likely that natural sources will become increasingly important in the future. The balance and integration of all these approaches is shown in Fig. 5. Clearly, there is a gap between targeted and complete random synthesis but both approaches are linked.

It must also be remembered that however sophisticated the chemistry or imaginative the biochemistry, the cost-effective biological effect is what the farmer buys. Huge sums of money are spent annually by agrochemical companies in the search for a new product but at the end of the day, if the farmer sees no advantage in terms of cost or biological effect he is unlikely to be persuaded to use it.

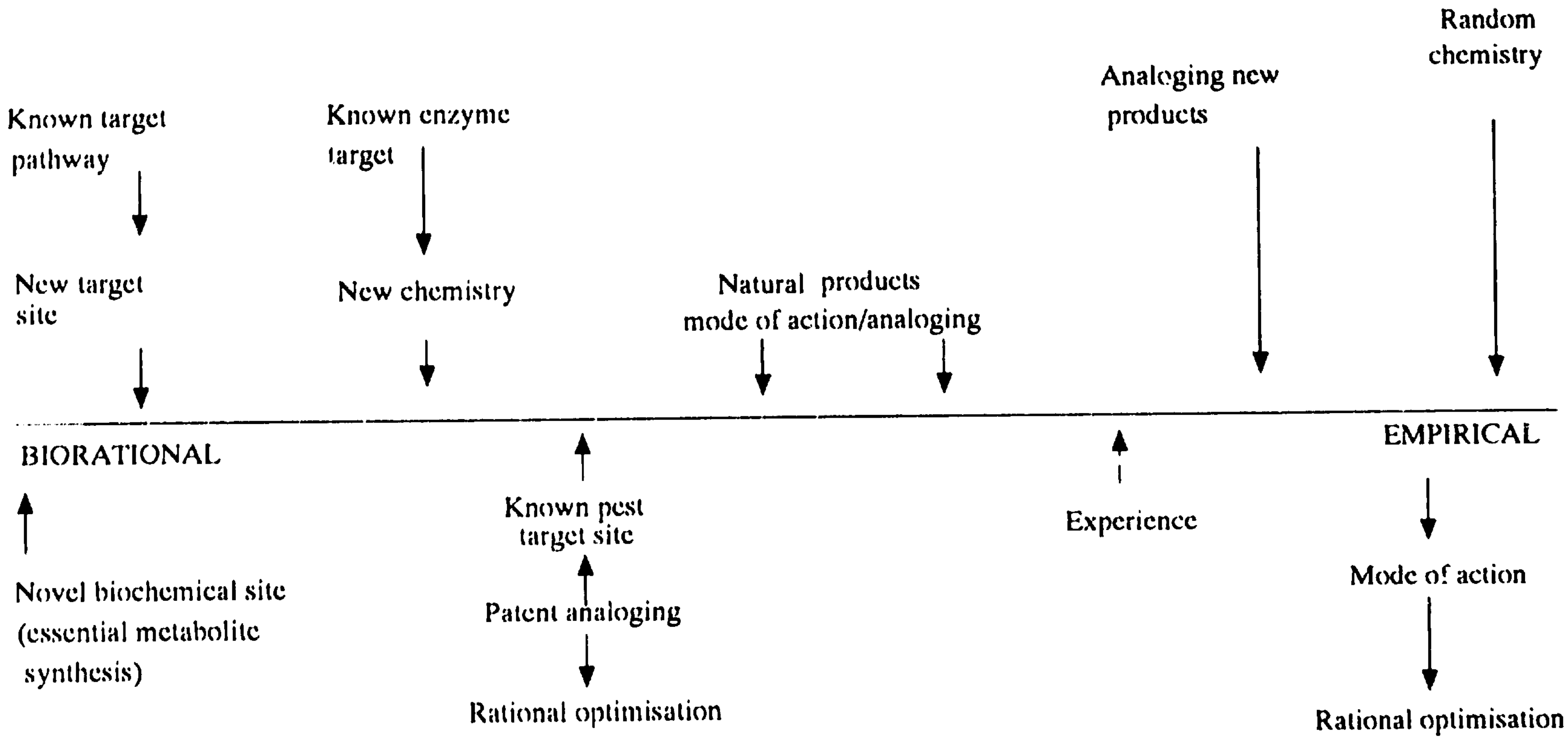


Figure 5. Relationship between empirical and biorational approaches to pesticide discovery

THE DEVELOPMENT OF A PESTICIDE - FROM CANDIDATE TO PRODUCT

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ABSTRACT

The development of a typical plant protection product is described. The global market for pesticides represents actually a volume of $ 21 billion. Expenditures for product development aggregate to approximately $ 80 - 90 million. About 36 % of this amount is related to chemistry, 30 % to biological development and 34 % to toxicological evaluations. Average time for development is 10 years.

INTRODUCTION

There is a tendency to underestimate the complexity of development work. So I have set out to review the focal points in general terms.

Assumed that we have arrived at a "candidate" compound - where in the complex course of the development of the future plant protection product do we stand, how do we go on and what are the requirements?

Before we embark on discussing further steps in detail, lets pause and recall some definitions first.

What actually is a pesticide?

In technical terms it is simply a tool for plant production systems. Such tools are supposed to

- reduce the expenditures of labour
- improve working conditions
- improve the quality of agricultural products
- increase the productivity at reduced input of raw materials, capital and labour
- support the creation of new products and/or techniques of production

The farmer buys effects and solutions to problems when he buys the product and not chemistry - this may be wise to remember.

But for the industry the definition of a pesticide goes much beyond that.

There simply is no product without the permission of the authorities to sell. This permission - the registration certificate - is the official judgement for acceptance of relevant properties of a compound.

It is required to demonstrate under German conditions (these requirements are more or less the same worldwide):

1. Physical and chemical properties, synthesis route and waste disposal

2. Efficacy against pests, diseases, weeds

3. Residues in and on plants, metabolism/degradation

4. Toxicity against man and animals

5. Behaviour in soil, air and water

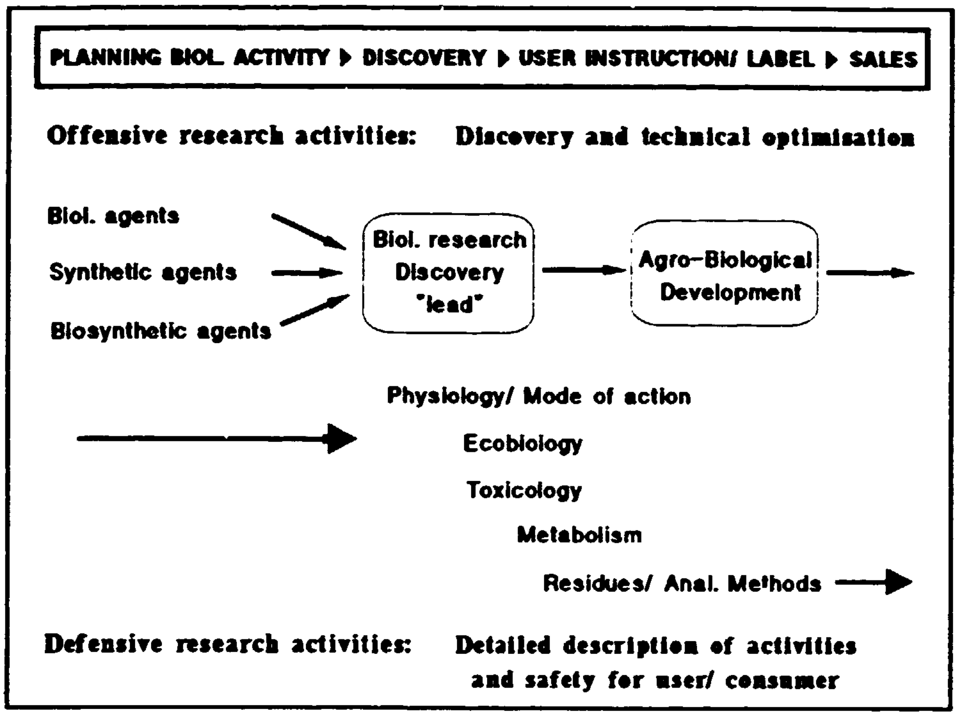
6. Effects on the environment

We realize that technical feasibility is but only one requirement - out of six - which we have to go after to make a product available to the farmer.

PRODUCT GENERATION

The product generation process is summarized in Table 1.

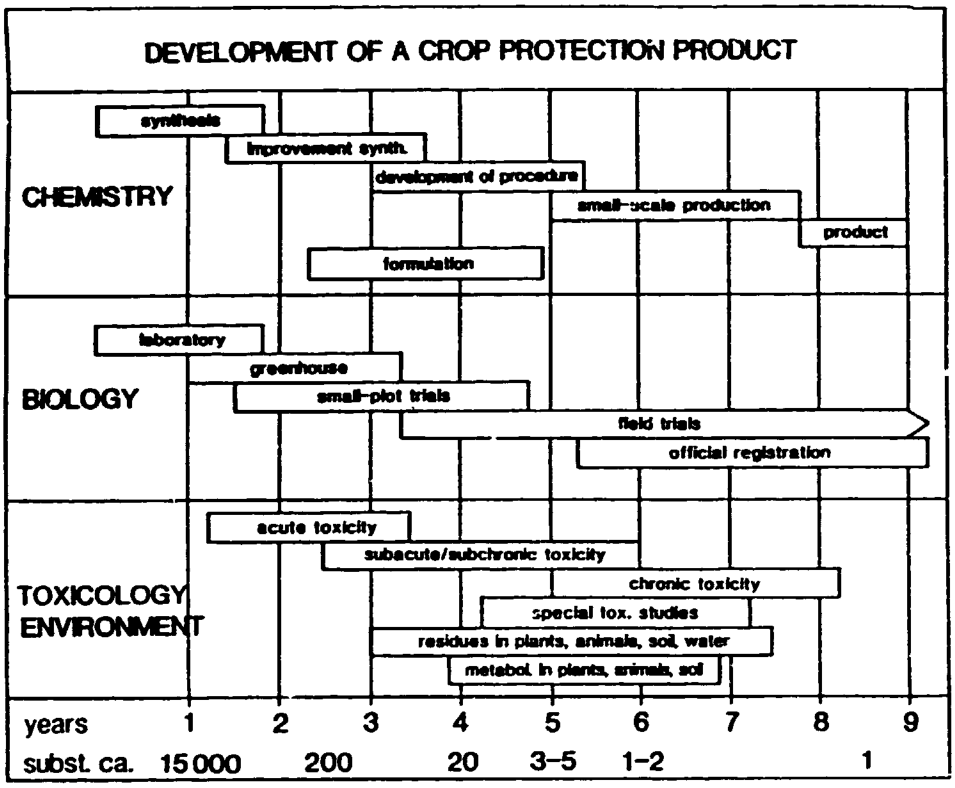
TABLE 1:
THE PRODUCT GENERATION PROCESS



Here, two kinds of activities may be distinguished. There are activities that cover new aspects of technology and performance - this is the "offensive part".All other activities which are to safeguard applicator and consumer constitute the "defensive" part of the work ahead.

This situation is described in Table 2 in more precise terms.

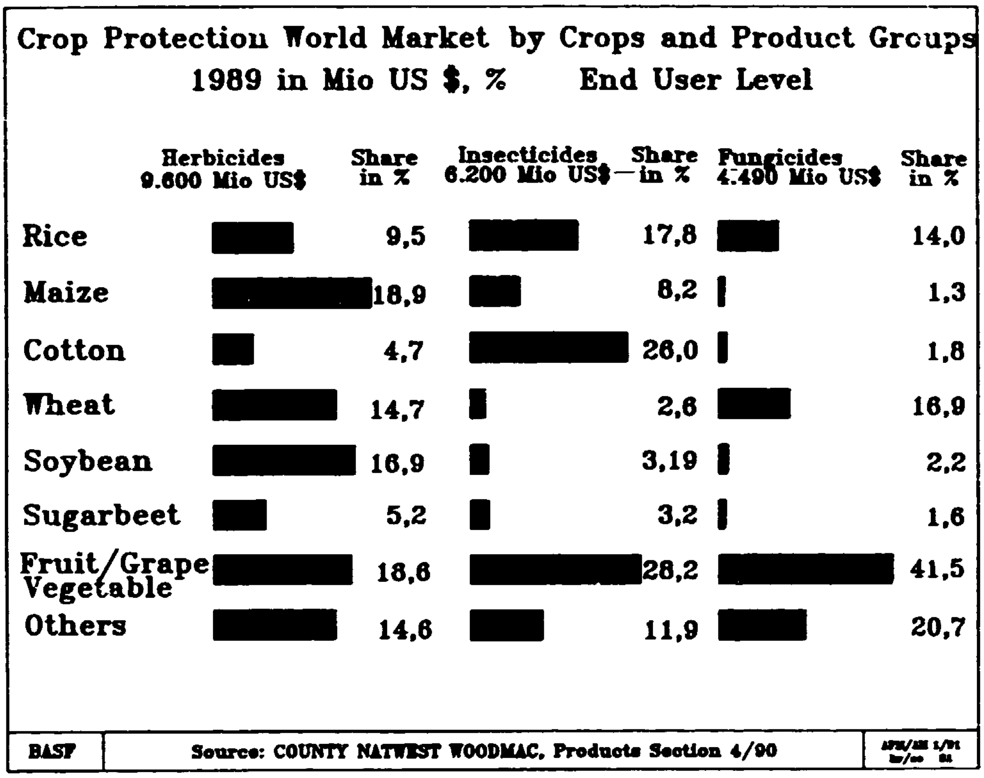
TABLE 2:
THE DEVELOPMENT OF A PLANT PROTECTION PRODUCT



Within a time frame of up to 10 years some \$ 80 - 90 million have to be spent - 36 % of which is related to chemistry, 30 % to biological development and 34 % to toxicological evaluations.

These expenses have to be seen against the total pesticide market which is in the \$ 21 billion bracket (Table 3). Incidentally the pharmaceutical market is ten times larger.

TABLE 3 :
THE WORLD PESTICIDE MARKET BY CROPS AND PRODUCT GROUPS 1989 IN MILLION US-$, % (END USER LEVEL)



PRODUCT DEVELOPMENT

I intend now to track the course of our candidate compound which is likely in the second year after discovery. The process is a model of multidisciplinary proceedings.

Let me first turn to technology and performance assessment - second in the list of requirements. The process is generally called "biological development".

Which questions have to be answered, which experiences will have to be gained? Important terms are certainly

- selectivity for crops and varieties
- definition of targets-activity; quantity per hectare and target
- method of application
- timing and window of application
- compatibility in product combinations
- yield and additional favourable effects

More questions relating to practical farming and the side effects are:

- drift and problems related to best application techniques
- carryover, persistence under field conditions
- effects on non-target organisms
- insensitive (target) populations

The final goal is the proper product label. Today it is to be a user instruction for "Precise Farming" and it should take into account all the factors that influence agricultural plant production - and conversely also all the factors which are affected by agricultural production in its environment.

Field trials

Table 4 lists the necessary field trial types and their purposes.

TABLE 4:
FIELD TRIAL TYPES

• Field screening	Microplots →	Effect, Efficacy - rough estimate
• Small plot trials - Series of trials - Regional specific trials	$5-50\ m^2$ →	Effect, Efficacy - precise evaluation (Remove unilateral influences) Centrally planned and evaluated
• Practical trials	acre/ha →	Real world AG Production conditions
• Demonstration trials	→	Instruction for advisors and customers

<u>Small plot trials</u> are the responsibility of advanced Field Development. They are to define exact quantities to be applied, optimal date and dependence on environmental factors, also the comparisons with competitive products and effects of combination with other products.

These trials have to be done in plots of 5 - 50 m^2 and treated and harvested under practical conditions.
As the data of only one trial are of limited value it is necessary to do the trial in various different locations to allow for exact comparison of yields and effects. Such trial series have to be adapted to the different climates and agricultural production systems of the world and they constitute the most important activity of advanced Field Development. They require special equipment.

"Practical or Farmer Usage Trials" are required for any product to be introduced into the market and are done in normal fields with standard agricultural machinery. They are to reveal "drift" problems, reaction of entire target populations, effects on non-target organisms and on non-sensitive genotypes. All of this may only be done on large areas of hectare size and above.

Demonstration trials finally are to demonstrate effects and methods as compared to standards to the farmer and of course to the advisory service.

Trial Layout and Evaluation

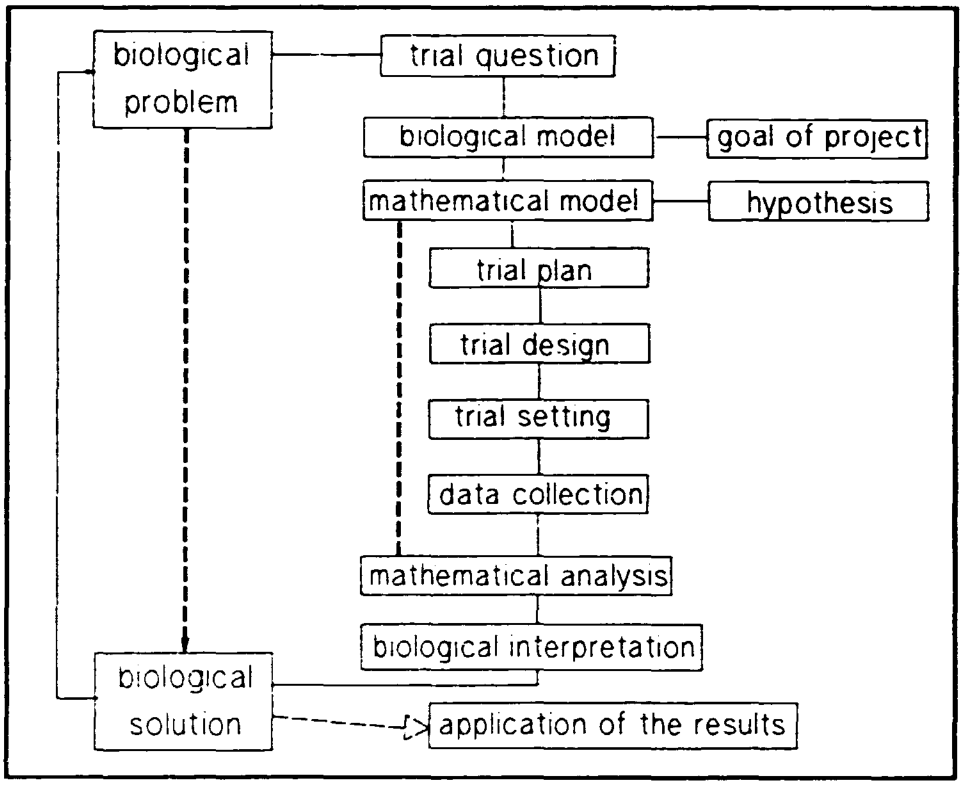
Small plot trials must be set up in accordance with the strict rules of biometrics for statistical evaluations if they are to lead to a reliable label. The basic requirements are

- common trial plan for various locations
- same trial design
- same evaluation criteria
- same evaluation methods
- equivalent evaluation timing
- on each location a different randomization of the plots must be used

First of all the precise layout of the trial in question is of crucial importance - whether it is a simple "one factorial" or a "multi factorial" design.

Let us consider the systematics (Table 5).

TABLE 5:
TRIAL PLANNING SCHEME



To eliminate chances of unilateral influences the trials are done in "blocks" with a randomized arrangement of plots within each repetition. The validation of results is emphasized by the principles of "repetition" and "randomization".

Additionally important for successful field trials are the

- selection of proper locations and fields
- availability of adequate field preparation-, application- and evaluation tools
- uniformity and high quality of crop growth
- availability of target organisms, homogeneity of weeds, pests, or diseases.

Before starting field trials the proper selection of a field and the allocation of the blocks by a skilled technician are the most important.

Layout and evaluation also depend strongly on proper specialized machinery for operation with precision on the relatively small plots. Precision of course is asked for in all stages of the operation inclusively of the standard agricultural measures such as

- seedbed preparation
- sowing of the crop
- fertilization
- plant protection and
- harvesting

A variety of application equipment can be used from a small plot log-sprayer to conventional tractor sprayers.

Assessment is by visual evaluation using standard criteria (Table 6).

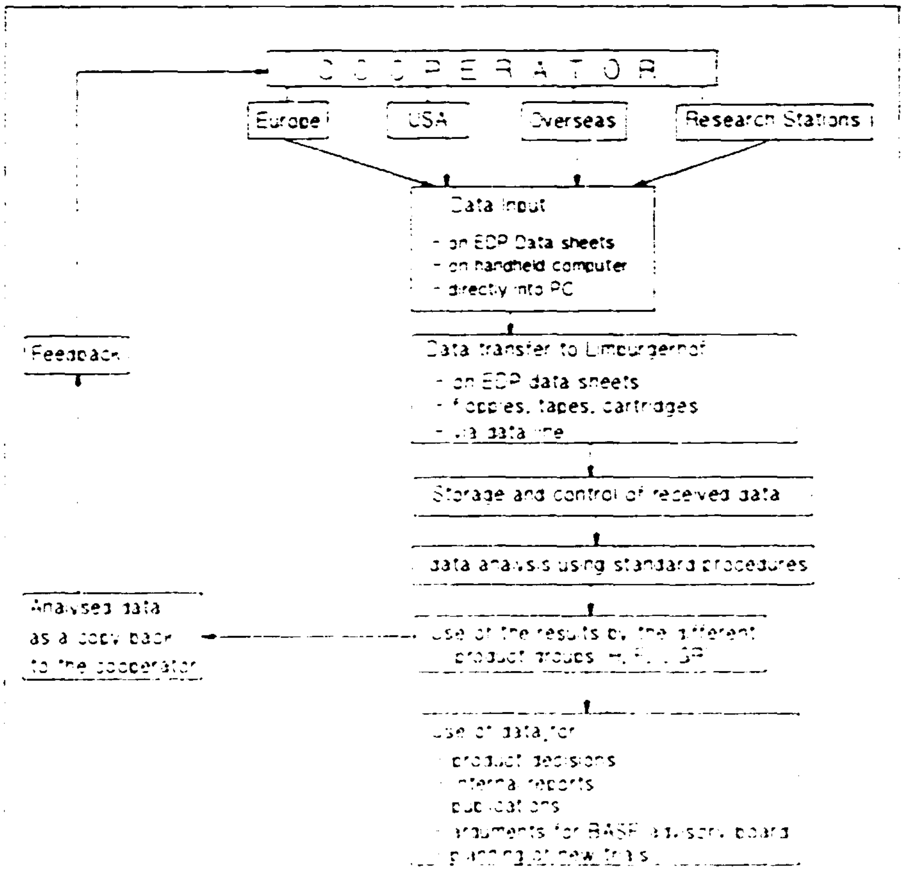
TABLE 6:
OUTLINE OF THE ASSESSMENT METHODS USED IN AGRICULTURAL TRIAL WORK

indication	variable	measurement method
HERBICIDES	weed control	direct estimation of control (%)
	grass control	direct estimation of control (%) or count of grasses
	plant injury	direct estimate (%)
FUNGICIDES	leaf diseases in field crops	visual estimate of disease incidence (%)
	ear diseases in cereals	visual estimate of disease (%)
	damping-off and root rot in cereals	classification of individual plants, of a random sampling into 4 disease levels
	Botrytis in strawberries	classification of individual plants, of a random sampling as "healthy" or "diseased"
	Sclerotinia spp. in oilseed and sunflowers	classification of individual plants, of a random sampling into 4 disease levels
INSECTICIDES	aphids on diverse crops	count of the living aphids in a random sample
	caterpillars	
	a) infestation	count of the living caterpillars in a random sample
	b) symptoms	classification of the caterpillars in a random sampling into 6 levels of infestation
BIOREGULATORS	germination density, crop stand	count of the plants, per area
	lodging	estimate of lodging in %
	plant height	measurement in cm or meters
	yield	weight of the yield in kg

Proper data sheets make sure that all the relevant data for trial evaluation are recorded from wherever the trials are laid out to make them available for biometrical evaluation.

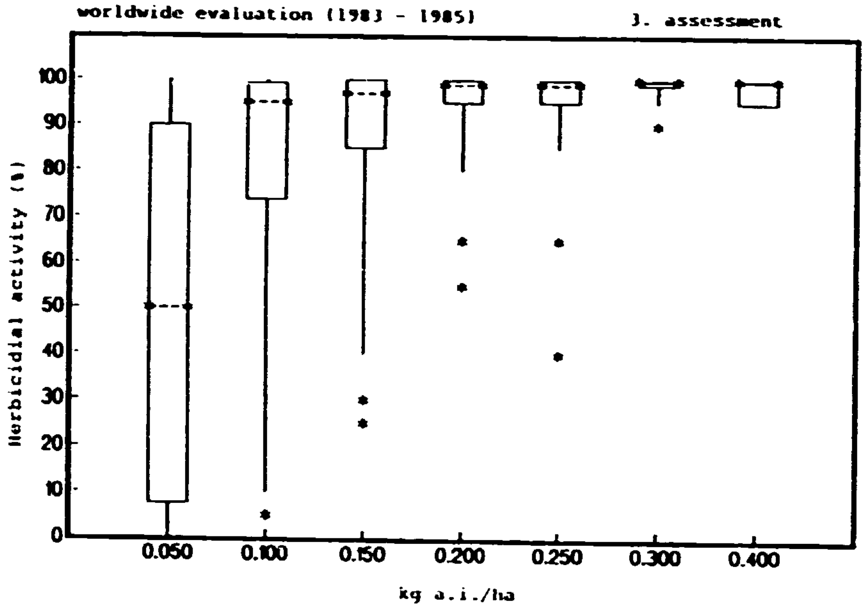
Data links to the central research location are established. Hand held computers provide for direct input in the field and specific programmes allow dialogue research in the data centre as well at the various research locations over the world. A scheme of the data flow is shown in Table 7.

TABLE 7:
FLOW DIAGRAM OF DATA PROCESSING



Results of these efforts are profiles of biological efficacy for the candidate (Table 8). Suitable graphical presentation allow for easy analysis of the results. Mean and standard deviation plots allow for fast comparison of the results.

TABLE 8:
PROFILE OF HERBICIDAL EFFICACY: ACTIVITY OF BAS 517..H AGAINST ALOPECURUS MYOSUROIDES

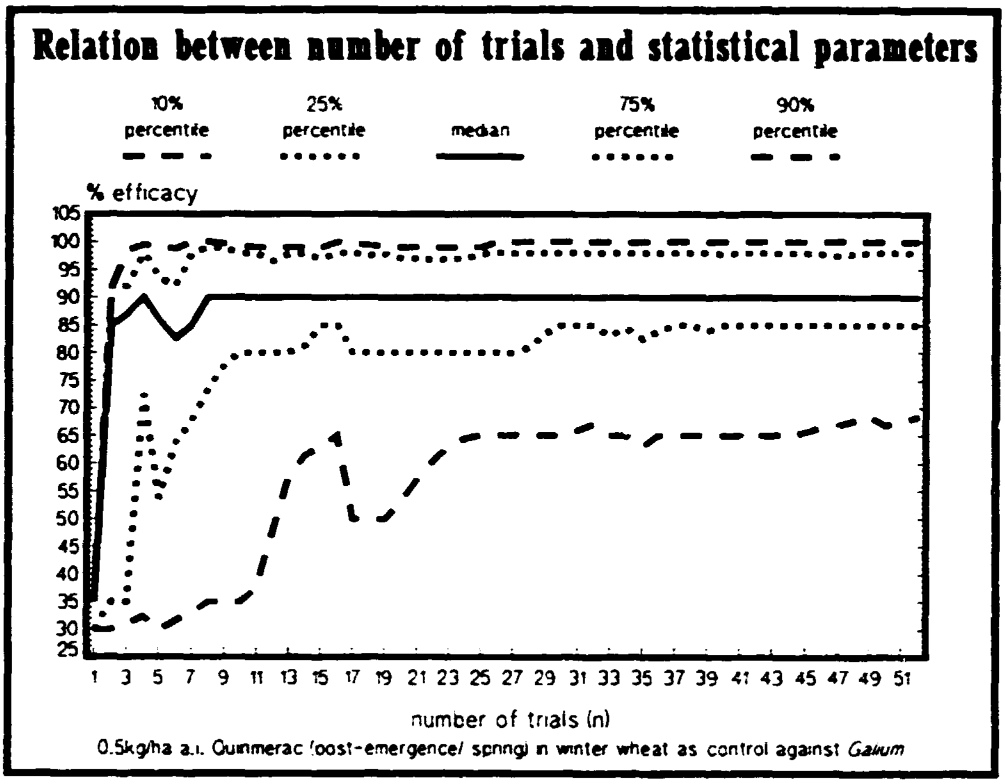


Amount of samples:	53	110	93	113	67	47	13

Box and whisker charts offer more information in that they describe the deviation from the mean value. A very helpful approach when it comes to assessment of herbicidal efficacy.

Table 9 indicates the number of trials necessary to answer the trial question reliably.

TABLE 9:
RELATION BETWEEN NUMBER OF TRIALS AND STATISTICAL PARAMETERS



A detailed look into the results areawise is quite revealing and underlines the necessity to do field trials in various regions for at least 4 years. The test volume is quite impressive. 2 800 trials with 8 500 plots on 85 hectares were executed in 5 years for the development of one cereal fungicide.

DEFENSIVE ASPECTS

We have now concluded the consideration of the "offensive work". Let us now turn to the activities, which are to protect finally the farmer, the consumer and the environment. This is what I called the "defensive part".

As we have seen a compound must be effective, but at the same time it must not be toxic, it must not leach, it must not evaporate, it must not be persistent, it must not upset the ecosystem beyond the limits imposed by the registration authorities. It is obvious that this can only mean to look for the best possible compromise.

It is therefore crucial that properties endangering such registration must be recognized as early as possible. This may avoid abandoning the project at a late and very costly stage.

The candidate is checked therefore early by studies (Table 10) which try to assure that full scale development is justified.

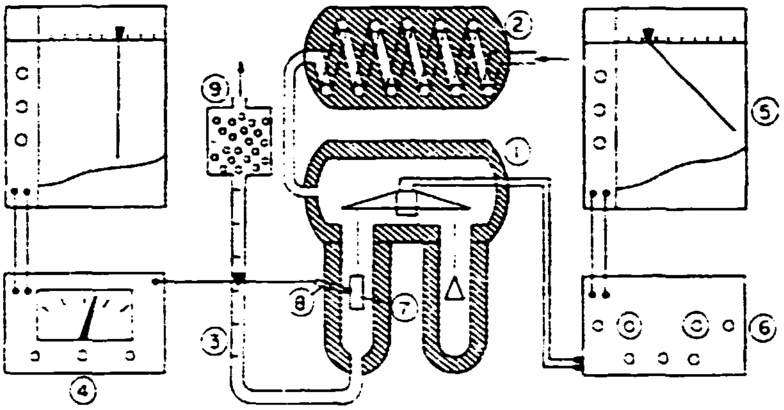
TABLE 10:
TESTING MEASURES TO DETERMINE THE ECOLOGICAL BEHAVIOUR OF PLANT PROTECTION COMPOUNDS WITHIN THE FRAMEWORK OF A SCREENING PROGRAM

	Test / Checking method		
A	TOXICITY		
1.	Acute oral toxicity (LD_{50} rat)		
2.	Acute peritoneal toxicity (LD_{50} rat)		
3.	Skin irritation (rabbit)		
4.	Irritation of mucous membranes (rabbit)		
5.	Cytotoxicity		
6.	Mutagenicity		
7.	Teratogenicity		
B	MOBILITY		
8.	Biological activity via the vapour phase		
9.	Leaching behaviour in soil		
C	BREAKDOWN / SORPTION		
10.	Loss of biological activity in at least two different types of soil		
11.	Sorption / desorption in different soil types.		
D	EFFECT ON SOIL MICROFLORA		
12.	Dehydrogenase activity		
13.	Ammonification		
14.	Nitrification		
E	SIDE EFFECTS ON NON-TARGET ANIMALS OR INSECTS		
15.	Earthworm	20.	Daphnia
16.	Honeybee	21.	Ramshorn snail
17.	Ladybird	22.	Ground beetle
18.	Lacewing	23.	Springtail
19.	Predatory mite	24.	Fish toxicity
F	SIDE-EFFECTS ON FLORA OF ARABLE LAND (ONLY IN THE CASE OF HERBICIDES)		
25.	Test of phytotoxicity to endangered species such as Pheasant's eye, Corn cockle, Hare's ear, Shepherd's needle, Large-flowered Orlaya, Hare's ear cabbage.		

Later in Field Development certain aspects of compound behaviour in the soil under field conditions is either investigated in lysimeter trials or in "field dissipation studies" e.g. with "suction candles".

When it comes to evaporation studies special laboratory equipment allows for an assessment (Figure 1).

FIGURE 1:
SCHEME OF AN APPARATUS FOR MEASURING THE EVAPORATION RATE



The apparatus for measuring the evaporation rate: 1, the electric balance; 2, the heat exchanger; 3, a rotameter; 4 and 5, chart recorders; 6, control device; 7, glass plate; 8, platinum temperature sensor; roughened and 9, sorption unit.

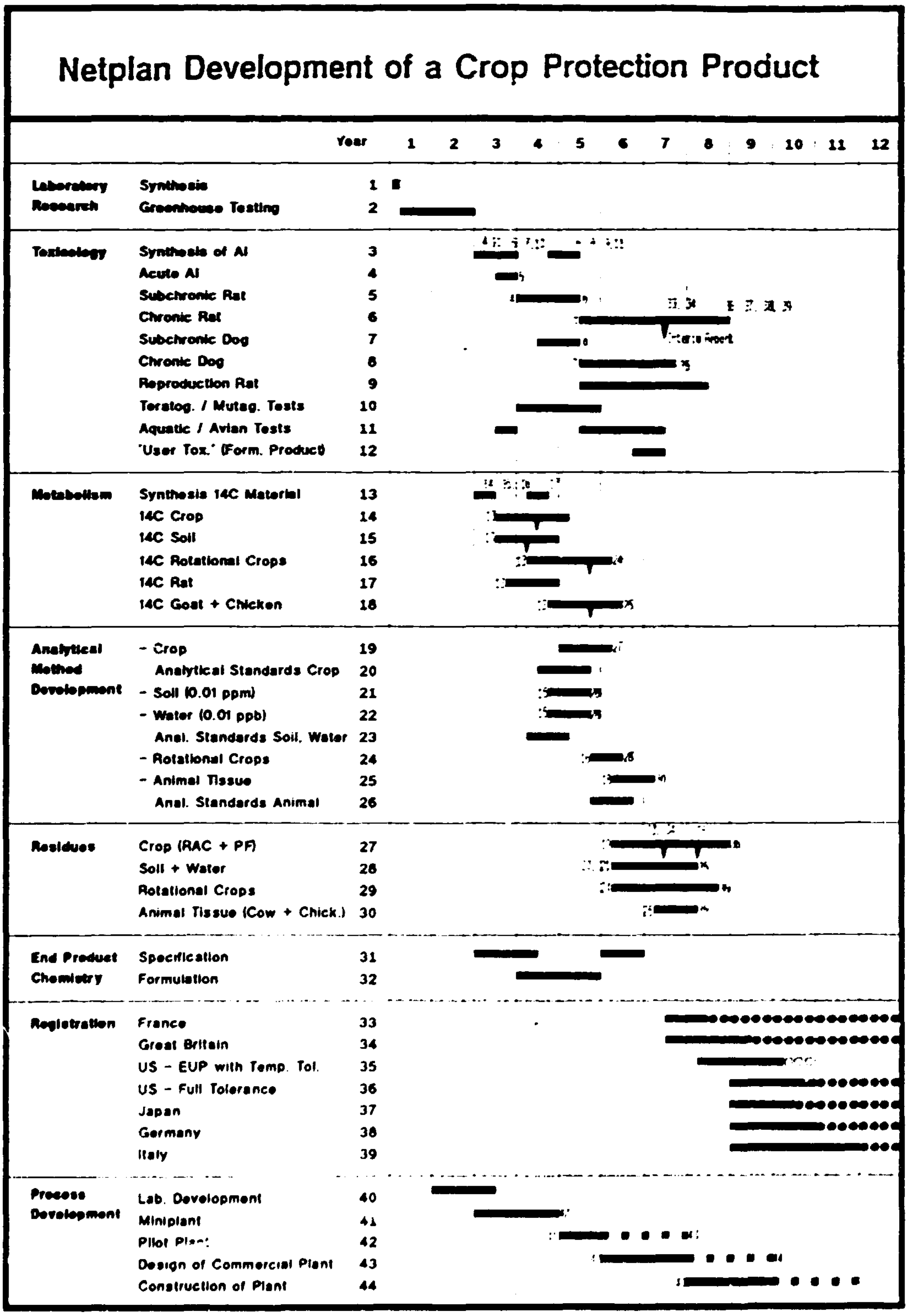
Impact on non-target organisms is studied in the above mentioned "indicator study phase" and of course in the phase of practical field trials.

It is essential that all these studies are be done under "Good Field Practice" conditions in order to make them acceptable to the registration authorities.

I will not go into the toxicity, residue and metabolism work in crop, harvest and all the compartments of the environment which is a lecture in itself: only that much of the respective investigations apply to the major metabolites of the compound. It must be noted that such "defensive" activities are continuously expanded and are about to consume the major part of the development expenses today.

It goes without saying that the development process - from candidate to product over a period of up to ten years and encompassing at least 1 000 required activities must be controlled as best as possible. This is achieved by Project Management Systems as exemplified in Table 11.

TABLE 11:
PROJECT MANAGEMENT BY NETPLANNING



OUTLOOK

Where do we go from here preparing for the "AGRICULTURE OF THE FUTURE"?

Developing products for advanced plant protection will be as important as ever.

By 2050 approximately 11 billion people will live on this globe (additional 1.6 million each week). Food production must increase by at least 70 % over the next 40 years. 1/3 of agricultural production increase will continue to come from plant protection along with plant breeding and plant nutrition.

Obviously further intensification of plant production is the answer - with as little environmental impact as possible in order to conserve the precious limited natural resources.

The best possible methods with the best possible products will have to be developed to allow for precision farming and overall input optimization into the production systems.

An integrated crop production will be called for - compatible with the ecosystems. This is to say that a good deal of additional detailed knowledge about these systems will be required if this is to be achieved.

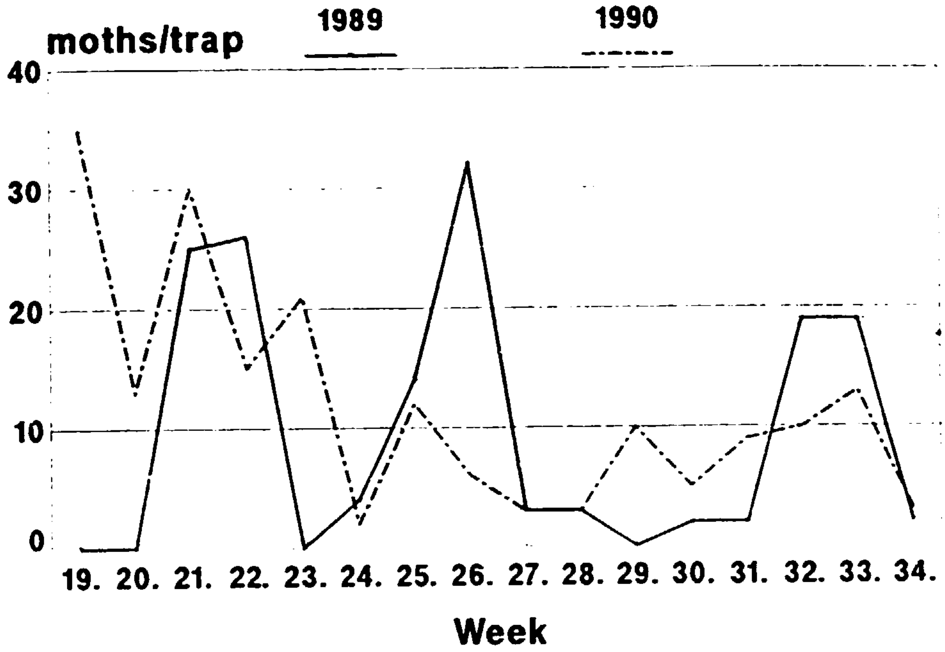
Evidently this calls for ever more complex and detailed advanced field development work to build an entire crop production system.

Complexities are easily demonstrated by pheromone trials / confusion methods where one has to cope with quite different flight periods over the years (Table 12).

TABLE 12:
FLIGHT ACTIVITY OF CYDIA POMONELLA
IN 1982/83

Cydia pomonella

(Bölingen)



How do we go on ?

There is no question in the expert's minds that plant agriculture will continue to rely mostly on chemicals, of course ever more advanced ones for plant protection.

These advanced chemicals will be applied on the new and more sophisticated varieties which will originate from plant genetics and advanced breeding. The new substances are expected

- to control and regulate crops rather than eliminate/kill weeds, pests or diseases
- to do so as low a rate as possible - but as much as necessary by bringing the right compound in the proper quantity at the right time to the proper spot.

The modern varieties on the other hand will require early integrated studies as to their plant protection needs.

Product development will have to be geared to strict observation of the limits imposed by registration to provide products that allow for the best production systems and best harvests possible in terms of quality and yield.

All this requires a continuous flow of innovation - in the face of major obstacles for the industry - the exploding R&D costs.

There is a big challenge both

- for the authorities to create proper environment encouraging R&D investments for plant protection and

- for the industry to create novel chemistry and novel techniques fast - and with improved methodology - at reduced costs.

There is reason for optimism - the industry certainly does not have a bad track record for continuous improvement. Quinmerac, the active ingredient of a new graminicide in rice suits surely here as a very good example amongst many others.

Acknowledgement

The help of Dr. V. Fischer and Dr. H. Bleiholder, BASF, Central Agricultural Research Station, Limburgerhof, in preparing and discussing the manuscript is gratefully acknowledged.

NATURAL AND SYNTHETIC PYRETHROID INSECTICIDES

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ABSTRACT

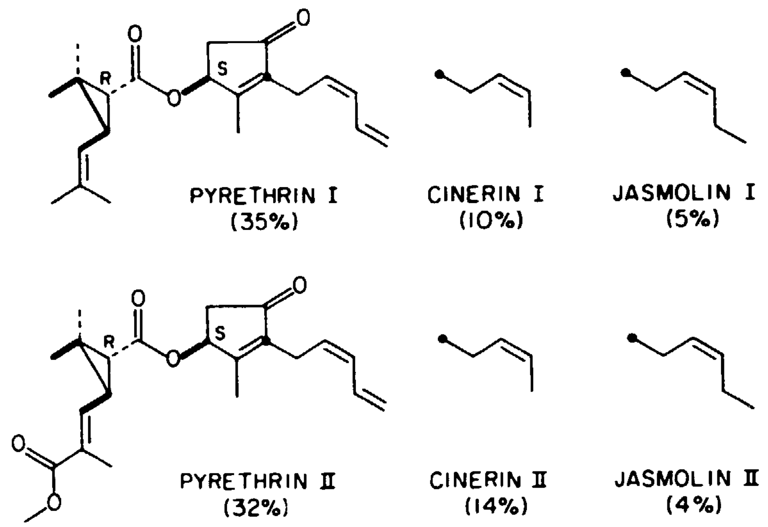
Synthetic variants, relatively more stable in air and light, were derived from the natural pyrethrin insecticides by a series of structural modifications. The main chemical, physico-chemical, biological and toxicological properties of the new compounds are described and their significance in present and future insect control is discussed.

INTRODUCTION

This contribution to the programme for the Opening Symposium of the Shenyang Research Institute of Chemical Industry will indicate how the structures of insecticides extracted from the mature dried flower of *Chrysanthemum (Tanacetum) cinerariaefolium* (1) became the basis for the development of commercial products now worth some U.S. $ one billion annually. These compounds, the natural pyrethrins, have been known for more than 100 years to act rapidly to kill or immobilize ("knock-down") a wide range of insect species yet to be harmless to mammals under all normal circumstances. Although the pyrethrins had been found to have a remarkable effect against obnoxious flying insects such as houseflies and mosquitoes, they were too unstable in air and light to control pests of agricultural crops efficiently and economically. These natural products could not therefore compete with synthetic insecticides such as DDT, HCH, aldrin, dieldrin and the organo-phosphate and carbamate insecticides for most general applications.

CHEMICAL STRUCTURES

The unique properties of the natural pyrethrins attracted the attention of organic chemists and entomologists in research stations and universities throughout the world. Over several decades workers in Japan, Switzerland, the United States and the United Kingdom (for details, see leading references cited in 1,2 and 3) established the structures of the natural esters shown.



FUJITANI (1909) YAMAMOTO (1919)
STAUDINGER AND RUZICKA (1924) (1910-1916)
LAFORGE *et al.* (1936-)
HARPER *et al.* (1942-)
CROMBIE *et al.* (1948-)

Figure 1. The structures of the six natural esters

Examination of the insecticidal activity of the natural esters and of related synthetic compounds then established some of the features (indicated in Figure 2) associated with potency (4).

DEVELOPMENT OF SYNTHETIC PYRETHROIDS

In 1948, at Rothamsted Experimental Station, Charles Potter, then recently appointed Head of the Insecticides and Fungicides Department, decided to use pyrethrum as the basis for a project to establish principles by which improved insecticides could be

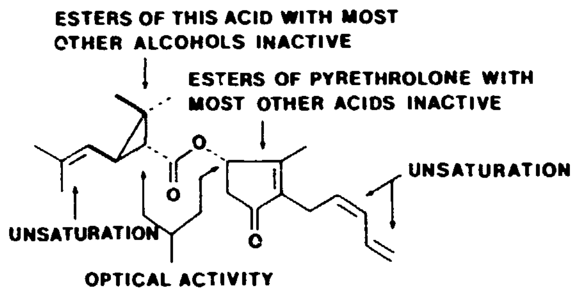
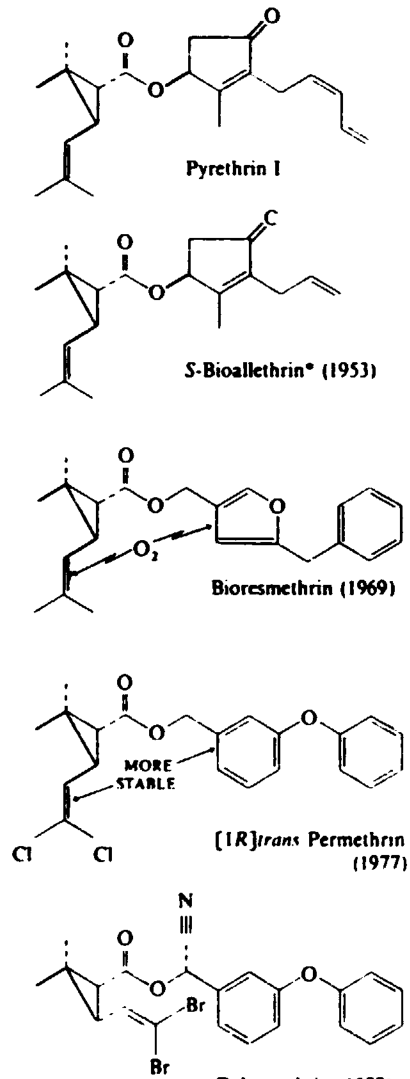


Figure 2. Structure and insecticidal activity

developed. At the start of the Rothamsted work on synthetic pyrethroids, Schechter, Green and LaForge of the United States Department of Agriculture at Beltsville, Maryland has just reported the first potentially commercial synthetic pyrethroid, allethrin (5). Unlike pyrethrin I and pyrethrin II, allethrin had only one double bond in the alcoholic side chain, so large scale synthesis was somewhat more feasible (6). Allethrin excited great interest because it acted more rapidly and five times more effectively than the natural compound (see Figure 3) against an established target for pyrethrum, the common housefly. However, after some time this outstanding performance was shown by tests at Rothamsted and elsewhere to be largely restricted to the housefly; against other insects (for example the beetle, *Phaedon cochleariae* L.) the natural compound was forty times more effective than allethrin (7). There was little practically significant difference in the toxicity to mammals of the natural and synthetic compounds and allethrin was still not stable enough in air and light to extend the range of applications much beyond those traditional for pyrethrum.

Several research groups continued to make synthetic pyrethroids, mainly cyclopentenolone esters, but none of the new compounds was significantly more active than allethrin and many were much less effective. At Rothamsted, based on our experience with pyrethrin I and allethrin against insects other than the housefly, we pursued the concept that for best activity more than one double bond in the alcoholic side chain of the molecule was necessary. Eventually, after synthesising and testing many structures, and with support (after 1962) from the British National Research Development Corporation, we reached the compound bioresmethrin, a molecule with similar overall size and shape to pyrethrin I but with a furan ring replacing the



Representative median lethal doses (mg kg⁻¹)

Compound	Insects, contact: *Musca domestica*	Insects, contact: *Phaedon cochleariae*	Mammals: Rats, oral	Typical field life, days
Pyrethrin I	30	0.3	420	<1
S-Bioallethrin* (1953)	6	12	800	<1
Bioresmethrin (1969)	0.6	0.5	8000	<1
[1*R*]*trans* Permethrin (1977)	0.7	0.1	2000	>20
Deltamethrin (1977)	0.02	0.008	~100	>20

Figure 3. Relative potency of some pyrethroids

cyclopentenone and a benzene ring simulating the Z (cis) dienyl side chain (8). The corresponding 2,5-disubstituted furan compound, which was more accessible synthetically, had been made before bioresmethrin and was moderately active. For us therefore the decision to invest time and effort into devising and executing a synthesis of the 3,5-substituted compound was a crucial one and in retrospect can be seen as the turning point on which our future progress depended.

In fact, bioresmethrin was the first synthetic pyrethroid to approach the potency of pyrethrin I to a range of insect species and an unanticipated, but most fortunate, bonus was that bioresmethrin was significantly less toxic to mammals than the pyrethrins and allethrin, which were already very safe.

However, in sunlight bioresmethrin was no more stable than the earlier synthetic pyrethroids, because both the furan ring and the isobutenyl side chain were vulnerable sites for degradative attack by oxygen in the presence of ultraviolet light (see Figure 3). These conclusions arose from detailed studies made in the laboratory of Professor John E. Casida in the University of California at Berkeley (9,10). Much more research then showed that both halves of the ester molecule could be modified for enhanced photostability whilst the stereochemical characteristics with which insecticidal activity was associated were maintained. Appropriate combinations such as biopermethrin (Figure 3) which had chlorine instead of methyl in the acid side chain and a meta-substituted phenyl ring instead of the furan in the alcohol had insecticidal activity comparable with or greater than that of the less stable related compounds (11). Moreover, these substitutions did not sacrifice the benefits of low mammalian toxicity.

Other modifications to the structure of biopermethrin and related compounds increased still further the levels of insecticidal activity. An α-cyano group, where shown, approximately trebled potency and was most effective with a dihalovinyl substituent *cis*, rather than *trans*, to the ester group. When all the optical centres were resolved and the halogen in the side chain was bromine, a highly crystalline insecticide, named deltamethrin (NRDC 161) was produced (12). This combined an exceptional level of insecticidal activity, the highest that had been reported for any compound at the time, with acceptable mammalian toxicity. Following its initial preparation at Rothamsted the advanced expertise of Roussel Uclaf brought this single isomer, the most active of eight possible, to full commercial production, as Dr Jacques Martel describes in ref (13). Deltamethrin was found to have appropriate stability in sunlight to control insects on agricultural crops, and, with application rates frequently below 50 g g ha^{-1}, in use it presented a very low hazard to mammals and to non-target species.

OTHER PHOTOSTABLE COMPOUNDS

Whilst the work described above leading to the photostable cyclopropane based synthetic pyrethroids was in progress, chemists of the Sumitomo Chemical Company in Japan had made the important and significant discovery that esters of some substituted phenylacetic acids, particularly with α-cyano-3-phenoxybenzyl alcohol, were very powerful insecticides. Figure 4 outlines the sequence of compounds involved in their research.

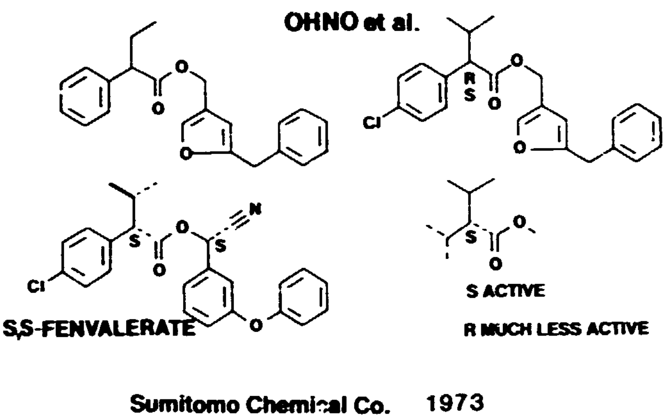


Figure 4. Development of Fenvalerate

This innovative work led in 1976 to the first commercial photostable pyrethroid, fenvalerate, a 4-isomer mixture, which has been followed (1986) by the single isomer Asana (14).

COMMERCIAL DEVELOPMENT OF PYRETHROIDS

Very rapid commercial development of synthetic pyrethroids followed when the first more photostable compounds (permethrin, cypermethrin, deltamethrin and fenvalerate) were found to be particularly effective against economically important pests such as lepidopterous larvae on cotton; these were controlled at exceptionally low rates of application. The new class of insecticides became available at a very opportune time when resistance developing in pest species was requiring unacceptably high rates of application for the established organochlorine and organophosphate insecticides.

Figure 5 shows the most active isomers in some of the cyclopropane based pyrethroids that have been developed. In addition to the compounds already mentioned, in cyfluthrin (15) a 4-fluoro substituent on the benzyl group enhances potency to a number of insect species. Crystalline equiproportion mixtures (alpha-cypermethrin (16,17) and lamda-cyhalothrin (18)) of the most active isomers in *cis*-cypermethrin and *cis*-cyhalothrin, respectively, with their inactive enantiomers, are very active insecticides manufactured without specific resolution steps.

The merits of commercial insecticides based on single isomers have been discussed (19).

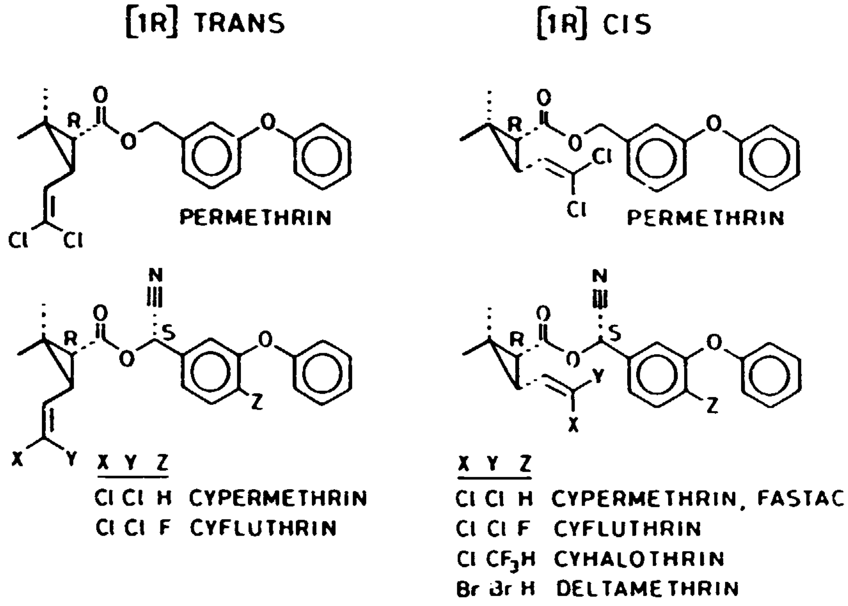


Figure 5. Active isomers in cyclopropane pyrethroids

The range of structures within the group which have useful insecticidal activity has continued to increase (Figure 6). Cycloprothrin (20) with diminished fish toxicity is valuable against pests of rice. Flumethrin, a compound with 4-chlorophenyl instead of chlorine in a *trans* acid side chain has exceptional activity against cattle ticks (21). Fluvalinate, extending the range of structural variations of fenvalerate, controls spider mites and is non-toxic and non-repellent to honey bees (22). Bifenthrin (23) is active against insects (including aphids) and mites (as is fenpropathrin (24); (Figure 7)). Tefluthrin (25) with a higher vapour pressure than most other pyrethroids is active against soil pests, such as the corn root worm, *Diabrotica baltcata.*

Many of the above developments have been more stable compounds suitable for agricultural applications; other products such as empenthrin (26) and prallethrin (27) (Figure 7) are particularly suitable for domestic applications, as indicated.

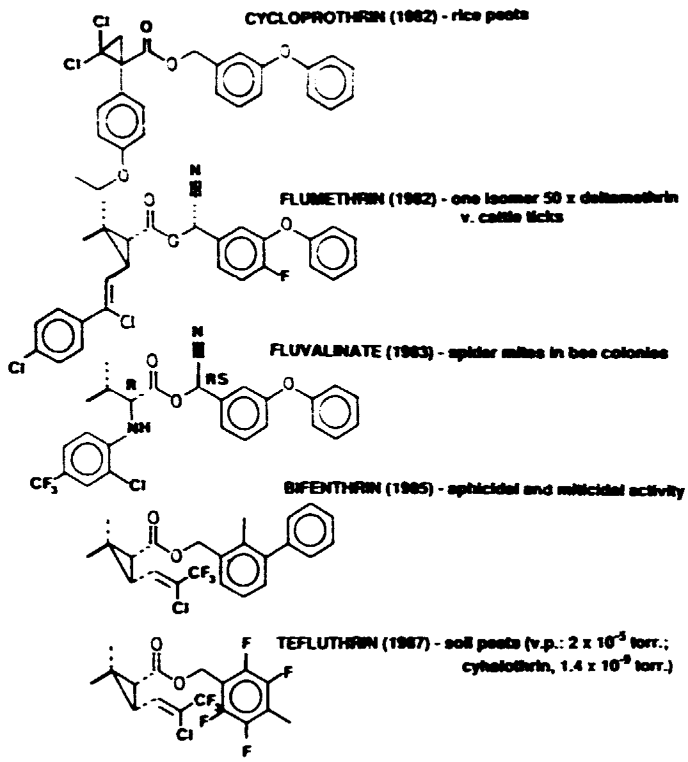


Figure 6. Halogenated pyrethroids

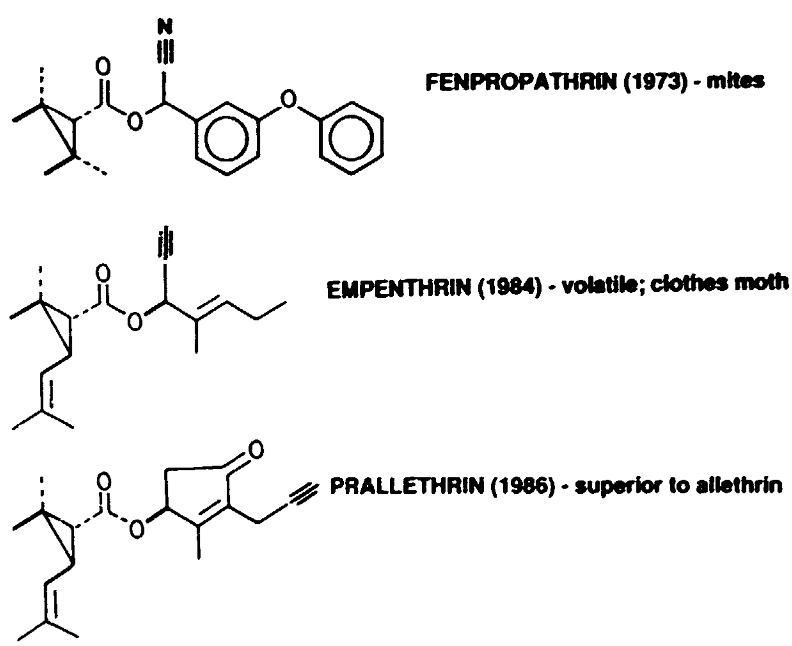


Figure 7. Cyclopropane esters without halogens

MORE RECENT DEVELOPMENTS

The survey above has been restricted to products developed commercially but many more related compounds have been synthesised in the process of optimising activity; the scope of this effort is indicated by Naumann (28). Active compounds (Figure 8) without ester groups such as oxime ethers (29) were challenging indicators of future advances, realized in one series as the innovatory compounds MTI 500 and MTI 800 (30), which amongst other valuable properties, have low toxicity to fish. Such non-esters, which are without centres of asymmetry, stimulated further research and thence products exemplified in Figure 8 (31;32,33;34). Significantly active silicon and tin derivatives (35) (Figure 9) suggest that other interesting compounds await discovery.

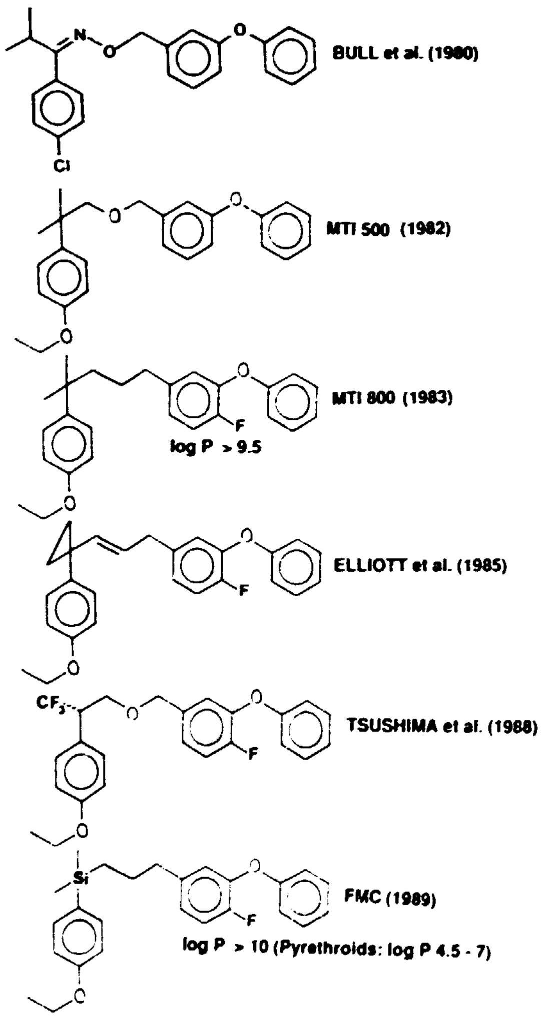


Figure 8. Non esters

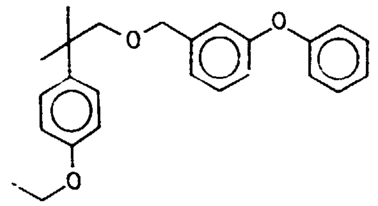
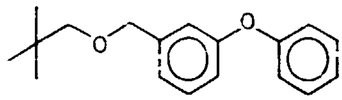
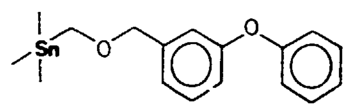
Tsushima et al., 1989	RELATIVE POTENCY	
	M. domestica	*C. suppressalis*
Permethrin	100	100
	26	77
	12	2
	120	190

Figure 9. Recent developments

ENVIRONMENTAL BEHAVIOUR AND TOXICOLOGY OF PYRETHROIDS

Pyrethroids such as pyrethrin I, allethrin and resmethrin are powerful insecticides with low toxicity to mammals, which metabolise pyrethroids at one or more sites efficiently (Figure 10). These insecticides are also degraded readily photochemically and are suitable for applications that do not require stability in light. The hazard associated with using permethrin, cypermethrin, deltamethrin, and related compounds is small because they retain multiple sites at which they are metabolized in biotic systems. They are still somewhat susceptible to photochemical degradation, but the reactions by which this proceeds are much slower, because the more stable compounds absorb light and transfer energy intramolecularly relatively less efficiently. These characteristics are the basis for the favourable combination of properties of the more photostable pyrethroids.

An important feature of pyrethroids is their differential potency between insects and mammals (36). These favourable toxicological properties depend on their ability to penetrate rapidly to, and interact with, sites of action in insects; these are probably sodium channels of the nerve membrane where compounds such as deltamethrin are active at concentrations as low as 10^{-12}M (37). In contrast, after external or oral administration to mammals, pyrethroids are largely converted by hydrolytic or oxidative

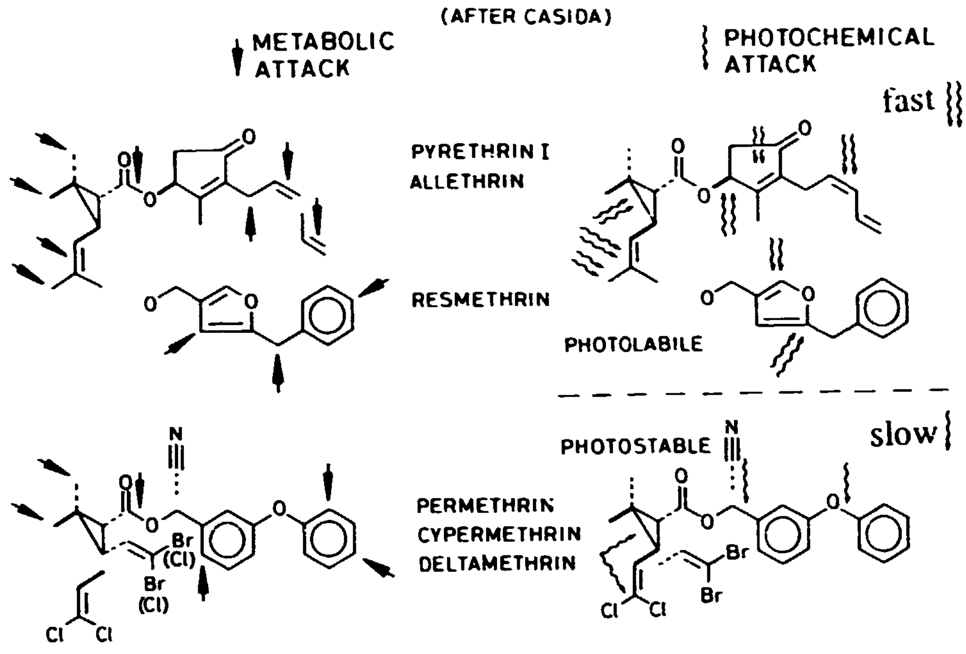


Figure 10. Metabolism and photochemistry of pyrethroids

attack to polar metabolites which are then eliminated in the faeces or urine, unchanged or as conjugates, before sensitive sites can be reached (38).

Commercially available photostable pyrethroids are effective in the field at rates of 200 g ha^{-1} or less, and with the most active compounds such as deltamethrin, alpha-cypermethrin or lambda-cyhalothrin 10-25 g or even 5 g ha^{-1} (for special applications) may be effective. In contrast, with organochlorine, organophosphate or carbamate insecticides rates of 1 kg ha^{-1} are common, frequently higher if pests are resistant. In the field the photostable pyrethroids persist on crops for 7-30 days whilst insect infestations are controlled; residues then reaching the soil are metabolized by routes comparable to those in mammalian systems and give polar products which are bound to soil particles, where they are further degraded. Residues of non-polar products do not therefore accumulate to contaminate the environment.

In some circumstances, pyrethroids are toxic to fish, probably because, as lipophilic compounds, they are adsorbed strongly by the gills even from low concentrations in water. In practice their impact is much less serious than might be predicted because their concentration in aqueous media is much diminished by adsorption onto river banks, pond sediments and organic matter with which they are in contact (39).

PRESENT AND FUTURE APPLICATIONS OF SYNTHETIC PYRETHROIDS

Insecticides such as DDT and other stable chlorinated hydrocarbon compounds, able to provide active residual films, transformed concepts of insect control and for a brief euphoric period, promised to provide the ultimate panacea. However the parent compounds and their degradation products proved in the long run too pervasive throughout the environment at the relatively high application rates their level of activity required. Because they are one or two orders of magnitude more active than DDT and not unduly persistent, pyrethroids can be considered as replacements for chlorinated hydrocarbon insecticides in applications from which they are not excluded by higher costs.

As well as being applied to agricultural crops (over 70 million ha are estimated to have been treated in 1987) including cotton, compounds such as cypermethrin and cyhalothrin are now used in the animal sector as ectoparasiticides and in the health and household insecticide market. Permethrin, which has the lowest mammalian toxicity of the more stable compounds, is formulated against human head lice and is proposed as an alternative for termite control.

Knowledge of how structure affects potency for important practical uses (activity against economically important pest species, acaricidal activity, selectivity between pests and beneficial species, persistence on crops and in the environment, rapidity of action, antifeedant or repellent properties, toxicity to mammals birds and fish etc.) is being rapidly accumulated. Strategies to guard against resistance developing (40) and to diminish adverse effects to biological systems by appropriate choice of timing and site of application are increasingly recognized as of outstanding importance. The prospects of developing pyrethroids with properties appropriate for particular insect control applications are therefore excellent, but the present range of compounds being already so potent, efficient exploitation of further improvements in intrinsic activity may not always be possible (41).

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DELTAMETHRIN - A CHALLENGE IN PROCESS DEVELOPMENT

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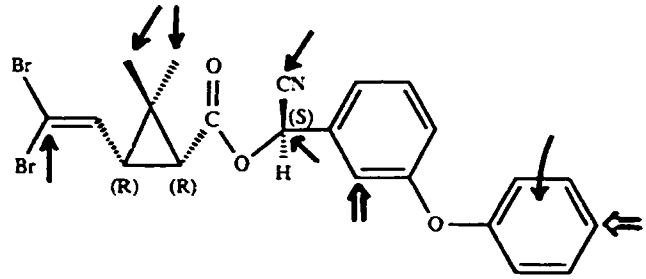
ABSTRACT

The industrial stereoselective route to deltamethrin was built taking advantage of the basic progress already accumulated in the S - bioallethrin synthesis. The stereospecific synthesis of the dl - trans-chrysanthemic acid discovered in 1967 was retained as well as the especially convenient resolution step. It remained to turn the advantageous production of either d or l - trans chrysanthemic enantiomer into a similar advantageous production of the chiral acidic moiety required for deltamethrin. This (1R, 3R) - 3 - (2,2 - dibromovinyl) - 2,2-dimethyl - cyclopropane - carboxylic acid belongs to the *cis series* and the forecast transformation of a trans derivative into a cis one had to be performed against the thermodynamical tendency of these structures. Production of deltamethrin should formally imply esterification of the chiral acid with α - cyano -m- phenoxybenzylic alcohol with the (S) configuration. Other challenges concerning deltamethrin synthesis deal with access to radiolabelled forms, which were required for different specific studies related to development, such as photodegradation, biodegradation, metabolism in plants and animals etc. Synthesis leading to 5 different 14C labelled deltamethrins and 2 other 3H labelled deltamethrins is briefly described.

INTRODUCTION

Deltamethrin (Figure 1) is an ester derived from a cyclopropanecarboxylic acid and a benzylic alcohol, which renders the compound sensitive to hydrolytic conditions. The double bond in the acidic moiety and the cyano-group in the alcoholic moiety enhance the fragility of the ester linkage. Aqueous acidic media are particularly detrimental to the cyano-group, which can afford a carboxyl group via the amide intermediate. Similar experimental conditions (Figure 2) may lead to double bond hydration, carbocation formation at one alpha-position of the cyclopropane and subsequent ring opening in an homoallylic type rearrangement.

Fig.1



Deltamethrin

(SITES OF CARBON-14 ↑ AND TRITIUM ⇑ LABELS)

Fig.2

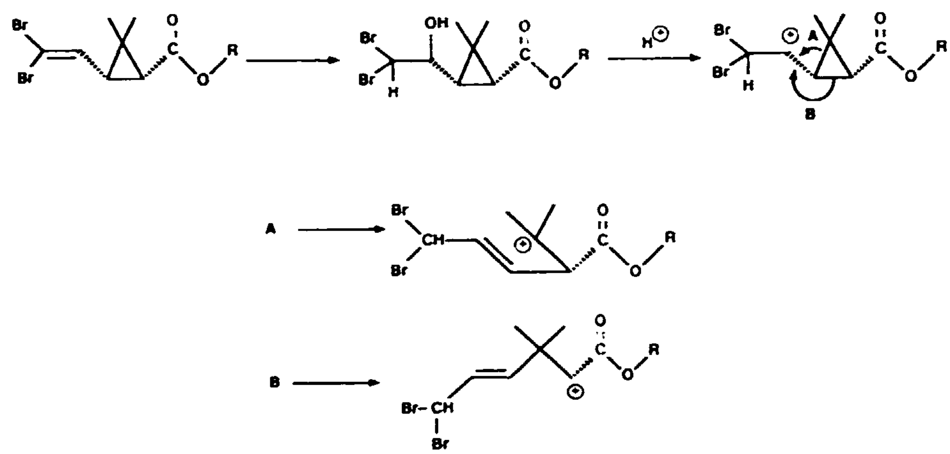
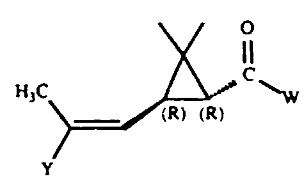
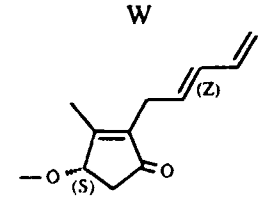
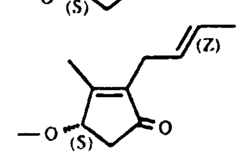
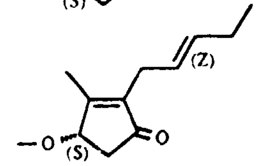


Fig.3



	Y series I	Y series II	W
Pyrethrins	$\cdot CH_3$	$\cdot CO_2CH_3$	
Cinerins	$\cdot CH_3$	$\cdot CO_2CH_3$	
Jasmolins	$\cdot CH_3$	$\cdot CO_2CH_3$	

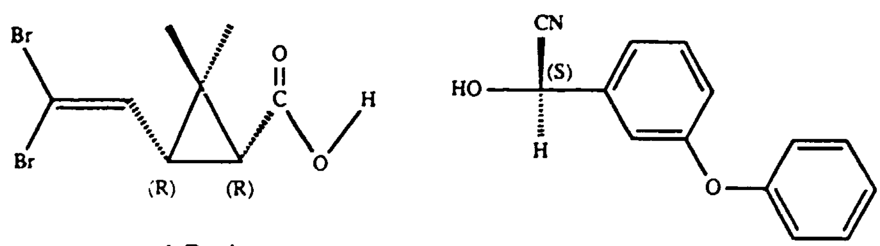
Comparative activity of deltamethrin and its 7 stereoisomers

C_1 configuration	C_3 configuration	C benzylic configuration	Insecticidal activity
R	R	R	0
R	S	R	0
R	R	S	+ + + + + (DELTAMETHRIN)
R	S	S	+ + +
S	R	R	0
S	S	R	0
S	R	S	0
S	S	S	0

0 = no activity

+ + + + + = maximum activity

Fig.4



1 R cis

Fig. 5

However, the main problem to be solved in the manufacture of deltamethrin arises from its stereochemical features. In this respect, the stereochemistry of deltamethrin is as complex as that of the natural pyrethrins of series I (Figure 3), which are derived from natural chrysanthemic acid. Pyrethrins II are derived from natural pyrethric acid and have an additional feature of asymetry around the double bond of the side chain. Thus, a non-stereoselective deltamethrin synthesis can generate 8 stereoisomers, since there are 3 asymetric centres leading to 2^3 different three-dimensional molecular arangements. Of these eight possible isomers only two are highly insecticidal, namely, deltamethrin and to a lesser extent its C-3 epimer, which is its 1R trans diastereoisomer (Figure 4). In practice, it is obviously sensible to use only the most potent isomer to avoid a useless dilution of activity by components of no insecticidal value, but which may have a detrimental impact on the environment.

SYNTHESIS STRATEGIES

From a general industrial point of view, expensive chemical reactions are only justified when they lead to the desired bioactive substance with the best transformation yield. This condition is systematically hampered when the desired substance is diluted by several worthless isomers of different chemical reactivity, resulting in a series of unwanted side-products. Since huge industrial investments are required for the large scale production of compounds, even when endowed with very high biological efficiency, several parameters have to be considered in the forecasting phase for a production plant. It is of concern to obtain the marketable substance at the highest concentration. Thereby, only the necessary minimum of industrial resource need be devoted to such manufacture. These general constraints justify an isomeric selection strategy, leading to the rejection of any non-specific synthesis generating the 8 forecast isomers (6 of them absolutely unwanted), in favour of a route leading to the single isomer deltamethrin, by far the most potent insecticide of the series.

Theoretically, such a synthesis requires total control of the stereospecific routes to the (1R, 3R) or 1R cis or d-cis-dibromo acid as well as of the (S) alcohol to be esterified (Figure 5). Based on our early experience in this field and on the thermodynamic considerations concerning the expected acid we did not try to solve access to the 1R cis dibromo acid by direct and stereospecific synthesis. Vinylcyclopropanecarboxylic acids of the cis- series are rather thermodynamically unstable isomers, very prone to an easy conversion into more stable trans isomers (Figure 6), either through inversion of configuration at C-1 (1R cis giving 1S trans derivatives) or by more complex mechanisms implying transient ring opening. In this case, racemization results.

In contrast, access to trans derivatives with high selectivity is secured when thermodynamic equilibrium is reached. Consequently, we chose in 1964 to replace the hazardous diazo synthesis of chrysanthemic acid by a safer novel route to thermodynamically expected trans derivatives, i.e., a one pot synthesis of dl trans chrysanthemic acid (Figure 7). This involves 1,4 - addition of a transiently activated isoprenoid moiety onto a β, β-dimethyl-acrylic ester, immediately followed by a 1,3-elimination of the activating group and formation of a cyclopropane ring. Arylsulfone is absolutely necessary for the 1,4-additon to β, β-disubstituted acrylic esters which are resistant to Michael reactions, even in Kohler conditions with copper chloride or other catalysts. This very efficient

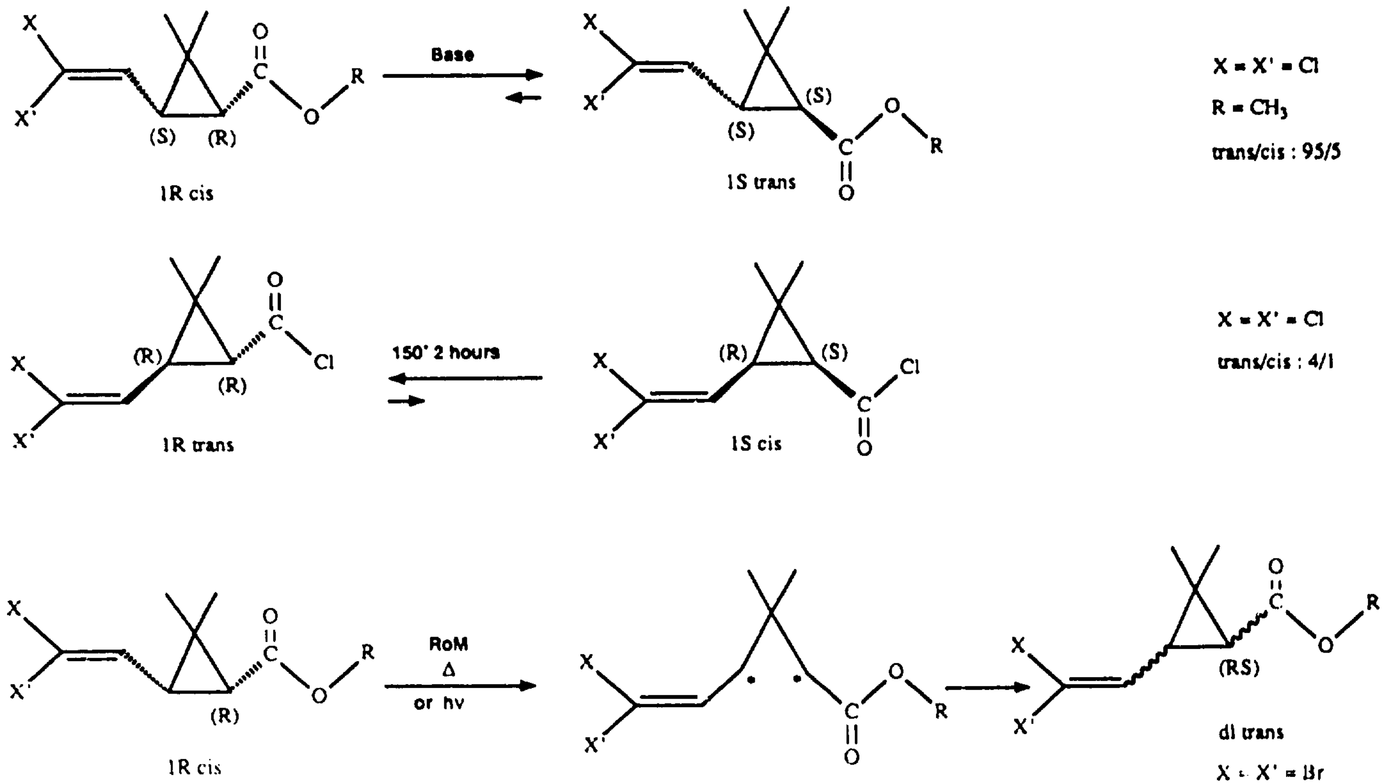
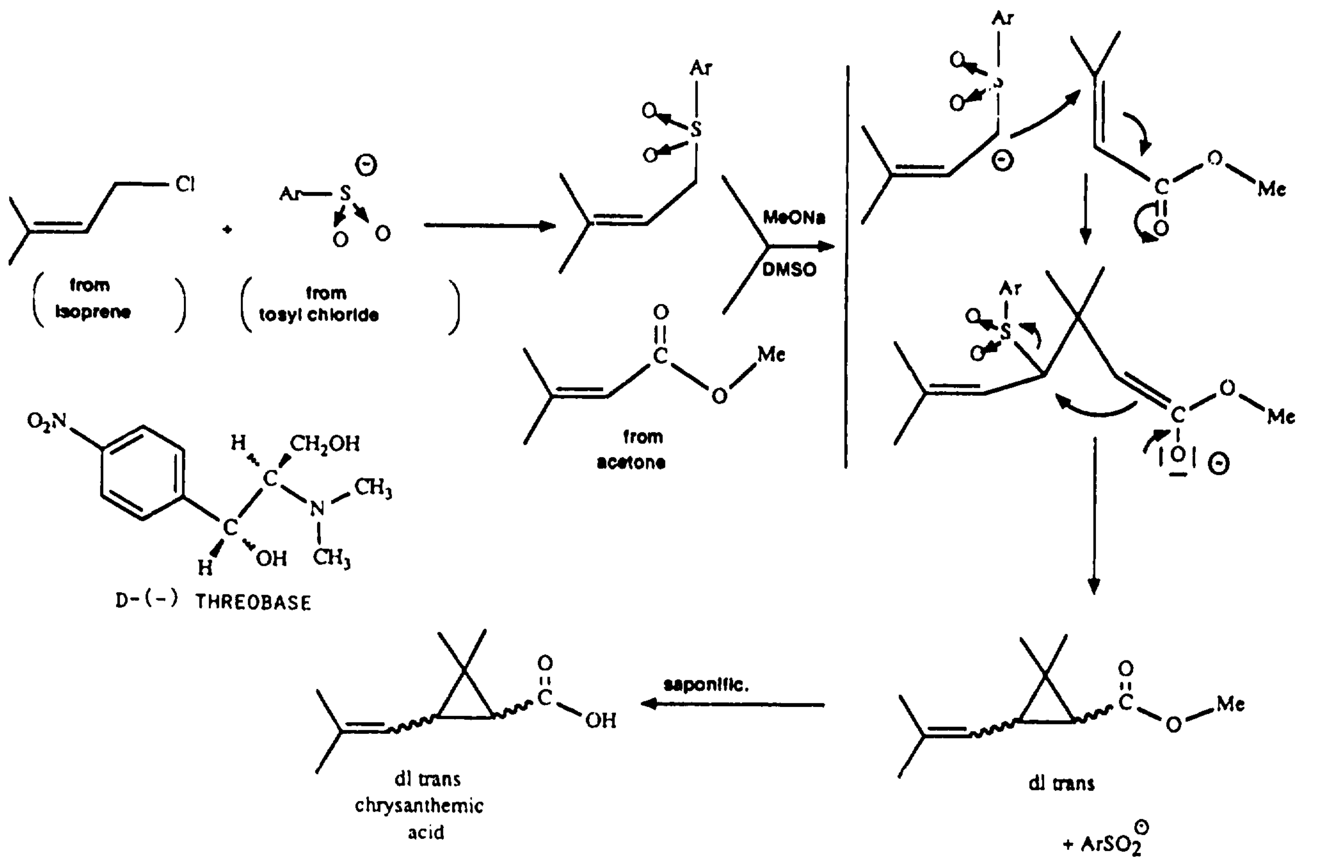
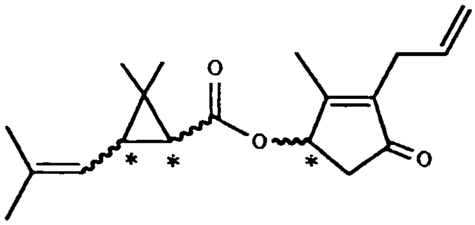

X
X'
(S) (R)
1R cis
Base
(S)
(S)
1S trans
R
X = X' = Cl
R = CH₃
trans/cis : 95/5
(R)
(R)
Cl
1R trans
150° 2 hours
(R)
(S)
1S cis
X = X' = Cl
trans/cis : 4/1
RoM
Δ
or hν
(RS)
dl trans
X = X' = Br

Fig. 6



Cl
from isoprene
from tosyl chloride
Ar
MeONa
DMSO
Me
from acetone
D-(-) THREOBASE
saponific.
dl trans chrysanthemic acid
dl trans
+ $ArSO_2^{\ominus}$

Fig. 7



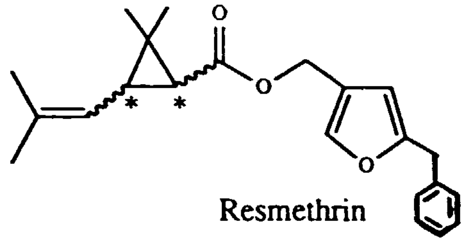
Allethrin

$2^3 = 8$ stereoisomers

allethronyl d trans

chrysanthemate content

about 20%



Resmethrin

$2^2 = 4$ stereoisomers

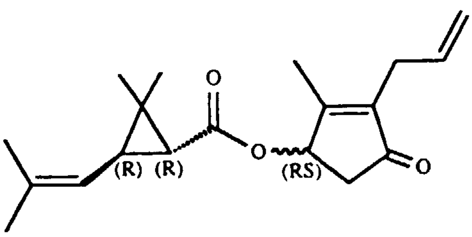
5-benzyl 3-furylmethyl d trans

chrysanthemate content

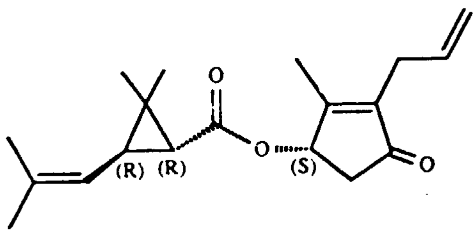
about 40%

* : unresolved asymetric centers

Fig. 8



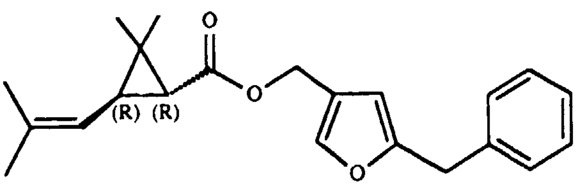
Bioallethrin



Esbioi

(S) allethronyl d trans chrysanthemate content

50% 100%



Bioresmethrin

5-benzyl 3-furylmethyl d trans chrysanthemate content

100%

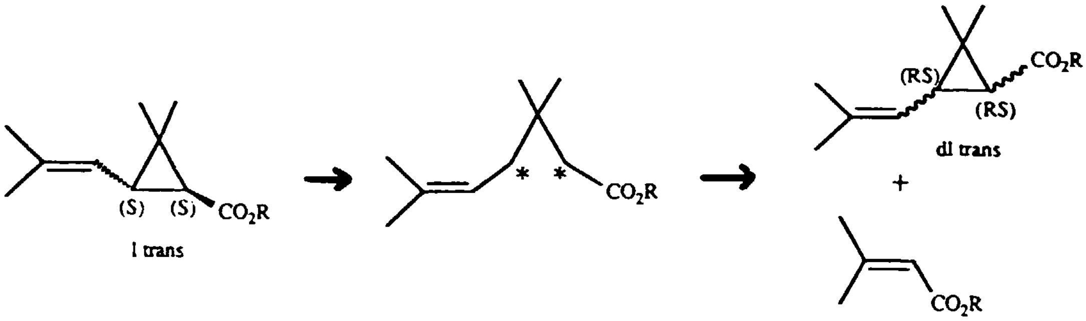
Fig. 9

synthesis of dl trans chrysanthemic acid offers many advantages for pyrethroid synthesis. The process is safe, starting materials are cheap and abundant, chemical yield and stereoselectivity are high, so that an easy resolution of the racemate leading to the natural trans isomer could be carried out. Industrial scale success of this delicate step is of prime importance for the application of isomeric selection to commercially existing pyrethroids (Figure 8), first for allethrin, then for resmethrin when it appeared and finally to NRDC 156, in which deltamethrin is entrained. At the esterification step, replacement of racemic dl cis trans acidic moieties by the single d trans isomer clearly more than doubles the content of the specially potent isomer (in each family) and thus should about double the insecticidal value of the resulting new ester.

For deltamethrin, which belongs to the d cis series, the isomeric selection results from other considerations but preparation of pure d trans chrysanthemic acid is another corner stone in the process we elaborated. The D (-) threo-derivative (Figure 7) from our chloramphenicol synthesis proved especially suitable for the resolution of our racemate. Following combination of the optically active base with the trans acid to be resolved, only one diastereoisomer crystallizes from solution while the other remains soluble. The solid material containing the natural chrysanthemic isomer can be filtered off and after acidification affords the pure d trans enantiomer with excellent yield and optical purity. After long standing or after several resolution runs, seeds causing crystallization of the second diastereoisomeric salt can appear, thereby preventing the enantiomeric separation. Fortunately, nothing similar happened in the present case since 1964, even under forcing conditions and after the manufacture of several hundred tons of the natural but synthetically produced isomer. Its esterification (Figure 9), first with racemic allethrolone then with the 4(S) alcoholic enantiomer, provided Bioallethrin, then Estiol, with complete isomeric selection. Bioresmethrin was produced similarly.

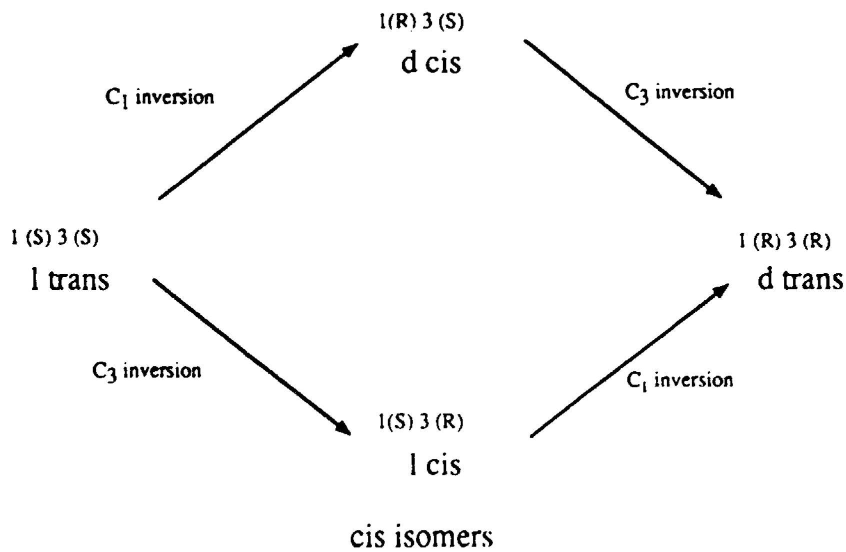
The above success in the trans series initiated application of isomeric selection to NRDC 156, the mixture of two diastereoisomers previously mentioned. The manufacture of natural chrysanthemic acid left an equal amount of resolved but unused l trans isomer. Inversion of both the cyclopropane asymetric centres from the wrong S to the desired R absolute configuration would convert this waste into the precious natural isomer. In similar cases one goes back to the racemate, which is then passed through the chemical reaction cycle again. Here, the chirality and trans optical isomerism are related to two asymetric cyclopropanic carbon atoms, implying that the return from one optical trans isomer to the racemate requires (Figure 10), a specific homolytic cleavage of the 1,3 cyclopropanic bond connecting the 2 involved atoms, a difficult reaction to perform efficiently due to complications attending radical formation. A better solution might be found in the successive inversion (or epimerization) of the two asymetric centres from S to R configuration (Figure 11). Theoretically, whichever chiral carbon atom we forecast to invert first (C-1 or C-3) requires passage through a cis derivative and this is not favoured thermodynamically. Some kind of ring stabilization of the cis structure as soon as it appears from the chemical reaction might overcome this problem. In the upper route (Figure 11) we obtained a lactonic stabilized cis structure in acidic medium (Figure 12), which also made available cis stabilized cyclic structures from trans isomers at the epimerization step and enabled us to study the insecticidal and already promising properties of the new unnatural d cis chrysanthemic acid derivatives.

To further the conversion of a l trans worthless enantiomer into the d trans one and to study the lower route of Figure 11, we faced the problem of the inversion at C-3. A Walden inversion by a preferential proton exchange at C-3 in a basic medium requires



(S)
(S)
CO₂R
l trans
CO₂R
(RS)
CO₂R
(RS)
dl trans
+
CO₂R

Fig. 10



1(R) 3 (S)
d cis
C1 inversion
C3 inversion
1 (S) 3 (S)
l trans
1 (R) 3 (R)
d trans
C3 inversion
C1 inversion
1(S) 3 (R)
l cis
cis isomers

Fig. 11

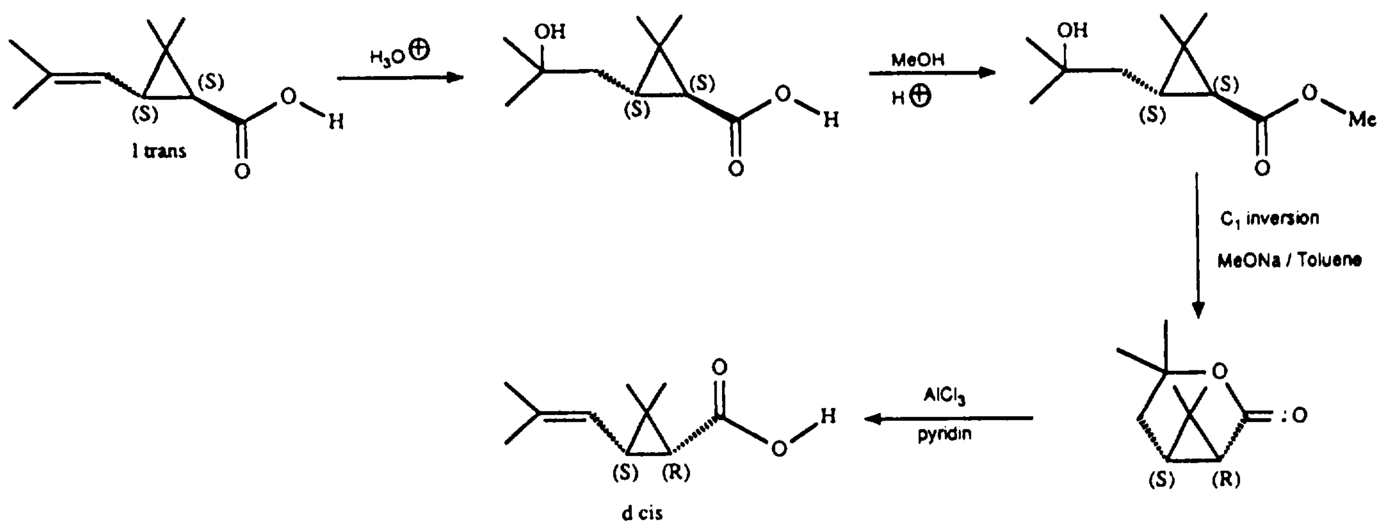

(S)
(S)
l trans
$H_3O^{\oplus}$
OH
MeOH
$H^{\oplus}$
Me
C_1 inversion
MeONa / Toluene
(R)
$AlCl_3$
pyridin
d cis

Fig. 12

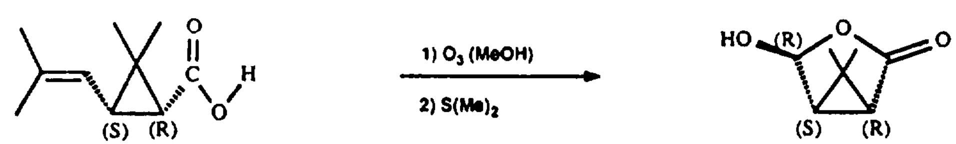
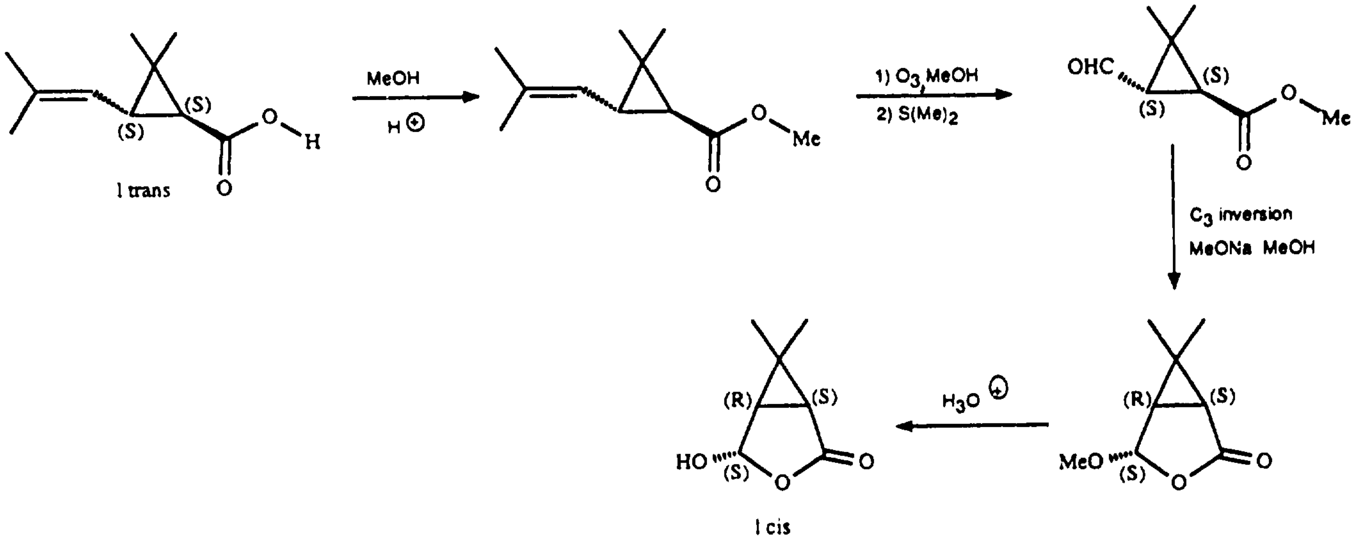

(S) (R)
1) O_3 (MeOH)
2) $S(Me)_2$
HO (R)

Fig. 13

Fig. 14


MeOH
H⊕
1) O3, MeOH
2) S(Me)2
OHC
(S)
O
Me
C3 inversion
MeONa MeOH
H3O ⊕
(R)
HO
MeO
l trans
l cis

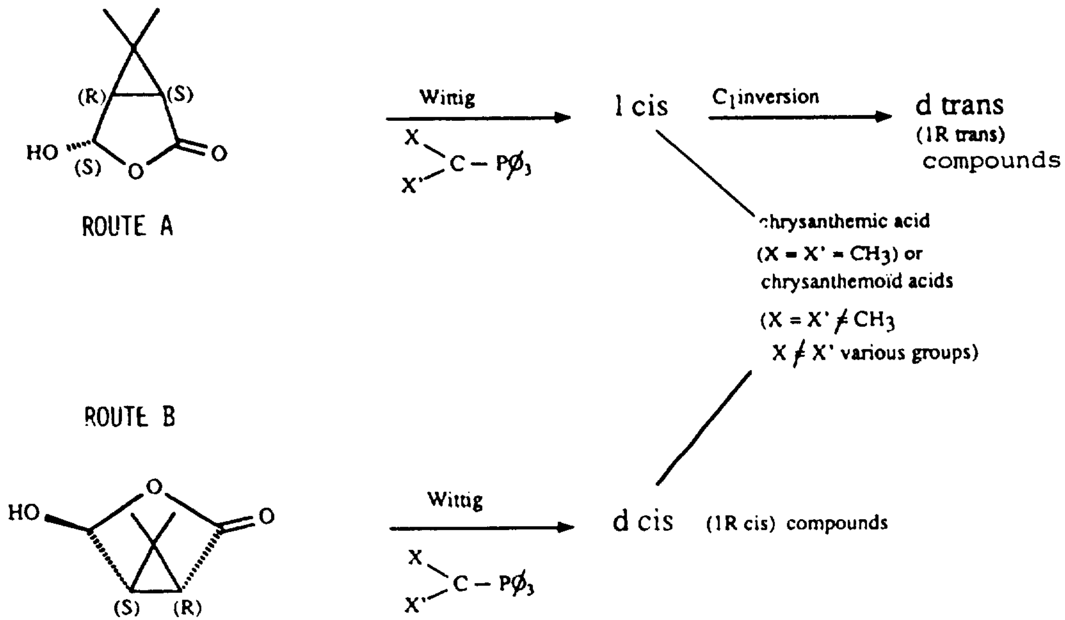

ROUTE A
ROUTE B
HO
(R)
(S)
O
Wittig
X
X'
C − PØ3
l cis
C1 inversion
d trans
(1R trans)
compounds
chrysanthemic acid
(X = X' = CH3) or
chrysanthemoïd acids
(X = X' ≠ CH3
X ≠ X' various groups)
d cis
(1R cis) compounds

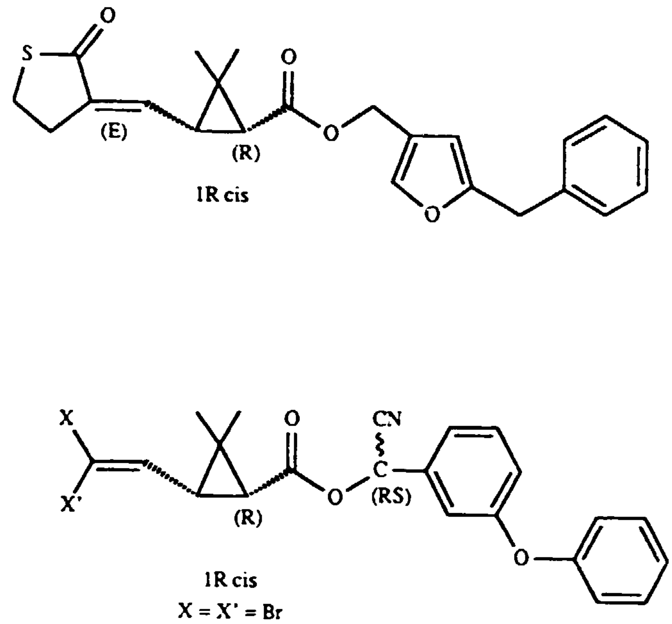
Fig. 15

activation in the alpha-position of the chosen site. This requirement at C-3 must be compatible with the presence of a carboxylic activating group at C-1. An aldehydic function resulting from an oxidative splitting of the double bond in the side chain could very probably fulfil these requirements. Ozonolysis of the now accessible d cis chrysanthemic isomer (Figure 13) followed by reduction in situ of the transient methoxyhydroperoxide gives effectively the crystalline hemicaronaldehyde of the d cis structure stabilized by its cyclic lactolic arrangement. Furthermore, only one single isomer corresponding to the exo-derivative with its hydroxyl group of (R) configuration was thereby produced. Under alkaline conditions the 1 trans hemicaronaldehyde from 1-trans chrysanthemic acid ozonolysis (Figure 14) easily underwent a C-3 epimerization through which the enantiomeric lactolic arrangement 1 cis (1S 3R) is expected, validating the lower route of Figure 11. Wittig reactions with phosphorous ylides (phosphoranes or phosphonates) carried out on the lactolic masked form of the aldehyde function (Figure 15) are possible with full retention of the absolute configurations of the asymetric centres included in the starting lactolic material. In route A, C-1 inversion gives access to the natural d trans chrysanthemic or chrysanthemoid acids, while route B is especially convenient for exploration and preparation of numerous novel and promising d cis insecticides.

In this way, we discovered (Figure 16) the very powerful knock-down properties of kadethrin while, at Rothamsted Experimental Station using our route B, Dr Elliott discovered the powerful killing properties and photostability of various halogenated derivatives in the dihalovinyl series, among them the two diastereoisomeric mixture coded NRDC 156. From the mixture obtained by esterifiction of the d cis acidic moiety, in which $X = X^1$ = bromine, with the racemic cyanohydrin alcohol, one diastereoisomer partly crystallized. This was NRDC 161 momentarily named by ourselves decamethrin, then deltamethrin for registration reasons. The insecticidal potency of the two diastereoisomeric mixture resides in the crystals in which the asymetric centre of the alcoholic moiety has the (S) absolute configuration. We were evidently in an undisputable position for industrial scale access to deltamethrin isomers but we had to solve two industrial problems, of which the first involved replacing the final Wittig reaction for the acid component by a cheaper method allowing also for the instability of the dibromomethylene ylide. Bromoform addition (Figure 17) onto the lactolic form of the d cis hemicaronaldehyde leads once again to the lactonic stabilized cis form of an α-tribromocarbinol, from which acetylbromide can be eliminated by acetic acid/iron treatment after acetylation. Figure 18 shows the complete scheme for the synthesis of the deltamethrin acidic moiety.

A convenient industrial access to deltamethrin requires combination of the optically pure d cis acidic component with the pure S-cyanohydrin alcoholic isomer, a benzylic cyanohydrin, weakly stable even in weak acid medium and readily hydrolysed to the corresponding amide and carboxylic acid. We reached several original solutions relevant to S-isomer access by chemical means but the question is not conveniently solved at an industrial level even with biological or enzymatic implementations. Practical and cheap results can be obtained for deltamethrin production based on its properties:

1. There is an especially mobile benzylic proton α to the cyano group.
2. The desired ester (i.e., deltamethrin) is crystalline.
3. There is a marked difference in the solubility between deltamethrin and its diastereoisomer arising from the R alcoholic moiety.



Kadethrin

NRDC 156

Fig. 16

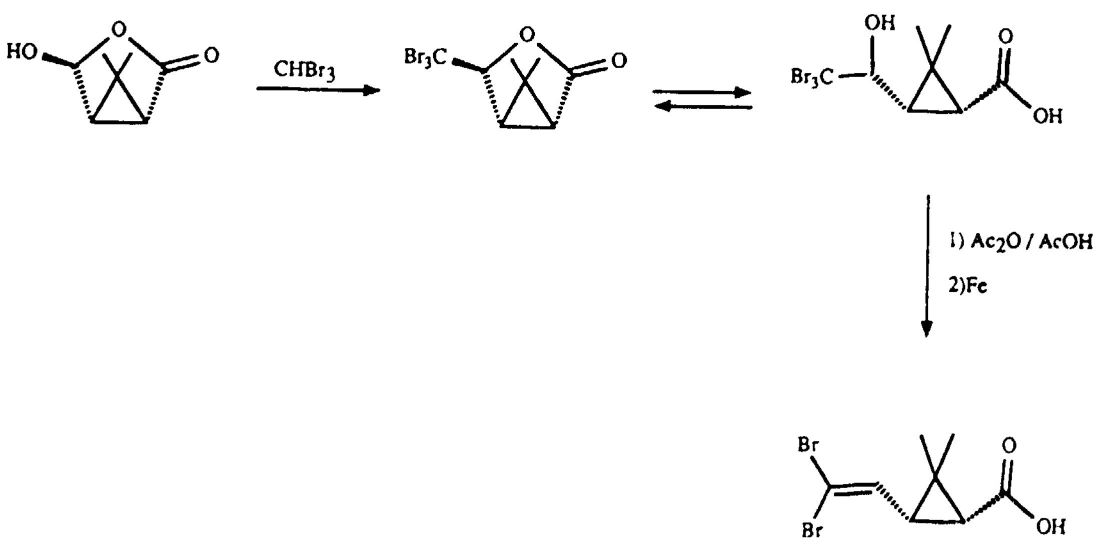


Fig. 17

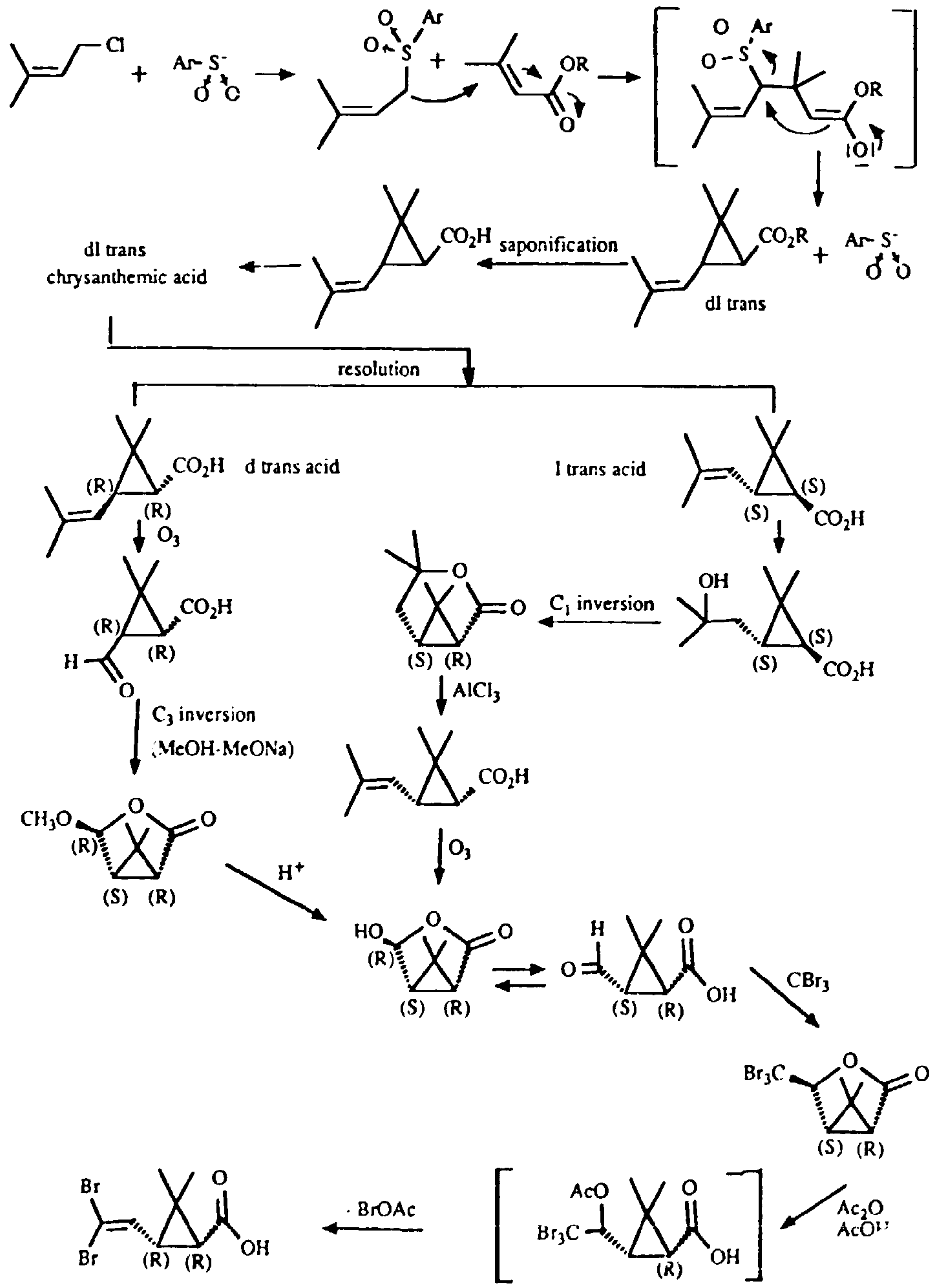

saponification
dl trans
dl trans
chrysanthemic acid
resolution
d trans acid
l trans acid
C$_1$ inversion
AlCl$_3$
C$_3$ inversion
(MeOH-MeONa)
H$^+$
CBr$_3$
Ac$_2$O
- BrOAc

Fig. 18

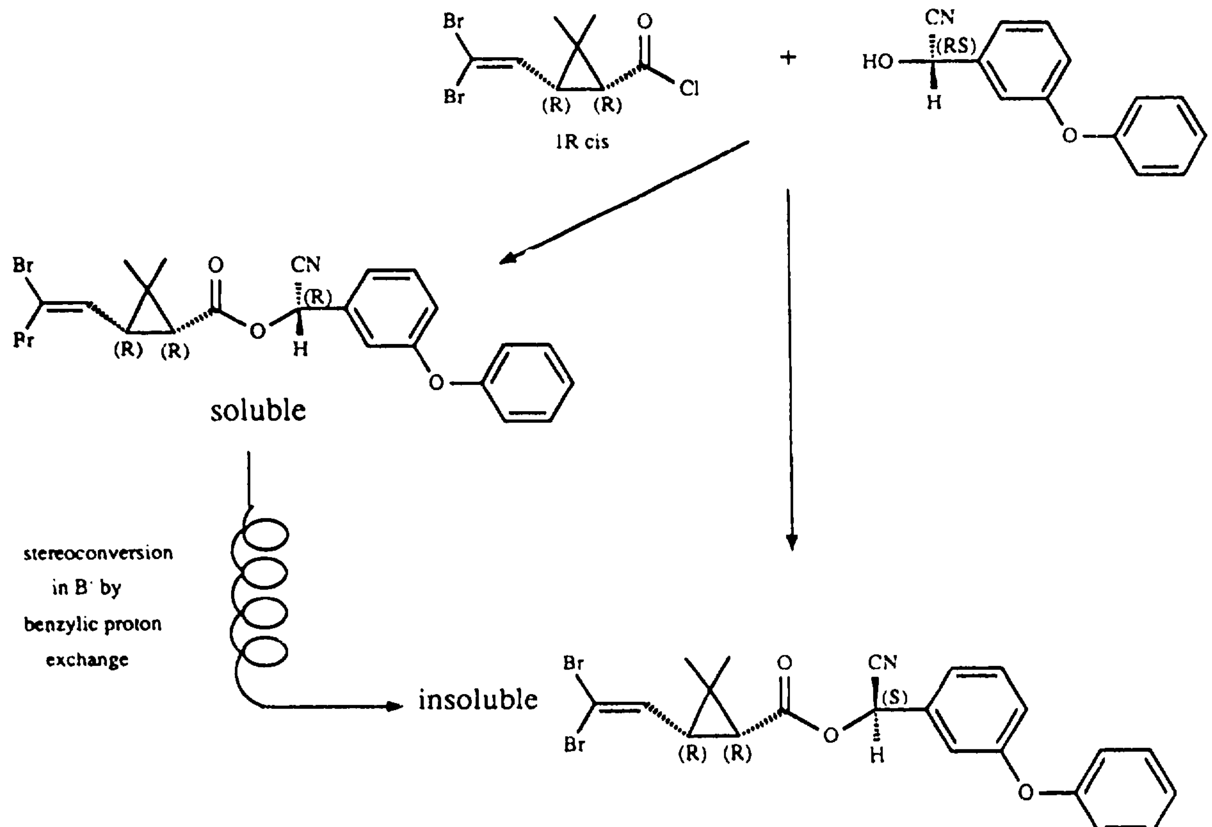
On the basis of these factors, we achieved the direct incorporation of the racemic alcoholic moiety and its complete transformation into the single (S) expected configuration (Figure 19). The racemic cyanohydrin combined with optically pure d cis dibromo acid gives a crude esterification product which, when totally dissolved, consists of about equimolecular proportions of two diastereomers, i.e., 1R cis ester of S-alcohol (deltamethrin) and 1R cis ester of R alcohol (worthless). From a mixture of these two esters in a carefully chosen base solvent pair (e.g., triethylamine in isopropanol), partial crystallization of deltamethrin occurs. The remaining soluble phase momentarily enriched in the wrong diastereoisomer, then promotes benzylic prototropy to restore continuously the original equimolecular equilibrium representative of the dissolved state. However, deltamethrin crystallizes out again, so there is a continuous stereoconversion of the wrong isomer into the required one (R into S); the very low solubility of deltamethrin in the chosen medium forces a 'second order resolution', or 'deracemization' to go to near completion. A critical consequence of the high insolubility of deltamethrin in the chosen experimental medium is that the very fragile ester from a benzylic cyanohydrin can be handled in an alkaline medium without the chemical degradations that this structure is prone to in solution.

Thus, the final industrial stereospecific synthesis of deltamethrin (Figure 20) produces only the required isomer among the 8 possible ones, despite the involvement of two racemates (dl trans acid and dl cyanohydrin alcohol). The stereospecific synthesis of dl chrysanthemic acid has been converted into a very efficient and wholly stereospecific access to d cis pure derivative. Finally, both racemic constituents are used in the synthesis without rejection of any material.

SYNTHESIS OF RADIOLABELLED DELTAMETHRIN

Synthesis of the Five ^{14}C-Derivatives (Figure 1)

Radionuclide in the side chain of the acidic moiety. Dr Elliott described in 1976 an indirect route for preparation of the dichloro analog. It consists of elaboration of the 1S trans isomer which was partially converted into the desired 1R cis system by thermal epimerization of the acid chloride. We adopted the direct approach (Figure 21) via addition of labeled bromoform to the 1R cis hemicaronaldehyde lactolic masked form. Deshydratation of the halohydrin provides the ring stabilized cis lactone which was reduced to the expected 1R cis dibromovinylic acid with zinc in acidic medium. ^{14}C-labelled bromoform is obtained from ^{14}C-α,α,α-tribromoacetophenone. For the latter, ^{14}C-methylmagnesium iodide (from ^{14}C-barium carbonate) is condensed with benzaldehyde, followed by α-bromination of the resulting ^{14}C-acetophenone. Here, the main difficulty lies in the instability of labeled bromoform, which undergoes radiolytic degradation. The last step of bromoform synthesis involved alkaline treatment of the labeled acetophenone diluted with cold acetophenone and even with a low specific activity of 5mCi/mmol, partial decomposition occurred. However, the C-2 labeled deltamethrin with a specific activity of 5 mCi/mmol was finally obtained in this way.



NRDC 161 DELTAMETHRIN

Fig. 19

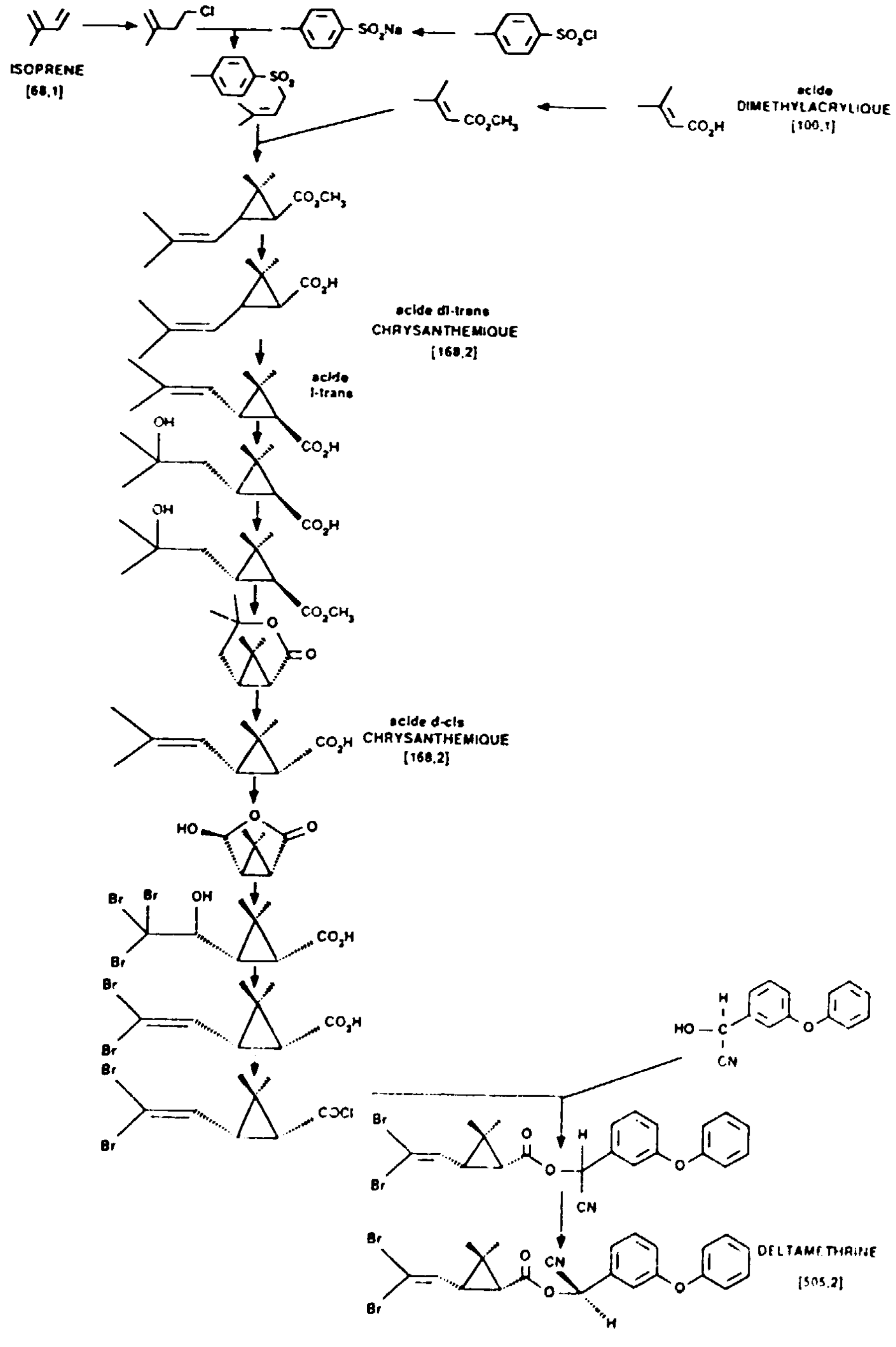

ISOPRENE
[68,1]
acide
DIMETHYLACRYLIQUE
[100,1]
acide dl-trans
CHRYSANTHEMIQUE
[168,2]
acide
l-trans
acide d-cis
CHRYSANTHEMIQUE
[168,2]
DELTAMETHRINE
[505,2]

Fig. 20

Fig. 21

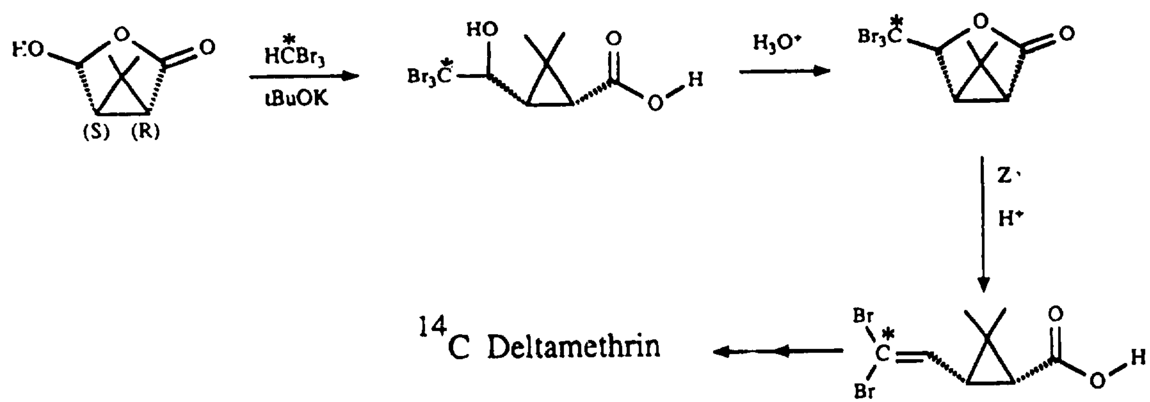
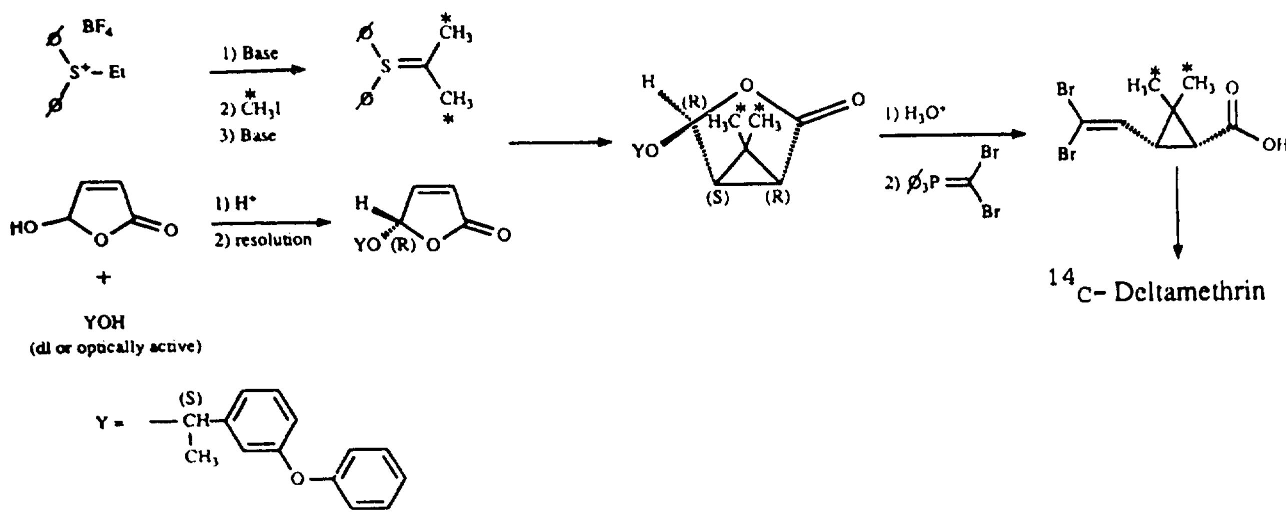

HO
(S) (R)
HC*Br3
tBuOK
Br3C*
H3O+
Z
H+
14C Deltamethrin

Fig. 22


BF4
S+– Et
1) Base
2) C*H3I
3) Base
HO
+
YOH
(dl or optically active)
1) H+
2) resolution
YO (R)
(S) (R)
1) H3O+
2) ∅3P
Br
14C- Deltamethrin
Y =
(S)
CH
CH3

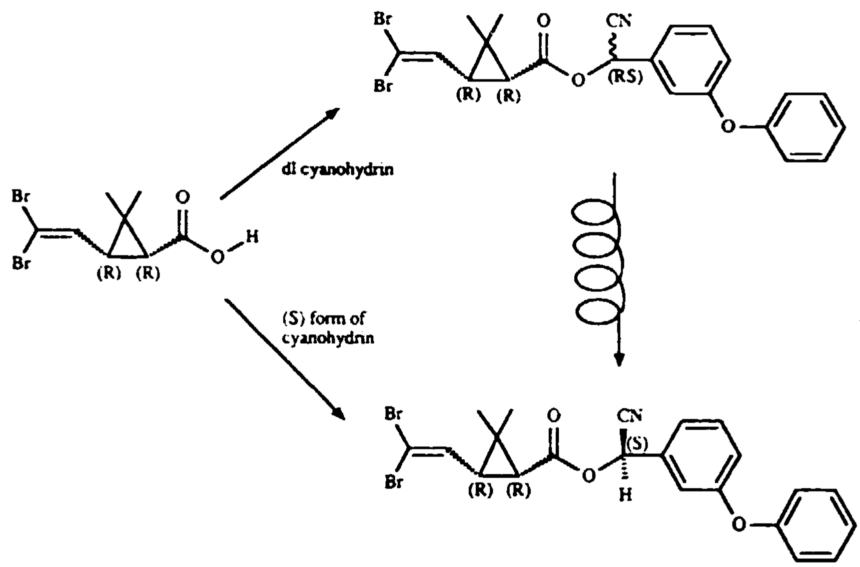


Fig. 23

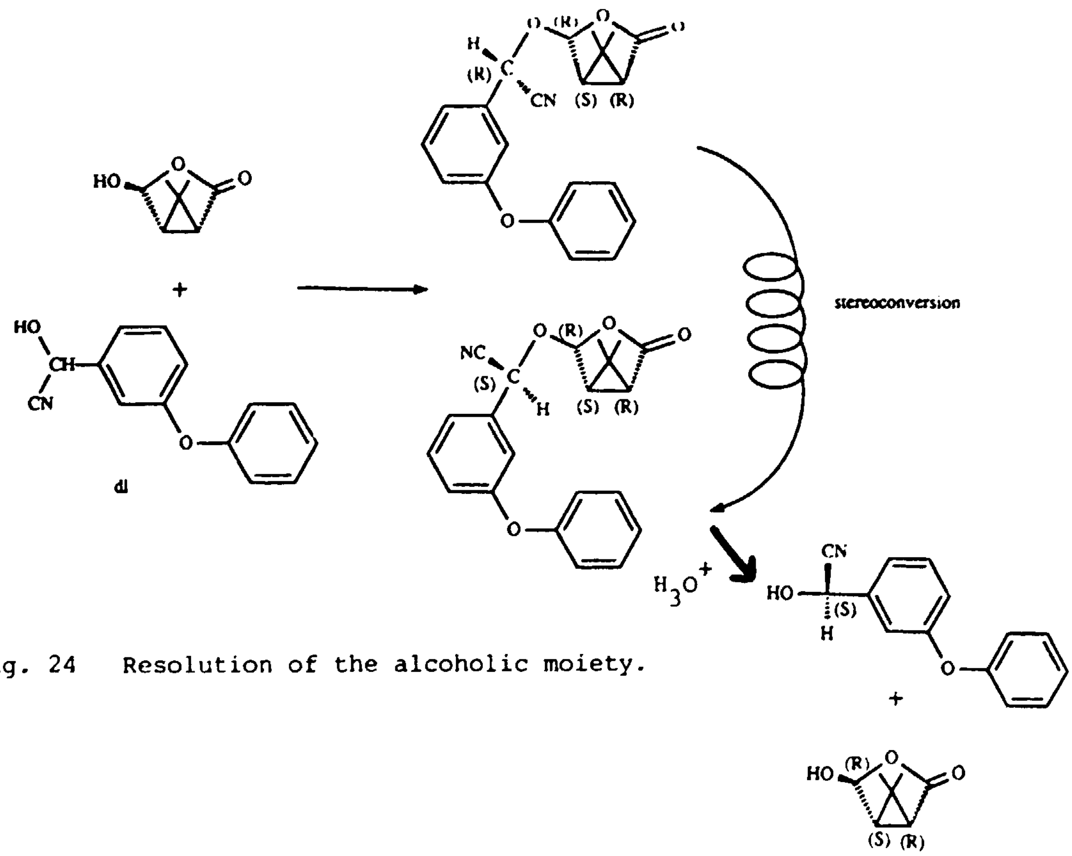


Fig. 24 Resolution of the alcoholic moiety.

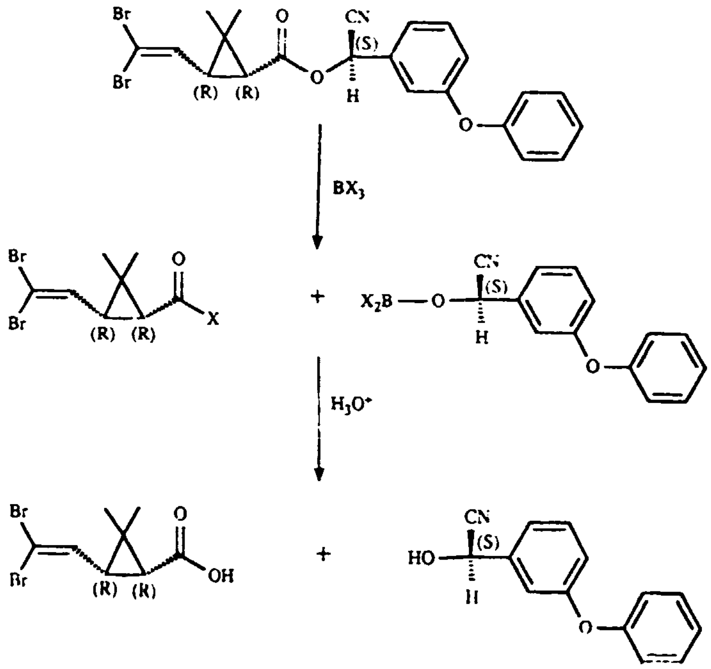

Br
Br
(R) (R)
O
CN
(S)
H
O
BX3
Br
Br
(R) (R)
O
X
+
X2B — O
CN
(S)
H
O
H3O+
Br
Br
(R) (R)
O
OH
+
HO
CN
(S)
H
O

Fig. 25

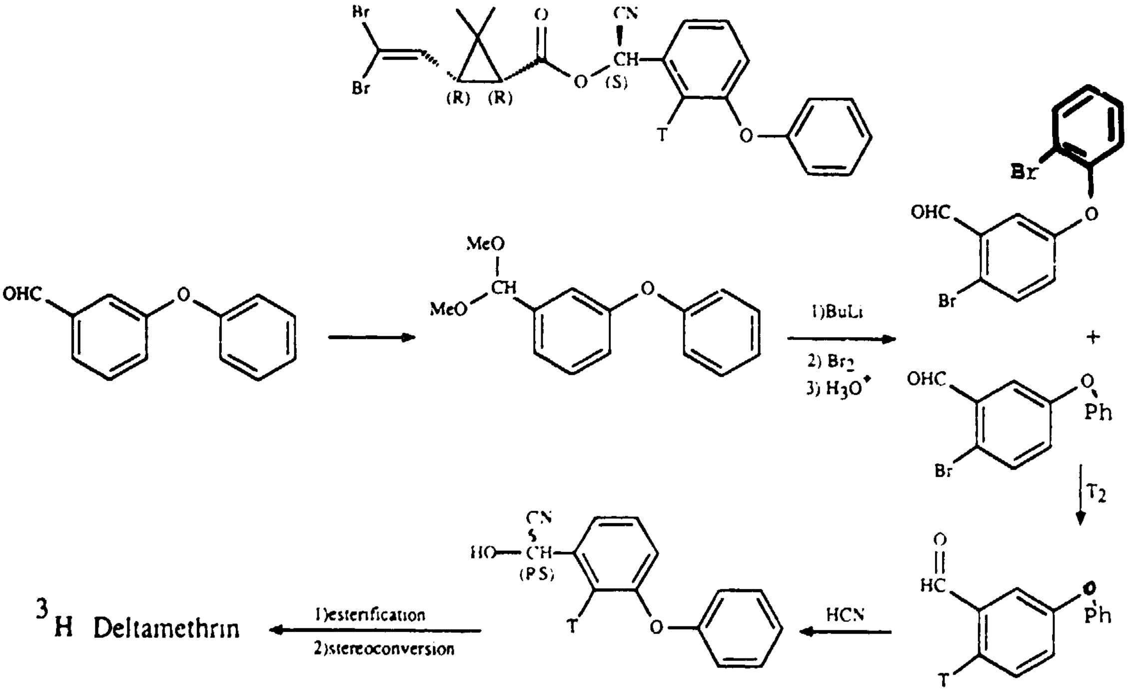

Br
Br
(R) (R)
O
CN
CH
(S)
T
O
Br
OHC
O
Br
OHC
O
MeO
CH
MeO
O
1)BuLi
2) Br2
3) H3O+
+
OHC
O
Ph
Br
T2
O
HC
O
Ph
T
HCN
CN
HO— CH
(RS)
T
O
1)esterification
2)stereoconversion
3H Deltamethrin

Fig. 26

Radionuclide in the gem dimethyl cyclopropanic group (Figure 22). This synthesis is based on a cyclopropanation method described by Corey in 1967. It involves addition of the diphenylsulfonium isopropylide to the conjugated double bond, here of a hydroxyfuranone derivative. To avoid the loss of the labeled 1S cis enantiomer at the necessary resolution step after cyclopropanation, we performed an asymetric synthesis starting from an optically active 5R diastereoisomer. A convenient derivative was finally obtained by chromatographic separation of the two isomeric mixture from reaction of the racemic 5-hydroxyfuranone with the S form of the phenoxyphenethyl alcohol. The radioactive reagent was prepared by alkylation of the diphenylsulfonium ethylide with ^{14}C-methyl iodide at -70°C in dimethoxyethane. The isopropyl sulfonium salt is immediately deprotonated in the same medium without separation and added to the furanone ether derivative. The fast and very stereospecific reaction provides only one bicyclo-compound with the exo-alkoxy group, the result of a trans addition. In the key cyclopropanation step, the configuration of the two chiral centres created is imposed by that of the furanone asymetric carbon atom. Thus, starting from the pure 5R ether, the single reaction product is the 1R cis caronaldehyde derivative.

The two methyl groups in Figure 22 are marked as labeled but in fact only one ^{14}C-methyl group is present per molecule and can be in either the endo or exo position. Hydrolysis of the ether group gave the acid aldehyde which was then subjected to a Wittig reaction to introduce the dibromo side chain. Pure deltamethrin can be obtained from the racemic cyanohydrin via our stereo-conversion process (Figure 23). For radiosynthesis it is sometimes easier or faster to use the pure S alcoholic form. We obtained this by two different chemical routes: (1) resolution of the racemic alcohol via ether derivatives of the 1R cis caronaldehyde (Figure 24) a new method based on the ability of lactolic forms of chiral acid aldehydes to produce ketals with the racemic forms of different alcohols. This affords directly the diastereoisomer pair that was sought previously through derivatizations, mainly via hemiester formation, then combination with a chiral base. The diastereoisomers may sometimes be separated by mere crystallization. Taking advantage of the acidity of the α-proton to the ketal linkage it is also possible to turn an oily unwanted stereoisomer into the crystalline desired one with reverse configuration at the alcoholic asymetric centre. Lastly, this method is especially convenient for fragile alchohols such as cyanohydrins because they are also handled free in soft acidic media: (2) deltamethrin itself can be split by a borontrihalide under mild conditions, the only known reaction which breaks the ester function without damaging the cyano group (Figure 25).

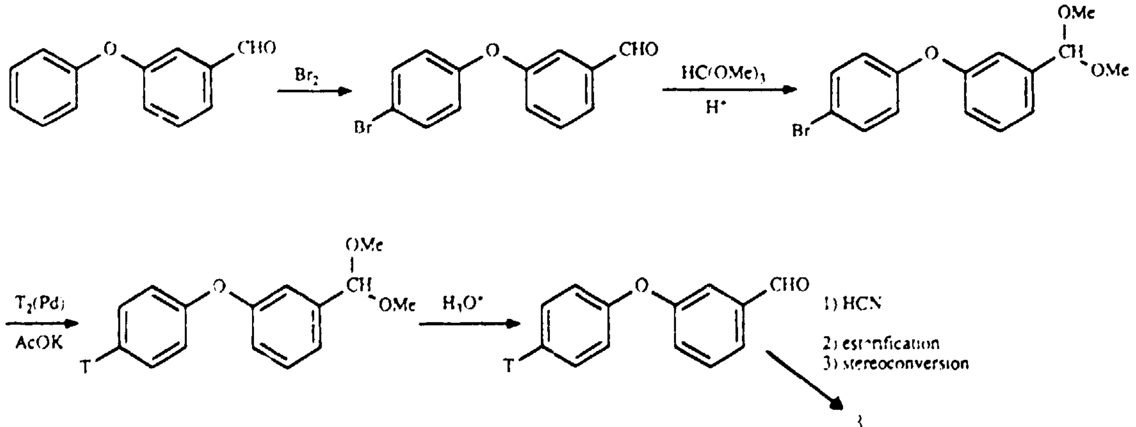


Fig. 27 4'-[^{3}H]Deltamethrin

Radionuclide in the alcohol moiety. (a) On the cyano group; the labeled cyano group is easily introduced by addition of ^{14}C-sodium cyanide to the 3-phenoxybenzaldehyde. (b) in the benzylic position; carbonation of the Grignard reagent from 3-phenoxy bromobenzene with $^{14}CO_2$ gave the ^{14}C-acid, then aldehyde and benzylic labeled cyano-alchohol (RS) for conversion into deltamethrin, as in the method described by Elliott for the radiosynthesis of permethrin.

Radionuclide in the terminal aromatic ring. Randomly labeled ^{14}C-phenol is condensed with 3-bromobenzaldehye for conversion into terminal ring-labeled cyano-alcohol and hence terminal ring labeled deltamethrin.

Synthesis of Tritium labeled Derivatives
The two tritiated derivatives (Figure 1) are obtained by hydrogenolysis with tritium gas of the appropriate bromo-precursors (Figure 26). The anion from butyllithium action on 3-phenoxybenzaldehyde dimethylacetal reacts with bromine at low temperature to give, depending on the experimental conditions, bromo-derivatives from which the pure 2-bromo-aldehyde is separated by column chromatography, then reacted with tritium gas and palladium catalyst to give the pure 2-tritiated aldehyde. Alternatively, 3-phenoxybenzaldehyde is brominated (Figure 27) followed by tritium exchange on the corresponding dimethylacetal to give a mixture of tritiated molecules from which 4^{1}-[^{3}H]-3-phenoxybenzaldehyde is readily obtained, for conversion into deltamethrin as described.

ACKNOWLEDGEMENTS

The chemical work summarised represents only part of that accomplished in promoting the success of deltamethrin. Success resulted from the cumulative efforts of numerous very skilled people in all areas of the Company's activities. I cannot name them individually as the list would be endless but I am glad to acknowledge their contribution and to thank all of them warmly.

DEVELOPMENT OF AZOLE FUNGICIDES

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ABSTRACT

In respect to the number of commercially available compounds, and their importance in the market, the azole fungicides are the most important group of specific fungicides. This article reviews the special properties which are the basis of this success. The discussion includes the modes of action, resistance and the systemic movement of these compounds in plants.

INTRODUCTION

Specific fungicides have been available to agriculture for about 25 years. Up to the late sixties, only the so-called 'conventional' or 'multisite' inhibitors, such as the dithiocarbamates and the phthalimides, were at the disposal of the farmer.

Among the specific fungicides, the azole group seems to be outstanding in view of their importance to the market, and the number of compounds which have been introduced into the market since the early seventies. Azole fungicides consist of the two subgroups, the triazole compounds and the imidazole compounds. Although only 5 imidazole compounds are currently available, more than 20 compounds of the triazole subgroup were available in 1989 (Table 1). The following short article attempts to describe some of the reasons for this obvious success. More detailed information is available from other recently published review articles [1] [2], [3].

TABLE 1

Azole fungicides

common name	code no.	company	year
IMIDAZOLES			
imazalil	R 23979	Janssen	1972
prochloraz	BTS 40542	Boots / Schering	1977
fenapanil	RH 2161	Rhom & Haas	1978
triflumizole	NF 114	Nippon Soda	1983
	UHF 8615	Ube / Hokko	1988
TRIAZOLES			
fluotrimazole	BUE 0620	Bayer	1973
triadimefon	MEB 6447	Bayer	1973
triadimenol	KWG 0519	Bayer	1977
bitertanol	KWG 0599	Bayer	1978
propiconazole	CGA 64250	Ciba-Geigy	1979
etaconazole	CGA 64251	Ciba-Geigy	1979
diclobutrazole	PP 296	ICI	1979
	BAS 45406F	BASF	1983
penconazole	CGA 71818	Ciba-Geigy	1983
	PP 969	ICI	1983
flutriafol	PP 450	ICI	1983
diniconazole	S 3308	Sumitomo	1983
flusilazole	DPX H6573	Dupont	1984
tebuconazole	HWG 1608	Bayer	1986
hexaconazole	PP 523	ICI	1986
cyproconazole	SAN 619F	Sandoz	1986
myclobutanil	RH-3866	Rohm & Haas	1987
difenconazole	CGA 169374	Ciba-Geigy	1988
imibenconazole	HF-6305	Hokko	1988
tetraconazole	M 14360	Montedison	1988
furconazole	LS 840606	Rhone-Poulenc	1988
fenethanil	RH-7592	Rhom & Haas	1988
	SSF 109	Shionogi	1988
bromuconazole	LS860263	Rhone-Poulenc	1990*
	BAS 480F	BASF	1990*

* added in proof

CHEMISTRY AND STEREOCHEMISTRY OF AZOLE FUNGICIDES

Within the azole fungicides, a very diverse range of chemical structures exists. These are usually arranged according to their functional groups. I. Azoles with keto groups are represented by the first systemic triazole fungicide, triadimefon. This compound set new standards for disease control. II. By reduction of triadimefon, triadimenol is prepared. This compound introduces another important subgroup of the triazoles, the azoles with hydroxy groups. Other members of this large group are bitertanol, tebuconazole, diniconazole, cyproconazole and hexaconazole. III. Triazoles with ketal groups are represented by propiconazole and etaconazole, the first of which has been shown to be a highly active broad spectrum compound. IV. Examples for azoles without other functional groups are penconazole and fluotrimazole. The latter was the very first triazole fungicide and is chemically related to clotrimazole (an imidazole derivative, patented in 1967 by Prof. Büchel from Bayer). Today, clotrimazole is one of the most successful antimycotic compounds in medical use.

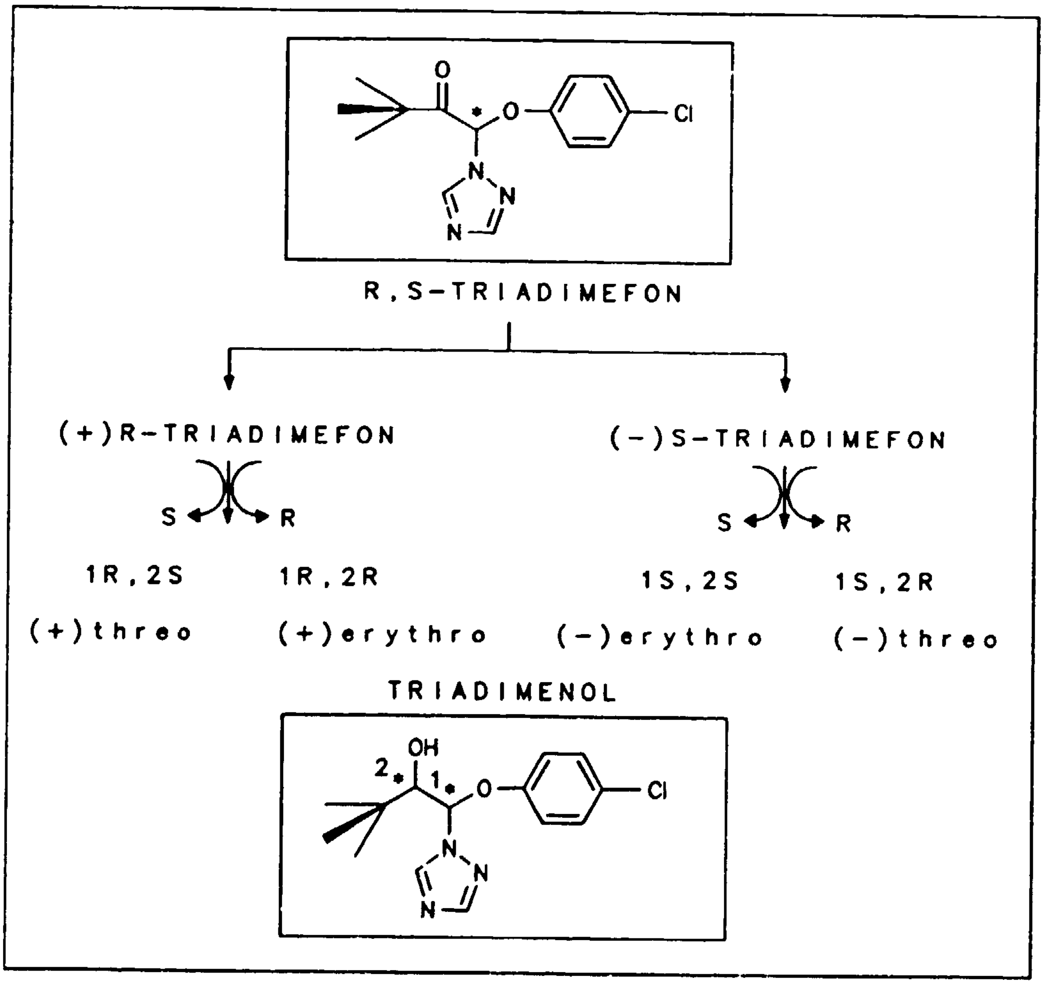

Figure 1. Reduction of triadimefon enantiomers to triadimenol enantiomers. Chiral centers are marked with an asterix.

Many of the azole compounds have at least one chiral carbon atom. The question concerning the influence of stereochemistry upon biological activity is therefore of particular interest. Well documented examples for significant differences in activity of stereoisomers are the triazole compounds etaconazole, propiconazole, diclobutrazol, bitertanol and triadimenol. As an example, the synthesis of triadimenol will be examined in more detail (Figure 1). Triadimefon, the parent compound, has one chiral carbon atom resulting in two optical enantiomers (R and S) which hardly differ in biological activity. The reduction of the keto group, which leads to triadimenol, results in the introduction of a second chiral carbon atom and therefore leads to the formation of two diastereomeric pairs each of which is composed of two enantiomeric forms. The resulting four enantiomers of triadimenol have different fungicidal activities. It can be clearly demonstrated, that the 1S,2R enantiomer (often designated as threo(-)) generally has the best fungicidal activity. The effect of the other enantiomers differs considerably. The 1R, 2R-form has the next strongest biological activity, while the other two enantiomers are less active. It must be mentioned, that with different fungi, different relative fungicidal activities of the enantiomers are found.

BIOCHEMICAL MODE OF ACTION

Together with some pyridine, pyrimidine and piperazine derivatives, the azole fungicides, e.g. imidazoles and triazoles, have been shown to belong to the so-called sterol-biosynthesis-inhihibitors (mostly abbreviated as "SBI"). Like phospholipids, sterols are functional components in cell membranes of animals, plants and fungi. Starting from acetate units, sterols are synthesized in cells by the terpenoid pathway to yield finally the last common metabolite of animals and fungi, lanosterol. Whereas animals use cholesterol as their final membrane sterol and plants stigma-, sito-, and campesterol, most fungi need ergosterol (or nearly related sterols). The biochemical pathway from lanosterol to ergosterol is, therefore, a target for specific inhibitors for fungi, which do not affect animals and plants. In Figure 2, the general sites of inhibition of most SBI--fungicides are given. The inhibition of demethylation in the C-14 position of 24-methylenedihydrolanosterol is the common site of action of the so-called "DMI"-fungicides (demethylation inhibitors) which include all SBIs with the exception of the morpholines. As shown in Figure 1, the morpholine fungicide, fenpropimorph, mainly blocks the reduction of the Δ^{14} double bond of 4,4-dimethyl $\Delta^{8,14,24(28)}$-ergostatrienol whereas another morpholine, tridemorph, predominately inhibits the Δ^{8} -> Δ^{7}-isomerisation of $\Delta^{5,8}$-4-ergostadienol.

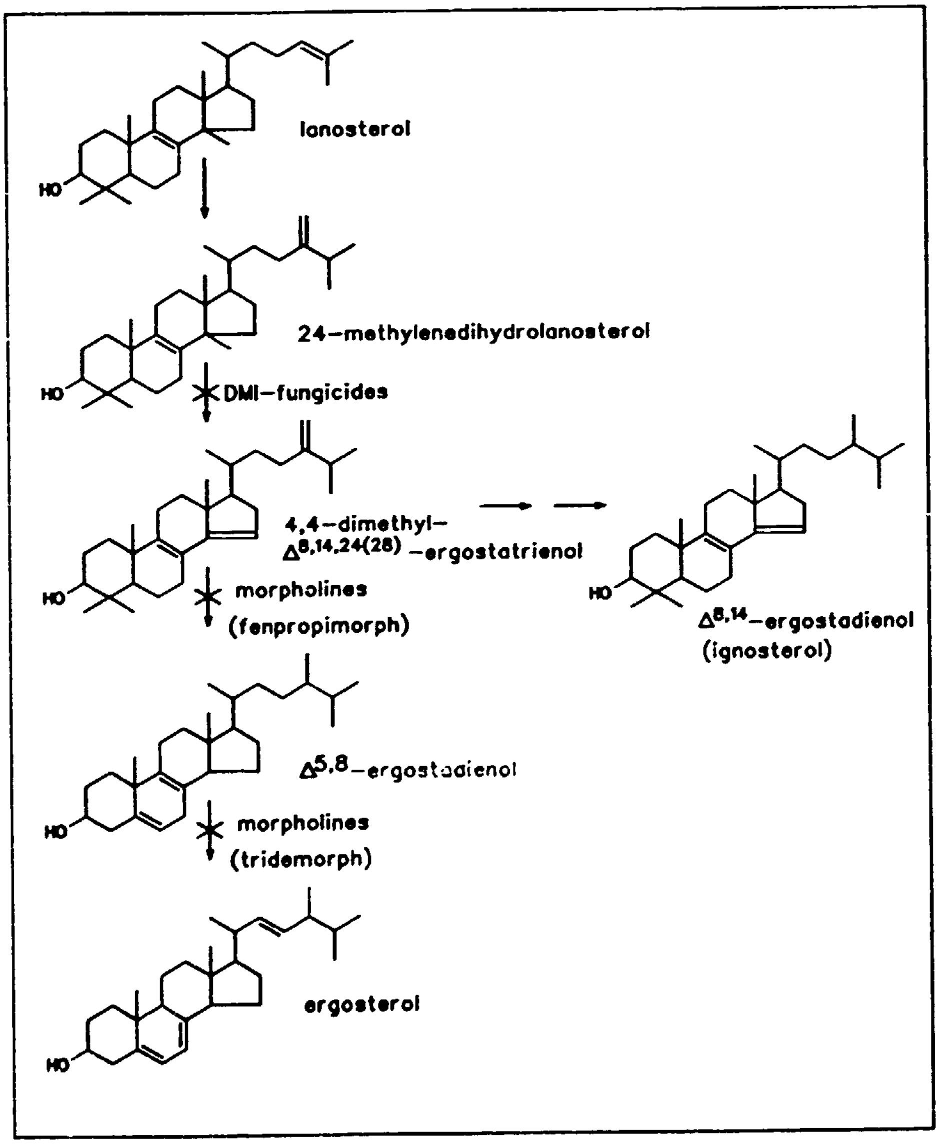

Figure 2. Sites of action of DMI-fungicides and morpholines in the fungal biosynthesis of sterols.

Analytically, the target site of a given SBI-fungicide is mostly proved by the concurrent accumulation of precursors due to a block within the metabolic pathway. For example, the inhibition of demethylation at the C-14 position leads to a marked increase in the concentration of 24-methylendihydrolanosterol. It is currently not known whether the lack of ergosterol, which is the final product, or the accumulation of harmful precursors is the toxic principle which finally prevents the further growth of an azole-treated fungus.

RESISTANCE RISKS

Due to the broad use of azole fungicides in agriculture, the question of the specific risk for resistance development of azole fungicides has been thoroughly studied during the last decade. In view of the paper of Dr. K. Brent (see this volume), which deals specifically with resistance problems of fungicides, only some general remarks shall be made here.

In spite of intensive studies, the mechanism of resistance of fungi to azole fungicides is still unclear. Some researchers, like de Waard (cited in [2]), found a reduced uptake of azole fungicides into the fungal mycelium. Others stated a slightly reduced sensitivity of the target enzyme. Today, most scientists believe in a combination of several independent changes in fungal metabolism, each alone having only minor effects. These biochemical results are supported by genetic studies of Hollomon and others (cited in [2]), who showed that resistance of fungi against DMI-fungicides has a multigenic basis.

This interpretation correlates well with epidemiological studies on the selection type of different classes of fungicides. In cases where the mutation of a single gene is sufficient to generate a high degree of resistance, the so-called "disruptive type" of resistance selection is found. Field studies on the degree of sensitivity of a great number of individual fungal isolates revealed that, typically, two unconnected populations can be found whose sensitivities towards a given fungicide differ greatly.

Azole fungicides, on the contrary, are normally characterized by a "directional type" of selection. Initially, only one homogenous population can be detected. The possible result of repeated fungicide applications may be, in this case, that a gradual "shifting" of sensitivity occurs due to the fact that the more sensitive part of the fungal population is reduced to a greater extent than the less sensitive one.

Due to the multigenic basis of azole resistance in fungi, serious resistance problems have seldom been seen in the field. In spite of a very broad, worldwide use against a wide range of different fungal species, only in few cases have serious problems been seen. The most important examples of resistance under practical conditions are the powdery mildew fungi, and especially those of cereals ard cucurbits.

Meanwhile, effective strategies are available to prevent a further build-up of resistance. According to the recommendations of the Fungicide Resistance Action Committee (FRAC), alternation with non-crossresistant fungicide groups, or the use of mixtures is generally recommended.

FUNGICIDAL SPECTRUM OF ACTIVITY

In spite of their chemical heterogeneity, the fungicidal spectra of azole fungicides have some similarities. *In vitro* studies have shown that, in general, most Ascomycetes, Basidiomycetes and Fungi Imperfecti are sensitive. The only important class of phytopathogenic fungi which is generally not sensitive is the Oomycetes. Table 2 shows an *in vitro* analysis of the ED50 values of the new triazole fungicide tebuconazole. In addition to the fungi listed in the table, the powdery mildew fungi, which are obligate parasites, are affected to some extent by nearly all azoles.

Under field conditions, some of the azole fungicides such as triadimenol, propiconazole, prochloraz and especially the new compounds flusilazole and tebuconazole can be used as broad spectrum fungicides to control a multitude of fungal diseases.

From the diseases which are actually controlled by the application of azoles, only the most important ones can be mentioned here.

TABLE 2

In vitro spectrum of the fungicidal activity of tebuconazole

fungus	ED50 [ppm]	fungus	ED50 [ppm]
OOMYCETES		BASIDIOMYCETES	
Phytophthora megasperma	114.00	*Rhizoctonia solani*	0.64
		Puccinia graminis	<0.01
ASCOMYCETES			
Pyrenophora graminea	0.06	DEUTEROMYCETES	
Pyrenophora teres	0.09	*Alternaria solani*	0.62
Helminthosporium tritici-repentis	0.08	*Cladosporium cucumerinum*	0.05
		Fusarium culmorum	0.13
Septoria nodorum	0.11	*Pseudocercosporella herpotrichoides*	0.29
Fusarium nivale	0.81		
Botrytis cinerea	0.15		

In cereals, rust and powdery mildew fungi as well as leaf spot pathogens such as *Pyrenophora* and *Septoria* species are controlled by many modern azoles. In contrast to this, eyespot (*Pseudocercosporella*) can be controlled only by very few compounds (prochloraz, flusilazole).

In grapes and fruits, powdery mildews (*Uncinula sp.*; *Sphaerotheca sp.*), apple scab (*Venturia inaequalis*) and *Monilinia* species are important targets of several azoles, some of which (e.g. penconazole) have been developed especially for this market segment.

In tropical and subtropical crops, important targets are black and yellow sigatoka, caused by *Mycosphaerella sp.*, in bananas. Furthermore, rust and *Mycosphaerella* diseases of peanuts and coffee rust can also be controlled.

In the field of cereal seed treatment, azoles have been able to replace mercury-based seed dressings in many countries. DMI-fungicides provide control of a broad complex of seed- and soilborne diseases such as smuts, bunts and *Pyrenophora* species. In addition, some systemic compounds have an effect against early plant infections by powdery mildew and rust via seed treatment.

Examples of further important applications against numerous fungi are those in ornamentals, vegetables and sugarbeet.

SYSTEMIC PROPERTIES

The introduction of systemic fungicides at the beginning of the seventies has considerably facilitated and improved the control of plant diseases since it enabled the use of curative and eradicative treatments.
The fact that all azoles are at least partially able to penetrate the plant cuticle is a major reason for the success of these fungicides. Therefore, at least translaminar or locosystemic action, which is a prerequisite for curative treatments, can be expected.

In view of the chemical heterogeneity of azole compounds, a great degree of variability in the capacity to be further distributed in the plant after having penetrated the plant surface is not surprising. Terms such as "highly mobile" or "medium systemic" are, therefore, used to differentiate further the degree of systemic translocation of azoles within the plant.

From the available literature [1] [2], it can be seen that the azoles can roughly be grouped in 3 categories. The first one includes the so-called "locosystemic" (or translaminar) compounds (such as prochloraz, bitertanol, triflumizole and diniconazole), which penetrate the cuticle but hardly move over greater distances in the plant. Examples for azoles with medium mobility are propiconazole, tebuconazole and flusilazole. Triadimefon, triadimenol, cyproconazole and myclobutanil are representative of the third category, which include highly mobile azoles that are relatively quickly translocated over greater distances in herbaceous plants.

All azole compounds are translocated predominantly in the apoplast, the non-living parts of the plant. Their mobility in the symplast (the living part of the plant such as the phloem) is thus far minimal. As a consequence the translocation of azoles within the plant is confined to the acropetal direction. Systemic protection is, therefore, limited to such cases where sufficient quantities of active ingredient have been applied to the basal parts of a leaf, shoot or seedling.

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THE EFFECT OF MOLECULAR STRUCTURE ON THE TRANSLOCATION OF PESTICIDES

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ABSTRACT

The distribution of a chemical applied to a plant depends on the molecular structure of the chemical and the nature of the plant. There are two long distance translocating mechanisms in the plant, the apoplast and the symplast, which are separated by a single membrane. If the chemical remains mainly in the external wall and xylem water of the apoplast it will only be able to move with the transpiration water from the direction of the roots to the leaf margins, but if it is able to cross the membrane and accumulate in the symplast, then it may translocate to the meristems and storage tissues.

Solutes may be retained in the symplast by at least four mechanisms, adsorption or partition within the cell, response to the cell electrical potential, differential permeability of weak acids, and active transport. Adsorption and partition are most likely to reduce translocation, and the cell potential is most important for ionic compounds, especially cations. Most xenobiotics are probably retained by the symplast because they are weak acids, but there is increasing evidence that some herbicides and plant growth regulators are held in the symplast by active processes.

To understand the factors controlling translocation requires an understanding of the structure of the plant and, in particular, the chemical interactions between the xenobiotic and the different components of the apoplast, symplast and membranes.

INTRODUCTION

Biocidal activity is the product of inherent activity and concentration at the site of action, NOT the concentration in the spray tank or on the surface of the organism. If the site of action is in the tissues beneath the spray deposit then **contact** action, where the biocide simply crosses the outer tissues to reach the site of action, may be sufficient, but most types of pesticidal activity are improved if the compound can move in the plant to reach parts that did not receive any spray deposits. Compounds that can move in this way are described as **systemic**.

There are two kinds of systemic compound, xylem systemic and phloem systemic, which differ fundamentally in the way they move. Xylem systemic compounds move with the transpiration water from the roots to the leaves. Such compounds, when applied to the leaf, move towards the leaf margins or tip, but do not move out of the leaf to which they are applied. They do not need to accumulate behind membranes in order to move in the plant, but they do need to cross membranes to reach the site of action. Phloem systemic compounds must accumulate behind the membranes of the phloem cells in order to translocate with the products of photosynthesis from the leaves to the developing tissues, meristems and the storage organs. When translocating from the leaves to the roots they will be moving in the opposite direction to xylem systemic compounds, but when translocating from the leaves to the apical meristem of a dicotyledonous plant, they will be moving in the same direction as xylem systemic compounds.

The properties that confer xylem or phloem mobility on a compound are not exclusive, any phloem mobile compound should also be xylem mobile, and many compounds that are not usually regarded as phloem mobile may show traces of such mobility under some circumstances. There are also important differences between species caused not by significant differences in the molecular requirements for translocation, but by quantitative differences in the composition of the tissues. For example, the types of compounds that can translocate in the phloem may be universal but there will still be major differences in the mobility of the same compound in different plant species, because some plants will have thicker cell walls or a higher tannin content, etc which may prevent the compound penetrating as far as the phloem tissues. This makes it very difficult to compare data from different species or environmental conditions.

A MODEL OF PLANT STRUCTURE

Figure 1 shows a simplified model of a plant that illustrates the possible destinations of a pesticide molecule moving from the leaf surface into the inner tissues. The first barrier to translocation is the cuticle, which must be crossed before the compound can enter the aqueous phase of the wall. There is no significant barrier to solute movement between the aqueous phase of the cell walls and the aqueous phase of the xylem, because the xylem tissues are dead at maturity, lacking membranes, and with connections to the wall free space via large pores and permeable wall sections. The aqueous continuum of the cell walls and xylem is termed the apoplast. The apoplast is adapted to the transport of water and solutes from the roots to the leaves and shoots, but it does not always permit the efficient transport of xenobiotics because wall components, especially the pectins, lignins and tannins, contain carboxyl and hydroxyl groups that can bind organic cations. There are big differences in the levels of the polyphenolic lignins and tannins between species.

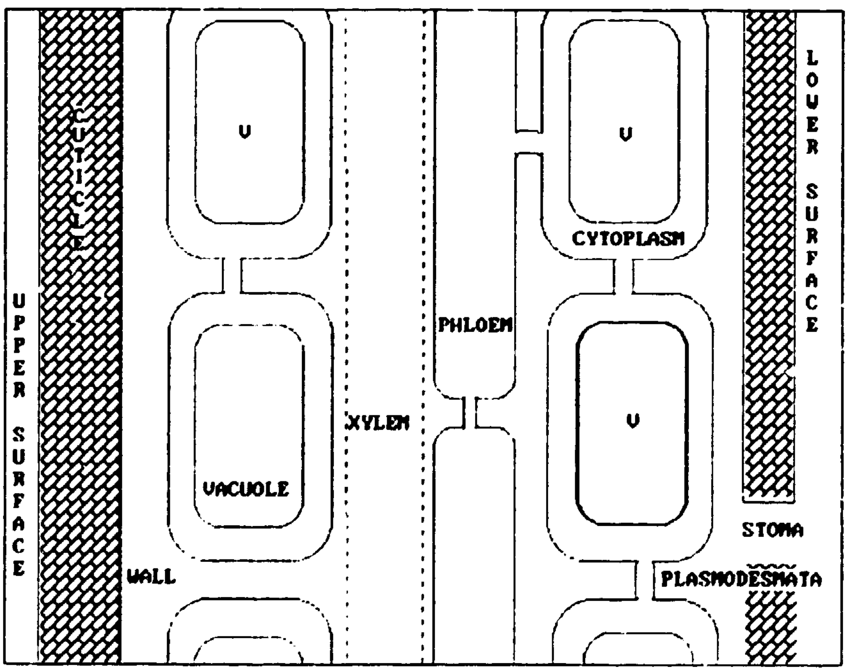

Figure 1 Plant structure model

Adjacent to the cell wall is the plasmalemma, the membrane which surrounds the cytoplasm. Any biocide must be capable of crossing or damaging the plasmalemma in order to damage the cell. The plasmalemmas of adjacent cells are joined by tubular connections, the plasmodesmata, giving cytoplasmic continuity between cells, including the phloem cells. This cytoplasmic continuum is the symplast. Membrane bounded organelles within the cell, such as the mitochondria, chloroplast and vacuole, are not strictly a part of the symplast because penetration into them requires transport across an additional membrane. Also, these organelles are not interconnected so they are not relevant to translocation, except where they reduce mobility. Accumulation in mitochondria and chloroplasts is important for the biocidal activity of some herbicides, but accumulation in the vacuole may be particularly important in reducing the translocation of many compounds, both in the symplast and the apoplast.

There is evidence that the apoplast may play a role in the transfer of sugars from the photosynthetic cells to the translocating cells of the phloem [1]. It is, therefore, realistic to assume that xenobiotics can also move from the apoplast directly into the translocating tissues. There is no evidence that herbicides or pesticides accumulated in the symplast of the epidermal or mesophyll cells will necessarily be transported in the symplast of the phloem tissues.

PENETRATION INTO THE PLANT TISSUES

Transport across the cuticle is by diffusion [Equation 1].

$$J = (Co - Ci)\ \frac{kB\ T\ K}{dx\ 6\pi r\ l\ n} \qquad [1]$$

J	Rate of diffusion
kB	Boltxman constant
l	Tortuosity factor
T	Absolute temperature
K	Partition coefficient
dx	Thickness of the cuticle
r	Radius of the diffusing molecule
n	Viscosity of the diffusing medium
C	Concentration outside/inside the cell

The most important molecular parameters are size, solubility in water, and partition coefficient [2]. There are reports that uptake improves with increasing partition coefficient [3] or that uptake is optimum when the partition coefficient is between zero and 2.5 [4]. The impact of partition coefficient on uptake is greatly reduced by adding a surfactant [4] and even highly polar compounds such as 4(4-trimethylammonio phenyl)-1-methyl-pyridinium chloride can achieve more than 95% uptake when suitably formulated [5]. Water solubility has also been found to be relatively unimportant for uptake, but compounds with a high partition coefficient and low water solubility will tend to remain in the cuticle and not enter the aqueous phase of the wall. Some 2,4-D esters have partition coefficients close to six [2], but there is evidence that such esters may be hydrolysed to their component acids and alcohols by enzymes located within the cuticle [6]. The molecular dimensions of pesticides have been reported to be more important in limiting uptake [7], but Price and Anderson [2] found this to be significant only for polar compounds.

APOPLAST MOVEMENT

Any compound that is able to dissolve in the transpiration water of the free space of the walls and the xylem will be systemic, unless it is prevented by adsorption onto cell wall components, or retained behind cell membranes. Typical examples are the herbicides atrazine and diuron, the fungicide ethirimol and the insecticide pirimicarb. The rate of entry into the apoplast aqueous phase is determined by the rate of arrival at the inner surface of the cuticle and the partition coefficient of the compound. It is usually considered that compounds with a log partition coefficient of more than 4.0 will not dissolve sufficiently in water to give any systemic activity [8], but in theory the potential for systemic activity should also depend on the solubility of the compound, the rate of transpiration, and the intrinsic activity of the compound. Partition is an equilibrium distribution of solute between two immiscible phases, so no matter how soluble the chemical may be in the lipid phase of the cuticle, there will always be some in the aqueous phase. If, as in the case of the plant transpiration water, the aqueous phase is constantly renewed, there will be continuous redistribution between the phases, in this case transfer from the cuticle to the transpiration water. This also means that the extent of systemic activity will be reduced in plants with a high lipid content or when the rate of water movement is reduced.

Compounds that do dissolve in significant quantities in the apoplast water will be carried with the water flow to the main evaporation sites at the tips or margins of leaves, unless prevented by adsorption or absorbtion. Solutes dissolved in the apoplast water will constantly equilibrate with the adjacent tissue lipids, wall polymers, polyphenols and cells. Cationic compounds, such as paraquat, are particularly susceptible to adsorption by cell walls, especially of dicotyledon species with a high tannin content [9]. This may explain why paraquat is so much more active on low tannin plants, such as grass weeds, and plants growing in shade.

THE APOPLAST - SYMPLAST INTERFACE

The apoplast and symplast are separated from each other by a single membrane, the plasmalemma. Herbicides diffusing from spray deposits on the leaf surface must enter the apoplast water, where they are transported by a combination of diffusion and mass flow to the symplast membrane. Solutes inside the cell are not influenced by the apoplast water movement but move in the cell by diffusion and cyclosis, the energy dependent circulation of cytoplasm in the cell. Equilibrium between the solute in the cell and in the apoplast is maintained by changes in the net membrane flux, but nevertheless the membrane can maintain a high concentration gradient between the two phases.

The directions of net flux are illustrated in Figure 2. Water movement from the roots to the leaf tips and margins is often far more rapid than sugar movement from the leaves to the sink tissues. This means that the phloem and other cells of the symplast are constantly being washed by transpiration water, so solute in the symplast will efflux from the symplast into the apoplast in exactly the same way that solute is washed from the inner surface of the cuticle. If the solute is able to pass across the plasmalemma with equal ease in both directions it will be transported primarily in the apoplast, but if cell influx is more rapid than efflux, then the compound will tend to be either retained by the cell, making it non-systemic, or it will be translocated in the symplast, making it phloem systemic. All pesticides are capable of entering the symplast, but the high rate of water movement in the apoplast relative to the phloem means that a compound must be very strongly retained by the plasmalemma if it is to be phloem systemic.

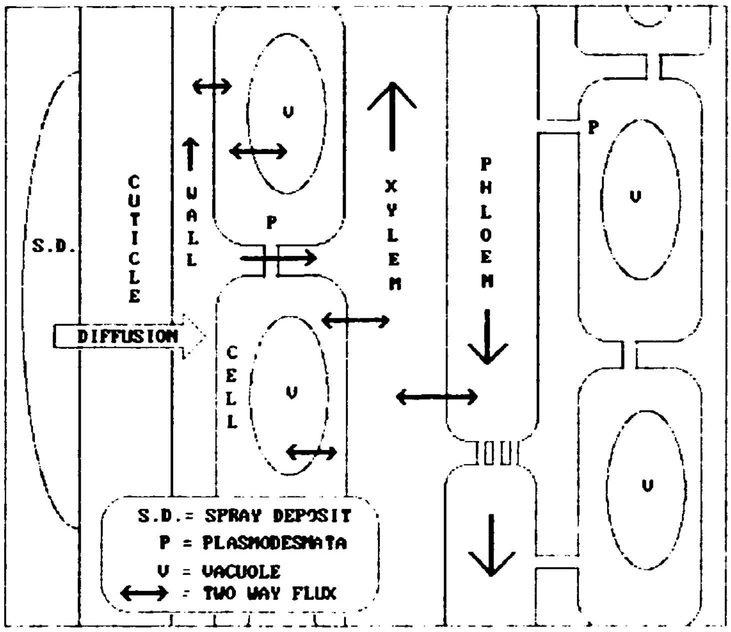

Figure 2 The apoplast - symplast interface

THE MOLECULAR REQUIREMENTS FOR PHLOEM MOBILITY.

There are four ways in which a compound can be retained by the symplast:

a) Adsorption or partition within the cell,

b) Cell electrical potential effects,

c) Differential permeability of weak acids,

d) Active transport.

Adsorption and Partition.

Compounds with a high partition coefficient will dissolve in lipid deposits within the cell, reducing the concentration in the aqueous phase of the symplast. This form of immobilisation is characteristic of compounds with a log partition near 4, and explains why such compounds may show systemic activity in some species [with a lower lipid content], but not in others. For example, bupirimate, when applied to wheat is relatively systemic but it is immobilised by apple leaves, even when applied to the thinner lower cuticle [9].

Many perennial and some annual plant species store tannins in the vacuole, and these may also retain xenobiotics. These compounds are particularly effective in binding cations, for example, paraquat is relatively ineffective on *Polygonum* species, which are known to have a high tannin content.

Cell Potential

The plasmalemma maintains an electrical potential gradient of approximately -150mv within the cell. The effect of this potential on ions is expressed by the Nernst equation [6]:

$$Ev = \frac{TR}{zF} \mathrm{Log}_e \frac{Co}{Ci} \qquad [2]$$

Ev Potential in millivolts
T Absolute temperature
R Gas constant
C Concentration of ion outside and inside the cell
F Faraday constant
z Valency

The negative internal potential means that cations are preferentially retained by the cell, while negatively charged compounds are excluded. This equation only strictly applies to compounds that can equilibrate, but it could have a very important effect on organic cations. For example a monovalent cation, such as 1-methyl-pyridinium cation [5], would have an equilibrium concentration 380 times higher inside the cell than outside, and is phloem mobile [9]. The corresponding concentration for a divalent cation such as paraquat would be 145,000 times higher inside than outside. In the case of this herbicide such distributions are meaningless because the membranes are rapidly damaged by herbicide action, but more than 85% of the non-herbicidal analogue 4-(4 trimethyl-ammoniophenyl)-1-methylpyridinium chloride was retained in soluble form in the cells of wheat plants, with negligible transport in the xylem or phloem, clear evidence that retention by cells does not necessarily mean phloem translocation. The effect of cell potential on the accumulation of organic anions is less clear because a wide range of acidic compounds are known to accumulate in cells.

Differential Permeability of Weak Acids

The pH of the cytoplasm is approximately 7.5 while the apoplast water is usually in the region of 5.5. The cytoplasmic pH is critical for many essential enzymic reactions and is maintained within close limits by a combination of metabolism and differential permeability of the plasmalemma and tonoplast. The phloem is a specialised type of cell, which lacks mitochondria, chloroplasts and vacuole, and has a cytoplasmic pH above 8.

Organic acids, with a pKa typically between 3 and 5, have a higher degree of dissociation in the symplast [pH 7.5 - 8.2] than in the apoplast [pH 5.5]. If the dissociated and undissociated forms of the acid differ significantly in lipid partition coefficient, it will enter the symplast more easily than it leaves it. This can result in the establishment of a higher concentration of the acid in the cell or phloem sieve tubes than in the external apoplast. If the concentration difference can be maintained, the acid will move in the phloem instead of the xylem [Figure 3]

The essential prerequisites for the phloem mobility of a weak acid are moderate to high lipid solubility of the undissociated acid, and low lipid solubility when ionised. The ratio of the two forms of the acid are independent of pH [Henderson-Hasselbach equation] and pKas in the range of zero to 14 have been quoted as suitable for phloem translocation, with zero to 7 as optimum [8], but this does not take into account the quantitative and non-equilibrium aspects of phloem accumulation. If the pKa is very low the concentration of undissociated solute available for diffusion and accumulation in the lipid phase of the membrane is also low, while if the pKa is very high the concentration of undissociated acid in the cell will also be high, facilitating efflux. For example, benzene sulphonic acid [pKa <1] is not phloem mobile, unlike the carboxyl and phosphonic acid analogues [pKas >2] [9].

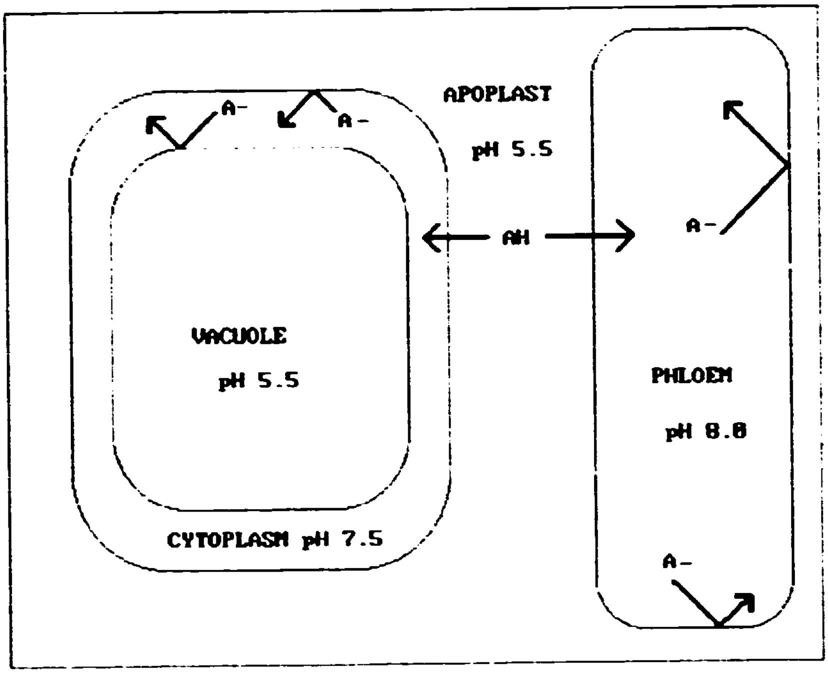

Figure 3 The distribution of weak acids

The lipid solubility of the undissociated acid is also relevant to the pKa limits, a high solubility compensating for a lower pKa; however, if the partition coefficient is too high, the acid will be retained by the cuticle and other lipids, and be unavailable to the phloem. The phloem mobility of weak acids is probably most effective when the pKa is between 2 and 6.5 and the partition coefficient of the undissociated acid between -1 and 3. Many phloem mobile herbicides and plant growth regulators fall into this range.

Most of the herbicides and plant growth regulators that are phloem mobile are weak acids, including such important groups as the phenoxyacids and sulphonyl ureas, the imidazolinones, the picolinic acids, and the diarylether graminicides, but other important herbicides, such as glyphosate and a number of model compounds, do not appear to conform to the requirements of the weak acid hypothesis. The translocation of substituted N-methyl-pyridinium compounds showed that, while the addition of a single carboxyl group to the parent pyridinium [MPC] improved translocation, a second carboxyl reduced it [5]. The substitution of a sulphonic acid group for the carboxyl gave very similar results, despite the fact that benzene sulphonic acid was not phloem mobile. There is also very little difference in the partition coefficients of the carboxypyridiniums with changes in pH because even the unsubstituted MPC has a log partition of -3.8 [2]. Glyphosate is very similar in that it is a zwitterion.

Active Transport

There is some evidence that a small number of xenobiotics may be taken into the cell by active transport mechanisms. Unlike diffusion, energy coupled transport mechanisms are affected by metabolic inhibitors, and are concentration dependent, showing reduced rates of transport when the system is saturated, or when a competing compound is present. Conclusive evidence using metabolic inhibitors is difficult to obtain because inhibitors can prevent the normal functioning of the membrane, but αamino-isobutyric acid [9] has shown saturation kinetics for cell uptake, while glyphosate uptake has been shown to demonstrate saturation kinetics and competitive inhibition [10]. Maleic hydrazide and 2,4-D may also enter plant cells by an active transport process [11]. There is still the need to show that active cell uptake is related to phloem translocation. It is probable that compounds that rely on existing active transport mechanisms for phloem mobility will be more selective in their molecular requirements than compounds relying on the physico-chemical process of ion trapping.

CONCLUSIONS

Many of the ground rules for the phloem translocation of pesticides are sufficiently well understood to permit the synthesis of novel compounds with predictable translocation properties. The main target now is to combine these properties with those of the active component in such a way that the biocide is delivered to its site of action in an active state.

ACKNOWLEDGEMENT

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SPRAY FORMULATIONS

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ABSTRACT

Many pesticides are applied as aqueous sprays that are produced by dilution of a concentrate. The latter could be wettable powder (WP), a granule, an emulsifiable concentrate (EC), suspension concentrate (SC) or an oil in water emulsion (EW). In this paper, I will discuss the factors that govern the stability of SCs and EWs since these are becoming more applied in recent years. This is due to their advantages over the more conventional WPs or ECs. Both SCs and EWs have to be prepared in a colloidally stable form by using powerful dispersing agents and emulsifiers. Of these, nonionic surfactants, block copolymers and polyelectrolytes are the most commonly used. They improve stability either by creating an electrical double layer at the particles or droplets, by steric repulsion (resulting from the adsorbed layers) or combination of both. The main parameters that control the stability of these systems are: zeta potential, electrolyte concentration, adsorbed layer thickness and particle size. Once stable suspensions and emulsions are prepared, it is essential to control their sedimentation behaviour. This is achieved by the addition of an antisettling system. The latter could be a high molecular weight polysaccharide, a swellable clay (such as sodium montmorillonite), silica or a combination of these materials. In all cases, it is essential to produce a gel network in the continuous phase that prevents sedimentation (or creaming) and hence little or no separation occurs on standing. The physical characteristics of the system can be investigated using various techniques such as particle size analysis and rheology.
On application of a spray formulation, it is essential to ensure the adhesion of the spray droplets to the target. It is also important to enhance the wetting and spreading of the spray droplets in order to ensure even coverage. To control these processes, one usually includes surfactants in the formulation which may also enhance the penetration of the chemical. The various physical processes involved will be discussed and guidelines for optimisation of spray application will be given.

INTRODUCTION

Many pesticides are applied as aqueous sprays that are produced by dilution of a concentrate. The latter could be a wettable powder (WP), a granule, an emulsifiable concentrate (EC), suspension concentrate (SC) or an oil in water emulsion (EW). The formulation of pesticides as SCs or EWs has attracted considerable attention in recent years. Both these formulations are sometimes referred to as flowables (particularly in North America). Such formulations offer a number of advantages for the user, being easy to measure, not dusty and readily dispersible on dilution. Moreover, being aqueous based they produce much less hazard to the operator in handling and they always have high flash points. In addition, since the formulation either contains no oil (with an SC) or a relatively small amount (with some EW formulations), they cause less damage (phytotoxicity) to the plants and to the environment. These types of systems are also suitable for optimisation of biological efficacy by controlling particle or droplet size, adding surfactants to enhance biological activity and film forming agents to improve adhesion and, in some cases, provide controlled release.

In this overview, which is by no means exhaustive, I will summarise the basic principles involved in the formulation of SCs and EWs. Particular attention will be paid for the basic colloid and interface science principles involved in their preparation and their subsequent stabilisation. This is then followed by a review of the application of these systems as sprays. This involves a number of interfaces, where interaction with the formulation plays a vital role.

SUSPENSION CONCENTRATES (SCs)

Suspension concentrate formulations are by far the most developed systems, both practically and fundamentally (1-3). Two main requirements are needed for formulation of an SC. Firstly, one needs a good dispersing agent to maintain colloid stability. Secondly, a suitable antisettling system is required to prevent sedimentation and formation of a dilatant (hard) structure at the bottom of the container. The dispersing agent should satisfy the following main criteria: (a) a good wetting agent for the pesticide powder (both external and internal surfaces of the powder aggregates and agglomerates must be spontaneously wetted); (b) be a good dispersing agent to break such aggregates and agglomerates into smaller units and subsequently help in the wet milling process (one usually aims at a dispersion with a mean volume mean diameter of 1-2 μm); (c) have good stability in the colloid sense, i.e. providing sufficient repulsion between the particles to maintain them as individual units. Powerful dispersing agents are particularly important for the preparation of highly concentrated suspension concentrates. Any flocculation will cause a rapid increase in the viscosity of the suspension during preparation and this makes wet milling a difficult job. Moreover, in most cases, one needs to start with a highly concentrated suspension for further formulation of the final product in which other ingredients such as surfactants and antisettling systems have to be added.

The function of the antisettling system is to provide a kind of "gel network" in the continuous phase. This is essential for the prevention of "caking" or "claying" which is the result of settling of suspensions as a consequence of the density difference between the particles and the medium. Since the particle size is outside the colloid range (usually greater than 1 μm), the very weak thermal (Brownian) motion is insufficient to overcome the gravitational force. As a result of the repulsive force between the particles (which is essential for maintaining colloid stability) in a sediment, these particles are able to move past each other forming a hard sediment (which in rheological terms is shear thickening or dilatant). As a result of the small spacing between the particles such "cakes" or "clays" are difficult to redisperse and, therefore, they must be avoided. Apart from prevention of claying, the antisettling systems should also reduce the overall separation in the formulation. Large separation usually makes it difficult to homogenise the final suspensions, unless the sediment is weakly gelled.

Choice of Dispersing Agent:

Various agents may be used to disperse the particles into water, e.g. ionic and nonionic surfactants, nonionic polymers and polyelectrolytes. Examples of such dispersing agents are given in Table 1.

Ionic surfactants and polyelectrolytes which become adsorbed on the hydrophobic particle surfaces provide a repulsive force as a result of double layer interaction. When the particles approach to distances that are smaller than twice the double layer extension, strong repulsion occurs. The double layer extension depends on electrolyte concentration, being larger the smaller the electrolyte concentration. For example in a 1:1 electrolyte such as NaCl, the double layer extension is 100 nm in 10^{-5} mol dm^{-3} electrolyte and 10 nm in 10^{-3} mol dm^{-3} electrolyte. At such low electrolyte concentration, double layer repulsion is effective at separation distances where the van der Waals attraction is relatively weak. Under these conditions (of low electrolyte concentration) the double layer repulsion predominates, at intermediate separation distances between the particles. This is illustrated in Fig.1a which shows the energy distance curve for the case of electrostatically stabilised suspensions at low electrolyte concentrations. This curve has characteristically an energy maximum, which if high enough (> 25 kT, where k is the Boltzmann constant and T the absolute temperature) prevents particle aggregation into the primary minimum. It should be mentioned, that when using ionic surfactants and polyelectrolytes one should make sure that the electrolyte content in the medium is reduced to a minimum. This is particularly the case with polyvalent ions such as Ca^{2+} or Mg^{2+} which tend to cause flocculation at lower concentration when compared with monovalent ions.

Nonionic surfactants and polymers provide an alternative (and possibly more effective) method for stabilisation of suspension concentrates. These molecules adsorb with the hydrophobic groups on the particle surface, leaving the hydrophilic chain (such as poly(ethylene oxide) or poly(vinyl alcohol) dangling in solution. They provide repulsion as a result of two main effects. When the particles

TABLE 1
Dispersing Agents for Suspension Concentrates

Ionic Surfactants:	e.g. Sodium dodecyl benezene sulphonate $C_{12}H_{25} - C_6H_5 - SO_3Na$ Cetyl trimethyl ammonium chloride $C_{16}H_{33} - N(CH_3)_3 - Cl$
Nonionic Surfactants:	e.g. Alcohol ethoxylates $R-(CH_2CH_2O)_x-OH$ Alkyl phenol ethoxylates $R-C_6H_5-(CH_2CH_2O)_x-OH$ Alkyl phenol propylene oxide ethylene oxide $R-C_6H_5-(CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-O)_y-(CH_2CH_2O)_x-OH$
Nonionic Polymers:	e.g. Block copolymer of ethylene oxide and propylene oxide $HO-(CH_2-CH_2O)_x-(CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-O)_y-(CH_2-CH_2O)_x-OH$ Polyvinyl alcohol/polyvinyl acetate $HO-(CH_2-\underset{\displaystyle OH}{\underset{\vert}{C}}H)_x-(CH_2-\underset{\displaystyle OCOOH_3}{\underset{\vert}{C}}H-\ )_y-(CH_2-\underset{\displaystyle OH}{\underset{\vert}{C}}H)_z-OH$ Graft copolymers "comb" e.g. polymethyl methacrylate with polyethylene oxide side chain.
Polyelectrolytes:	Naphthalene formaldehyde sulphonated condensates Lignosulphonates

approach each other to distances smaller than twice the chain extension of the surfactant or polymer (usually referred to as the adsorbed layer thickness δ), the chains undergo overlap and/or compression, both of which are unfavourable when the chains are in good solvent conditions. As a result of overlap and/or compression, the osmotic pressure in between the particles becomes larger than in bulk solution. This results in diffusion of solvent molecules from the bulk thus separating the particles. The second effect that results from chain overlap and/or compression is the reduction in configurational entropy of the chains which leads to repulsion between the particles. This combination of osmotic and entropic repulsion is usually referred to as steric stabilisation (4). It is characterised by an energy-distance curve illustrated in Fig. 1b. As can be seen, this curve contains only one minimum, which is usually shallow when the adsorbed layer thickness is larger than say 5-10 nm. Thus, with most nonionic surfactants and polymers, repulsion is very strong at distances of separation comparable to twice the adsorbed

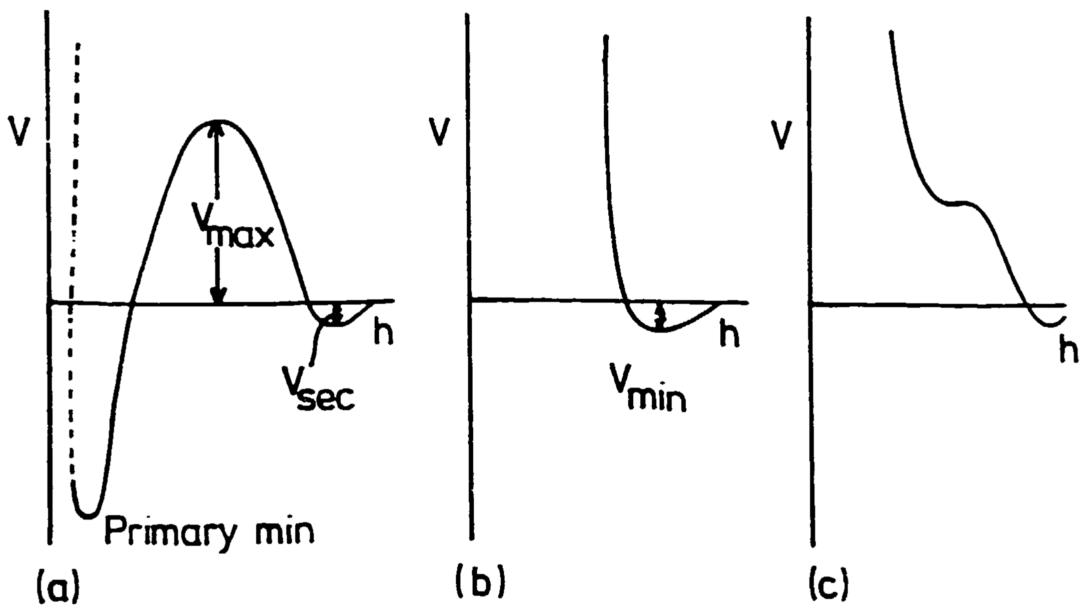

Figure 1. Energy-d.:tance curve for three different stabilisation mechanisms: (a) electrostatic; (b) steric; (c) electrostatic + steric.

layer thickness. The major requirement in this case is to have a polymer that adsorbs strongly on the particle surface. In this respect block and graft ("comb" type) polymers are the most suitable. These systems consist of A and B units combined together in A-B, A-B-A or BA_n fashion. B represents units with high affinity for the particle surface and basically insoluble in the continuous medium, thus providing strong adsorption ("anchoring" units). A, on the other hand represents units with high affinity for the medium (high chains - solvent interaction) and little or no affinity to the particle surface. An example of such powerful dispersant is a graft copolymer of poly methyl methacylate-methacrylic acid (the anchoring portion) and methoxy polyethylene oxide (the stabilising chain) methyacrylate (5). Adsorption measurements of such a polymer on a pesticide, namely ethirimol (a fungicide) showed a high affinity isotherm with no desorption. Using such an agent a suspension with high volume fraction (> 0.55) could be prepared.

The third class of dispersing agents which is commonly used in SC formulations is that of polyelectrolytes. Of these, sulphonated naphthalene-formaldehyde condensates and lignosulphonates are probably the most commonly used. The energy-distance curve for such systems is illustrated in Fig.1c. This shows a shallow minimum, a shallow maximum, and strong repulsion at short distances. Thus, these polyelectrolytes offer some versatility in SC formulations.

Choice of Antisettling Systems

As mentioned before an antisettling system is required to reduce separation and prevents the formation of a dilatant system. The most commonly used method is to add to the continuous medium a high molecular weight water soluble material, e.g. hydroxyethyl cellulose or Xanthan gum (a polysaccharide). Alternatively one may add a finely divided inert substance such as sodium montmorillonite (bentonite) or silica which produces a gel network in the continous phase. A more robust antisettling system consists of a mixture of bentonite or silica and a polysaccharide like Xanthan gum. The optimum concentration and composition of an antisettling system can be obtained from rheological measurements (see below).

Although the above systems are the most currently used materials, some potential alternatives could be applied for SCs. The first method depends on controlled flocculation of electrostatically stabilised suspensions by addition of electrolytes (6) or for sterically stabilised suspensions by reducing the adsorbed layer thickness (1). The second method is based on the addition "free" (non-adsorbing) polymer to a sterically stabilised suspension. This was illustrated by using an ethirimol suspension stabilised with a "comb" stabiliser to which poly(ethylene oxide) (PEO) with various molecular weights was added to the continuous phase (5). Rheological measurements showed that above a critical PEO concentration, weak flocculation of the suspension occured with the result of formation of a gel-like structure with a measurable yield value. This gel structure is sufficient for prevention of caking or claying.

Assessment of the State and Long-term Physical Stability of Suspensions

Various states of SCs may be identified and these are schematically represented in Fig.2. The first three states (a-c) represent three cases of a colloidally stable suspension of which only state (a) is uniform since the particles are very small (Brownian diffusion overcomes any sedimentation). States (b) and (c) represent "clayed" suspensions. Such clays or cakes can be felt using a glass rod whereby resistence to penetration can be felt. Clearly, these suspensions are unacceptable and they require addition of an anti-settling system. States (d) - (f) represent three cases of unstable (coagulated) suspensions which again are undesirable. The most acceptable cases are those represented by (g) - (i) which produce a kind of controlled flocculation. State (g) is the case whereby the particles of the suspension produce the gel, i.e. those produced by secondary minimum flocculation. State (h) is that produced by bridging flocculation using a high molecular weight polymer, whereas state (i) is that produced using depletion flocculation.

The above different states can be assessed using different techniques. The most common procedures are those based on particle

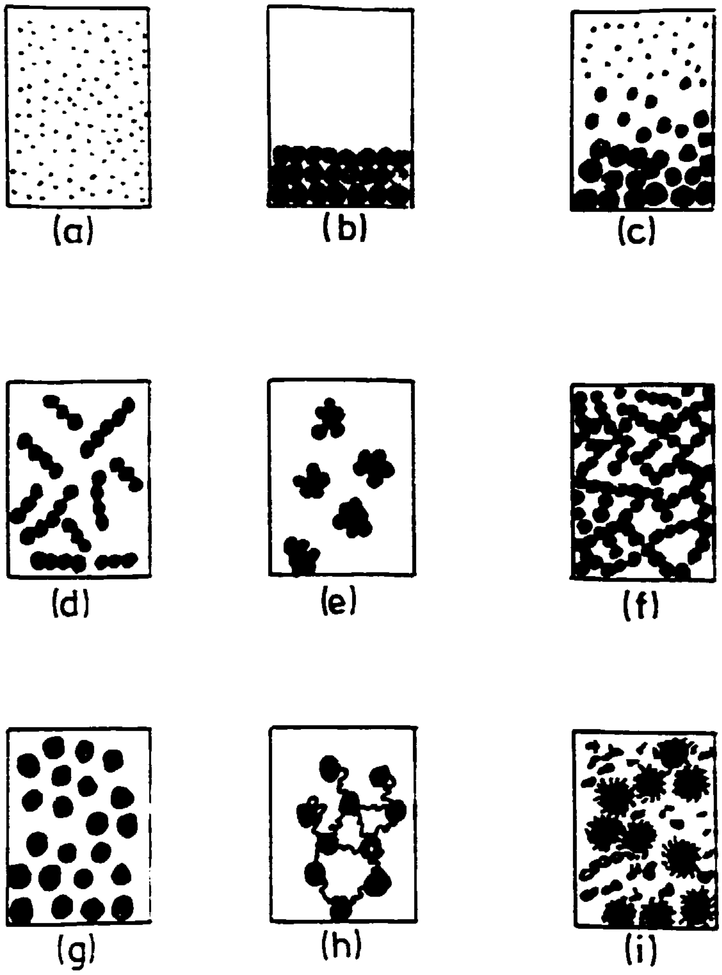

Figure 2. (a) Stable colloidal suspension; (b) stable coarse suspension (uniform size); (c) stable coarse suspension (size distribution); (d) coagulated suspension (chain aggregates); (e) coagulated suspension (compact clusters); (f) coagulated suspension (open structure); (g) weakly flocculated structure; (h) bridging flocculation; (i) depletion flocculation.

size measurements and rheology. For particle size analysis one needs to carefully dilute the suspension and then observe the particles under the optical microscope or use particle size analysis instruments. Any strong flocculation can be observed under the optical microscope since on dilution, the strong aggregates are not broken down. Coulter counters and laser diffraction techniques can also be applied for particle size analysis and these could also give information on flocculation of the system.

For assessment of the bulk properties of the suspension (without diluting it) one uses rheological methods. These methods require modern rheometers that can be used to obtain steady state (shear stress - shear rate), oscillatory and constant stress measurements. The steady state shear stress - shear rate results are schematically shown in Fig.3. From these data, one can obtain the extrapolated yield stress τ_B using a Bingham equation, (7).

$$\tau = \tau + \eta_{pl} \dot{\gamma} \qquad (1)$$

Alternatively, the data could be analysed using a Casson's equation (8)

$$\tau^{1/2} = \tau_c^{1/2} + \eta_c^{1/2} \dot{\gamma}^{1/2} \qquad (2)$$

It can be seen from Fig. 3 that the viscosity of the suspension

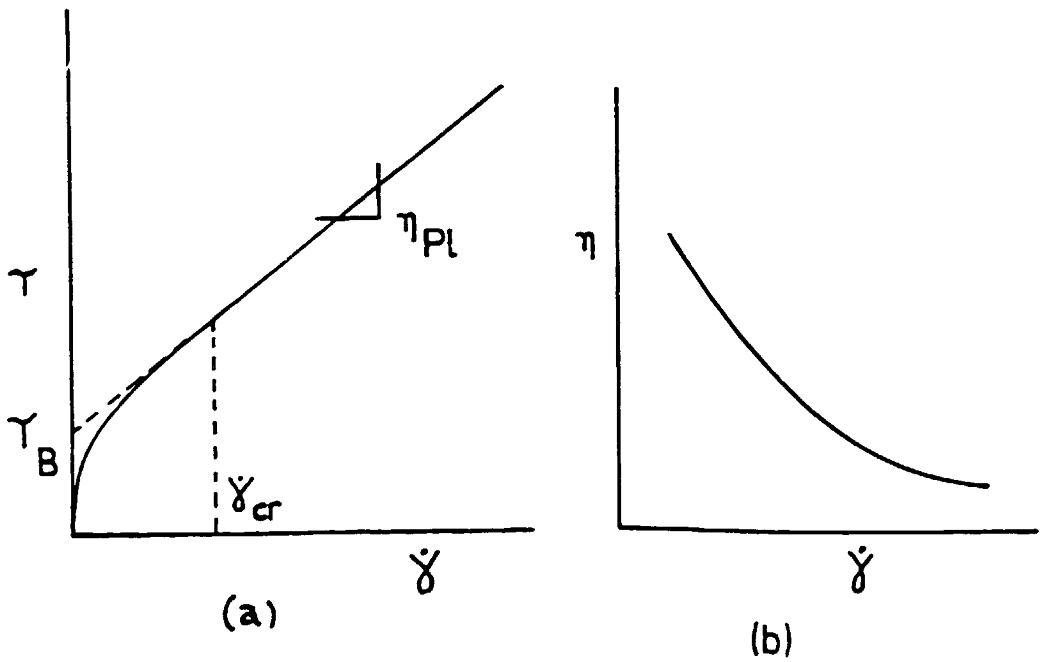

Figure 3. (a) shear stress - shear rate and (b) viscosity - shear rate relationship for a typical SC.

increases with decrease of shear rate and indeed at very low shear rate ($\dot{\gamma} \rightarrow 0$), the viscosity reaches a limiting value, referred to as the residual or zero shear viscosity $\eta_{(o)}$. The latter can be obtained from constant stress (creep) measurements. Basically one measures the creep curves at various stresses and then obtain the viscosity as a function of applied stress to obtain the limiting value $\eta_{(o)}$ at a stress approaching zero. The residual viscosity $\eta_{(o)}$ is an important parameter that determines settling of the suspension (9).

Another useful rheological method is the oscillatory (dynamic) technique. In this case a small amplitude sinusoidal strain (or stress) is applied on the system and the stress and strain compared over a wide range of frequencies. From the phase angle shift between stress and strain δ, and the amplitudes of stress and strain (τ_0 and γ_0 respectively) one can calculate the complex modulus G*, the storage modulus G′ (the elastic component) and the loss modulus G″ (the viscous component) i.e.

$$G^* = \tau_0/\gamma_0 \quad (3)$$
$$G' = G^* \cos \delta \quad (4)$$
$$G'' = G^* \sin \delta \quad (5)$$

Both G* and G′ give a measure of the elasticity in the system which control separation of the suspension concentrate. Thus, by combining the various rheological methods, one is able to assess and predict the long term physical stability of suspension formulations.

EMULSIONS (EWs)

As mentioned in the introduction, oil-in-water emulsions of pesticides offer an alternative to SCs. If the pesticide is a liquid, with relatively low viscosity, it can be directly emulsified into water using suitable surfactants or polymers. However, in most cases, the pesticide oil is viscous and hence a small amount of an oil, such as xylene or isoparaffinic oil, is added to lower the viscosity. This is also the case with low melting point solids which can be dissolved in an oil.

Emulsification is a non-spontaneous process whereby the bulk oil phase is subdivided with small oil droplets. When the bulk oil phase (with area A_1) is changed to emulsion droplets (with area A_2 that is much larger than A_1), a large increase in surface area occurs. The free energy of emulsion formation is given by the expression (10)

$$\Delta G^{form} = \Delta A \, \gamma_{12} - T \, \Delta S^{conf} \quad (6)$$

where $A = A_2 - A_1$, γ_{12} is the interfacial tension, T the absolute temperature and ΔS^{conf} is the configurational entropy for the relatively large number of droplets formed.

Most emulsifiers reduce γ_{12} to values that are seldom below 1 mNm^{-1}. In all cases, $\Delta A \, \gamma_{12}$ is much larger than $T \, \Delta S^{Conf}$, since the droplet size is also not very small (usually above 1 μm). This means that G^{form} is positive and hence energy is required for emulsification. However, in some cases, particularly when using mixed emulsifiers, γ_{12} can reach relatively low values (< 0.2 mNm^{-1}) and the droplet size can become small (submicron). Under these conditions, emulsification may be spontaneous requiring little or no energy. If this is not the case, high speed mixers (e.g. Silverson, Ilado or Ultraturrax stirrers) or valve homogenisers must be used to produce the emulsion.

Factors responsible for Emulsion Instability (Breakdown Processes)

Various breakdown processes may be identified and these are schematically illustrated in Fig.4. States (a) and (b) are the result of the effect of gravity, when the density of the oil phase is

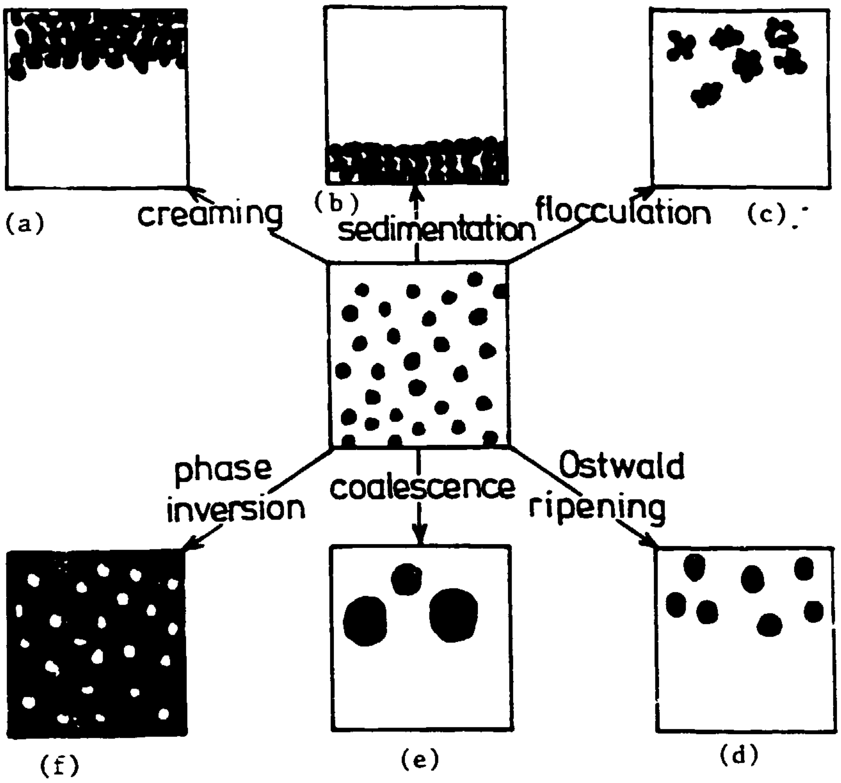

Figure 4. Various breakdown processes in emulsions

different from that of the continuous phase and the droplet size distribution is outside the colloid range (10). In this case the mild thermal motion (weak Brownian diffusion) is insufficient to counteract the gravitational force. If the density of the oil is lower than that of the continuous medium the droplets move to the top of the container, a process referred to as creaming (10). On the other hand, if the density of the oil phase is higher than that of the medium sedimentation occurs (b). The process of creaming or sedimentation results in no change in droplet size but the close approach of droplets in a cream or sediment may lead to enhancement of coalescence (see below).

State c, where the droplets aggregate together is the result of lack of sufficient repulsion to counteract the van der Waals attraction. This process, referred to as flocculation is similar to that obtained with unstable suspensions. The forces responsible for flocculation have been discussed before in the section on SCs.

State d, is the result of Ostwald ripening, the driving force in this case is the difference in solubility between small and large droplets. This process, which may also occur with SCs, results when the pesticide has significant solubility in the continuous medium. The process may also be enhanced by the presence of surfactants which cause solubilisation of the pesticide.

State e, is the result of the thinning and disruption of the liquid film between the droplets resulting in their coalescence. The latter process, which does not occur with SCs, can lead to dramatic instability with the result of separation of oil and water into two layers. The driving force for coalescence is the thinning and disruption of liquid films between droplets which results from thermal or mechanical fluctuations. The latter produce surface waves which may grow in amplitude resulting in close approach between the crests and joining of the oil droplets. Alternatively, film fluctuation may result in formation of thin films which below a critical thickness may rupture as a result of the strong van der Waals attraction.

State f, is the result of phase inversion whereby an oil-in-water emulsion inverts to a water-in-oil (w/o) emulsion. The resulting w/o emulsion is usually more stable than the o/w oil. Such process of inversion may result when the oil volume fraction is increased above a critical value, or it may result from change in the conditions (e.g. temperature increase) whereby the emulsifier becomes more suitable for the inverted emulsion.

Emulsifier Selection

A useful (although empirical) procedure for emulsifier selection has been introduced by Griffin (11) and is referred to as the hydrophilic-lipophilic balance (HLB index). This empirical HLB number is based on the relative proportion of hydrophilic and lipophilic groups in the surfactant molecules. For example, for a surfactant having the structure $R-(CH_2CH_2O)_x-OH$, the HLB number is simply given by the equation,

$$HLB = (E + P)/5 \qquad (7)$$

where E and P represent the weight per cent of ethylene oxide and polar hydroxyl groups respectively. Emulsifiers with HLB number 3-6 usually produce w/o emulsion, whereas those with HLB number 8-18 produce o/w emulsion. The exact HLB number for a particular oil is usually established by a trial and error procedure. Two nonionic surfactants with low and high HLB are mixed in various proportions to produce a range of HLB numbers. These surfactant mixtures are then used to prepare a number of o/w emulsions and their stability assessed by standing or by using droplet size analysis (using the Coulter counter). In this way the optimum ratio of the two surfactants for the particular oil in question is obtained. Once this ratio is established, emulsions are then prepared using various surfactant concentrations in order to establish the optimum concentration for maximum stability.

Stabilisation of Emulsions

Creaming or sedimentation can be significantly reduced by reducing the droplet size of the emulsion, e.g. by using valve homogenisers or appropriate surfactants. By using oils of various densities one could match the density of the oil and continuous medium (at least at one temperature) thus reducing creaming or sedimentation. However, in most practical emulsions, it is neither possible to reduce the droplet size sufficiently, nor it is possible to match the density. In these cases, creaming or sedimentation may be reduced by addition of thickeners e.g. polysaccharides in the same manner as described for SCs.

Irreversible flocculation can be prevented by creating sufficient energy barrier to prevent close approach of the droplets. In this respect, steric stabilisation produced by using nonionic surfactant or polymers (block or graft copolymer) is the most efficient procedure. As mentioned above, one usually uses a mixture of two emulsifiers, e.g. Spans and Tweens to optimise the stability of the emulsion (12). To prevent coalescence, one needs to dampen the surface fluctuations which occur when the droplets approach each other. This can be achieved by using surfactant mixtures or polymers that enhances the Gibbs elasticity. The latter results from the interfacial tension gradients that occur on stretching of a surfactant film. The Gibbs dilational elasticity ε is given by the expression,

$$\varepsilon = d\gamma/d \ln A = A(d\gamma/dA) \quad (8)$$

As a result of the Gibbs elasticity, surfactant molecules diffuse from bulk solution to the o/w interface and these molecules cause a liquid flow to the film between the droplets (the Marangoni effect). This process results in the formation of thicker films and hence coalescence is prevented.

Ostwald ripening is usually reduced in the presence of surfactants which are effective in lowering the interfacial tension and produce a high Gibbs elasticity. The process of Ostwald ripening can also be reduced by incorporation of a small proportion of highly insoluble oil in the emulsion (13). When oil molecules diffuse from smaller droplets, the activity of the insoluble oil molecules increases and this reduces further diffusion, thus reducing Ostwald ripening.

Phase inversion may be prevented by reducing the oil phase volume fraction well below the maximum packing fraction for the o/w emulsion; and by proper choice of the surfactants. One should ensure that when the conditions are changed (eg. by increase of temperature), the HLB number of the surfactant does not reach values that are more suitable for producing w/o emulsions.

Assessment of Emulsions

For assessment of the physical stability of emulsions, one uses the same procedures described above for SCs, i.e. droplet size analysis, microscopic investigation and rheology. Droplet size analysis is usually carried out using a Coulter counter, whereby one measures the droplet size distribution as a function of time. This allows one to obtain the flocculation and coalescence rates, as well as any Ostwald ripening process. Rheological measurements can also obtain information on coalescence since the process usually results in reduction of the viscosity of the emulsion. In addition, low shear rheology can obtain information on creaming and sedimentation in the same manner as described for SCs.

SPRAY APPLICATION

As mentioned in the introduction, spray application involves a number of interfaces, where interaction with the formulation plays a vital role (14). The first interface during application is that between the spray solution and the atmosphere (air) which governs the droplet spectrum, rate of evaporation, drift, etc. In this respect, the rate of adsorption of the surfactant or polymer at the air/liquid interface is of vital important. The second interface is that between the liquid droplets and the leaf surface, whereby the droplets impinging on the surface undergo a number of processes that determine their adhesion and retention and further spreading on the target surface. The rate of evaporation of the droplet and the concentration gradient of surfactant across the droplet governs the nature of the deposit formed. Below a summary of the various processes involved will be given.

Interactions at the Air/Solution Interface and their Effect on Droplet Formation

In a spraying process a liquid is forced through an orifice to form droplets by application of hydrostatic pressure. If the time of formation of a drop is large (greater than 1 minute), the volume of the drop depends on the properties of the liquid such as its surface tension and viscosity and the dimensions of the orifice, but is independent on the time of its formation. However, at short times of formation (less than one minute) the drop volume depends on the time of its formation. As the speed of formation of the drop is increased, its volume increases, passes through a maximum and then decreases. The maximum time at which the droplet volume is a maximum increases with increase of viscosity and decrease of surface tension. Thus loosening of drops which happens when its weight W exceeds the surface tension force (i.e. $w > 2 \pi r \gamma$, where r is the radius of the drop and γ is the surface tension) progresses at a speed that is determined by the viscosity and surface tension of the liquid.

At short t values, W is again smaller since the liquid in the drop has a considerable kinetic energy even before the drop breaks loose. The liquid coming into the drop imparts downward acceleration and this may cause separation before the drop has reached the value that is determined by surface tension forces.

When the hydrostatic pressure is raised further, i.e. when attainment of even shorter t values is attempted, no separate drops are formed at all and a continuous jet issues from the orifice. Then at even higher hydrostatic pressure, the jet breaks into droplets, the phenomenon usually referred to as spraying. The process of break-up of jets (or liquids sheets) into droplets is the result of surface forces. The surface area and consequently the surface free energy (area × surface tension) of a sphere is smaller than that of a less symmetrical body. Hence small liquid volumes of other shapes tend to give rise to spherical droplets. For example, a liquid cylinder becomes unstable and divides into spherical droplets as soon as the length of the liquid is greater than its circumference (15).

Let us now discuss how surfactants and polymers (which are present in most pesticidal formulations) affect the droplet size spectrum of a spray. As we will see in the next Section, the droplet size of a spray droplet, everything else being equal, determines its adhesion and capture. Since surfactants lower the surface tension of water, one would expect that their presence in the spray solution would result in the formation of smaller droplets. However, the actual situation is not simple since one is dealing with a dynamic situation. In a spraying process, a fresh liquid surface is continuously being formed. The surface tension of that liquid should depend on the relative ratio between the time taken to form an interface and the rate of adsorption of the surfactant from bulk solution to the air/liquid interface, which depends on the rate of diffusion of the adjuvant molecules.

The rate of surfactant adsorption increase with increase of its diffusion coefficient (which in turn increases with decrease of molecular weight of the surfactant) and its concentration. Clearly, if the time of formation of an adsorbed surfactant layer with sufficiently low surface tension is much larger than the time of disruption of the liquid into droplets, then the effect of addition of that surfactant on the droplet spectrum will be insignificant. The faster the adsorption of the surfactant, the more the effect in reducing droplet size.

The influence of polymers on the droplet size of spray liquids is far from being clearly understood although it is well known that thickening agents (high molecular weight polymers) are beneficial in reducing drift, i.e. they favour the formation of larger droplets. The most likely explanation of how polymers affect droplet size is in terms of the viscoelastic behaviour of polymer solutions. Many high molecular weight polymers adopt a random coil configuration which is characterised by a root mean square radius of gyration Rg. At low polymer concentration, the polymer coils are separated from each other by solvent molecules and the viscosity of the polymer solution increases gradually with increase of the polymer concentration, until a critical concentration, C*, is reached above which the polymer coils begin to overlap. Above C*, the viscosity of the polymer solution increases much more rapidly with further increase in its concentration. This polymer coil overlap opposes liquid instability of spray jets, thus resulting in the formation of larger droplets.

Spray Impaction and Adhesion

When a drop of a liquid impinges on a leaf surface, one of several states may arise depending on the conditions. The drop may bounce or undergo fragmentation into two or more smaller droplets which in turn may bounce back or return to the surface with a lower kinetic energy. Alternatively, the drop may adhere to the surface after passing through several stages, where it flattens, retracts spreads and finally rests to form a hemispherical cap. In some cases the droplet does not adhere but floats as an individual drop for a fraction of a second or even several seconds and can either adhere to the surface or leave it again.

The most important parameters which determine which of the above stages is reached are: (i) the mass (volume) of the droplet, its velocity in flight and the distance between the spray nozzle and the target surface, (ii) the difference between the surface energy of the droplet in flight E_0 and its surface energy after impact E_s (16), (iii) displacement of air between the droplet and the leaf.

Droplets with diameters in the region 20-50 µm do not usually undergo reflection if they are able to reach the leaf surface. Such droplets have a low momentum and can only reach the surface if they travel in the direction of the air stream. On the other hand, large droplets of the order of a few thousand micrometer diameter undergo fragmentation. Droplets in the range 100-400 µm, which cover the range produced by most spray nozzles, may be reflected or retained depending on a number of parameters such as the surface tension of the spray solution, surface roughness and elasticity of the drop surface. For any given spray solution (with a given surface tension), a critical droplet diameter exists below which adhesion is high and above which adhesion is low. This critical droplet size increases as the surface tension decreases. The viscosity has only a small effect on adhesion of large spray droplets, but with small droplets adhesion increases with increase in viscosity. As expected, the percentage of adhered droplets decreases as the angle of incidence of the target surface increases.

Droplet Sliding and Spray Retention

Many pesticidal applications involve high volume sprays, whereby with continuous spraying the volume of the drops continue to grow in size by impaction of more spray droplets upon them and by coalesence with neighbouring drops on the surface. During this process, the amount of spray retained increases provided the liquid which impacts is retained. However, with further spraying the drops grow in size reaching a critical value, above which they begin to slide down the surface and "drop off", the so called "run-off" condition. At the point of "incipient run-off" the volume of spray retained is a maximum. The retention at this point is governed by the movement of liquid drops on the solid surface. The percentage of droplets sticking to a plant after having touched it should depend upon the tilt of the leaf, the size of the droplets and the contact angle at the plant leaf/droplet/air interface. However such a process is complicated and is governed by many other factors (17) such as droplet spray spectrum, velocity of impacting droplets, volatility or viscosity liquid and ambient conditions.

Wetting and Spreading

Another factor which can affect the biological efficacy of foliar spray application of pesticides is the extent to which the liquid wets and covers the foliage surface. This in turn governs the final distribution of pesticides over the areas to be protected (18). Many leaf surfaces are difficult to wet since they are covered with crystalline wax (straight chain alcohols in the range 24-35 C atoms) that renders them very hydrophobic. When a water drop is placed on a leaf surface, it takes the form a spherical cap that is characterised by the contact angle (fig.5). From the balance of tensions one obtains

$$\gamma_{SA} = \gamma_{SL} + \gamma_{LV} \cos \theta \qquad (9)$$

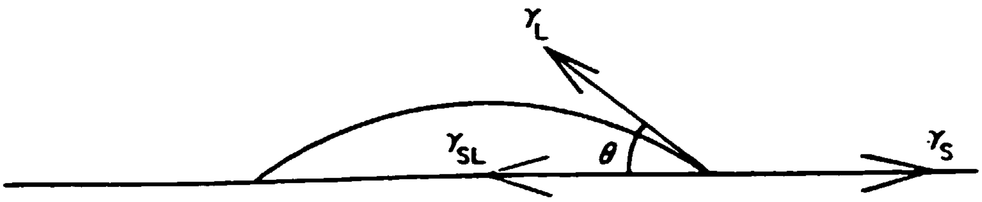

Figure 5. Schematic representation of a drop on a leaf surface.

Wetting is sometimes assessed by the value of the contact angle; the smaller the angle the better the liquid is said to wet the solid. Complete wetting means that the contact angle is zero, whereas complete non-wetting dictates an angle of 180°. In most practical systems, the angle exhibits hysteresis, i.e. its value depends upon the history of the system and varies according to whether the given liquid is tending to advance across or recede from the solid surface. One of the most important factors that causes hysteresis is surface roughness which for most leaves is the rule rather than the exception.

Several indices may be used to describe the wetting of a leaf surface, of which the spread factor (SF) and spreading coefficient (S) are the most commonly used

$$SF = D/d \qquad (10)$$

where D is the area wetted on the leaf and d the droplet diameter.

The spread factor can be calculated from the contact angle,

$$SF = [4 \sin^3 \theta/(1 - \cos \theta)^2 (2 + \cos \theta)]^{1/3} \quad (11)$$

The spreading coefficient S is given by the expression,

$$S = \gamma_{SA} - (\gamma_{SL} + \gamma_{LA}) = \gamma_{LA} (\cos \theta - 1) \quad (12)$$

If S is positive, the liquid will spread until it completely wets the solid. If S is negative the liquid forms a non-zero contact angle (partial wetting).

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MODERN FORMULATIONS - KEY TO SAFER PLANT PROTECTION

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ABSTRACT

The development of safer and more effective products through improvement in formulation and packaging is described. Innovations with emulsions in water, water dispersible granules, effervescent tablets, water soluble bags, seed treatment and microencapsulation are presented.

INTRODUCTION

In 1988 the world's farmers and fishermen provided approximately 4.3 billion tons of food, twice as much as they harvested in 1963, twenty five years earlier. If the current per capita consumption remains constant, population growth will require food and fibre for 6 billion people by the year 2000 and for 8 billion by 2025. The annual world food demand by 2025 could be 9 billion tons.

Fortunately there are several agricultural technologies available or well advanced in the development pipeline that can be employed to raise crop yields in low-income, food deficit countries, by 50-100%. One of the inevitable, yet increasingly unpopular means for productivity improvement will be the intensive use of plant protection agents.

The trend in the development of formulations goes towards safer formulations both biologically and from the viewpoint of the operator. Regulatory pressure from environmental and consumer areas is expected to continue.

The role of the formulation chemist in developing safer, more revolutionary types of products will become increasingly important to counterbalance stringent registration requirements.

ADVANCES IN PACKING DEVELOPMENT

Squeeze Bottles

Squeeze bottles represent a relatively simple yet effective means of improving the accuracy of dosing liquid pesticide formulations and at the same time, reducing the danger of accidental spillage of product. Different models are available on the market (Fig. 1).

TOP PAC

Another new, improved package for flowable formulations is the 'TOP PAC 5 L' container. It is an environmentally friendly design, easily rinsable, i.e. less than 0.01% of the product is left inside after triple rinsing with water. It has a 63mm standard neck, to fit European Closed Application Systems. HF-induction sealing provides high safety and tamper-proof standard.

EMULSIONS IN WATER AS REPLACEMENT FOR EMULSIFIABLE CONCENTRATE FORMULATIONS

One of the most marked changes in the popularity of conventional formulations towards the development of newer, safer products is the trend away from solvent-based towards water-based and solid agrochemical products. Emulsifiable concentrates (EC) are flammable and dermally more toxic than other formulations. In the formulation segment water based, liquid formulations we have on the one side well established over 20 years the very successful suspension concentrates (SC) which are feasible for almost all solid active ingredients with low water solubility. For the formulation of liquid active ingredients, emulsions in water (EW) can partially replace ECs. Water-based emulsions offer an improvement over emulsifiable concentrates in that they are of lower toxicity, flammability, are less irritant and utilise little or no solvent. For the formulation chemist, aqueous emulsions do pose more difficulties. The limiting factor for the successful development of EWs is the hydrolytical stability of the active ingredient (a.i.), which is especially critical for organophosphorous esters.

In the product range of Ciba-Geigy, the following EWs have been developed as replacement for EC s: isazophos 500 EW, diazinon 600 EW, furathiocarb 500 EW, cypermethrin 300 EW, metolachlor 720 EW and pretilachlor 300 EW.

Fig. 2 demonstrates different ways of improving handling- and user- safety of agrochemical products by appropriate changes in the types of formulations.

WETTABLE POWDERS IN WATER SOLUBLE BAGS

There is a move away from wettable powders (WP) and powder seed treatments as they are dusty, difficult to measure and bulky. However their safe use will be prolonged by the strongly increasing popularity of water soluble packagings made from polyvinylalcohol (PVA) and polyesters.

The advent of water- soluble bags (WSB) for pesticides is breathing new life into the use of wettable powder formulations.

The advantages of water-soluble packaging include:

- environmental acceptability, since the bag dissolves completely and the remaining packaging material contains no residues so is not classed as hazardous waste

- user safety, since direct contact with the product is avoided

- precise dosage of the pesticide, with no waste.

Water-soluble film is somewhat more expensive than conventional packaging materials but many farmers are prepared to pay a small premium in view of the associated health and safety benefits.

The concept of water-soluble packaging is now very well established in the United States of America, in Switzerland, Denmark, France, Germany and the United Kingdom.

WATER DISPERSIBLE GRANULES

Another way of avoiding dustiness and low bulk density of WPs is the presentation of agro-products in the form of water dispersible granules (WG). Water dispersible granules, which do not use solvents, are non-dusty, free-flowing and allow easy pack disposal; they are a desirable formulation and preferable to wettable powders. They have been developed in the 1980s and have become more important, particularly in the last five years. However, they have proved more expensive and more difficult to manufacture than WPs. In principle, WGs combine essential advantages of emulsions and powders (Fig. 3).

Basically there are two main technologies for the production of WGs: powder granulation and suspension granulation (Fig. 4). Production of WGs by powder granulation comprises the following basic technology steps: mixing, milling, feedstock wetting, granulation in a pan, Schugi Flexomix or extruder, drying and classification. Today, for each step, several producers offer technologically mature solutions according to the special needs of the producer. Suspension granulation relies on the use of flowable technology, comprising stirring kettles for the preparation of suspensions, wet mills such as delivered by Netzsh, Bachofen (Dynomill) or Boesch (Cobol mill), and spray driers or fluidized bed driers as those produced by Niro, Glatt, Alpine, Anhydro etc.

WGs differ somewhat in their physical properties according to their technology of production. When obtained by powder granulation, WGs generally have a larger diameter, lower bulk density, slower dispersion time and lower dust content than when produced by suspension granulation.

In contrast to WPs, WGs can be measured volumetrically like liquid formulations but the advantage of correct and easy dosing can still be enhanced by packaging them in WSB. One example introduced very successfully is primisulfuron (TELL 75 WG), a highly active corn herbicide delivered to the customer in 40g portions in water soluble bags. The contents of one WSB will treat 2 hectares.

EFFERVESCENT TABLETS

Further modern solid formulations, which can potentially replace wettable powders, are effervescent tablets. The technology for their production can basically benefit from the experience of pharmaceutical tablet producers with the difference that tablets for agricultural use are larger in size to avoid accidental swallowing. Nevertheless they have in common with effervescent vitamin tablets a short dissolution time of 1-2 minutes. In addition they must form a very fine dispersion in the spray liquid in order to pass nozzles as small as 120μm in diameter. Examples of this new product type are tablets of the penconazole fungicide introduced in 1990 in France and triasulfuron, a sulfonylurea for weed control in cereals. The farmer applies 4 tablets of the former per hectare and for the latter only one tablet per ha.

EMULSIFIABLE CONCENTRATES IN WATER SOLUBLE BAGS

It is possible that the trend away from solvent based formulations may be arrested by packaging ECs in water soluble sachets, such as one manufacturer has done for the herbicide mixture containing bromoxynil octanoate + ioxynil octanoate. As secondary packaging a yoghurt beaker is used. However, this new way of improving the handling safety of an EC- formulation still suffers from essential drawbacks. Firstly the inflammability of the formulation is not changed and secondly the physical strength of the product i.e. the entity of formulation plus packaging is too weak. If the package is dropped from 1.2 metres, the outer package and the water soluble bag will break. Therefore this type of product does not fulfil United Nations transport regulations but is an interesting new "lead".

SEED TREATMENT FORMULATIONS AND TECHNOLOGIES

From the ecological standpoint, pesticide application by seed treatment is a very elegant method of plant protection. Applying a fungicide or insecticide directly to the seed means placing the pesticide exactly to the location where it is needed for protection of the growing crop and avoiding unnecesary excessive quantitites of a.i. in soil and water.

The first and oldest type of seed treatment formulations was a dust formulation, the DS (dust for seed treatment). It is a solid formulation of an active material adsorbed or mixed with a finely ground carrier like silica. DS formulations are designed to be used without the addition of water to powder the seed. Today this formulation is old fashioned.

The next step in the development of safer seed-treatment formulations are water dispersible powders (WS formulations). They are in principle classical wettable powders. Slurry concentrations of about 30-40% are used in comparison to 0.5 to 1% WP application on crops or soil.

More modern formulation types for seed treatment are liquid, water based (LS) formulations. LS are true solutions of the active material in a solvent. This solvent is preferably water or a hydrotrope such as cumenesulfonate which can enhance the solubility of active materials which are normally not water soluble.

Emulsions for seed treatment (ES) consist of finely dispersed droplets of a normally liquid active material in water and correspond to EWs in conventional r[illegible] protection.

Flowable concentrates for seed treatment (FS) are suspensions of fin[illegible]y dispersed solid particles of active material in water, corresponding to suspension con[illegible]ntrates (SC).

Seed treatment is a cheap and simple method of application for the small farmer. Water based seed treatment formulations, such as of the fungicide fenpiclonil and of the insecticide furathiocarb can be applied to the seed by simply mixing in an Erlenmeyer flask for 1-2 minutes.

The use of a Hege seed treater is a more sophisticated method suitable for the laboratory and the small farmer. The applied liquid is distributed on the seed by spreading it with a spinning disc.

The 'Amazone' is a very good batch treater. It can be used with about 50kg of seed and offers a very homogeneous treatment. It is preferably used on farm sites for direct pre-sowing application.

Heid and Gustafson and other companies produce continuous treatment machinery for large scale application in specialised treatment plants.

Ciba-Geigy has sucessfuly entered the seed treatment market with modern active ingredients such as the fungicides metalaxyl (APRON), fenpiclonil (BERET) as well as the insecticide furathiocarb (PROMET).

With fenpiclonil, toxicological data show the FS formulations to be no more toxic than technical fenpiclonil. Different FS formulations of fenpiclonil alone or in mixture with imazalil and carboxin have been developed for cereals (wheat, rye, barley and oats), used at 400ml per 100kg of seed, and for leguminous crops, rape and potato.

Furathiocarb entered the seed treatment market in 1985 with two PROMET DS formulations, followed by solvent based formulations in 1987. 'ROMET 300 ES was introduced in 1986. It is purely water-based formulation with very good oral and dermal toxicological values (Fig. 5).

However, this year Ciba-Geigy has introduced a new type of seed treatment product: PROMET 400 CS. This formulation contains the a.i. in microencapsulated form. It has a large insecticidal spectrum, can be used in cereals, corn, rape, vegetables and sugar beet at amounts of 250-6000 ml/kg seed, and is very safe as demonstrated by the favourable toxicity values of Fig. 5.

MICROENCAPSULATION TECHNOLOGIES

Microencapsulation is a powerful tool for getting safer plant protection products. All modern methods of formulations, mentioned so far, can effectively improve product safety during storage, transportation, handling and dosing. However, all those methods do not improve unwanted physical and biological properties of the a.i.. Yet this is possible by controlled release technologies listed on the right hand side of Fig. 6. These not only improve hygiene and comfort during storage, transportation, handling and application but also influence and change properties of the active ingredient - such as acute mammalian and fish-toxicity, evaporation loss, duration of biological efficacy, phytotoxicity, leaching into soil and groundwater.

Under the headline of controlled release all technologies which can delay the immediate availability of the full dose of an a.i. may be grouped. Various technologies are available to the formulation chemist, of which microencapsulation is considered in detail.

Microencapsulation by 'Interfacial Polymerisation' can yield formulations of considerably reduced mammalian toxicity as already demonstrated with the example of PROMET 400 CS (CS = capsule suspension) for seed treatment. In order to be successfully applied through controlled release technology, interfacial polymerization requires a.i.s of low water solubility which are liquids or can be molten at temperatures not higher than 70°C. The basic chemical reaction leading to polyureas or polyamides is described in Fig. 7.

The production technology as schematically shown in Fig. 8 requires as critical pathways very precise dosing of reaction compounds (rc) and high efficiency stirring for the formation of small droplets in the range 2-20μ diameter.

Fig. 9 shows microcapsules of isazophos (MIRAL) with a medium diameter of 6μ in the electron microscope.

In Fig. 10 comparative toxicological data of different isazophos formulations are presented. Isazophos, an excellent phosphorus ester insecticide can be formulated as EC, GR and CS. The improvement in toxicity from liquid EC 500 to solid GR 3 and encapsulated CS 500 is obvious, although the low percentage granules and the capsule suspension could not be meaningfully tested in acute dermal studies.

Reduction of evaporation losses by microencapsulation is demonstrated in Fig. 11 in the example of different microencapsulated isazophos formulations. Whereas the relatively volatile a.i. evaporated almost completely from a teflon strip within 4 hours at 40°C, it is strongly retained with increasing capsule diameter.

If a product has a short effective life in the field, its biological activity can be extended to some degree by microencapsulation. If biological activity is extended, fewer applications need to be made.

CONCLUSIONS

The above examples of modern product presentations demonstrate that the formulation chemist can successfully accept the challenge of improving the environmental and user safety of agrochemical products. We hope to convince an increasing opposition of environmentalists that chemical plant protection is beneficial, safe and remains essential to the maintenance of our quality of life.

Since the chance to discover and develop successfully new plant protection molecules is decreasing, product enhancement with existing and registered compounds by improved formulation and packaging will play an increasingly important role in the marketing of safer, tailor-made plant protection products.

However, the design, development, scale up and construction of production facilities for these new formulation technologies are costly and time consuming. It may, as in the case of microencapsulation technologies, take up to 7 years from the first idea to the market introduction and large scale production of the new product. Therefore, industry must seek to protect these technological inventions as well as new active ingredients by adequate patents.

Figure 1. Typical squeeze bottles

Figure 2. Potential ways to improve safety of formulations

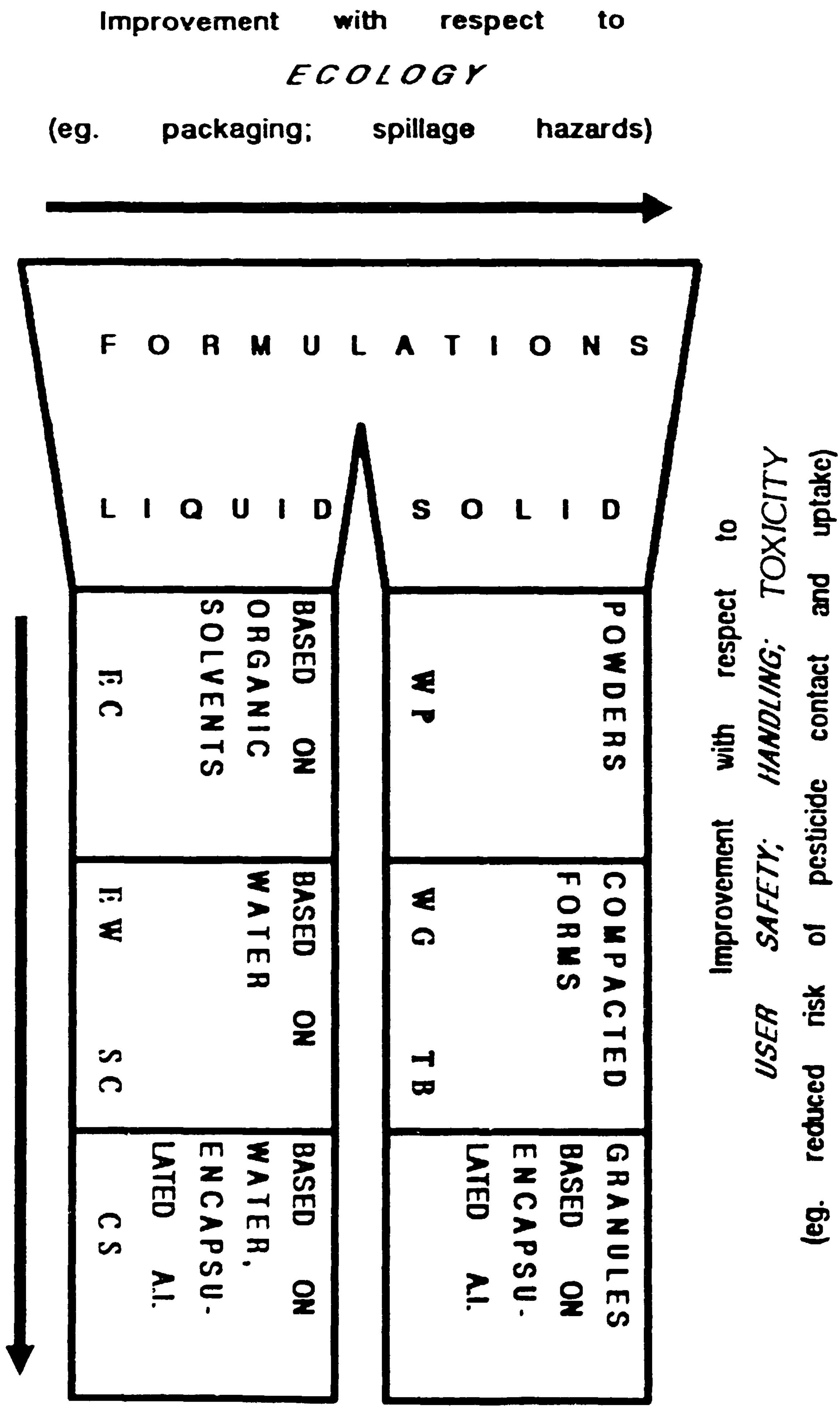


Figure 3. Advantages of water dispersible granules.

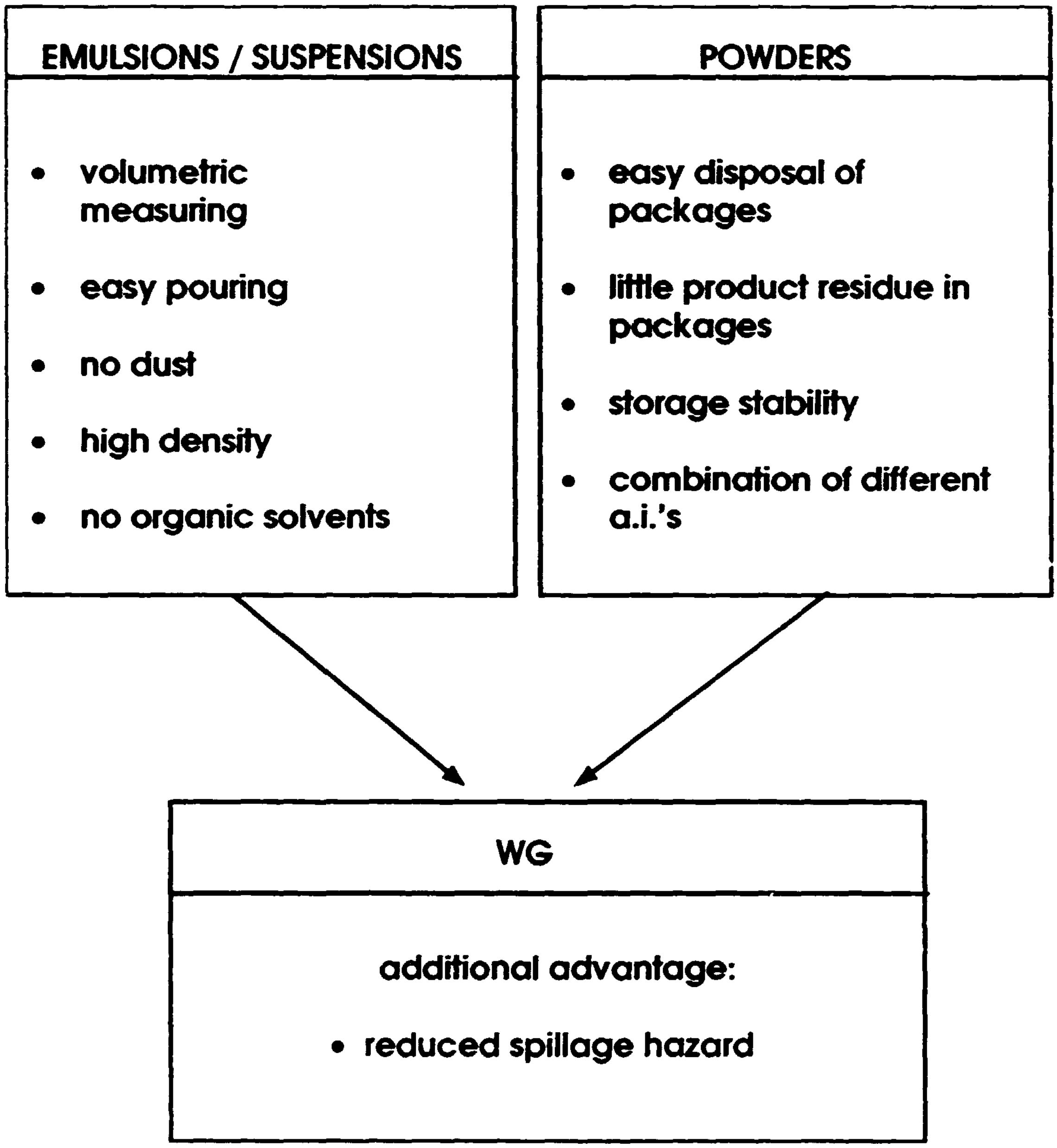


Figure 4. Technologies for production of water dispersible granules.

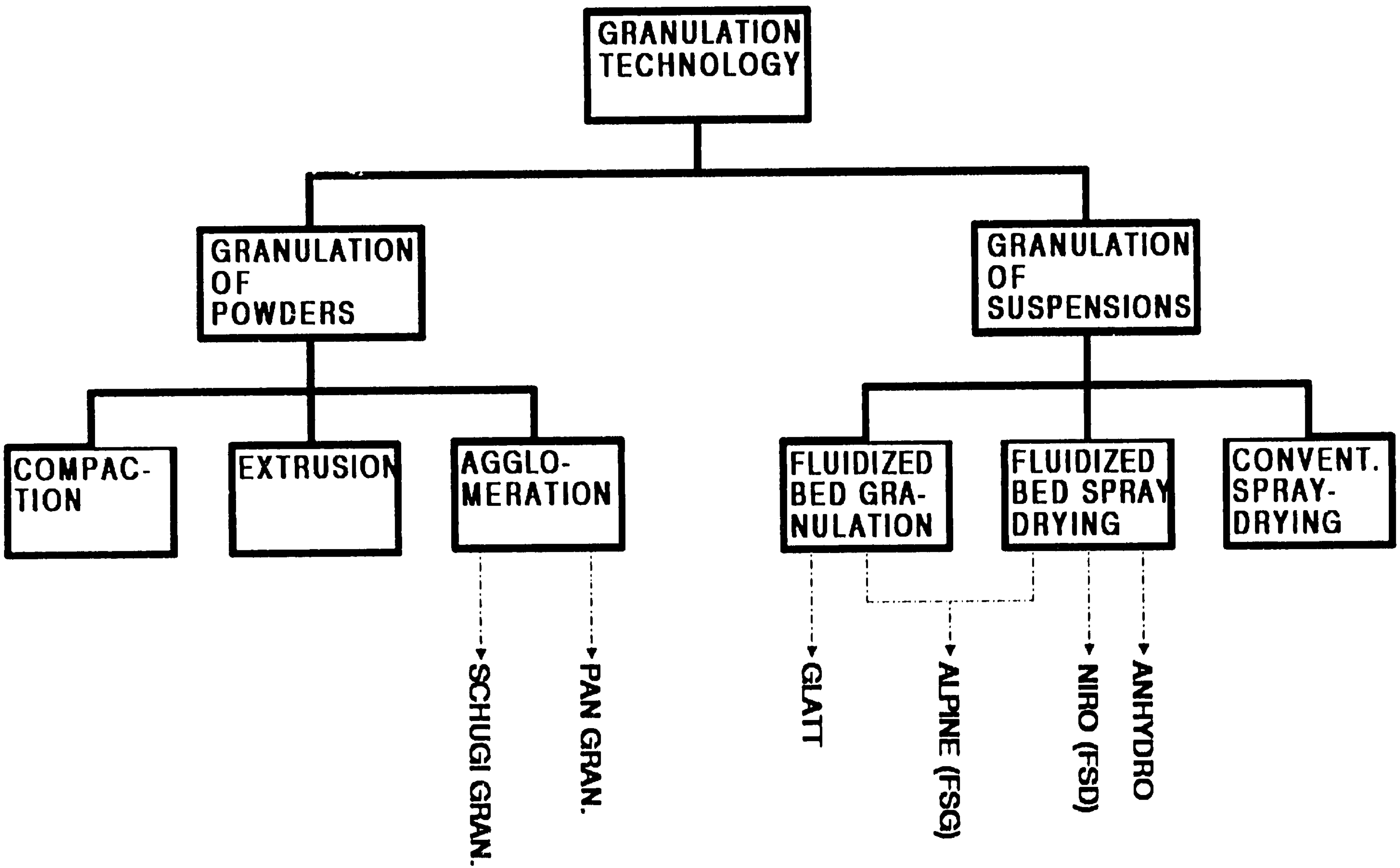


Figure 5. Profile of seed treatment formulations of furathiocarb.

Common name	furathiocarb	
Efficacy spectrum	sucking and biting insects	
mode of action in plants	systemic	
vapour pressure (Pa 20©)	8.4×10^{-5}	
water solubility (ppm)	10	
Formulations	ES 300	CS 400
LD_{50} rat oral in mg/kg	> 2000	> 3000
LD_{50} rat dermal in mg/kg	> 2000	> 4000
LD_{50} rat Inhalation in mg/kg	?	> 1270
skin irritation (rabbit)	none	none
eye irritation (rabbit)	none	none
bird toxicity (LD_{50} in mg/kg) quail	4	416
WHO class	IB	III

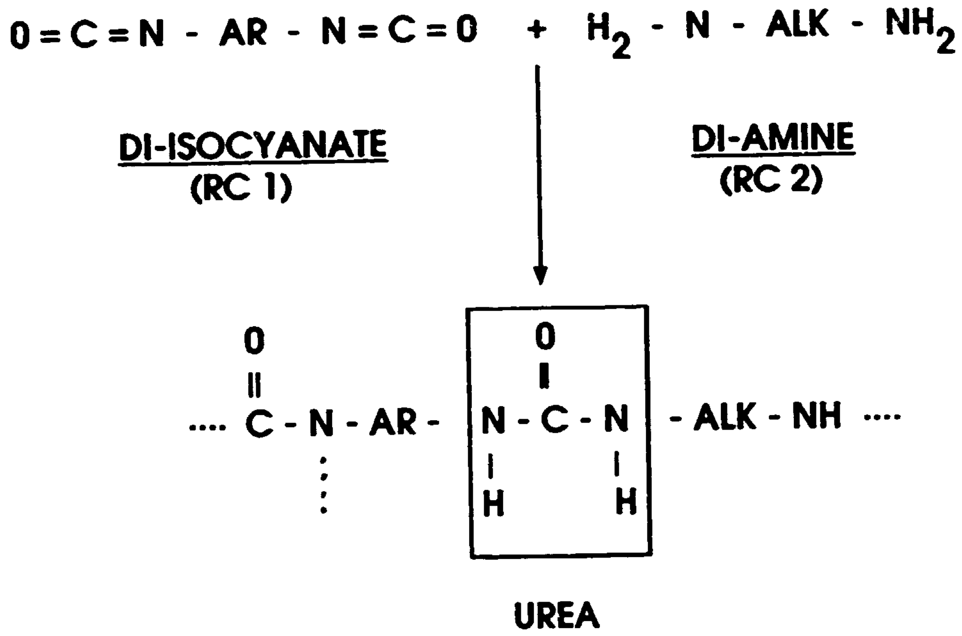
Figure 6. Summary of improvements in product presentation.

A: Handling, dosing hygiene, disposal	B: Biology, Toxicology Ecology(e.g. leaching)
• squeeze bottle	• Microencapsulation
• EC → EW	• Coated Powders
• EC → GR	• Polymer matrix GR
• water soluble bag	• Microcapsules → GR
• WP → WG	
• WP → TB	
• Seed treatment	

TB = tablet GR = granule

Figure 7. Interfacial polymerisation: basic chemical reaction.

1. POLYUREAS FORMATION



2. POLYAMIDE FORMATION

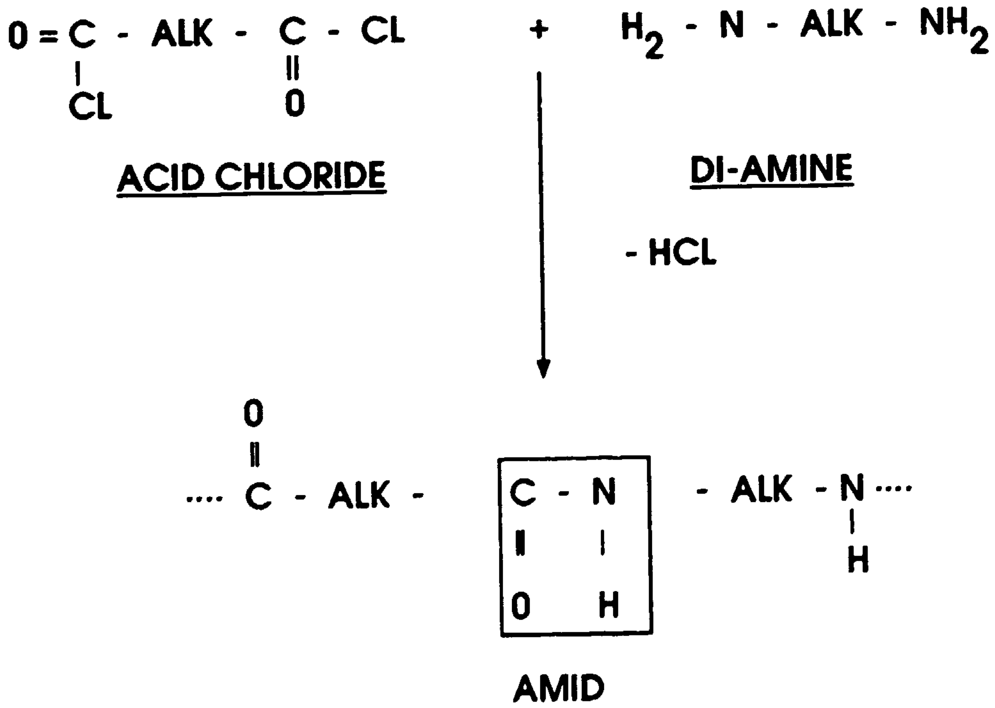


Figure 8. Interfacial polymerisation: basic production technology.

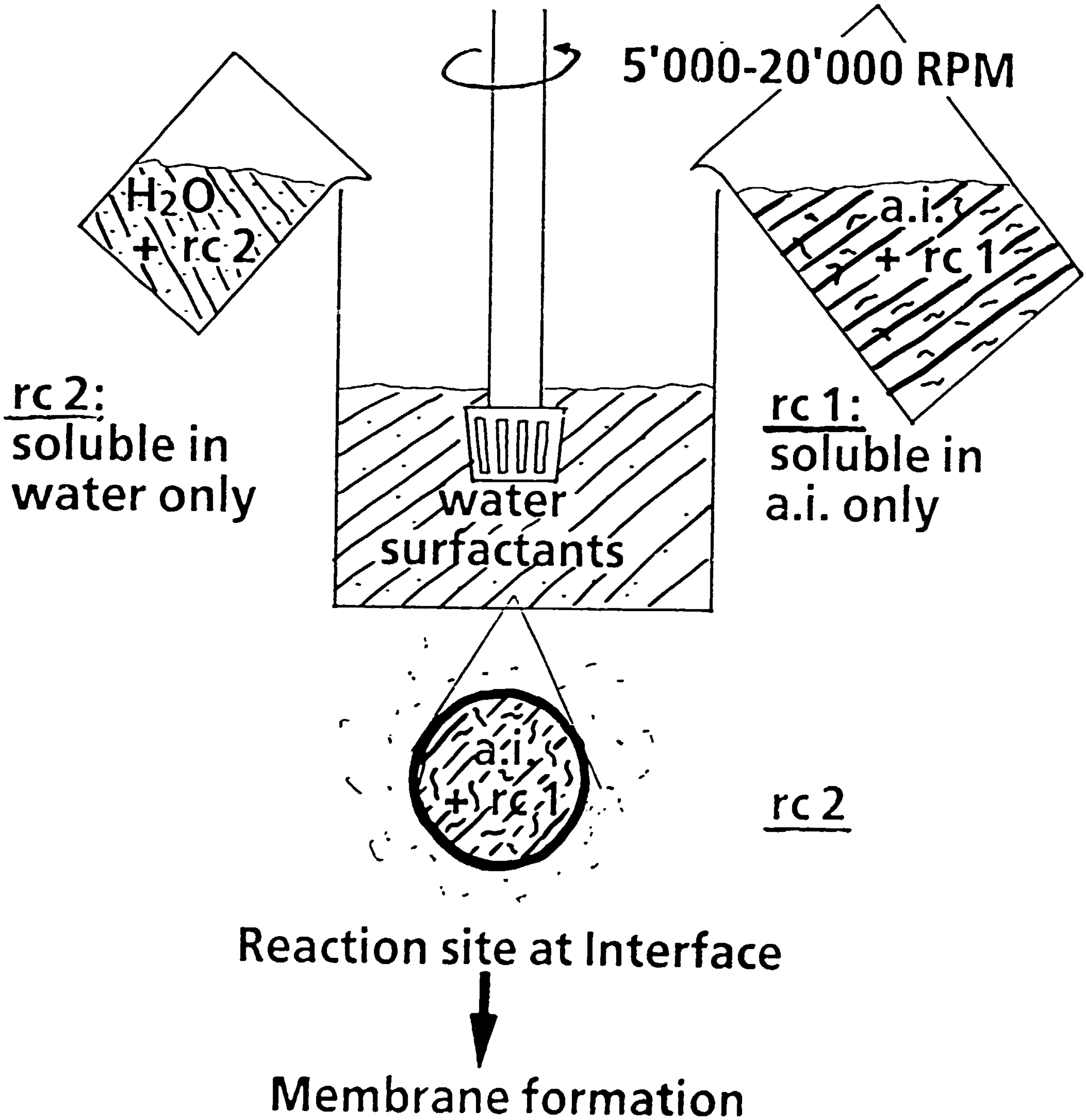
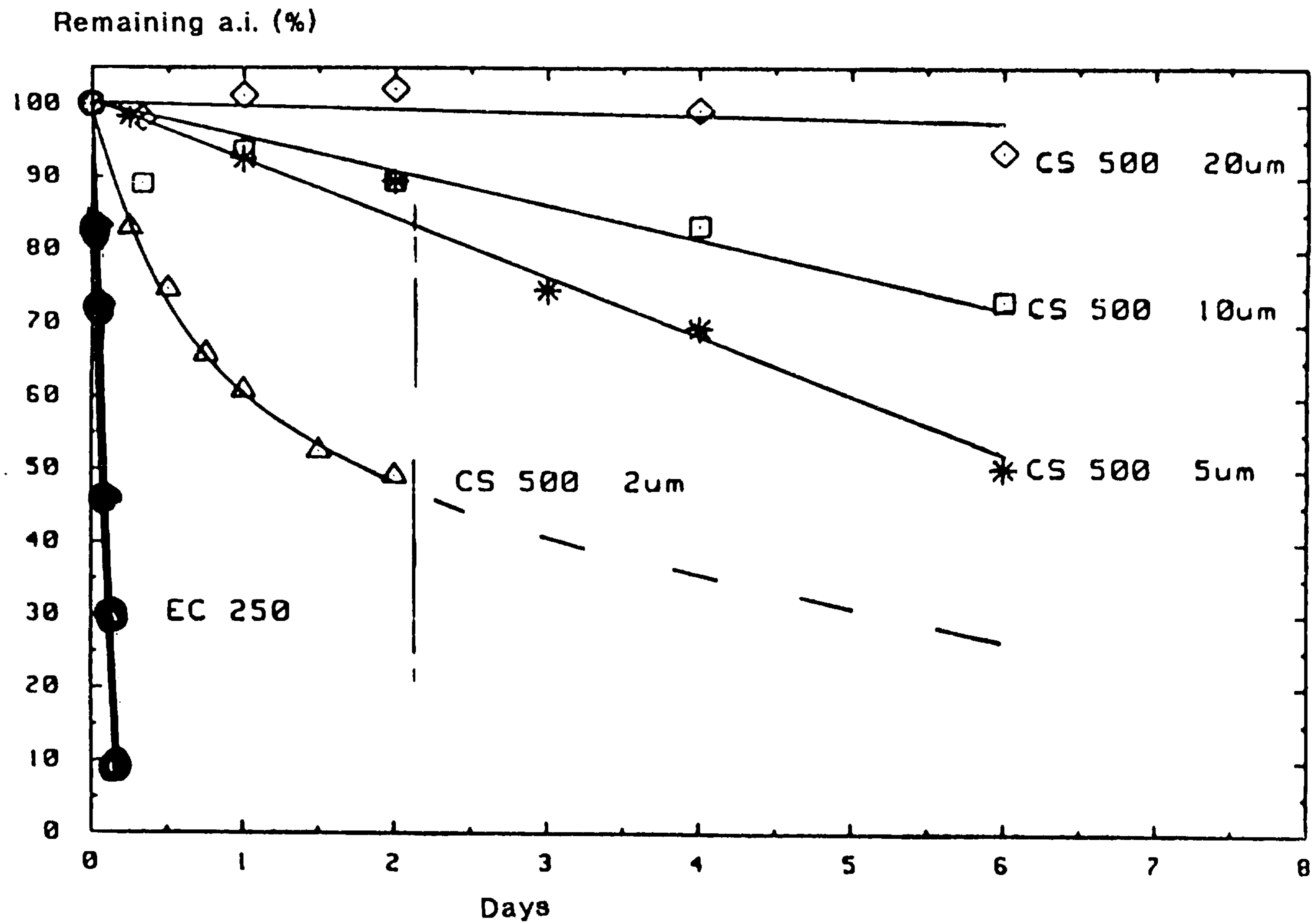


Figure 9. Electron microscope photograph of capsules of 'Miral 500 CS' formulation of isazophos.

Figure 10. Comparison of toxicity of formulations of isazophos

PRODUCT	RAT LD_{50}, DERMAL (MG/KG)	RAT LD_{50}, ORAL (MG/KG)	FISH (C.CARPIO) CL_{50} IN VITRO	BIOLOGICAL ACTIVITY
MIRAL 500 EC	747	74	< 0.1 mg/kg	IN VITRO EFFICACY OF CS EQUAL TO EC NILAPARVATA + WHORL MAGGOT FLY
MIRAL 3 GR	> 2'000	> 3'000	----	
CGA 12223 CS 500 (10 % Polymer; 6 μ)	> 2'000	> 5'000	> 10 mg/kg	Equal control of EC and CS in field trials (Gallmidge & Stem-borer)

Figure 11. Reduction of evaporation losses by microencapsulation of isazophos



PLANT PROTECTION IN TROPICAL COUNTRIES

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ABSTACT

The main aim of plant protection is to prevent losses by pests, diseases and other environmental influences in agricultural production and storage and in this way help to solve world food problems. The yearly losses in quantity as well as quality range between 10% and 50% of the potential yield of different crops of which the highest rates are in developing countries of the tropics and subtropics. Plant protection does not mean the application of pesticides but the use of prophylactic measures (especially in the form of cultural methods), protection activities, the introduction of biological control measures and the selection and use of pesticides that are environmentally friendly. In view of these aspects a number of approaches have been taken into consideration in the paper.

Plant protection means in general all activities to prevent losses caused by pests, diseases and other environmental influences in agricultural production and storage, thus helping to solve world food problems. Unfortunately there is a misunderstanding especially in tropical countries where crop protection is seen from the aspect of pesticide application. Who induced this point of view? Not the native people but supervisers in different fields, either from pesticide industries or agricultural project managements. They propagated the use of pesticides from the standpoint of quick and impressive effects without considering the side effects and their influence on the environment. This resulted in an inappropriate application of pesticides, wrong in type and dose, unnecessary environmental pollution and poisoning of animals and human beings.

Let us come back to the main aim of crop protection, i.e. to prevent losses. To prevent them presupposes knowledge about their origin and economic significance. In this connection we will pay attention to three main points: the ecological situation, the susceptibility of the plants and the local conditions.

TABLE 1

Yield losses, world average in % [1]

	Wheat	Rye	Barley	Rice	Sorghum/millet	Maize	Potato	Sugarbeet	Sugarcane	Fruits	Citrus	Coffee	Cocoa	Tea	Tobacco	Soybean	Groundnut	Cotton
Pests	5	2	4	27	10	12	7	8	20	7	8	13	13	8	10	5	17	16
Diseases	9	3	8	9	11	9	22	10	19	8	10	17	21	15	12	11	12	12
Weeds	10	9	9	11	18	13	4	6	16	2	4	15	12	9	8	14	12	6
Total	24	14	21	47	39	34	33	24	55	17	22	45	46	32	30	30	41	34

1. In a basic natural ecosystem there is a dynamic biological balance. There are no disease epidemics and no pest gradations but agricultural productivity is low and yields are insufficient compared with needs. In the interest of increasing agricultural production this balance is shifted, depending on the intensification of production. In developed countries with industrialized agriculture this trend led to a very high intensity and consequently to surplus production. In developing countries, and these are mostly countries of the tropics and subtropics, this strong deformation of the ecological balance is still only limited. This means that the greater the destruction of a natural ecosystem the more the need for intensive crop protection measures and vice-versa. However, low productivity is associated with low yields. Therefore, it is necessary to increase productivity but it seems unnecessary to use in developing countries the same methods as are used in developed countries. Measures used have to be adapted to the existing local conditions.

2. It should be mentioned that the native types of our agricultural crops had a high resistance to environmental influences, but their yield was low. In the interest of increasing yields, plant breeders developed high yielding varieties with increased susceptibility to pests and diseases. In connection with the "Green Revolution" it was shown that the sole use of high yielding varieties is insufficient, if the other intensification measures like mechanization, fertilizer use and even crop protection were neglected. This means that the greater the distance of a variety from its origin, the greater the need to protect it against pests and diseases.

3. Agricultural crops in their original environment are more or less protected against pests and diseases by natural enemies and other environmental influences. If we shift them to new locations they are faced with a new ecosystem; new conditions to which they may not be sufficiently adapted. In conclusion, the shift from the natural ecosystem to the agro-ecosystem disturbs the established balance. The change from native type to high yielding varieties confers a decrease of natural resistance. The main aim of crop protection is to compensate these negative influences on agricultural crops.

These ideas suggest that the use of pesticides is not the first task in crop protection. The analysis of a given situation, including ecological and sociological analysis, will lead to other possible solutions in tropical countries that are also applicable in countries with intensive agricultural production. The above facts show that careful handling of the ecosystem by plant hygiene measures is of great importance. This means the selection and preparation of the proper location for the production of a given plant, the use of modern cultural methods, and full attention to the breeding of resistant varieties should be preferred. The second method should be the management of the ecosystem to support natural enemies, to increase the antiphytopathogencity of the soil, to introduce and release natural enemies from other locations, to stimulate viral, bacterial or fungal epidemics in insect populations and the like. Within this ecological management the application of chemical pesticides for controlling pests and pathogens should be included.

The second question which arose at the beginning was the economic significance of yield losses in agricultural production. According to Cramer [1] and other sources [2, 3, 4], the yearly yield losses of agricultural crops caused by pests, diseases and weeds, in terms of world averages, range between 10 and 50% of the potential yield (Table 1). Highest losses are noted in sugar cane production (55%), cocoa and rice (46%), coffee (45%) and groundnut production (41%) mainly cultivated in tropical and subtropical countries, in contrast to rye production (14%), citrus (22%), wheat and sugar beet production (24%). These and other figures show higher yield losses in developing countries of the tropics and subtropics especially in Africa and Asia. The reasons for this situation are not only changes in the ecosystem caused by breeding of high yielding varieties, or transfer to new locations, but also the particular socio-economic conditions in these countries, including farming systems, farm size, income of the farmers and their level of knowledge.

The lowest type of farming system is subsistence farming with exploitation of natural resources and the so-called shifting cultivation with fallow. Under these conditions there is no danger of accumulating pests and diseases on plants. The only exception may be grass-hoppers, weaver birds or sparrows. The productivity is very low considering the yields obtained.

The next step to increase productivity is land rotation with bush or grass fallow. For plant protection in regions with such a farming system it is advisable to use pesticides for the disinfection of seeds and planting materials, with special regard to damping off and smut diseases in sorghum, corn and other cereals and vegetables. In addition we have to mention the migration of pests from surrounding fallow areas into the fields.

These primitive kinds of cultivation make few demands on plant protection. Only the intensification of production can promote its development. In crop farming this implies crop rotation as a production system, which means the continuous use of available land. The level of intensification resulting from this kind of cultivation depends on both the socio-economic structure and the developmental stage of the production technology, including all measures for soil improvement, plant nutrition and cultivation, and using more and more sophisticated equipment. In this process of obtaining the best output per hectare by means of a comprehensive input of labour and a reasonable organization of work, the demands on plant protection become increasingly evident. For the time being we have to accept that mixed cropping and similar arrangements will dominate in the farming systems of developing countries.

Summarizing, we have pointed out that the application of plant protection measures including pesticides depends essentially on the actual production level. For rain-field cropping plant protection measures are only efficient with the beginning of crop rotation, and for the cultivation of permanent crops are only efficient if the plantations are established systematically. Irrigated farming occupies an important position and involves larger investments. Therefore, from the very beginning one should strive for an intensive production and a developed plant protection in accordance with the actual level of mechanization and organization.

Another factor which influences the activities in crop protection is farm size or size of the cultivated area. If we look at several developing countries in Africa and Asia we find that individual or family sized farms between 1 and 4 hectares represent 80 to 95% of the total available farmland. Thus, even in medium sized farms only simple and inexpensive plant protection measures can be introduced. Farmers have to understand that crop protection is not a job for one person but a joint activity. Cooperative work is necessary to overcome the problems. A simple step may be the so-called common crop rotation. This means that neighbouring farmers produce the same crop in a given area and at another place they produce together different crops. Through this proposal the field size for one crop increases, making it easier to observe and control pest and disease attacks.

Another approach is seen in settlement schemes like Gezira in the Sudan. Such schemes offer more favourable prerequisites for the intensification of production, including the application of appropriate plant protection measures.

Finally we want to mention the formation of agricultural multipurpose co-operatives. They can be organized as follows:

- central seed cleaning and seed dressing,
- protection methods for stored products,
- training and advice for farmers in simple plant protection operations within the range of the general production technology,

- organization of specialized groups for field operations, including pesticide application and the permanent training of farm workers.

One limiting factor in using expensive pest control measures is the yearly income of the farmers. Statistics of the Food and Agricultural Organisation (FAO) and other institutions show a range between $110 (e.g. India) and $650 (e.g. Argentina) under subsistence conditions. Only with the production of cash crops is there a little surplus and some possibility for the application of pesticides, as we found in banana production in Guinea, West Africa.

In this connection the qualification of the producers in general may be of far more importance. We are aware of literacy campaigns in developing countries and of activities for training people in several fields. These activities may reduce the illiteracy but this needs time. Crop protection, especially the use of pesticides, is a present-day problem and requires knowledge and qualification. Under these conditions we should classify crop protection measures into two groups:

1. Measures which are part of the general production technology, available to all producers, e.g. the selection of pest and disease-free seeds and seedlings; plant hygiene methods like the destruction of plant residues after harvest by deep ploughing in order to control rice stem borers, or against the same pest by flooding the field for 3 to 6 weeks; the planting of catch crops for controlling plant hoppers and aphids; the arrangement of mixed cultures, e.g. of maize and sweet potatoes for controlling *Diabrotica* - beetles, etc.

2. Measures and methods which demand special knowledge, materials and machinery. To this group belong:

   - breeding of resistant varieties,
   - biological methods for controlling pests and pathogens e.g.,
     . mass-rearing and release of parasitoids, such as the egg-parasitoids of the genus *Trichogramma*;
     . confusion techniques with pheromones to disturb mating within a given pest population;
     . sterilization techniques, also called the autocide method;

treatment of epidemics in pest populations with viruses, bacteria or fungi. Already well known is *Bacillus thuringiensis* and its different subspecies. application of pesticides. Unfortunately the danger they may represent is underestimated and everybody believes it is correct to use them. Although no farmer will give his cow any medicine without the advice of the veterinarian, it seems that the use of pesticides in fields and plantations does not merit the same care. Therefore we welcome the activities of FAO, Groupement International des Association Nationales de Fabricants de Produit Agrochimiques (GIFAP) and other organizations in promulgating instructions about pesticide use like "Guidelines for the safe transport of pesticides", "Guidelines for the avoidance, limitation and disposal of pesticide waste on the farms" [3, 4]. In this connection the "International Code of Conduct on the Distribution and use of Pesticides" is of very great importance. The purpose of this Code is to ensure the more effective and safe use of pesticides, especially in countries with insufficient regulations provided by government, insufficient infrastructure for controlling pesticide use and insufficient instructions for application by producers.

In conclusion we can state:

A low level of production on small farms and a low income of farmers, as in developing countries of the tropics and subtropics, force on the one hand the selection of simple but effective control methods and, on the other, joint working efforts within the communities, a strategy which should be supported by the government. With the increase of productivity in relation to the cultivation of high yielding varieties, mechanization, use of fertilizer and other activities, plant protection with a higher intensity and efficiency is needed.

In the situation found in the tropics for crop protection the following points should be taken into consideration:

1. Local traditional methods in plant and storage protection should be analyzed from the beginning so that they fit into a supervised crop protection scheme including surveillance, determination of economic loss etc., up to the level of integrated pest management (IPM).

2. Training and advising farmers in applicable control methods especially in cultural practices and the training of interested farmers within the community to establish special application teams for biological and chemical control. Information about protective clothing should be included in this training.

3. Introduction of simple but modern methods to improve plant protection, e.g., surveillance of fields and plantations with respect to attack by pests, as in the use of pheromones in searching for economic losses and the optimal time for control.

4. Selection of pesticides with high insecticidal and fungicidal effects but very low human toxicity, including chemosterilants, insect growth regulators, inhibitors of metabolic processes, plant extracts like neem seed oil, derris, or quassia, and other materials, to reduce pest epidemics.

5. Organizing locally supervised crop protection with the aim of establishing IPM programmes.

IPM will become the strategy in crop protection, rather than the one-sided application of pesticides.

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CHANGES IN APPLICATION TECHNOLOGY TO MEET OPERATOR AND ENVIRONMENTAL SAFETY STANDARDS

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ABSTRACT

Concern about environmental pollution, crop residues and operator safety has led to new regulations governing the application of pesticides. In response to this, two lines of development of equipment have been pursued - namely the improvement of existing technology based on hydraulic spraying and, secondly, efforts to develop alternative technology, including seed treatment, granule application and different spraying systems.

Much emphasis has been given by the agrochemical industry to improving safety, through changes in formulation and packaging to reduce operator contamination. This has been accompanied by new sprayer designs which also improve safety and research is examining methods to facilitate mixing and transfer of pesticides by closed systems. In the United Kingdom definition of spray quality and improved selection of spray nozzles has been directed at reducing environmental contamination by drift. At present areas of concern include air-assisted spraying to protect trees where spray droplets are more likely to be carried by air movements out of the treated area. Recent research has led to the development of active boom suspensions, and extensive studies have examined different methods of electrostatically charging sprays, although there has been little adoption of this new technology in Europe.

A range of equipment to suit different size farms is now available and to ensure that this equipment is correctly used, training is now mandatory in the United Kingdom, so that accuracy of pesticide application will undoubtedly improve, particularly through better calibration.

All these changes do not overcome the inherent low efficiency of pesticide application, so alternative techniques, albeit less universal, aim to improve the targeting of spray deposits and timing of applications in response to pest monitoring. Reduced volumes using hand-carried spinning disc sprayers and electrostatically charged sprays are now used principally to control cotton pests in the semi-arid tropics in Africa and South America. The role of extension services in introducing new technology is discussed.

Charged sprays reduce the amount of pesticide that fails to reach its intended target and is ideal for small areas of crops where drift to other crops must be minimised. Progress for new techniques will depend on the development of new more active molecules that are not

only acceptable environmentally, but can be formulated in relation to developments in application technology. More interdisciplinary research is needed to develop more efficient delivery systems, but at the same time, regulatory authorities need to be receptive to the introduction of innovative technology.

INTRODUCTION

Man's quest to control pests in not new. 'Shifting Agriculture' opened up new land to avoid weeds and soil-borne pests, and farmers rotated their crops in different fields. However, many centuries ago man started to use chemicals; there are early records of using sulphur to protect the vine from fungal pathogens and the dried flowers of Chrysanthemum cinerariaefolium were used to protect stored grain. Lhoste [1] states that the insecticidal activity of pyrethrum was known in China in the first century A.D. In recent times the discovery of synthetic pesticides, starting with DDT and 2,4-D, led the way to an over-optimistic view that man could easily use chemical weapons to defeat the pests. To-day the overuse and mis-use of many pesticides has aroused considerable public concern about environmental pollution, the risk of residues in food to human safety and the hazards for those working directly in the fields.

In many countries legislation has now been introduced to improve safety and reduce the risks; thus in the United Kingdom there is the Food and Environmental Protection Act (FEPA) together with the Control of Substances Hazardous to Health (COSHH) regulations which have introduced statutory requirements for the safe and judicious use of pesticides. This includes mandatory training of those who apply pesticides on farms. Other papers at this conference will consider the legislative aspects in more detail, but this trend has implications in the way pesticides are applied and the design of equipment.

Traditionally most pesticides have been formulated so that the active ingredient can be mixed and diluted with water and sprayed through hydraulic pressure nozzles. Alternatively some chemicals especially the most hazardous have been applied as granules and a few have been used as dusts. Equipment used for their application was described by Matthews [2]. The two previous papers at this conference have referred to the changes in formulation technology. with greater emphasis on the application of suspension concentrates or dispersible grains rather than emulsifiable concentrates or wettable powders. Such changes are also being accompanied by the introduction of new methods of packaging including standardized containers with an opening to suit closed filling systems that eliminate the exposure of the operator to the most hazardous operation, namely the measuring out of the concentrate and transferring the product to the sprayer.

In the United Kingdom, efforts to reduce the risk of environmental pollution by spray drift have led to the introduction of a standard system of nomenclature for nozzles to indicate the type (fan, cone, deflector...), spray angle, output and operating pressure, without advertising any particular manufacturer's nozzle.

Thus a F/110/1.5/3 indicates a fan nozzle with a 110° spray angle emitting 1.5 litres per minute at 3 bar pressure.

This has enabled the agrochemical industry to be much more precise in recommending how their pesticide product should be applied, instead of giving a rather vague volume application rate. Alternatively the pesticide label may refer to a particular spray quality (very fine, fine, medium, coarse and very coarse) which in effect limits the choice of operating pressure in relation to a particular nozzle selected to give the appropriate output.

The adoption of criteria for spray quality has been made possible by advances in the methodology for measuring droplet spectra [3]. Computerized laser light diffraction and other measuring instruments enable a sample of spray to be measured within minutes. Most sprays in the United Kingdom will be applied with 'medium' sprays but some pesticides may require a 'fine' spray with smaller droplets, whereas if there is any risk of damage to a susceptible crop in an adjacent field, a coarse spray will be recommended. However it is essential to remember that all hydraulic sprays will contain a range of droplet sizes so even a coarse spray will contain some fine aerosol droplets. These smaller droplets are very liable to shrink in hot dry air, and become dry particles that are liable to drift over considerable distances. In practice drift is reduced if there is a slight wind which increases the proportion of droplets that are impacted on to nearby vegetation, so there has been a move away from the more traditional recommendation of saying the ideal conditions for spraying are 'calm' conditions, and now a wind speed of 2-5 m/s is recommended. Advice on the selection of nozzles for the farmer is now available in 'user-friendly' handbooks, published by the British Crop Protection Council.

For the large scale farmer with mechanised equipment, recent developments have included the introduction of design changes to facilitate transfer of the pesticide into the sprayer, for example suction probes or a low level mixing tank. Ideally the sprayer would be a closed system in which the tank would only contain water; the pesticide would be injected into the water as close to the nozzle as possible. Such a system needs to be designed to apply a range of dose rates with formulations of different physical properties [4], and at present there are very few sprayers of this type available. In the meantime conventional sprayers can be fitted with a rotary washer to clean the inside of the sprayer with minimal quantities of water after spraying has been completed and spray the washings on the edge of the treated field.

Some farmers have, however, adopted the use of air assistance in atomisation and delivery of the spray. One nozzle incorporates a baffle plate which breaks up the liquid into droplets that are mixed in a swirl chamber with compressed air, before being emitted from a deflector type nozzle. Studies have shown that the aerated droplets travel slower than conventional liquid droplets of a similar size, but are entrained in the air from the nozzle and get carried into the crop with less downwind drift. Sufficient power is needed to operate the compressor and care is needed to avoid excess air pressure which could produce too many small droplets.

Another type of air-assistance on sprayers designed for field crops is using a large fan to deliver air through an inflatable or rigid sleeve mounted just above the spray boom. Air escapes from the sleeve through apertures or a thin slit above and to the rear of conventional hydraulic nozzle so that the air projects the spray into the crop. The air assistance provides better penetration of crop foliage and has been used where control of whiteflies has been needed on cotton, in preference to aerial applications. The machine also allows spraying when wind might cause drift from a conventional spray boom.

Rotary nozzles designed originally for fitting to aircraft have been used on tractor mounted spray booms together with a hydraulically driven propellor to project the spray into the crop. Adjustment of the pitch of the propellor blades and speed of rotation can control the airflow. The swirling air flow is expected to improve the air turbulence within the foliage and provide better coverage of complex crop canopies.

Spray drift is clearly an important issue and much more work is needed to improve pesticide deposition on some crops. In particular, orchard crops are perceived to be more environmentally polluting as spray is often projected up into a crop canopy. However new agronomic practices and cultivars are providing smaller trees which are much easier to protect.

On the large tractor-mounted sprayers there have been changes in the design of boom suspensions, including the use of active boom suspensions to ensure nozzles are kept at the correct height above the crop.

Apart from these changes which affect the design of the larger mechanised hydraulic sprayers, there have been a number of developments of manually carried and more specialized equipment, several of which are particularly relevent to the many small-scale farmers in China.

MANUALLY OPERATED SPRAYERS

The earliest attempt to distribute a liquid pesticide over foliage was to dip a brush into an open bucket and splash droplets over the leaves. This method is still in use in many areas, but the idea of carrying the liquid in a container on the operator's back was soon taken up some 100 years ago [5]. The basic design of the lever-operated knapsack sprayer has remained unchanged to this day, although manufacturing techniques have changed and plastic materials have largely replaced most metal components.

It is unfortunate that the main criterion in selecting a knapsack sprayer, whether it is a continuously pumped lever-operated sprayer or a compression sprayer, has been its price, so sprayers are made in many countries as cheaply as possible. Such equipment often fails after relatively little use and may not be repaired easily if the user cannot obtain spare parts or lacks the knowledge needed to repair it. Spray is often spilt over the container, leakages occur and the lance is invariably held in front of the operator, who can get heavily contaminated with the pesticide. This has led to increasingly vocal criticism of pesticides in the hotter climates in developing countries where farmers cannot afford or wish to wear protective clothing.

Operator contamination can be reduced by better design of individual components on the sprayer For example the lid of the knapsack sprayer has always had a small hole to allow air to enter the tank during spraying, but if the operator bends down, liquid can spurt through the hole and contaminate his head. The hole can be simply blocked by a small valve that lets air in and prevents liquid escaping from the tank. Other design changes that some manifacturers are now adopting include improved design of straps and provision of a waist strap so that the container is held more firmly on the back and the weight is more evenly distributed. This allows a greater efficiency in transferring the effort of pumping into the pump action. A large air chamber to even out the pulsations in pressure with each pump stroke is essential but sprayers should also be provided with a pressure regulating valve that is easily set outside the container. This is needed so that the nozzle is operated at the correct pressure. A new design of 'spray management valve' is at present under development.

A major problem with these sprayers is the difficulty for farmers in applying the correct dosage, as the farmer has little idea how much liquid is applied on a given area of land or crop. The factors involved are walking speed, swath width (choice of nozzle and its position relative to the target) and output of the nozzle (nozzle orifice size, operating pressure). A simple method of calibrating the equipment is needed so that the farmer 'sees' the quantity of spray applied. One development has been the 'Kalibottle' graduated in litres per hectare, which is used to collect the spray while treating an area of $25m^2$.

Too often the cheaper sprayers are provided with only a single variable cone nozzle. Apart from the need to touch the nozzle tip to adjust the spray pattern, this type of nozzle is seldom set correctly for a particular type of pesticide. It is preferable to have a standard nozzle that can be fitted with one of a range of different types of nozzle tip to obtain the correct pattern and spray quality.

Efforts are needed to encourage operators to hold the lance downwind while spraying to avoid walking into the spray, or to accept mounting the nozzle on a boom to the rear of the spray tank. In Africa, several types of rear-mounted boom have been used. In West Africa preference was given vertical (referred to as a tailboom) so that nozzles could be set at different heights during the season and adjust the spray volume to the increase in height of cotton plants. This provided protection of bolls on the lower canopy at the same time as buds on the top of plants. Walking away from the spray emitted between the rows of cotton resulted in far less operator contamination.

SPINNING DISC SPRAYERS

In many of the semi-arid areas of the world, farmers were unable to find or transport sufficient water to use with knapsack sprayers so an alternative technique was urgently needed to protect their crops. Efforts to control the desert locust in the 1950's had led to the concept of ultra-low volume spraying. This was followed by the development of small light-weight electrically operated spinning disc sprayers [6] which enabled farmers to apply as little as 2 - 3 litres of oil-based pesticide.

These sprayers produce a much narrower range of droplet sizes and rely on natural dispersion by gravity and air turbulence to distribute the spray into the crop canopy. A sequence of overlapping swaths builds up a deposit downwind of the operator while moving progressively upwind through the field. Experiments in Africa confirmed that farmers could obtain as high a yield of cotton without the drudgery of carrying water and pumping it [7, 8]. This technique has now been most widely used in West Africa, but also in The United Republic of Tanzania and Indonesia. However, the cost of the 3 litres of oil-based formulation has led to farmers in some countries reverting to the conventional water-based formulations diluted in only 15 litres of water per hectare or as little as 5 l/ha if an evaporation retardant is added to the spray. In Zimbabwe, molasses was used as this also acted as feeding stimulant and increased the stomach activity of the pesticide. Considerable moth mortality was recorded on the night after application. Emulsified vegetable oils and other adjuvants have been used as an anti-evaporant.

Using a slower disc speed to obtain larger droplets (c.250 μm) that are rapidly deposited with little downwind movement, spinning disc sprayers are also used to apply herbicides, but the adoption of this technique has been far less than the application of insecticides. Nevertheless the potential to increase weed control at the start of a season when water supplies are poor, suggests that more efforts are needed to do research and show farmers the benefits of early weed control, while reducing the risk of soil erosion that frequently occurs after hoeing has loosened the soil. In practice much of the expansion in the use of spinning disc technology for weed control has been in the amenity area, as local authorities have welcomed the increase in work-rate and reduction in the drudgery of carrying heavy loads of water. The use of a shrouded disc enables the swath width to be controlled as well as droplet size.

ELECTROSTATIC SPRAYING

Concern that the insecticide spray is applied from spinning disc sprayers by a downwind drift technique led to the research on using an additional force - electrostatic - to increase the deposition of the spray droplets. This research led to several developments in which an electrostatic charge was added to spray from existing nozzles [9, 10, 11, 12] or the electrostatic forces were also used to create the spray droplets [13]. For the small-scale farmer the latter system has been developed to a commercial hand-carried 'Electrodyn' sprayer, that is now increasingly used by cotton farmers [14]. In this system four 1.5V batteries are used to power a solid-state generator that provides a 24kV source to the specially designed nozzle. This nozzle is incorporated into a pre-packed container, referred to as a 'Bozzle'. Liquid formulated in an oil and solvent to provide the appropriate resistivity is fed by gravity through the nozzle. The charged liquid emerges as regularly spaced ligaments that break up into droplets within a very narrow size range. The size of droplets can be altered by adjusting the flow of liquid so some products are available in 'Bozzles' with different restrictors identified by a colour-coded cap.

This sprayer is used in much the same way as the hand-carried spinning disc sprayer with the nozzle held downwind of the operator, but as the spray is deposited with minimal downwind drift, the farmer has to walk through the crop more times with a narrower swath. Battery life is much longer as the power requirement is only 0.1 watt. The use of a pre-packed container eliminates the need for the mixing of pesticide, so operator contamination is generally far less than with any other technique provided the farmer understands how to hold the nozzle relative to the crop. However, the operator can get contaminated if there is no earthed object nearer to the nozzle.

Using an electrostatically charged spray, most of the pesticide is deposited on the exposed outer foliage of the crop canopy, with droplets on both upper and lower surfaces of leaves. The amount of penetration into a crop canopy depends on the amount of air turbulence as well as the volume of air space between the rows and within the plant structure, so the technique is best suited to the semi-arid crops which have relatively small plants. Irrigated crops with tall lush foliage are not suited to the method.

Foliage collects most of the charged spray, so very little pesticide is deposited on the soil under the foliage, and this enables many of the predators such as carabids and ants to survive in contrast to the conventional spraying systems where much of the pesticide is wasted on the soil [15]. Where only small plots are treated with the pattern of discrete droplets, there is also some evidence now that parasitoids can recolonise a treated crop, thus Plutella xylostella on brussels sprout plants were parasitized by Diadegma fenestralis one week after spraying [16]. The spraying method is therefore also suited to intercropping systems to treat individual crops grown in relatively narrow beds, as spray drift to the adjacent crops is less than with uncharged sprays.

Development of the 'Electrodyn' sprayer was initially based on the pyrethroid insecticide cypermethrin, but there is now an extended range of different insecticides, including chlorpyrifos, profenophos, carbosulfan, pirimicarb, lambda-cyhalothrin and bromopropylate [17], so that choice of pesticide can be made in relation to crop monitoring and resistance management policies.

ADOPTION OF NEW TECHNOLOGY

Farmers need a system of chemical control which is easy to use and will decrease a pest population rapidly and subsequently increase crop yields significantly. Initially crop protection chemicals were formulated as dusts, as this technology was already established for fertilizer use. However, it was soon appreciated that toxic dusts could be blown by the wind and drift on to neighbouring fields and contaminate the environment. Spray application using water to dilute the pesticide product was soon accepted as more efficient than using dusts, so that the majority of pesticide products are formulations for application with a hydraulic sprayer. There is therefore theoretically a universal system with equipment ranging in size from small hand-operated machines to large mechanised self-propelled sprayers capable of applying most pesticides; a few highly toxic compounds being only applied as granules. Unfortunately hydraulic sprays, while being effective, are not efficient in terms of transfer of the active ingredient, and in many situations less than 1 per cent of the pesticide actually reaches the site of action in the pest. In consequence spray technology remains one of the least efficient processes used by man.

In view of the need to avoid some of the consequences of pesticide use, such as selection of resistant pests, resurgence of pest in the absence of natural enemies and wastage of pesticide in the environment, there is a need for more efficient application delivery systems to fit in with the integrated pest management approach. The difficulty in getting any new application technique accepted is that in most cases a new technique will be more specialized. In this paper reference has been made to very-low or ultra-low volume spray techniques, but their use has been confined almost entirely to the semi-arid areas where cotton is severely damaged by a range of insect pests. Special formulations for ultra-low volume require separate registration, and in some cases only a limited range of active ingredients can be used, thus the more active molecules requiring only a few grams per hectare are more suitable than certain of the older, less active pesticides. Other specialized techniques include seed coatings and granule application, and there will be increasing demand for application of pheromones and pathogens such as Bacillus thuringiensis and baculoviruses, which may require very specific types of equipment and formulation.

To gain acceptance of a new technique clearly needs a sufficiently large research programme to devise the appropriate technique for a given pest species and product, but that is only the beginning of the problem of technology transfer to the farmers. The most successful implementation of a new application technique, or indeed the adoption of an integrated pest management programme has usually followed a crisis, when existing methodologies have failed. There is then the climate for a consensus to get together so that the results of research can be taken up by the extension services in close collaboration with industry and the representatives of the farmers. Research, extension, industry and the farmers must rely on integrating their efforts. Each trying to work alone is doomed to failure! Unfortunately in many countries the extension service does not have the same prestige as the more academic research, and in consequence there is insufficient communication between research scientists and extension staff to ensure that a new technology is fully understood. Lack of feedback to the researcher from the farm will also cause problems if adjustments to the technology are needed to make it more acceptable to the farmer. Training individual small-holder farmers in new techniques with equipment that they may share in a village is clearly an important part of improving the application of pesticides, reducing environmental pollution and ensuring the appropriate selection of chemicals.

Application technology faces an interesting challenge as new molecules, such as the acylureas are discovered, there is greater interest in applying microbial pesticides and there is a need to apply very specific chemicals such as the pheromones. In many cases only a few grams of active ingredient will be required per hectare so they will require more selective placement with significantly less wastage compared with the relatively simple and inexpensive products like DDT. Registration authorities will need to consider novel techniques to provide a range of different application techniques to suit particular pest management programmes, as well as new chemical or microbial products.

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IMPLICATIONS OF BIOLOGICAL AND PESTICIDAL BEHAVIOUR IN CHEMICAL CONTROL OF PESTS

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ABSTRACT

It is well established that under general practical conditions of application, the pesticide used is estimated to be only a mere fraction of the actual amount applied. Such poor efficiency stems from an inefficient application system which delivers a very low quantity of pesticide onto target organisms and wastes most of it into the environment. The so called target spraying could be successful if the biological and pesticidal properties are brought into consideration. The paper gives examples of phosphamidon as ultra low volume spray used on rice for protection against *Cnaphalocrocis medialis* in China, and it is also used on cotton in Thailand for protection against *Heliothis armigera*. Depending on the requirements, the droplet size and deposit densities are important factors. Among the methods that have been developed for target spraying in recent years is a hand-held mist blower called 'HANDIMIST' developed in China for small-scale farms. It could be used to save expensive pesticide active ingredients and would provide protection of the environment.

GENERAL CONSIDERATIONS

It is well established that pesticide requirement is only a mere fraction of the actual amount applied in practice. Such poor efficiency stems from an inefficient application system which delivers a very low quantity of pesticide onto target organisms and wastes most of it into the environment. The so called target spraying could be successful if both pest biology and pesticide properties are brought into consideration. In this paper examples are given on the utilization of the behaviour of air-borne organisms and pesticide particles and their behaviour on plant surfaces. Depending on the requirements, the droplet size and deposit densities are important factors. Among the methods that have been developed for target spraying in recent years is a hand-held mist blower called 'HANDIMIST'* developed in China for small scale farmers. It could be used to save expensive pesticide active ingredients and would provide protection of the environment.

*'HANDIMIST' is a [illegible] name of a hand-held mist blower developed in China.

Pesticides play an important part in agricultural pest management. The global yearly output of chemical pesticides has been estimated to be more than 2 million tonnes, but unfortunately, the application efficiency is very low. On average merely 1 in 10^7 of applied insecticide is received by the pest insects according to the recovery of chemicals extracted from insect bodies collected from the treated crop area.

This surprising information focused the attention of scientists of different disciplines on the efficiency of chemical control methods and we are now under pressure to face the urgent problem of how to increase the efficiency of pesticide usage.

It is very difficult, if not impossible, to focus on the target organisms accurately during pesticide application without any loss of the chemicals, but there would be much improvement if both pest biology and pesticide behaviours were brought into consideration. What is a target? Against the background of pesticide application technology, a target is a place or site on which the applied pesticide should deposit in order to induce a prompt or residual response from the pest, whether the pest is in situ or will come to the treated place later.

Accordingly, there are two different types of targets; direct targets, e.g., pest insects, pathogenic diseases, weeds, harmful vertebrates, etc., and indirect targets e.g., crop plants, soil. etc. Indirect targets are most important targets in pest control, because a residual spray on plant surfaces is generally capable of protecting the crop plant for a relatively long time, so that the repeated attack of the pests can be avoided. However, it is not necessary to spray heavily or thoroughly, i.e., to give a blanket spraying. More than 60% of the chemicals would be lost under such a high volume spray, which takes the whole crop or whole crop field as its target. A correct and rational strategy for chemical control is to reduce the target area as much as possible to avoid any meaningless loss of pesticides in non-target areas. Pests usually have their own habitat as shown in Table 1, and this habitat can be called the effective target area (ETA).

TABLE 1
Effective Target Area (ETA)

Part of The Canopy	Pests and Pathogens
Top	Wheat Scab, English Grain Aphids, etc.
Middle	E. pseudoconspersa, etc.
Basal	Brown Planthopper, Rice Sheath Blight, etc.
Terminal Bud	Cotton Aphids, Cotton Bollworm, Apple Powdery Mildew, etc.
Fruit	Peach Fruit Borer, Lima Bean Pod Borer, etc.

An ETA is a certain part of a plant where the pests live and develop, and once the ETA is covered by sufficient pesticide deposit, an effective control of the pests will then be achieved, no matter whether the other part of the crop plant is covered by the chemicals or not. Such a reasonable technique cannot be successful if we are ignorant of the behaviour of the pests and the characteristics of the pesticides, especially the movement and behaviour of pesticide droplets and particles. It will also be impossible if we lack suitable application equipment and sensible operation systems.

BEHAVIOUR OF AIR-BORNE ORGANISMS AND PESTICIDE PARTICLES

The famous Porton Method developed in 1945 for swarm control was based on the locusts migratory behaviour and the spray droplets' physical behaviour. A droplet size of 100-300μm was suggested to be the effective air-borne pesticide droplet size which was capable of forming a spray cloud or a toxic curtain in the air ahead of a swarm. Since the swarm has a positive anemotaxis behaviour, the spray droplets could be easily captured by the locusts. Three to five drops each containing 50μg of toxicants were enough to kill an adult.

This technique had been improved [1] in a project for spruce budworm control in Canada. Fine droplets (30-60μm) of phosphamidon (Dimecron) solution were emitted into air to form a spray cloud about 250m high from the ground. The spray cloud remained in air as long as 50 min so that the fine droplets had sufficient time to be captured by the flying moth. By this method merely 2g (a.i.) of phosphamidon per hectare (ha) was enough, while 200g (a.i.)/ha is generally necessary for conventional aerial application.

A number of the adults from Noctuidae fly at night, such as the rice leaf roller, the cotton boll worm, etc. Rendal [2] described an interesting system for control of cotton boll worm, *Heliothis armigera*, in Thailand. An ultra low volume application spray unit was set up in the field and connected to an automatic control system, so that the unit could spray automatically at night at intervals of 1 hr, forming an intermittent spray system.

We have tried to make the adults of rice leaf roller take off from the rice canopy in daytime and have then sprayed with fine droplets. This proved successful when a hand-operated mist blower, the HANDIMIST was used. The swinging of the nozzle and the air stream of the mist blower disturbed the rice canopy so that the moths took off from the canopy and impinged with the spray cloud. By this method a dosage of 255g (a.i.)/ha was enough to give an excellent efficacy [3]. This application method also proved useful in wheat bulb fly (*Belia coarctata*) control when a motorized knapsack mist blower or a HANDIMIST was used [4].

Flying adults may more easily entrain fine droplets of pesticide solution because adult antennae are easily impacted by the fine droplets [5]. On the other hand, there are many chemoreceptive sensilla located on the antenna surfaces making it very vulnerable to contact insecticides.

The sensitivity of antennae to pesticides is seen in Table 2. The adult of litchi stink bug (*Tessaratima papillosa*) was tested by topical application of trichlorfon solution (in acetone) onto different parts of the adult's body. A 0.1% dilute solution of trichlorfon in acetone (2.0μl) was applied to the selected part or organ, and one group of bugs treated with acetone only was kept as controls.

The movement of fine droplets or particles is strongly affected by meteorological conditions, especially air turbulence. In daytime the fine particles move upward with the ascending air current and the deposit efficiency will doubtlessly be decreased. Inversion condition is helpful to increase the deposit efficiency. For example, serious drift will occur if pesticide dust is applied in daytime, but it will form a stable cloud within the inversion layer at dusk. We have succeeded in applying a dust of trichlorfon-malathion combined at dusk to control the cotton boll worm [7].

TABLE 2
The sensitivity of different part of the litchi bug body to trichlorfon [6]

Part treated	Adults treated	Mortality of the adults %	
		after 24 hr	after 48 hr
Antennae	30	70.0	83.3
Protergum	30	40.0	53.3
Tarsus	30	50.0	70.0
Sterna	30	26.7	40.0
Control	30	0	0

A very interesting phenomenon induced by the behaviour of smoke particles attracted our attention. We found that the efficacy of Daconil Smoke Pellet (active ingredient: chlorothalonil) in the green house is much better at night or in early morning. This was not caused by the influence of temperature upon biological activity but stemmed from deposit characteristics. The very fine aerosol particles could be captured by a target which is cooler than the ambient air but if the target is warmer than the environment air, the deposit will be far less than that on a cooler target (see Figures 1 and 2). This phenomenon was early discovered by Tyndall and termed the thermophoresis effect.

Making use of this phenomenon we have been able to improve the efficacy of cucumber downy mildew control with Daconil Smoke Pellet in vinyl house by treating the house at nearly midnight, because the temperature of leaves is lowest then [8].

BEHAVIOUR ON PLANT SURFACES

The behaviour of pest organisms and pesticide particles appears to be much more complicated on plant surfaces. Prior to deposition, the pesticide particles must first impact with the plant surface. The mechanism of impaction has been studied by many research workers [9-13]. Bouncing of droplets on target surface, which usually occurs when the spray liquid lacks wetting ability, is an unfavourable behavioural factor which may reduce the depositing ability of spray droplets. Brunskill found that a droplet bigger than 100μm would bounce from a pea leaf but a wetting agent could prevent this. This was confirmed by Lake on barley and the so called critical droplet size was suggested, to express the stability of droplet on a plant surface. The critical droplet size of water was said to be 100μm and could be enlarged by certain wetting agents. However, drainage may happen if the concentration of the wetting agent is too high or the volume of applied liquid too great (Figure 3), because an overdose of the surfactant reduces the contact angle of the spray liquid (Table 3), so that a rather smaller volume of the liquid could be kept on the surface.

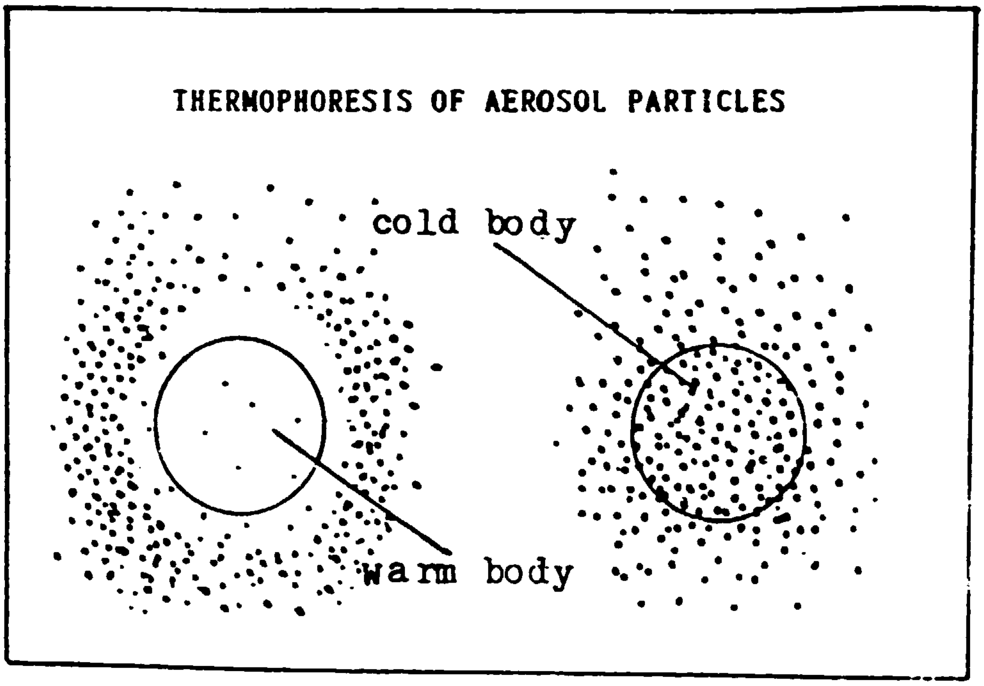

Figure 1. Thermophoresis effect

According to Young's opinion three situations of bouncing may occur:

1. Low energy situations: the impacting droplet undergoes elastic oscillation and then detaches from the leaf.

2. Medium energy situations: the droplet impacts and progressively flattens over the leaf surface. The expanded drop may only contact the adjacent ridges, leaving air-gaps in between.

3. High energy situations: in this case the radial expansion is so rapid that the liquid perimeter is ruptured and satellites are thrown out. The remaining liquid recoils and may detach from the leaf.

Fine droplets have smaller terminal velocity and undergo flow energy impaction; no radial expansion or secondary disintegration will happen. Therefore fine drop spraying usually produces a more stable and steady deposition. However it was found that the deposit of fine drops was not uniform on the leaf. The droplets captured by the top third of a rice or wheat leaf is usually 2-3 fold more than that captured by the basal third of the leaf and double that of the middle third. This is valuable in control of pests such as rice leaf roller, leaf blight, thrips, etc., and more than 25% of the pesticide could be saved [14].

Courshee [15] reported that the deposit pattern within a wheat canopy could be changed by selecting the spray angle. A spray angle of 60^0 made the deposit-density on the upper third of a 30cm tall wheat canopy double the density on the ground, and 2.34 fold higher than that on the bottom third. Spraying perpendicularly (0^0) reduced the deposit

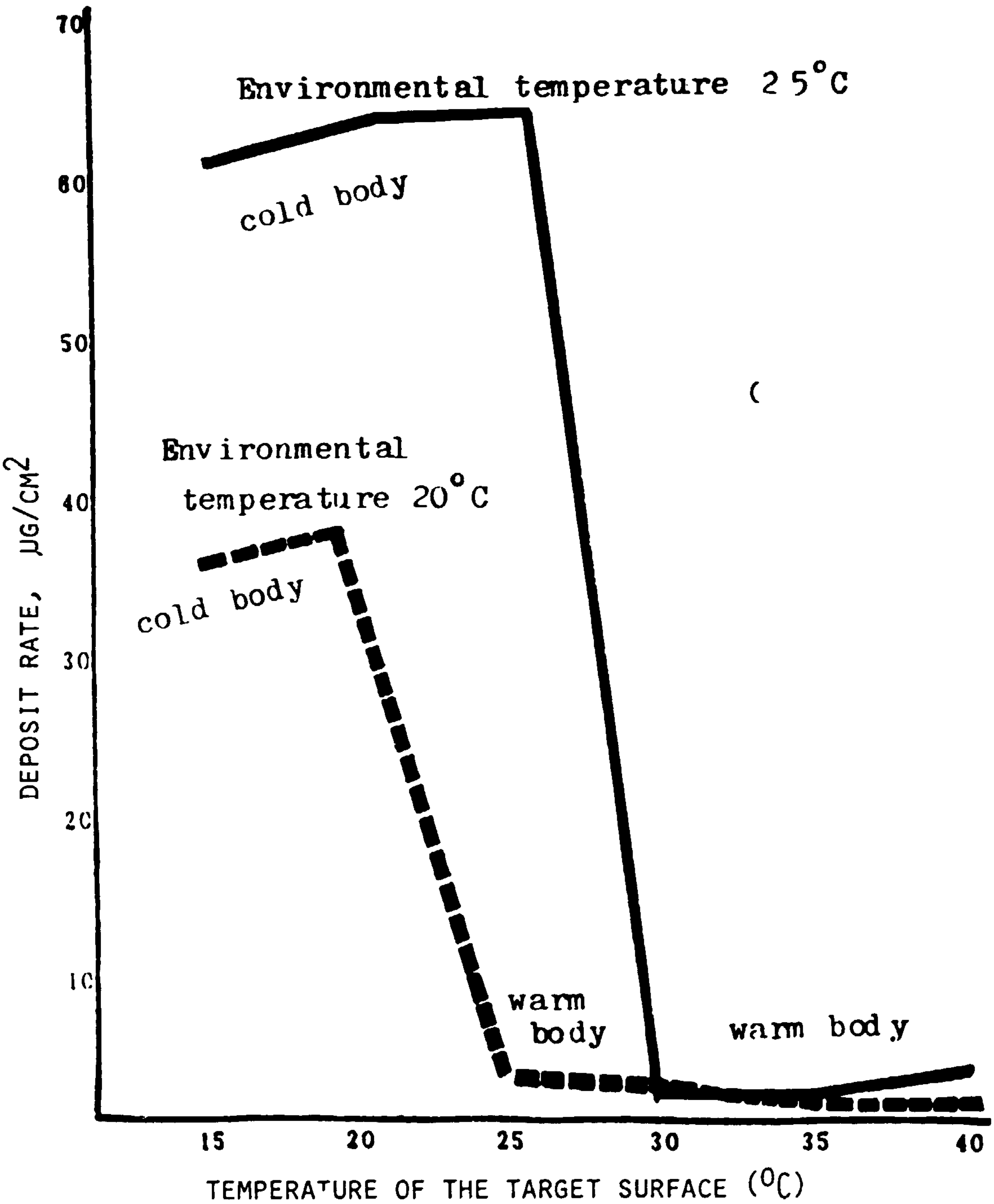

FIGURE 2. THERMOPHORESIS ON ARTIFICIAL TARGETS (8)

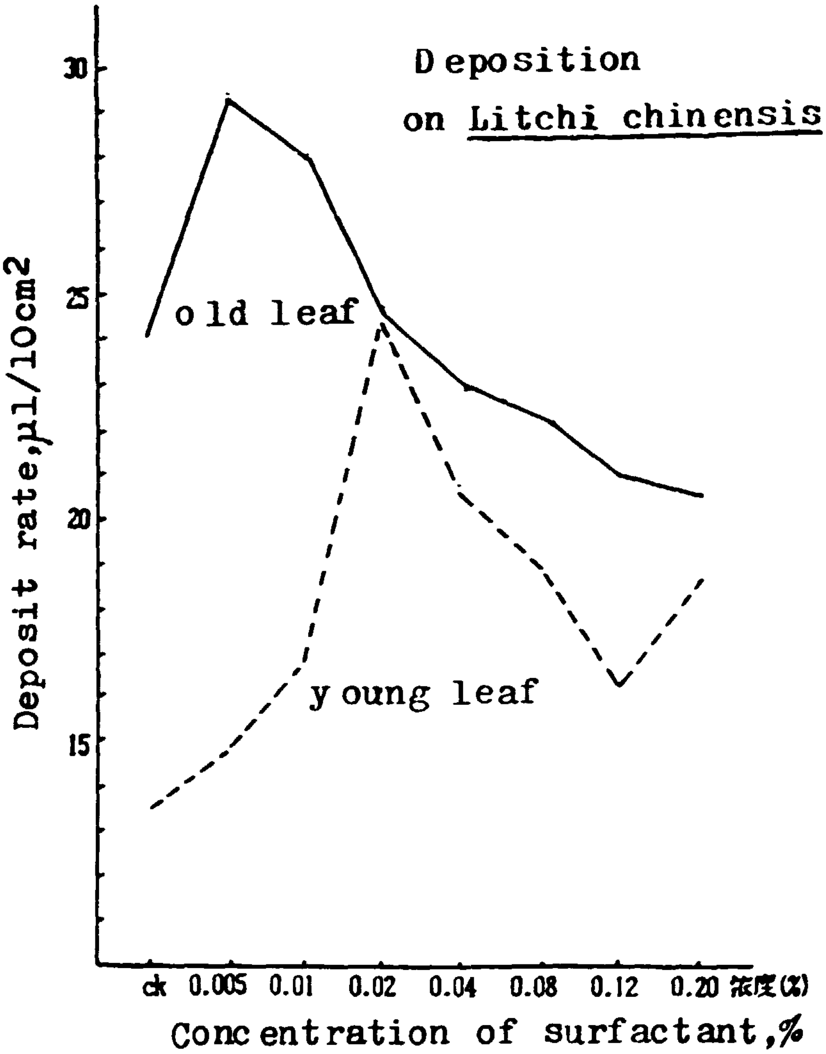

Figure 3. Relationship between rate of deposition and surfactant concentration (surfactant used: ABS-Na) [6]

density on the upper third of the wheat canopy sharply to 1/15 of that deposited on the ground and about half of that on bottom third. However, this was never possible if a hollow cone nozzle was used with a wide spray angle.

A new hand-operated mist blower, the HANDIMIST, as mentioned in preceding part of this text, gives good results. With a narrow-angled solid cone nozzle, the HANDIMIST is able to deliver fine drops onto a relatively narrow target area, and the spray angle is adjustable by turning the nozzle upward, downward or sideways as required. This equipment has proved successful in the control of wheat aphids, wheat scab, rice blast, rice leaf roller and thrips locating at the top of the canopy, using a side-ways spray.

Due to its very low application rate, i.e. 15-37 L/ha, HANDIMIST appears to be very handy and easy for use if compared with a conventional hydraulic knapsack sprayer which is so far still the predominantly used equipment in China. Accordingly HANDIMIST appears to be a rational hand-held spray equipment for small-scale peasant farmers.

A number of pest organisms localize on abaxial surfaces of plant leaves, such as aphids, white flies, pathogen of downy mildew, etc. It is very difficult to deliver spray drops onto abaxial surfaces, especially when the crop density is high, e.g. the full-bloom stage of cotton plant. At this stage the cotton field is fully stocked and a serious shielding effect occurs between cotton leaves, which reduces the penetration ability of spray drops into the cotton canopy, and allows still less deposition on abaxial surfaces. However, we found a possibility to make use of such behaviour of cotton leaves.

Cotton leaves have a phototaxic behaviour which makes the leaves declined with their adaxial surfaces toward the sunlight, so that their abaxial surfaces will then be exposed to spray cloud. Thus the collonial structure of the cotton field changes from an enclosed system to an open system, permitting the spray cloud to penetrate easily into the cotton canopy [16, 17]. The declination angle can be found from Table 4.

TABLE 3
Contact angles of surfactants on litchi leaves (*Litchi chinensis*) [6]

Concentration of surfactant's solution (%)	Contact angle on adaxial/abaxial surface					
	ABS-Na		Tween-20		OP-10	
	Adax.	Abax.	Adax.	Abax.	Adax.	Abax.
0.001	60.0	111.3	66.3	112.7	57.0	91.7
0.002	49.2	100.3	60.0	86.0	52.7	68.3
0.005	47.3	76.0	56.0	72.0	50.0	59.7
0.01	38.3	52.3	50.3	69.3	46.3	51.0
0.02	32.0	37.3	48.7	58.7	43.7	48.3
0.05	28.3	31.0	43.3	56.3	40.0	41.3
0.10	27.7	26.7	36.3	53.0	33.8	33.7

TABLE 4
Declination of cotton leaves toward sunshine (D^0) in summertime (July, Beijing)

Location of the leaves	Declination (D^0) at different time							
	6:30	7:30	8:30	9:30	16:30	17:30	18:30	19:30
Upper part	0	33	45	41	35	41	45	42
Middle part	0	25	40	35	33	38	40	36
Lower Part	0	15	25	20	15	20	25	25
	Eastwards				Westwards			

An interesting phenomenon was also found in peanut canopy. The peanut plant possesses opposite leaves which used to close together face-to-face at night and open again from dawn till dusk. Doubtlessly this behaviour could be made use of when the pesticides are required to be applied onto the abaxial surfaces.

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NATURAL PRODUCTS AND THEIR POTENTIAL AS PEST CONTROL AGENTS: FOCUS ON PESTICDES OF MICROBIAL ORIGIN

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ABSTRACT

While the selective activity of certain microbial products against a wide range of plant pests and diseases is well known, relatively little use has been made of them in agriculture. In this field, keen interest is at present largely restricted to Japan where blasticidin S and kasugamycin are used to control blast disease in rice and polyoxins and validamycins are effective against rice sheath blight. Recent co-operative work between Chinese and Japanese scientists succeeded in discovering several new microbial substances active against plant diseases. The pesticides of microbial origin apparently have the advantage of target specificity and of being biodegradable.

Although pesticides have played an indispensable role in preventing crop losses caused by pests and diseases to meet the increasing population in the world, there is growing concern about pesticides on their side effects on non-target organisms and from environmental viewpoints. This points to the need for selective pesticides with higher degradability in nature. Some older conventional pesticides such as DDT and BHC are hazardous to mammals through their biological concentration in the food-chain and they remain in the natural environment for a long period. On the contrary, naturally occurring pesticides are generally specific for target organisms and are supposed to be inherently biodegradable since they are synthesized biologically. Thus worldwide interest in pesticides of microbial origin has lately been renewed.

The use of microbial products to protect crops against plant pathogenic bacteria originated in Europe and the United States, applying medicinal antibiotics such as streptomycin, tetracycline, or chloramphenicol. Then, cycloheximide and griseofulvin were introduced for the control of fungal plant diseases. The use of these compounds was, however, not extensive. Later, many attempts were made to find microbial products for the prime purpose of plant disease control, but most compounds had no practical promise because of their instability in field use or phytotoxicity. In Japan, however, an epoch-making substance named blasticidin S (Fig.1) was discovered in 1958 (Takeuchi *et al.*, 1958), and it exhibited high efficacy in controlling rice blast disease, the most serious and damaging of all diseases of rice in temperate and humid climates found in Japan. The success of blasticidin S in practical use inspired further research for new pesticides of microbial origin, leading to the development of excellent antifungal substances such as kasugamycin (Umezawa *et al.*, 1965), polyoxins (Isono *et al.*, 1965; Fig. 2 & 3), validamycins (Iwasa *et al.*, 1970) and mildiomycin. In addition, microbial products with insecticidal and herbicidal activity have also been found; tetranactin (Ando *et al.*, 1971) as a miticide and bilanafos (Fig. 4) as a herbicide. If gibberellins, well-known plant growth regulators, are included in this category, microbial products are being used in every sphere of pesticide use. Table 1 shows the main pesticides of microbial origin practically used in Japan (for fuller details of the characteristics of substances see [Misato *et al.*, 1977]). It might be surprising that seven compounds out of ten were discovered in Japan.

In recent years, standards for the disposal of industrial wastes have become more and more strict, and consequently the manufacture of synthetic chemicals becomes quite expensive if waste disposal facilities, as well as production plants, must be set up for each new product. In this concern, pesticides of microbial origin have an economic advantage, since a variety of substances can be manufactured using one set of equipment and facilities. Additionally, they are produced not from limited fossil resources but from renewable agricultural products through fermentation by microorganisms. From these aspects, pesticides of microbial origin would be more advantageous especially for developng countries, and bettter results can be expected there in the future.

As is true for every scientific technique, their use also has limitations. One disadvantage is the difficulty in their microanalysis, especially when they consist of many components. The second demerit is that, because of their highly specific mechanism of action, they are apt to suffer from the emergence of resistant strains. To cope with this problem, it is sometimes a requisite to combine the agents with other chemicals having different action mechanisms or to use them in rotation. Further, the biggest limitation to the use of microbial products in agriculture would be a concern that their wide use might create resistant strains which could hinder medical treatment of humans. This concern seems particularly noticeable in advanced Western countries, where the use of microbial products started by an application of medicinal antibiotics as mentioned earlier. Fortunately, the use of pesticides of microbial origin in Japan for more than 20 years has never met any problem involving cross-resistance with medicinal antibiotics. Naturally, sufficient precautions must be taken not to cause any resistance in human pathogens in the future. However, this approach should not be limited to pesticides of microbial origin. There should be no difference between microbial products and synthetic chemicals in this respect and the important point is whether or not any pesticides may induce resistance to medicines. At present, the use of microbial products in agriculture is subjected to rigid regulations and restrictions apparently because they are called "antibiotics". This should be reconsidered from scientific points of view and it can be argued that they should be treated in the same way as synthetic chemicals.

Among the pesticides listed in Table 1, polyoxins and validamycins are quite safe pesticides; non-phytotoxic, and non-toxic to humans, livestock, and wildlife. Such excellent characteristics seem to be due to their modes of actions. Polyoxins selectively inhibit the synthesis of fungal cell wall chitin, which does not exist in mammalian cells (Hori *et al.*, 1974). Validamycins have exceptional characteristics, i.e., they are not fungicidal but only deteriorate the normal mycelial growth of the pathogen on plants. Probably because of such moderate activity, no occurrence of resistant strains have been reported following validamycin treatment, despite the largest consumption among pesticides of microbial origin. Further, components of avermections (Dybas, 1983), insecticidal microbial products discovered in the US, were successfully transformed into significantly more active derivatives by chemical modification of the original structures. These findings leave considerable scope for future prospects of microbial products. In addition new microbial products with novel characters may be found against those pests and diseases such as soil borne diseases and viral diseases which are difficult to control by synthetic chemicals at present.

It was envisaged by Dr. H. Geissbuhler (1986) that crop and pest biochemistry and molecular biology will make rapid further advances, new biotechnology will be an important factor of future plant protection research and strategy. For example, more efficient production of microbial products will become possible by modern gene engineering. By the extensive use of computer and data processing procedures, biorational approaches will also become feasible in the design of new pesticides from microbial products.

Blasticidin S has broad antimicrobial activity but occasionally exhibits an adverse phytotoxic effects on some broad-leaved plants. The structural gene, *bsr*, of an inactivating enzyme (Yamaguchi *et al.*, 1972, 1985, 1986) has been cloned and introduced into tobacco plants using the Ti plasmid vector system, which demonstrated that the *bsr* gene afforded a blasticidin S resistant phenotype to the plants (Kamakura *et al.*, 1990). This gives an example for a new approach to the solution of phytotoxic problems with some fungicides. In addition, a tabtoxin resistance gene *ttr* isolated from the pathogen *Pseudomonas syringae* pv. *tabaci* was also introduced into tobacco cells. The transgenic tobacco plants showed high specific-expression of the *ttr* gene and no chlorotic symptoms caused by tabtoxin treatment or with infection by the pathogen (Anzai *et al.*, 1989). These plant genetic studies may demonstrate another new approach for plant protection research.

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Table 1 Microbial Products Used in Agriculture in Japan

Substance	Effective against
Antifungal	
Blasticidin S*	Rice blast
Kasugamycin*	Rice blast
Polyoxins*	Rice sheath blight, Fungal diseases of fruit trees and vegetables
Validamycins*	Rice sheath blight
Mildiomycin*	Powdery mildew
Antibacterial	
Streptomycin Oxytetracyclin	Bacterial diseases of fruit trees and vegetables
Novobiocin	Bacterial canker of tomato
Insecticidal	
Tetranactin*	Mites of fruit trees and tea plants
Herbicidal	
Bilanafos*	Weeds in mulberry field and orchard

*Compounds discovered in Japan.

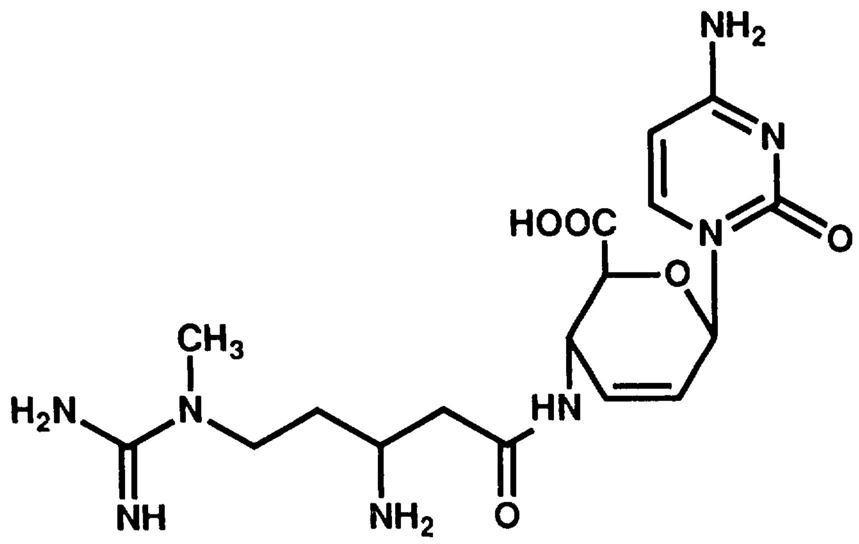
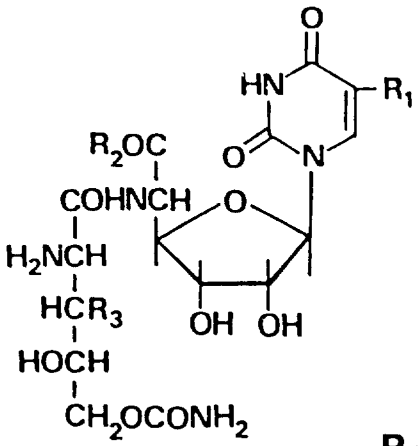
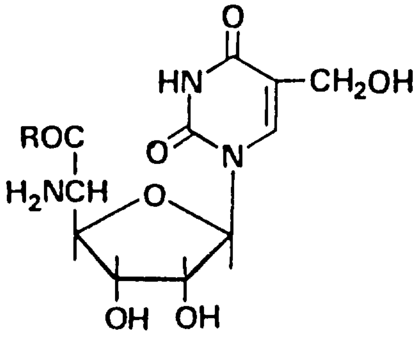


Figure 1 Chemical structure of blasticidin S



	R_1	R_2	R_3
Polyoxin A	CH_2OH	x	OH
B	CH_2OH	HO	OH
D	COOH	HO	OH
E	COOH	HO	H
F	COOH	x	OH
G	CH_2OH	HO	H
H	CH_3	x	OH
J	CH_3	HO	OH
K	H	x	OH
L	H	HO	OH
M	H	HO	H



Polyoxin C R= OH

I R= x

(x = )

Figure 2 Chemical structures of polyoxins

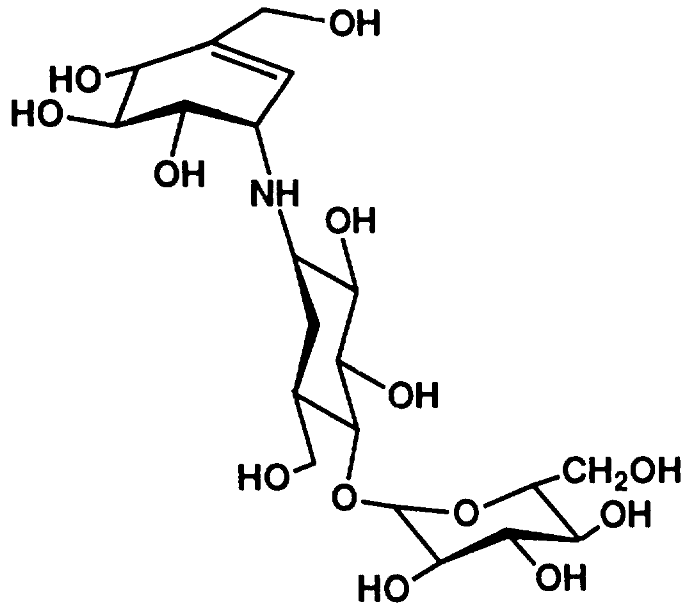


Figure 3 Chemical structure of validamycin A

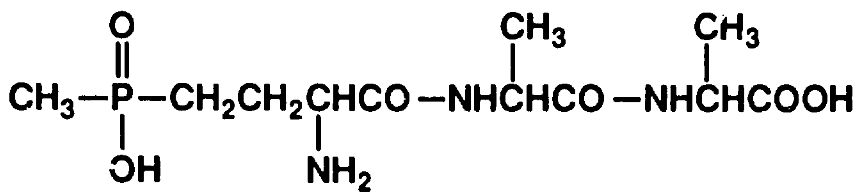


Figure 4 Chemical structure of bilanafos

NATURAL PRODUCTS AND THEIR POTENTIAL FOR ASIAN REGIONS

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ABSTRACT

Pesticides will continue to be needed in the near future to control at least half of the insect problems affecting agriculture and public and animal health. At the same time, the problems of insecticides resistance and detrimental effects on humans and other non-target organisms associated with the large-scale use of broad-spectrum synthetic insecticides cannot be overlooked. This has led to a decline of the discovery rate of synthetic insecticides. Fortunately alternatives exist within natural products. The paper reviews the status and potential of insecticides of plant, insect, and microbial origin in the context of current pest control challenges and future biotechnological opportunities.

INTRODUCTION

More than one-third of world crops are destroyed by insects, plant pathogens, and weeds (Pimentel & Pimentel 1979). An additional 10 to 20% of crops is lost to insects, microorganisms, rodents, and birds during postharvest operations and storage (Pimentel & Andow 1984). Thus almost one-half of the potential world food material is damaged or destroyed annually. Pesticide use has therefore become indispensable to modern, high performance agriculture. Without pesticides crop losses would escalate further. Crop losses would be even greater in developing countries where alternate crop protection measures are still being strengthened.

Averting crop losses caused by pests is a high priority in Asia with 60% of the global population. The tropical environment is conducive to insect multiplication and enhances their capacity for destruction. The current agricultural practice of planting large acreage to standardized crops offer optimum conditions for the development and spread of destructive insects. Insects also affect public and animal health and transmit some highly debilitating diseases. Insecticides will therefore continue to be needed to control at least some, if not all, the insect pest problems in Asia.

Although only 21% of the pesticides produced worldwide are used in developing countries (Berry 1979), the incidence of human poisoning is disproportionately high in developing countries. Poisoning occurs mostly during handling and application of pesticides. The poisoning of livestock, fish, wildlife, and other beneficial organisms are hidden costs in pesticide use. The inherent problem lies in the nature of pesticides used. Most insecticides developed after DDT have been synthetic, nonselective, neurotoxic chemicals.

Insecticide resistance is a major problem associated with the use of toxic, synthetic insecticides. Numerous pest species have become resistant to insecticides. Also the problem has manifested itself in a widening circle of cross and multiple resistance. In 1954, there were only ten insect species known to be resistant to insecticides; by 1980 and 1986, the figure rose to 432 and 447, respectively (Georghiou 1986). The decreasing effectiveness of insecticides is exemplified by the diamondback moth, *Plutella xylostella*, which in the Philippines and Thailand has become resistant to all major classes of insecticides. The discovery rate of new insecticides has declined in recent years due to an exponential increase in the cost of developing synthetic insecticides (Metcalf 1989).

Resurgence of insect pests associated with insecticidal destruction of natural enemies and development of insecticide resistance has necessitated frequent applications of insecticides at higher rates, ending in an insecticide treadmill. This is uneconomical and exacerbates the problem.

Complex insecticide resistance management programs, comprising alternation of insecticides across generations, nonpersistent formulations, and the use of pesticides conferring only low magnitudes of resistance have been recommended (Roush 1989). However, they deal with only one aspect of the multifaceted insecticide problem.

Clearly, new insecticides are needed which are pest effective, nontoxic to humans and beneficial organisms, economical, biodegradable, less prone to development of insecticide resistance, and less expensive. Such insecticides are the dreams of applied entomologists. Fortunately, a few natural products may qualify for some of the attributes of ideal insecticides. This paper reviews the status and potential of plant-based, insect-based, and microbial insecticides.

PLANT-BASED INSECTICIDES

Plants are rich in bioactive organic chemicals. About 10,000 secondary plant metabolites have been chemically identified; their total number may exceed 400,000 (Swain 1977). They include defense chemicals, comprising repellents, feeding deterrents, growth inhibitors, sterilants, toxicants, etc. Some of the oldest and most common insecticides (nicotine, pyrethrins, and rotenone) were derived from plants. Before the advent of synthetic insecticides, it was common practice in China and India to use plant derivatives for warding off attacks by household and agricultural pests.

Plant species reportedly screened for insecticidal properties exceeded 6,000 by 1971. Of these 2,400 species have been recorded to possess measurable to considerable activity (Grainge & Ahmed 1988). Plants that are amenable to commercial exploitation have generally received greater attention.

Nicotine and Other Alkaloids

Long before nicotine was identified as the principal toxic alkaloid of tobacco, farmers were using tobacco leaf powder or leaf extract as an insecticide. Nicotine kills insects upon contact and as a fumigant and stomach poison. It occurs in varying concentration in about 18 *Nicotiana* sp. (Solanaceae). The commercially important species *N. tabacum* and *N. rustica* contain between 6 and 18% nicotine. Nicotine though toxic to insects has little advantage over synthetics because of its high production costs, disagreeable smell, and insecticidal activity limited mostly to soft-bodied insects, such as aphids. Commercial production of nicotine is greatest in the United Kingdom, India, Germany, and the Netherlands. On a worldwide basis, around 600,000 kg of nicotine sulfate and 75,000 kg of pure nicotine are produced annually.

Rotenone and Rotenoids

Rotenone and rotenoids, derived from certain legumes, called *toeba* or *tuba* (*Derris* sp.) in the Malay archipelago, and *timbo* or *cube* (*Lonchocarpus* sp.) in Central and South America, were used for centuries by the natives as fish poison or to poison arrows or spearheads. About 100 years ago, the Chinese in Singapore used *tuba* root as an insecticide. The bioactive component isolated from *Derris chinensis* was called *roten* in Formosa. Being a ketone, it was named rotenone. The commercially important species *D. elliptica* and *D. malaccensis* contain 4-5% rotenone; *Lonchocarpus utilis* and *L. urucu* contain 8-10% rotenone in dried roots. The plants are allowed to grow for 2 to 3 years before they are uprooted. The roots, averaging about 1 kg each, are washed, cut, dried, and processed. A few *Tephrosia* species are rich in rotenoids.

Rotenone dusts, dispersible powders, and sprays have been used in crop and health protection, and against household pests. The mammalian toxicity is low. Crystalline rotenone is used for mothproofing. Rotenone acts as a slow contact insecticide and as a stomach poison. The toxic principals deteriorate rapidly in sunlight and air. The complex structure of rotenone precludes commercial synthesis, but simpler, more cost-effective analogs can possibly be developed in the future.

Pyrethrum

Pyrethrum is derived from dried flower heads of *Chrysanthemum cinerariaefolium* (Asteraceae), which is native to Yugoslavia and Albania. Pyrethrum is a safe insecticide that has been used to control insects in the Middle East since ancient times. In the 19th century, it was introduced in Europe, the United States, Japan, East Africa, and South America. The commercial importance of pyrethrum declined with the popularity of DDT, but as insects became resistant to DDT and other insecticides, and the hazards of their continued use were recognised, the demand for pyrethrum rose again.

Worldwide annual production of pyrethrum averages 30,000 t. Kenya is the largest producer of high quality pyrethrum in the world. The United Republic of Tanzania, Rwanda, Zaire, Japan, and India also produce pyrethrum.

Casida (1973) has reviewed pyrethrum as a safe insecticide. The insecticidal principals in pyrethrum extract comprise pyrethrins I and II, cinererins I and II, and jasmolins I and II. Pyrethrin I is the most potent. Insect susceptibility to pyrethrum is due to high cuticular permeability and action on the central nervous system. Their activity is markedly enhanced by piperonyl butoxide. Pyrethrum products containing 0.03 to 0.1% pyrethrins and 5 to 10 times as much synergists are applied as oil- or water-based sprays. Dusts are made by mixing pyrethrum extracts with clay or talc carriers, but deteriorate rapidly. Pyrethrum-based insecticides are used mainly against household insects, flies pestering livestock or cattle, stored grain insects in mills and warehouses, pests of vegetable and fruit crops, and against forest defoliators.

Pyrethrins do not affect certain natural enemies of pests. They are nonpersistent and effects are short-lived. Pyrethrum does not harm bees, birds, fish, and warm-blooded animals. Pyrethrin resistance has been recorded in cockroaches, bedbugs, houseflies, cattle ticks, and body lice, but these species are also resistant to common synthetic insecticides.

The uses of natural pyrethrins are restricted by their high costs and instability under field conditions. Several synthetic analogs, called pyrethroids or synthetic pyrethroids (Elliott 1977), are now available that possess the desired properties of higher toxicity to pests, lower cost, reduced mammalian toxicity, and greater stability. Their greater insecticidal activity, permitting fewer treatments at lower doses, confers advantage over conventional pesticides. Allethrin, deltamethrin, permethrin, cypermethrin, and bioallethrin are some of the popular synthetic pyrethroids.

Other tropical plants with insecticidal properties

Custard-apple. The dried seeds of *Annona* spp. (Annonaceae) have long been used as an insecticide throughout many tropical countries. The insecticidal property is attributed to annonine, a benzylisoquinoline alkaloid. *Annona* extracts act both as a contact and a stomach poison to insects. Annonaceae comprises about 2000 species of tropical and subtropical trees and shrubs which produce highly bioactive annonaceous acetogenins (Rupprecht et al. 1990).

Neem and chinaberry. Centuries before synthetic insecticides became available, farmers in the Indian sub-continent protected crops with natural repellents in the fruits and leaves of Neem *Azadirachta indica*. The potential of natural insecticides from neem and other tropical plants has been reviewed (Schmutterer et al. 1981, Schmutterer & Ascher 1984, 1987 Arnason et al. 1989).

The active principles in neem have been identified as limonoids, a group of stereochemically homogeneous tetranortriterpenoids. The most important bioactive principal is azadirachtin, although more than 50 metabolites have been identified, and more are being added to the list. Besides azadirachtin, meliantriol, and salannin are also feeding deterrents (Henderson et al. 1964).

In spite of high selectivity, neem affects more than 200 insect pest species belonging to Coleoptera, Diptera, Heteroptera, Homoptera, Hymenoptera, Lepidoptera, and Orthoptera, also some species of mites, and nematodes (Saxena 1989, Schmutterer 1990). In general, insects feed less, grow poorly, and lay fewer eggs on plants treated with neem oil, cake, or extracts. Predators are not very sensitive to neem derivatives and emergence of parasites is not much affected (Saxena et al. 1981, Schmutterer et al. 1983).

Azadirachtin acts principally as an insect ecdysis inhibitor. Neem compounds also affect insects in other important ways, such as antagonism towards pest endosymbionts, partial sterilization, disruption of pest mating behaviour, oviposition deterrence, and reduced hatchability of insect eggs (Saxena 1989).

The effects of neem derivatives on stored grain insects have been reviewed in depth (Saxena et al. 1989). Dried neem leaves, seed kernel powder, cake, oil, and others when mixed with grains in storage, not only protect them from damage, but also inhibit insect growth and development. This was confirmed in warehouse trials conducted in the Philippines where paddy rice mixed with neem derivatives suffered little pest damage even after 6 months of storage (G. Jilani & R. C. Saxena, IRRI, unpublished information).

Neem also affects mosquitoes; larvae die as intermediates during imaginal development (Zebitz 1987).

Neem derivatives have been used against various storage pests and crop pests either singly or in selected combination with other nonedible oils, insecticides, and synergistic compounds. Resistance to neem products has not been observed.

In field trials, neem derivatives were promising against several rice insect pests and virus diseases transmitted by them (Saxena, 1987). Neem as a seed treatment for rice before sowing produced vigorous seedlings that resisted the development of homopterous pests (Abdul Kareem et al. 1989).

The chinaberry trees *Melia azadarach* and *Melia toosendan* also occur in much the same areas as neem. Several of the limonoids in chinaberry seeds are common to neem seed, except azadirachtin. Another triterpenoid, toosandnin, occurs in chinaberry bark (Shin-Foon 1989). Chinaberry seed oil and extracts are repellent and toxic to insects. Unlike neem, chinaberry has limited scope for development as a natural insecticide: fruits do not drop off when ripe, making seed collection laborious; seeds are stone hard, kernel size is small, and oil and extracts are toxic to warmblooded animals. However, the fast-growing, insect resistant tree is valued for timber.

Other nonedible seed oils. Several other tropical trees produce nonedible oil seeds. For example, India alone has more than 150 species of forest and roadside trees that produce highly odoriferous nonedible oils which are unfit for use without processing. Nevertheless, they contain valuable active principals and chemical components reputedly useful as medicines and pesticides. 'Mahua' *Maduca longifolia* var. *latifolia*, 'Karanj' (Indian beech) *Pongamia glabra*, and 'pinnai' (Alexandrian laurel) *Calophyllum inophyllum* are widespread in India and are sources of considerable quantities of nonedible oils. These oils are used mainly for illumination, low grade soaps and detergents. Only recently has their insect control potential been examined. (Mariappan et al. 1988).

Photoactivated Biocides from Plants

Some species of plants produce "photosensitizers" or phototoxins (Downum 1986). The metabolites are unique in that they become toxic in the presence of sunlight, being activated particularly by the UVA region of the spectrum. Such "solar-powered" defense agents may discourage insect attack. They comprise diverse groups of natural products. Members of Asteraceae and Rutaceae possess the widest range of phototoxic compounds. Their potential for insect control has not much been exploited.

Insect Resistant Crop Plants

Resistant varieties of some cultivated crops also possess chemicals that repel or affect insect pests. Toxins that act directly on insects can provide models for developing future insecticides. For instance, TKM6, a resistant rice variety from India contains n-pentadecanal that affects the development of rice stem borer larvae and deters moths from egg-laying.

INSECT-BASED INSECTICIDES

Many interactions between insect species, prey and natural enemies, and between sexes of insect species are chemically mediated. Also, insect behaviour, physiology, growth and maturation processes are regulated chemically by insect hormones.

Insect Venoms and Defense Secretions

A number of scorpions and spiders, and insects such as Hemiptera, Diptera, Coleoptera, and especially Hymenoptera, produce venoms or toxic secretions for self-defense against predators. Venoms and toxic secretions are some of the most pest-specific, most potent, and the fastest acting insecticides. These toxicants are effective only upon injection, and so find little use in insect control.

Insect Growth Regulators (IGR)

Though slow in action, IGRs selectively and specifically affect the growth, development, and maturation processes of insects. Their short environmental persistence, low toxicity to vertebrates, and other attributes make them potentially useful alternatives to common insecticides. However, their effectiveness depends on synchrony with certain metabolic events in insect life in which the absence or presence of the growth regulator is critical for normal development. Four groups of IGRs based on hormonal processes are known: molting hormones, anti-molting hormones juvenile hormones, and anti-juvenile hormones.

Molting hormones. These steroid hormones, found in insects and crustaceans, regulate molting, growth, and maturation patterns (Watkinson & Clarke 1973). Any disruption in their metabolism would affect the insect's control of its own hormonal system. Molting hormones include ecdysone, ecdysterone, and other ecdysteroids. They are derived from cholesterol (still retaining its C27 carbon skeleton). Although certain plants are rich in phytoecdysones, their extraction for insect control would not be economical unless highly effective. Also, steroidal insecticides would require careful testing for possible side effects, including affects on crustaceans. Consequently, molting hormones have low potential as control agents.

Anti-molting hormones. Some chemical antagonists for molting hormones have been identified (Staal 1976), but their use is still experimental. Certain azasterols and even non-steroidal secondary and tertiary amines disrupt the development of phytophagous insects that depend on dietary sitosterol for their cholesterol needs (Robbins et al. 1975). Such compounds may also interfere with steroid metabolism in higher animals. The high costs of azasterols limits any agricultural use; simpler antagonists may have some insect control potential.

Juvenile hormones. Insect juvenile hormone (JH) was described by V. B. Wigglesworth in 1935 as a metamorphosis regulating secretion of *corpus allatum*. In 1956, C. M. Williams suggested the possible use of JH to upset normal growth of insects. In 1967, Williams proposed JH-active substances as powerful "third generation pesticides" to which the pests may not be able to develop resistance.

Being terpenoidal in nature, exogenously applied JH can easily penetrate the insect cuticle and affect the target tissue. Four different JH (JH-0, JH1, JH2, and JH3), occurring naturally, singly or in combination, in different species, have been identified (Richards 1981). The number of carbon atoms ranges from 19 for JH-0, 18 for JH1, 17 and 16 for JH2 and JH3 respectively. The use of natural JH for insect control is not feasible due to reasons of instability, however, several highly active substituted aromatic terpenoid esters have been synthesized. That started the era of juvenile hormone analogs (JHA) with higher specific activity, greater stability, lower manufacturing costs, and enhanced selectivity (Staal 1976). The basic mode of action of JHA appears identical to that of exogenously applied JH, affecting metamorphosis, and causing embryonic inhibition, chemosterilization, and diapause disruption. Their systemic activity in plants has not been fully exploited.

Methoprene or Altosid[R], a promising JH compound, effectively controlled OP-resistant strains of floodwater mosquito *Aedes nigromaculatus* larvae, which develop synchronously. Slow-release microencapsulated formulations have been found to be effective against *Culex tarsalis* and *Culisita inornata*, which develop asynchronously, and several OP-resistant aquatic midges. Methoprene is not hazardous to fish. Methoprene has also been used in fly control in various ways and against some stored grain pests. Insensitivity of some species of grain weevils limits the potential of methoprene and other JH compounds for stored grain protection.

A few IGRs, such as kinoprene, are highly active against aphids, mealy bugs, scales and whiteflies, particularly on foliage ornamentals grown in greenhouses (Stall 1977). Low persistence of some IGRs in the field can be compensated to some extent by frequent applications and improved formulations. Epofenonane, an improved JHA with high activity and foliar persistence, is highly effective against insecticide-resistant scale insects (Stall 1977). It is also compatible with biocontrol agents. But the high cost is a constraint and prohibits their use in developing Asian countries.

Anti-juvenile hormones. Bowers et al. (1976) discovered two anti-JH (AJH) compounds, called 'precocenes 1 and 2' from extracts of the bedding plant *Ageratum houstonianum*. Contact with precocenes induced immature *Oncopeltus fasciatus* and *Dysdercus* bugs to skip succeeding instars and develop into tiny sterile female or male 'adultoids'. Bowers (1984) called JH-antagonists 'fourth generation pesticides.' The precocenes can readily enter the insect system, and penetrate into *corpora allata* which they destroy, thereby preventing biosynthesis of juvenile hormones. Although precocenes evoked much interest initially, they did not find practical applications due to high and narrow dose requirements and toxicity to vertebrates.

MICROBIAL INSECTICIDES

Arthropods, including insects, are attacked by more than 1000 pathogens, comprising bacteria, viruses, fungi, nematodes, and protozoa (NAS 1979). Microbial insecticides, comprising these microorganisms or the chemicals produced by them, have received more attention as a biological resource for developing environmentally rational insecticides (Burges & Hussey 1981, Kirschbaum 1985).

Bacteria

The spore-forming bacterium, *Bacillus popilliae* (the causative organism of milky diseases in scarabaeid beetles) and *Bacillus thuringiensis* (the crystal-forming bacteria that infect lepidopterous pests) have been developed as microbial insecticides. Some urea-forming strains of *Bacillus sphaericus* are also being considered for the control of mosquito larvae.

Dutky (1940) first described milky diseases in the Japanese beetles. The insecticide 'Japodemic' or 'Doom' comprising spores of *B. popilliae*, is still used for grub control in lawns and golf greens in the United States. Production of milky disease spores is somewhat expensive because of specificity of the bacterium isolates and the cultural requirements of living grubs. With advances in cell and tissue culture techniques, it should be possible to produce spores economically in culture media.

B. thuringiensis (Bt) was first isolated in diseased larvae of the flour moth *Anagasta kuhniella* in 1915. It is a complex species comprising more than 20 H-serotypes. These serotypes produce spores that contain β-exotoxin and δ-endotoxin which are used in agriculture. The β-exotoxin is a potent broad- spectrum insecticide, but its teratogenicity and possible mutagenicity in insects precludes its use in most countries.

The δ-endotoxin or the 'crystal' is highly valuable in the control of caterpillars and larvae of mosquitoes, aquatic midges, and black flies. Fast (1981) reviewed the biogenesis, chemistry, and mode of action of the crystal toxin. Once eaten by insects, the crystal causes gut paralysis. Genetic manipulation may further enhance the toxicity and the host range of Bt. The bacterium is produced by fermentation on semisolid or liquid medium and its products are sold under varied trade names. Production methods have been simplified for use at commune level in China (Hussey & Tinsley 1981). Efforts are underway in other countries for producing the bacterium.

The efficacy of Bt can be enhanced with adjuvants, such as 0.1% whole egg homogenate, 0.5% whole milk, or 5% neem seed kernel extract (DBT 1989). The spectrum of Bt activity can also be increased by hybridizing the strains with desired host range. However, concern has been expressed that certain nontarget species of Lepidoptera may be ecologically "at risk" in large- scale pest control programs based on Bt (Miller 1990).

Viruses

Several baculoviruses, cytoplasmic polyhedrosis viruses (CPV), entomopoxyviruses, iridoviruses, densoviruses, and small RNA viruses cause diseases in insects. Only baculoviruses, particularly the nuclear polyhedrosis (NPV) and one CPV, have been developed as viral insecticides. The NPVs invade the larval mid-gut epithelium and have been used in the control of *Heliothis, Lymantria, Neodiprion, Trichoplusia*, and a few other pests. The NPV of *Heliothis* ('Eclar' and 'Biotrol-VHZ') was the first viral insecticide used on cotton in the United States.

A baculovirus of the rhinoceros beetle *Oryctes rhinoceros* has been used extensively in pest control in Southeast Asia and the South Pacific (Bedford 1981). The virus is spread by releasing infected beetles in the wild beetle population. A CPV that caused flacherie disease of the pine caterpillar *Dendrolimus* has been registered for use as an insecticide in Japan (Katagiri 1981).

The cultural requirements for live hosts limits the production of viral insecticides and renders the system vulnerable to contamination. *In vitro* production of insect viruses in cells may overcome these problems. Persistence of viral insecticides may be improved with sunshields. Although insect viruses are safe to vertebrates, caution in their use for insect control will have to be observed as mass production of viruses may entail possible development of deleterious mutations which could survive in nature and affect nontarget insect species.

Fungi

Entomogenous fungi have attracted much attention because of their ability to decimate pest populations, especially during epizootics. As many as 750 fungi are associated with insects (NAS 1979); the important ones are: *Beauveria, Metarhizium, Verticillium, Hirsutella*, and *Nomuraea*. Environmental safety of insect fungi, particularly allergic reactions caused during production or use in dust form and suspected production of mycotoxins are matters of concern. But the important insect fungi have been found to be environmentally acceptable (Shadduck et al. 1982).

Beauveria bassiana has been mass produced in China and the USSR for the control of the European corn borer and the Colorado potato beetle, respectively. In Brazil, *Metarhizium anisopliae* is produced commercially for the control of spittle bugs on forage and sugarcane (Ferron 1981). Although not yet commercialized in India, the fungus has been tried successfully for the control of *Pyrilla* in sugarcane fields (DBT 1989). In the USA, *Hirsutella thompsonii* is used commercially to control the citrus rust mite (McCoy 1972). Control of mosquito larvae by *Culicinomyces*, *Lagenidium*, and *Coelomyces* has shown promise in Australia and America (Federici 1981). Some insect fungi produce metabolites highly toxic to insects, but their insect control potential has not been explored. In general, most work has been done on temperate or subtropical insect fungi. Research on identification of suitable tropical strains and standarization of procedures for commercial production is urgently needed to exploit their potential for insect control.

Genetic manipulation for modifying the virulence is expected to enhance the use of insect fungi. Also improved production techniques to prolong shelf life, and formulations containing nutrients and alginates need to be tested. Likewise, appropriate application methodology needs to be developed for efficient insect control using fungi.

Nematodes

Several species of mermithid, sphaerularid, and neoaplectanid nematodes parasitize insect pests in soil or aquatic habitats and even on low-growing plants (Nickle 1981). The mosquito mermithid *Romanomermis culicivorax* has been reared on *Culex pipiens quinquefasciatus* larvae at a cost of $10/10^6 preparasites. It was promising in small to large-scale field trials and has been produced commerically. Other nematodes tolerant to salinity, desiccation, pollution, and suited to mosquito breeding places are being developed. Mermithid parasitization of rice leafhoppers and planthoppers has been recorded in Japan and India, but not exploited for pest control. Improved culture methods, and better storage techniques would help in reducing production costs and maintaining infectivity. The use of formulations with antidesiccants enhances the infection period of neoaplectanid nematodes (MacVean et al. 1982). Better knowledge of host and parasite biology and physiological interactions should facilitate greater use of nematodes for pest control in Asia.

Protozoa

Potential of *Nosema* and *Vairimorpha* has been considered for insect control. Large-scale field trials with *Nosema locustae* were potentially useful in integrated programmes of rangeland grasshopper management in the Unites States of America. The microsporidian spores need to be mass produced in living hosts and stockpiled for large-scale and blanket treatment. Cell culture techniques may make production economical. Although *N. locustae* are considered safe, they need to be tested against grasshopper predators and parasites. Their potential for insect control in developing countries of Asia is low at present.

Vairimorpha necatrix is highly pathogenic to a wide range of lepidopterous pests, but does not affect hymenopterous parasites and other insects (Maddox et al. 1981). The spores are sensitive to sunlight and UV radiation, therefore use of baits or carriers should be more effective in field applications. Rickettsiae also infect insects, but pathogenicity to warm-blooded organisms renders their use unlikely. On the whole, little scope exists for the use of protozoa for insect control in Asia.

FUTURE CONSIDERATIONS AND CONCLUSIONS

Until now the control of agricultural pests and disease vectors has largely depended on the use of toxic, non-selective, synthetic insecticides. While the use of such chemicals cannot be totally avoided to avert crop losses or reduce risk to public and animal health, the naturally occurring bioactive pest control agents can be exploited to decrease our dependence on toxic insecticides. A large assemblage of botanical, microbial, and insect-based insecticides are available today to substitute for and reduce the dependency on synthetic, broad-spectrum insecticides. The selectivity of natural pest control agents or their bioactive products makes them valuable in integrated pest control. Examples of their successful use against insect pests have demonstrated their potential for development as future generation pesticides that are pest effective, nontoxic to humans and beneficial organisms, biodegradable, less prone to development of insecticide resistance, and are less expensive. However, production methods, formulations, and method and timing of application are more critical in the development and use of natural pesticides than of conventional pesticides.

The costs of petroleum-based insecticides has been increasing steadily. Their importation is a substantial drain on the meagre foreign exchange reserves of developing economies in Asia. This burden can be reduced if insecticides can be derived from locally grown plants. The technology need not be very sophisticated in order to be practical and effective. However, systematically accelerating the research and development of botanical insecticides at all levels will have a greater payoff. Farmers can make direct use of locally available known pesticidal plant material in developing countries, while the industry in advanced countries can conduct research on analysis, synthesis, and development of principal constituents. As plants are the richest source of organic metabolites on earth, the chances of discovering new chemicals with desirable bioactivity from them are greater than the serendipitous discovery of a novel chemical during the routine screening of synthetic compounds. Many potent chemicals have been discovered in plants which were not even thought to possess defense chemicals. For instance, an effective rice stem borer ovipositon deterrent was isolated from a rice variety 'TKM6' and identified as pentadecanal. Efforts are underway to synthesize and evaluate the novel chemical. On the other hand, several neem-based insecticides have been developed directly from neem oil or from enriched extracts. Trees as perennial sources of raw material for insecticide development have a distinct advantage over insecticidal plants that have to be cultivated seasonally or annually as crops. Besides providing large quantities of insecticidal material, they have multiple other uses, and can aid in rehabilitating degraded and denuded lands - a common scenario in many developing countries. It is heartening to see that large-scale planting of insecticidal trees, such as neem, is taking place not only in Asia, but also in Africa, the Middle East, and Latin America. Tree planting and collection of raw material for insecticide development will also generate opportunities for employment and additional income.

The chances of insect pests developing resistance to plant-derived insecticides comprising a complex array of chemicals are lower than with ordinary insecticides based on single active ingredients. Plant-based insecticides can further be fortified against dynamic insect pests by optimizing their use with microbials, such as Bt, NPV, entomophagous pathogens, synthetic insecticides, or plant derivatives.

The potential of microbial insecticides is also considerable. Many of them have already been developed commerically and their use appears to be increasing as a component in pest management programs. Pathogens in use have a clean safety record. In contrast to chemicals, when produced according to standardized procedures, they are virtually accident proof. Some of the insect pathogens are already being mass produced in developing countries using relatively simple technology. Biotechnological advances will help in developing superior insect pathogens amenable to mass production using cell and tissue culture techniques. Modern techniques of cellular and molecular biology have also been used for cloning Bt gene and introducing it into crop plants through transformation techniques, for control of lepidopterous pests. The tremendous heterogeneity of insect pathogens belonging to diverse plant and animal phyla, and variation within the species, make identification difficult. Proper identification is essential to avoid contamination in mass production of pathogens. Also a better understanding is required of their pathogenicity and the nature and mode of action of their toxins.

The insect based pesticides will be used against insect pests mainly as growth-disrupting agents. While some JHA have shown potential in the control of insect pests affecting public and animal health and stored products, their potential for crop protection will remain limited, particularly in developing countries. Also their high costs will restrict use for pest control in Asia. Neuroendocrinological research in advanced research centers may lead to some more novel approaches to pest control.

Insect control in the 21st century looks promising, as it will be based on ecologically sensible and chemically novel approaches.

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STUDIES OF PLANTS AS SOURCES AND MODELS OF INSECT CONTROL AGENTS

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ABSTRACT

Since the discovery of nicotine, pyrethroids and rotenoids as insecticides several thousand species of higher plants have been screened by many researchers for insecticidal activity. Today over 2000 species of plants are known to possess some specificity for target organisms and increased safety for non-target organisms when compared with neurototoxic action of conventional insecticides. The major part of the paper is concerned with some research of plant products carried out in our laboratory on *Rhododendron molle*, *Wikstroemia indica*, *Dictamnus dasycarpus* and *Tephrosia vogelii*. To our knowledge no report exists on these species as having insecticidal properties. It is hoped to find the bioactive components in these plants through the standard stepwise procedures and to characterize the biologically active components. The paper discusses the future potential of naturally occurring insecticides.

INTRODUCTION

Today in China there is an increased interest in the discovery of new means and chemicals for control of insect pests. It is clear that conventional synthetic insecticides are not entirely adequate for the needs of our country. Largescale investigations of insecticidal plants have received considerable attention in recent years. There is continuing research for natural materials that affect insects in a manner that might be useful in pest control. In many instances plants have been used as folk remedies in China [1, 2, 3].

The major scientific emphasis of our study is the isolation, purification chemical identification, bioassay and the mode of action of the natural products in several plants which were chosen because of their abundance and the lack of detailed research on these plants, especially the native species.

BOTANICAL ORIGIN AND TEST INSECTS

Some natural products from plant origin have already served as progenitors to commercial insecticides. Our research uses a bioassay-guided fractionation of the extracts from seven species of plants. There are -

1. *Rhododendron*
2. *Wikstroemia indica*
3. *Dictamnus dasycarpus*
4. *Tephrosia vogelii*
5. *Amorpha fruticosa*
6. *Ajuga niponensis*
7. *Plumbago zeylanica.*

In order to detect the presence of bioactive components in these plants, six species of insects were used to follow sequentially the various steps of the isolation procedures. The test insects were:

1. *Chilo suppressalis* (Rice stem borer)
2. *Nilaparvata lugens* (Brown planthopper)
3. *Mythimna separata* (Armyworm)
4. *Ostrinia furnacalis* (Asiatic corn borer)
5. *Pieris rapae* (Cabbage worm)
6. *Prodenia litura* (Cotton leafworm).

BIOASSAY METHOD

The bioassay methods of topical application, artificial diet, and leaf-disc method have been described previously by the South China Agricultural University.

Electrophysiological method

Physiological data from phytophagous insects stimulated by plant substances have become available in the last decade. A correlated electrophysiological study demonstrated that a chemoreceptive cell in the maxillary sense organs responds to sucrose. The sugar receptors were quite sensitive. The mouthparts of caterpillars are amply supplied by tactile receptors [4]. We have used the tip-recording technique to detect antifeedant activity. Glass pipettes, filled with stimulating chemicals of known concentrations, were employed as the stimulatory recording electrode. They were placed in contact with the tips of *sensillum styloconicum* of armyworm and corn borer larvae. The nerve action caused high frequencies of spikes to be recorded. (Figure 1).

RESULTS AND DISCUSSION

1. The discovery of rhodojaponin from the flowers and leaves of *Rhododendron molle*
Fractions were tested against the rice stem borer and armyworm to guide the fractionation and purification scheme. (Figures 2 and 3).

Three active fractions were obtained. The identification of the chemical structures of these components are shown in Figure 4. All of these compounds are from in the same chemical class.

The crude extract FC from flowers of *R. molle* was identified as containing R - III, R - II and R - V. FC-22 was identified as R - III. Fractions C-1, C-2 and C-3 from the leaves were identified as R - V, R - II, R - III respectively.

The crude extract FC, and FA and FB have distinct antifeedant effect on the larvae of *Mythimna separata, Prodenia litura, Pieris rapae* and *Nilaparvata lugens* (see Table 1, 2 and 3).

The mode of action
Rhodojaponin III (R -III) was more active against *Chilo suppressalis*, exhibiting strong contact insecticidal action. The LC_{50} was 451 ppm on the 3th instar larvae after 48 hours. R - III was found to be a growth inhibitor when incorporated into artificial diet and fed to larvae of *Ostrinia furnaculis*. It also showed antifeedant activity against larvae of *Mythimna separata, Prodenia litura, Pieris rapae* and *Nilaparvata lugens*.

The symptoms and mechanism of rhodojaponin were similar to neurotoxin. The results of electrophysiological studies showed that R - III inhibits the sugar receptors after 5 minutes on the larvae of *Mythimna separata*.

2. Rotenone and its analogs which were obtained from *Tephrosia vogelii* and *Amorpha fruticosa*
The insecticidal efficiency of *Derris* has a long history of use in China. Several groups of compounds have been isolated from various species of *Derris*. The fact, that rotenone is active as a contact and stomach poison against insects has been well documented. The bioactive constituents isolated and identified in these two species of plants were rotenone and an analog. (Figure 5).

The sugar receptor of *M. separata* larvae exhibited a considerably reduced sensitivity, after only 10 minutes. The sugar potential was inhibited very quickly. (Figure 6).

Similarly rotenone and its analog (AMF) were found to be more potent to *M. separata* in no choice leaf disk bioassays with AFC_{50} being 20.4 ppm and 21.1 respectively. Such efficiency is of interest since the concentration is over 10 times lower than that needed for contact application.

3. Fractionation of *Dictamnus dasycarpus*
Compound isolation from roots of *D. dasycarpus* is shown in Figure 7. Nine active compounds were obtained and the following 3 identified: dictamin (C_2), obacunon (C_5), limonin (C_7).

The sugar receptors of *M. separata* larvae showed a considerable reduction insensitivity when they were exposed to C_2, C_5 and C_7.
The observed responses of sugar potential were very inhibited after 5-10 minutes for C_2 and 50-55 minutes for C_5. Though C_2 or C_5 do not seem to interact instantaneously with sugar reception, but exert a long lasting after effect. This result compares well with the

antifeedant activity in the leaf disk bioassay. C_2 was more active than C_5 and C_7. See Figure 8.

TABLE 1
Bioactives of some components of *Rhododendron molle* following separation

Insect	Antifeeding ratio%[1]			
Army worm	FA 71.5		FC-21	86.0
(Mythimna separata)	FB 48.1	FC-1 53.0		
	FC 90.0 →	FC-2 94.5 →	FC-22	93.0
	FD 54.2	FC-3 29.2		
			FC-23	27.0
Rice stem borer	Mortality%			
(Chilo suppressalis)	FA 0		FC-21	90
	FC 30.0	FC-1 5.0		
	FC 90.0 →	FC-2 100 →	FC-22	100
	FD 0	FC-3 5.0		
			FC-23	95.0

[1]Antifeeding ratio

$$= \frac{\text{(Area consumed by untreated) - (Area consumed by treated)}}{\text{Area consumed by untreated}} \times 100$$

TABLE 2
Effects of some components from flower extracts of *R. molle* as antifeedants against the 5th nymph of brown planthopper

Crude extracts	Ave. area mm/nymph	Antifeeding ratio%	AFC_{50}[1]
FA 1%	0.96	95	0.25
FC 1%	0.58	97	0.27
FB 1%	11.32	64	-
Control	19.58	-	-

[1]Antifeeding ratio (A.R)% AFC_{50} - median antifeedant concentration

TABLE 3
Antifeeding ratio for some components in the flowers extract of R. molle tested on two cabbage worms

Crude extracts	*Pieris rapae* $cm^2/larva^1$	A.R.%	*Prodenia litura* $Cm^2/larva^1$	A.R.%
FA 1	0.73	94.5	1.16	90.1
FB 1%	-	-	3.30	71.1
FC 1%	0.44	96.7	0.77	93.5
Control	13.36	-	11.53	-

[1]leaf area eaten (cm^2/larva)

4. A number of "plumbagin" have thus far been isolated from the *Pumbago* sp. [5] as a model for insect ecdysis inhibition. We have isolated and purified plumbagin from the leaves of *P. zeylanica* and synthesized the chemical with the aim of testing the mode of action in different insects.

CONCLUSION

1. Biologically active chemicals occurring naturally are largely unidentified in China. We have isolated and identified over 20 antifeedant compounds from seven species of plants. Just as Copping [6] has pointed out that "This vast supply of uncharacterized and untested new chemicals must surely be the starting point for a novel product, a new synthesis lead or a new useful mode of action".

2. A careful choice of experimental technique is important, since the traditional bioassay methods have to be improved for antifeedant studies. Electrophysiological techniques require limited numbers of test insects and small quantities of chemicals, and the tests can be done in a short time. This method is very convenient and efficient [7]. Progress in the study of natural products are largely dependent on reliable bioassay techniques. Many workers have tried to fulfil this requirement, but many points remain to be improved.

3. Efforts towards the discovery of safer types of ideal botanical pest control agents require collaborative efforts between chemists and biologists [8]. In China there are very rich sources of plants. International cooperation and coordination is very important in the implementation of botanical pest control projects.

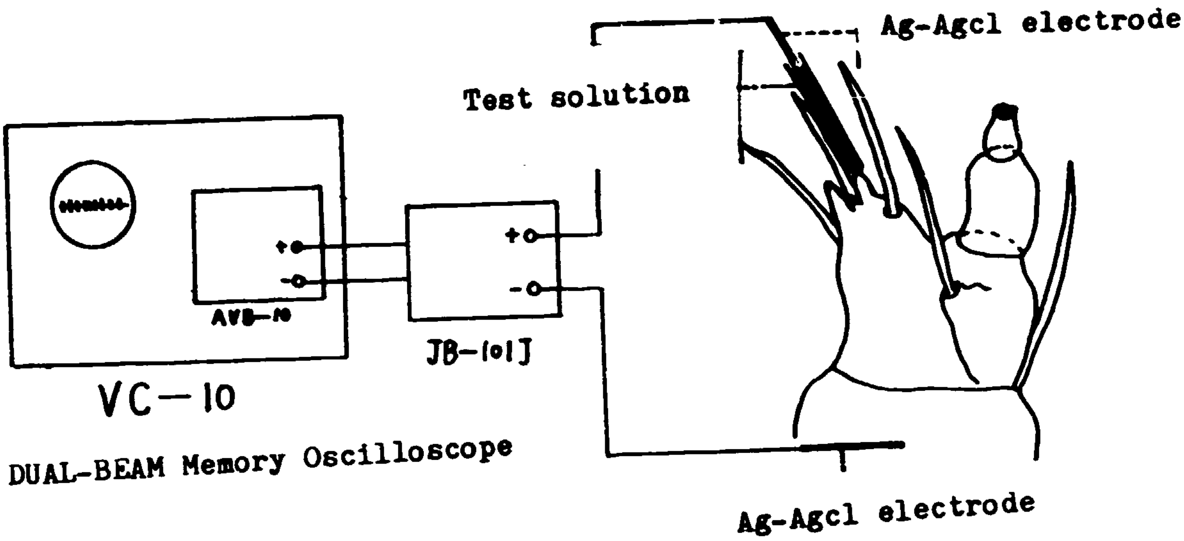


Figure 1. Diagrammatic illustration of the experimental arrangement for the tip recording technique

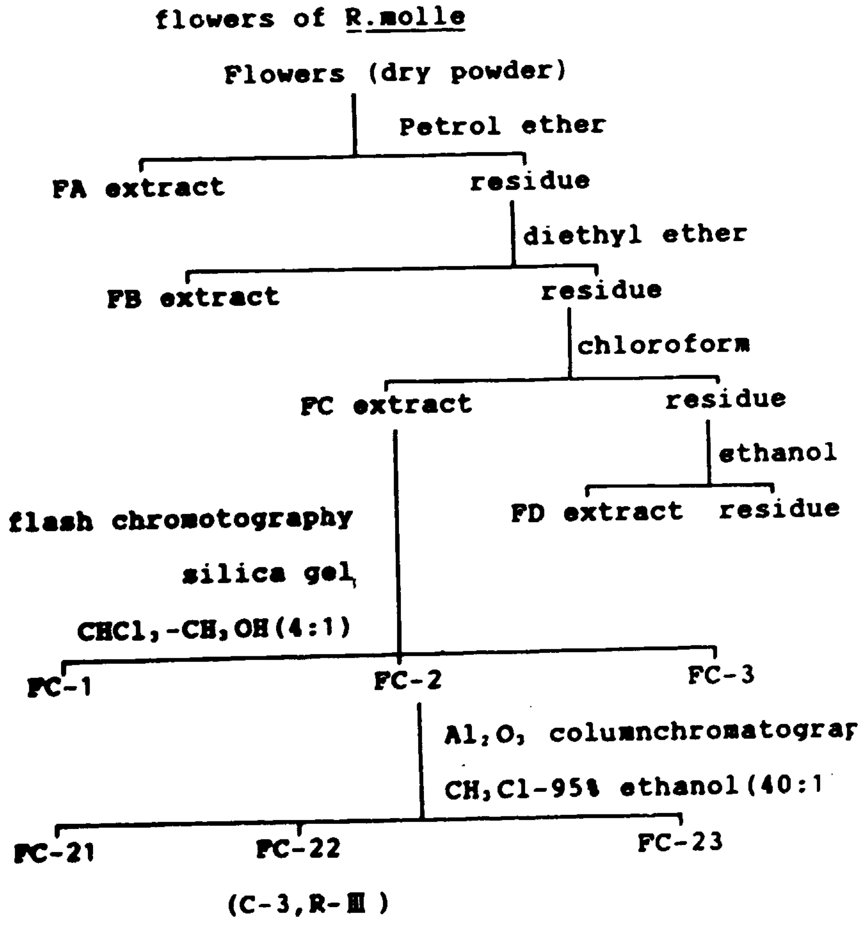


Figure 2. The isolation of the crude extracts from flowers *R*

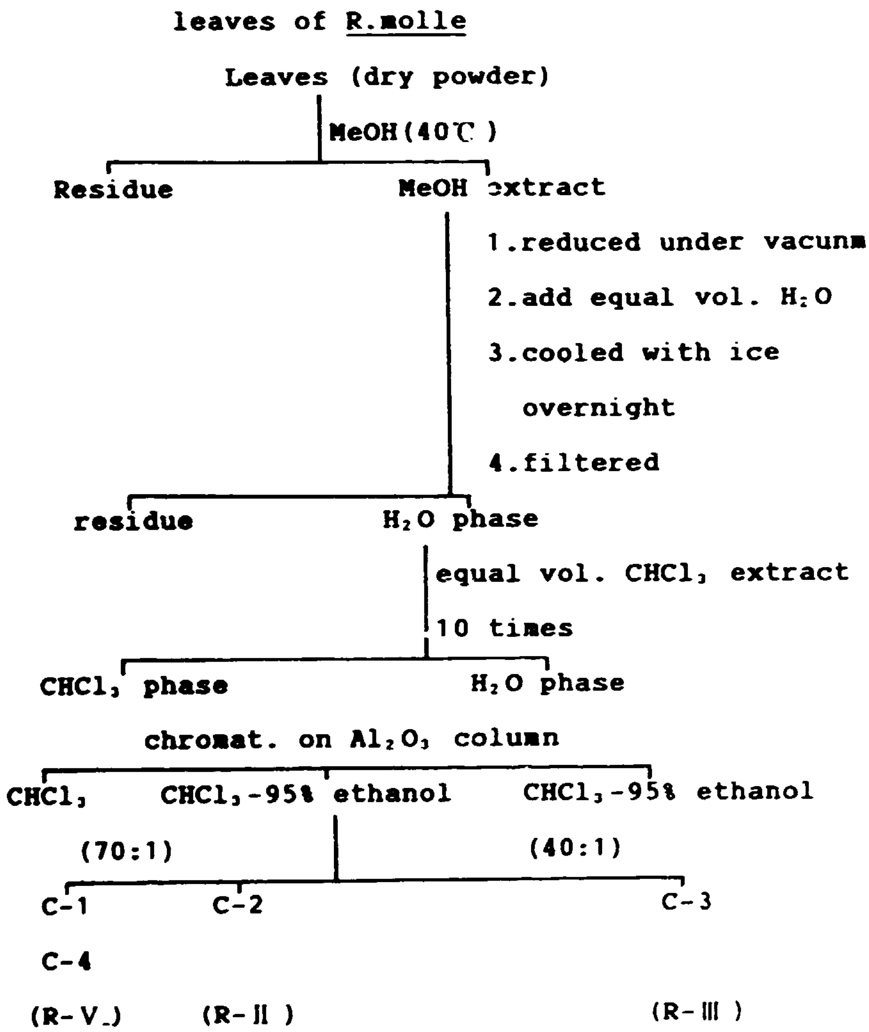
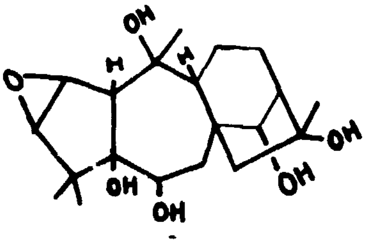
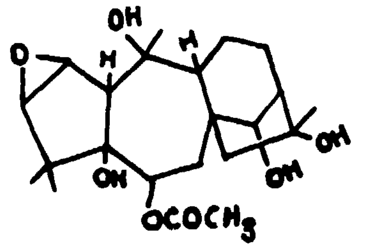


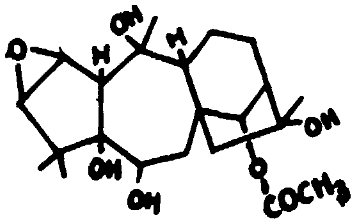
Figure 3. The isolation of the crude extracts from leaves of *R. molle*



Rhodojaponin-III (i.e.FC-22 or C-3)



Rhodojaponin-II (i.e. C-2)



Rhodojaponin-V (i.e. C-[illegible])

Figure 4. Chemical structures of rhodojaponin II, III and V.

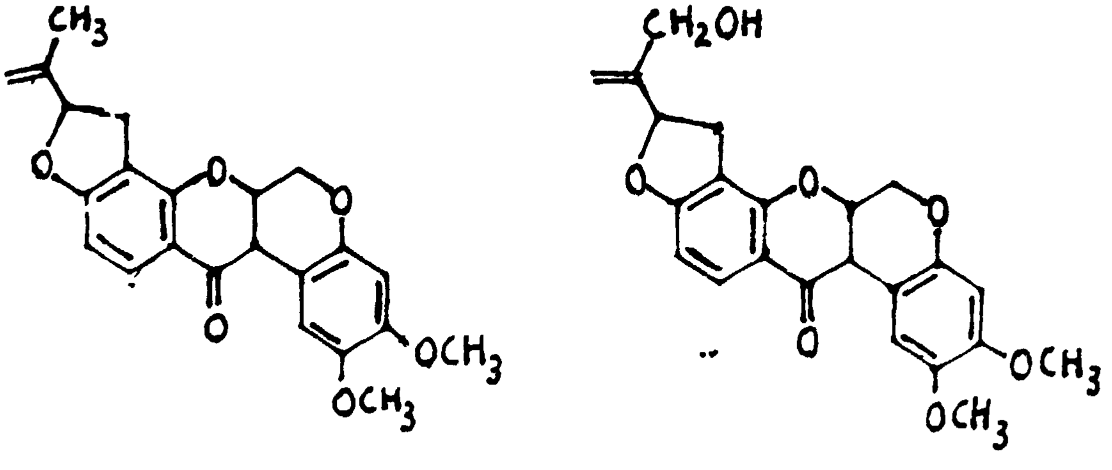


Figure 5. Chemical structure of rotenone and its analog (AMF)

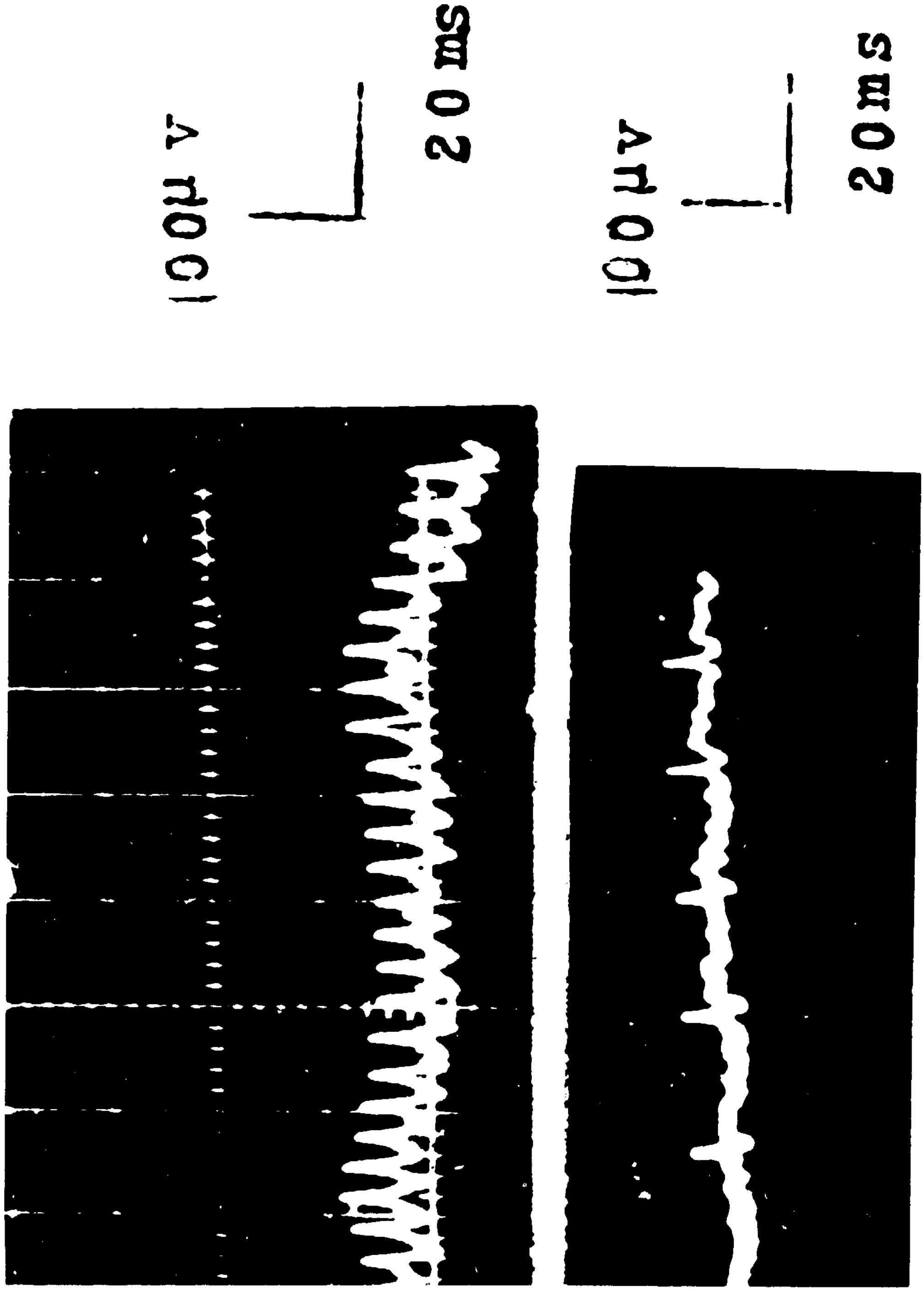


Figure 6. The responses of sugar potential inhibited by rotenone
above: before treatment
below: after 10 minutes

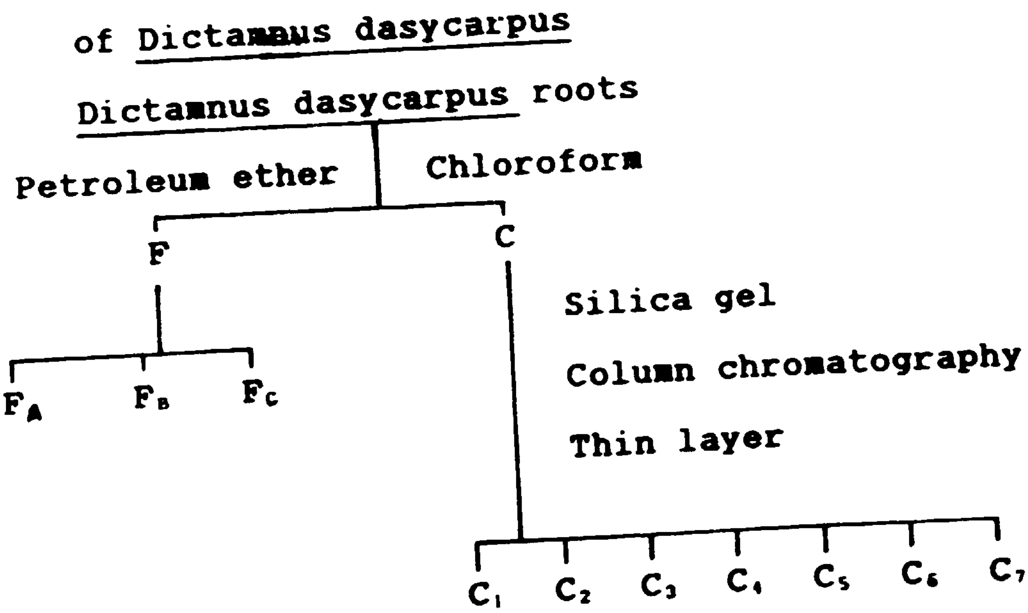


Figure 7. Separation scheme for dividing the extract of *Dictamnus dasycarpus*

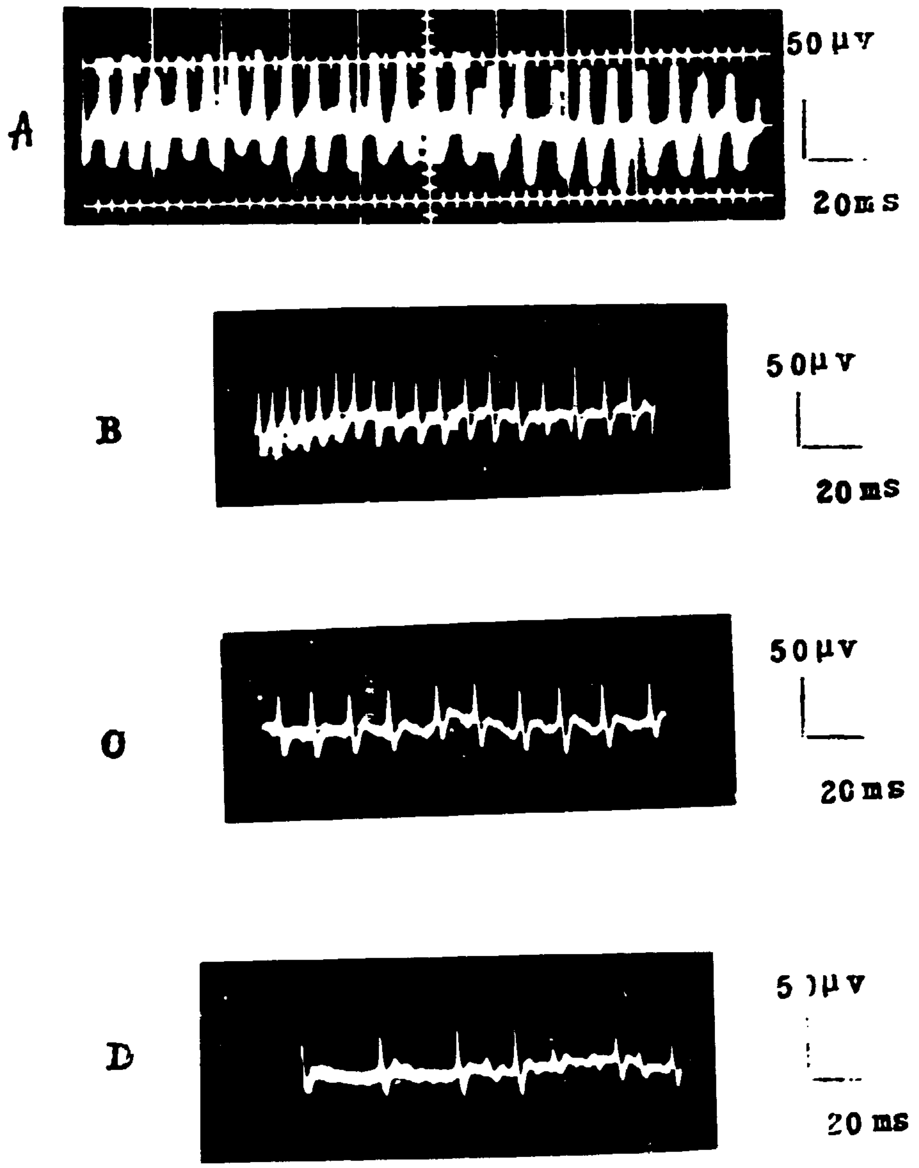


Figure 8. The sugar potential inhibited by dictamnin
A. before treatment
B. after 5 minutes
C. after 30 minutes
D. after 40 minutes

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NATURAL PRODUCTS AS PESTICIDES - THEIR POTENTIAL IN PAKISTAN

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ABSTRACT

Before the advent of synthetic insecticides, botanical pesticides such as pyrethrins, rotenone, nicotine, veratrum alkaloids and quassin were used. The paper reviews the various natural products that show biological activity and their future potential in Pakistan is discussed.

Prolonged use of synthetic insecticides proved to be ecologically deleterious and has led to insect resistance. Consequently, natural products are again of interest as pesticides. Monographs such as "Insecticides of Plant Origin" by American Chemical Society, 1989 [1], "Biologically Active Natural Products - potential use in Agriculture" by American Chemical Society, 1988 [2] "Natural pesticides from the Neem tree and other topical plants" by GTZ, 1984 [3] and "Handbook of Plants with pest-control properties" by Grainge and Ahmed, 1988 [4] during the last few years indicate intense research activity in the field. Grainge and Ahmed [4] list 41 plants as "Cream of the Crop" and the chemistry of some of these is briefly described here, by family (Table 1)

Justicia adhatoda and related species of the Acanthaceae have yielded justicidins A - E. Justicidin B (I) has shown piscicidal activity [5]. The related lignin podophyllotoxin (II) has shown high insecticidal activity [6]. *Annona squamosa* has yielded several annonins, a new group of acetogenins, among which bullatacin (III) is highly insecticidal against bean leaf beetle [7]. McLaughlin *et al* [8] isolated similar compounds from a number of other *Annonaceous* plants using the Brine shrimp lethality test. This simple bench-top test will stimulate much research activity on bioactive natural products.

An ethanolic extract of the fruit of *A. reticulata* exerts a juvenilizing effect on striped cucumber beetle adults [9]. This activity might be due to one or several of the kaurane and 16-kaurene diterpenes isolated from the bark of the plant. However, the results of McLaughlin *et al* [7], suggest that the activity might be due to annonins. Work on *A. recticulata* is in progress to isolate bioactive compounds. *Artabotrys hexapetalus;* may also contain annonins.

TABLE 1

List by family of "Cream of the Crop" plants [4]

I *Acanthaceae*

1. *Justicia adhatoda*

II. *Annonaceae*

1. *Annona reticulata*
2. *A. squamosa*
3. *Artabotrys hexapetalus*

III. *Apocyanaceae*

1. *Haplophyton cimicidum*

I.V. *Araceae*

1. *Acorus calamus*

V. *Asteraceae*

1. *Ageratum conyzoides*
2. *Chrysanthemum cineriaefolium*
3. *Tagetes erecta*
4. *T. patula*

VI. *Celasteraceae*

1. *Tripterygium forestii*
2. *T. wilfordii*

VII. *Clusiaceae (Guttifereae)*

1. *Mammea americana*

VIII. *Euphorbiaceae*

1. *Aleurites fordii*
2. *Croton tiglium*
3. *Ricinus communis*

IX. *Fabaceae* (Leguminoseae)

1. *Arachis hypogaea*
2. *Derris elliptica*
3. *Mundulea suberosa*
4. *Pachyrhizus erosus*
5. *Pongamia glabra*
6. *Tephrosia virginiana*
7. *T. vogelii*

X. *Flacourtiaceae*

1. *Ryania speciosa*

XI. *Lamiaceae*

1. *Pogostemon patchouli*

XII. *Liliaceae*

1. *Schoenocaulon officinalis (sabadilla)*
2. *Veratrum album*
3. *V. viride*

XIII. *Meliaceae*

1. *Azadirachta indica*
2. *Melia azedarach*

XIV. *Piperaceae*

1. *Piper nigrum (black pepper)*

The dried leaves of *Haplophyton cimicidum* (Apocyanaceae) yield "Cockroach powder", which is effective against flying insects [10]. A number of indole alkaloids have been isolated, such as cimidine (IV). Recent studies on *Rhazya stricta* in Pakistan have shown that the methanol extract had antifeedant activity against *Rhyzopertha dominica* [11]. It was further found that the activity resides in the most polar fraction. We have isolated rhazidigenine N-oxide (V) from its seeds, and the plant has already yielded more than 100 indole alkaloids [12]. Further studies are in progress using Brine shrimp lethality test for bioassay. Leaves and root stock of *A. calamus* (Araceae) make very effective insecticides for use against biting and sucking insects attacking field crops, stored grains, wool and against household pests like bedbugs, fleas and flies [13]. Malik *et al* [14] have found that an hexane extract of the rhizome of *A. calamus* has repellant activity. Further processing yielded β-asarone (VI) and methyl eugenol (VII) as the active principles. Jilani and co-workers [15] found that *A. calamus* proved promising against *Callosobruchus analis* and *Sitophibus oryzae* showing 100% mortality at 1% concentration in 3 and 6 days, respectively. Saxena has reported [16] the isolation of asarone, acoradin, 2,4,5-trimethoxy-benzaldehyde, Z-3-(2,4,5-trimethoxyphenyl)-2-propenal and 2,3-dihydro-4,5,7-trimethoxy-1-ethyl-2-methyl-3-(2,4,5-trimethoxyphenyl) indene from *A. calamus*, without bioassay results.

Sesquiterpene lactones isolated from a number of *Asteraceae* have proved to be excellent feeding deterrents for pest insects [17]. Unsaturated amides from some species of the family have shown strong larvicidal activity against Aedes mosquitoes [18]. *Ageratum houstonianum* has yielded 6,7-dimethoxy-2,2-dimethyl chromene (VIII), which has extremely high juvenilizing activity on several species of insects [19]. Little work has been reported on *Ageratum conyzoides* which may contain similar compounds. Dried flowers of *Chrysanthemum cinerariaefolium* have yielded a most economically important group of natural plant insecticides, pyrethrin I (IX), pyrethrin II (X) and relatives [20]. From the leaves of *Tagetes minuta*, 5-ocimenone has been isolated, which is responsible for repellant activity of the plant oil to *Anopheles* mosquitoes. The oil also possesses juvenilizing properties against *Dysdercus koenigii* [21]. *Tagetes erecta* and *T. patula* may contain similar compounds.

The powdered root bark of *Tripterygium forestii (Celesteraceae)* and *T. wilfordii* has been used as a garden insecticide in China. Five insecticidal ester alkaloids, called wilforine, wilfordine, wilforgine, wilfortine and wilforzine, have been isolated. On hydrolysis they yield the same polyhydric alcohol, but different acids [22]. *Mammea americana (Clusiaceae)* has been used as a source of insecticides. Mammein (XI) is the main insecticidal principle [23] and more than 20 coumarins have been isolated from the plant [24]. Recently, surangin C (XII) has been isolated from *M. longifolia* an Indian insecticidal plant [25]. The seeds and the oil extracted from *Croton tiglium* (Euphorbiaceae) are drastic purgatives. The isolation and structure elucidation of tumour promoting phorbol-12, 13-diesters (XIII) from the seed by Hecker *et al* [26] initiated intensive research into the pro-inflamatory and tumor-promoting diterpenes of the family Euphorbiaceae and *Thymeleaceae*. More than 200 diterpenes are known. *Aleurites fordii* has yielded 16-hydroxyphorbol esters (XIV) and more recently a coumarinolignan, (XV) has been isolated [27]. *Ricinus communis* contains castor oil and a diterpene casbene (XVI) has been isolated from an enzyme preparation of the seedlings [28].

Oil of groundnut *(Arachis hypogaea) (Fabaceae)* is reported to control the cowpea beetle, while cotton seed oil has completely controlled the Mexican bean beetle [29]. Groundnut oil has been found to protect maize from damage by the rice weevil *S. oryzae* [30]. Recently, a stilbene derivative (XVII) has been isolated from *A. hypogaea* which has inhibitory activity to both spore germination and hyphal extension of the fungus, *Aspergillus flavus*, at 14.0 and 11.3μg/ml [30]. It is interesting to point out that piceatannol (XVIII) is a potent inhibitor of protein-tyrosine kinases [31]. *Derris elliptica, Mundulea suberosa, Pachyrhizus erosus, Tephrosia virginiana* and *T. vogelli* all contain rotenone (XIX), a well

Pachyrhizus erosus, Tephrosia virginiana and *T. vogelli* all contain rotenone (XIX), a well known insecticide, which is extremely toxic to fish [32]. Seeds and roots of *Pongamia glabra* (syn. *P. pinnata)* are used as fish poison. More than 40 compounds [33] have been isolated from various parts of the plant including furanochalcone (XX), furanoflavone (XXI), chromenochalcone (XXII) and chromenoflavone (XXIII). The pisticidal activity may be due to these compounds. Work is in progress to identify to the piscicidal principle. *Ryania speciosa (Flacourtiaceae)* was found to have promising activity against assay insects. The alkaloid ryanodine (XXIV) is the active principle [34].

Pogostemon patchouli is a strongly aromatic herb. The dried leaves are extensively employed for scenting clothes to keep off insects from woollen shawls, [35]. It contains an essential oil which has yielded patchouli alcohol (XXV), eugenol, and two alkaloids patchoulipyridine (XXVI) and epiguaipyridine (XXVII), [36]. Clerodane diterpenes from various species of the family have been found to be feeding deterrents and to have juvenilizing effects on the Mexican bean beetle and the two-spotted spider mite [37]. The compound mainly responsible for antifeedant activity is ajugarin. Recently, four neo-clerodane diterpenoids have been isolated from aerial parts of *Scutellaria galericulata*. Among these jodrellin B is amongst the most potent neo-clerodane antifeedants so far described [38]. We have recently reviewed the chemistry of such diterpenes [39]. *Pogostemon patchouli* might contain such types of compounds and we have already undertaken a study of this plant. In the *Liliaceae* family *Schoenocaulon officinalis (sabadilla)*, *Veratrum album* and *V. viride* all contain veratrum type alkaloids such as cevadine (XXVIII), which are reponsible for their insecticidal activity [40]. The neem tree *(Azadirachta indica) (Meliaceae)* contains promising pest control substances found effective against many economically important pests. Azadirachtin (XXIX) is the active principle and effective as a feeding deterrent, repellent, toxicant, sterilant and growth disruptant for insects at dosage as low as 0.1ppm [41]. The difficulty encountered in the isolation of pure azadirachtin has led to standardized "neem rich" extracts, and azadirachtin-rich" formulations. A company in India is marketing "Repelin" and "Wellgro", two neem based formulations. Nimbosol and biosal, two oil-based, neem formulations are also being used for the control of whiteflies and *lepidopterous* pests. An "Azadirachtin-rich" formulation, Margosan-O, for use on nonfood crops and ornamentals has been registered in the United States. Efforts are being made in our laboratory in Pakistan to develop similar formulations, combining the methods developed by Nakanishi *et al* [42] and by Feuerhake [43].

Pepper oil distilled from fruits of *Piper nigrum (Piperaceae)* is used in perfumery. Piperine, an alkaloid from pepper, markedly increases the kill of house flies. It improves insecticidal activity of *Eucalyptus* oil. Piperine is synergistically insecticidal to rice weevil and cow pea weevils. Miyakado et al [44] isolated N-isobutyl-11-(3, 4-methylenedioxphenyl)-(2E, 4E, 10E)-2,4, 10-undecatrienamide (pipercide), the major insecticidal amide from the fruit of *Piper nigrum*. The amide has been synthesized. Pipercide (XXX) exhibits a paralysing effect and lethal activity against susceptible and pyrethroid resistant insects.

POTENTIAL IN PAKISTAN

Pakistan is keenly developing its agricultural resources by increasing areas under cultivation, because of increasing population pressure. To achieve these ends, pesticides are an essential element in controlling insects, pests, weeds and diseases. Use of synthetic pesticides, for control of pests of various crops has tremendously increased since privatization of their marketing in since 1981. However the use of chemical pesticides has resulted in a number of problems including pesticide residue on crops, in soil and air; particularly residues on food crops, fruits and vegetables.

In view of the above limitation and increased cost of synthetic pesticides, the use of botanical pesticides, which are usually safe and effective, have attracted priority attention by scientists. Work on botanical pesticides has resulted in identification of 2300 plants which have pest control properties and another 100 plants are being studied [4].

A list of insecticidal and insect-repellent plants of India and Pakistan is given in Table 2.

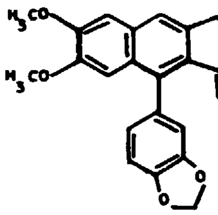
TABLE 2
Insecticidal and Insect-repellent plants

Acorus calamus Linn.	*Euphorbia thymifolia* Linn.
Acorus gramineus Soland.	*Gardenia campanulata* Roxb.
Adina cordifolia	*Gaultheria fragrantissima* Wall.
Agave americana Linn.	*Gloriosa superba* Linn.
Anacardium occidentale Linn.	*Gynandropsis gynandra*
Anamirta cocculus	*Hedera helix* Linn.
Andrachne cordifolia Muell.-Arg.	*Kalanchoe spathulata*
Annona reticulata Linn.	*Lagenandra toxicaria* Dalz.
Annona squamosa Linn.	*Madhuca latifolia*
Arisaema speciosum	*Madhuca longifolia*
Arisaema tortuosum	*Melaleuca leucadendron* Linn.
Aristolochia bracteata Retz.	*Milletia auriculata*
Artemisia absinthium Linn.	*Nicandra physaloides* Gaertn.
Azadirachta indica A. Juss.	*Nicotiana tabacum* Linn.
Bambusa arundinacea Willd.	*Nigella sativa* Linn.
Butea monosperma (Lam.) Kuntze.	*Ocimum gratissimum* Linn.
Calonyction muricatum	*Pachygone ovata*
Cannabis sativa Linn.	*Peganum harmala* Linn.
Cassytha filiformis Linn.	*Picrasma javanica* Blume
Centratherum anthelminticum	*Pieris ovalifolia* D.Don.
Chrysanthemum cinerariaefolium Vis.	*Pogostemon heyneanus* Benth.
Cimicifuga foetida Linn.	*Polygonum flaccidum* Meissn.
Cinnamomum camphora Nees & Ebern.	*Polygonum hydropiper* Linn.
Croton oblongifolius Roxb.	*Randia dumetorum* Lam.
Croton tiglium Linn.	*Ricinus communis* Linn.
Cucumis sativus Linn.	*Ruta graveolens* Linn
Curcuma longa Roxb.	*Santalum album* Linn.
Cymbopogon nardus	*Sarcostemma acidum*
Cyanchum arnottianum Wight.	*Saussurea lappa* C.B. Clarke.
Delphinium brunonianum Royle	*Schleichera oleosa*
Delphinium caeruleum Jacq.	*Scleria pergracilis*
Delphinium elatum Linn	*Sophora mollis* R. Grah.
Derris elliptica	*Tephrosia vogelii* Hook.

Eucalyptus globulus Labill
Euphorbia antiquorum Linn
Vitex neugundo Linn.
Zanthoxylum hamiltonianum Wall.

Of the various plants of Pakistan tested by Malik *et al* and Jilani *et al.*, [14, 15] *Acorus calamus L.*, *Zanthoxylum armatum* DC., *Rhazya stricta* and *Saussurea lappa* have been found to be active by Malik et al, whereas *A. calamus*, *Curcuma longa* and *Azadirachta indica* were found to be active against a number of pests by Jilani *et al*. We have initiated studies for general screening of plants using the Brine Shrimp lethality test (a bioassay which is indicative of cytotoxicity, various pharmacologic actions and pesticidal effects) and monitoring of frond proliferation in *Lemna* or duckweed (a bioassay for herbicide and plant growth stimulants) under a project approved by Pakistan Agricultural Research Council. "Neem-rich" and "Azadiractin-rich" formulations are being developed to commercialize such products in Pakistan.

We are thankful to PARC for nomination and UNIDO for support to attend the seminar.



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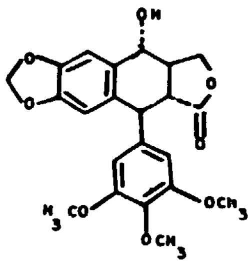

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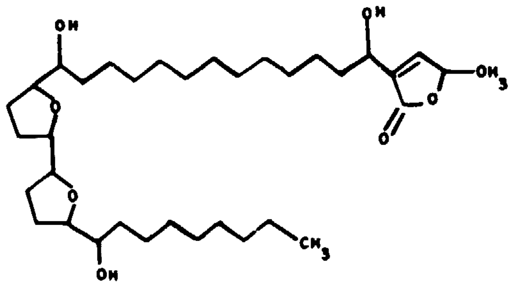

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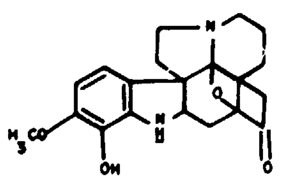

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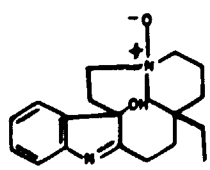

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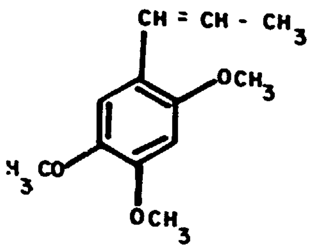

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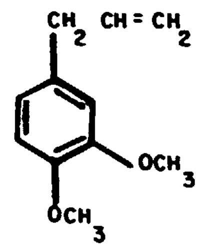

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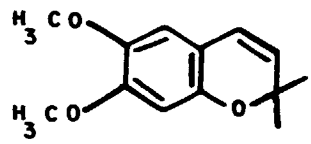

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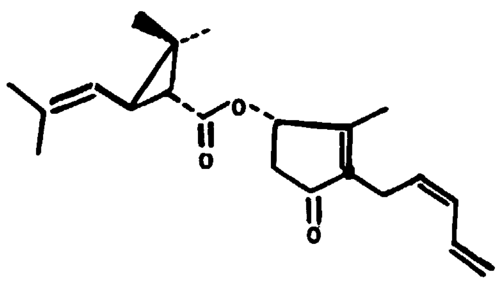

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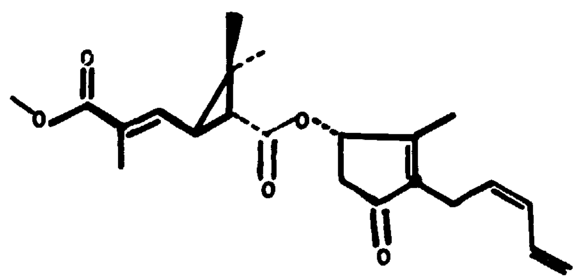

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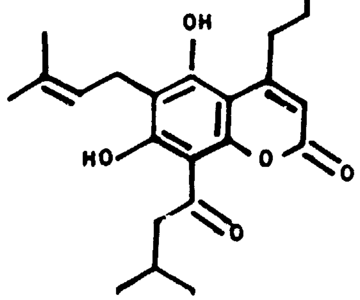

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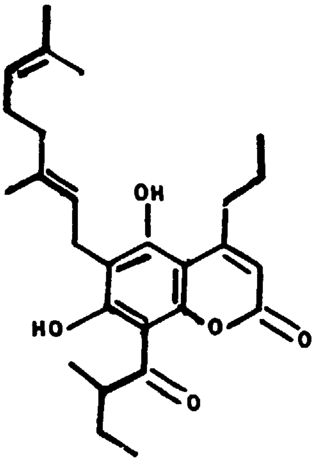

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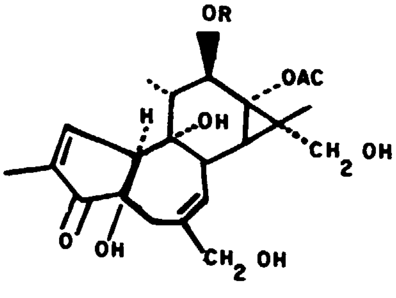

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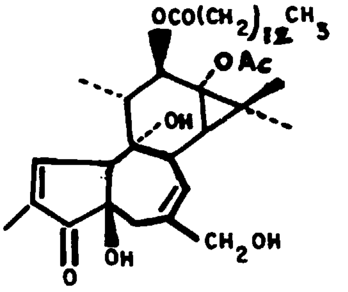

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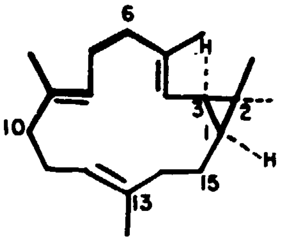

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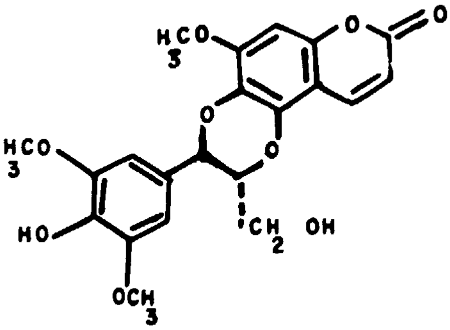

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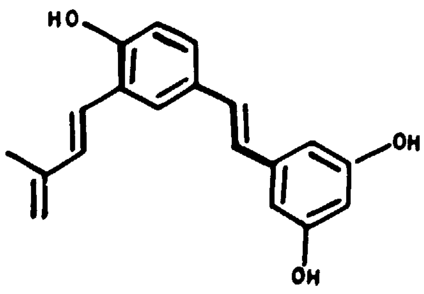

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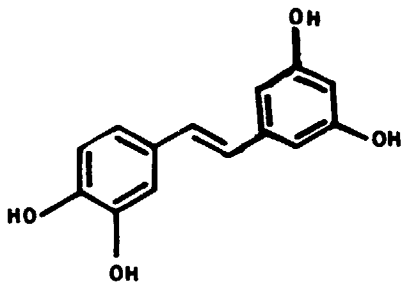

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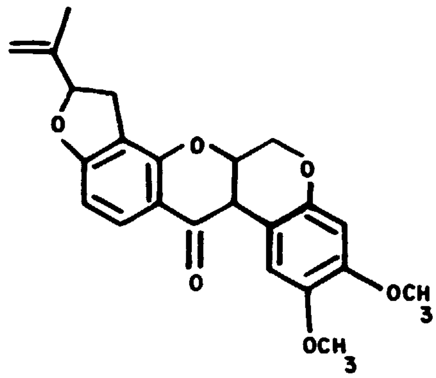

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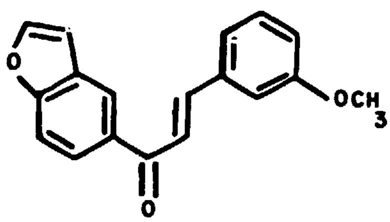

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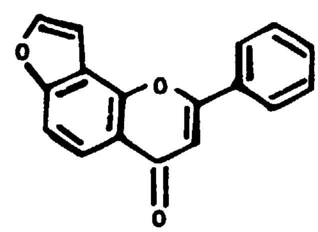

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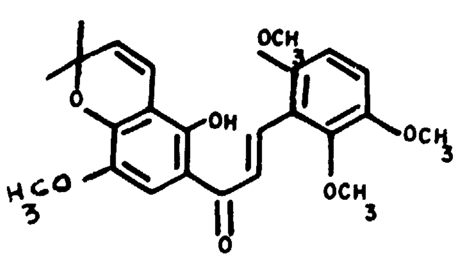

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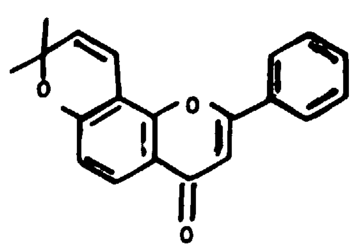

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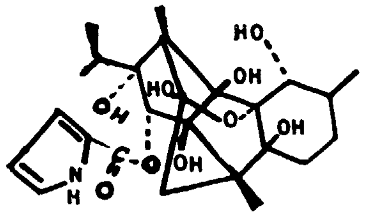

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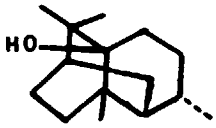

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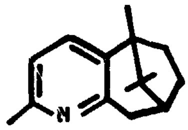

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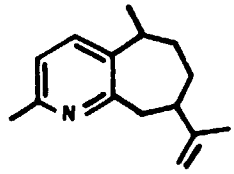

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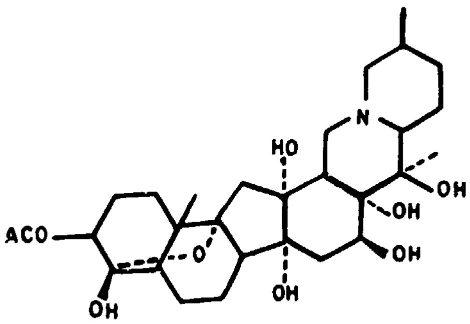

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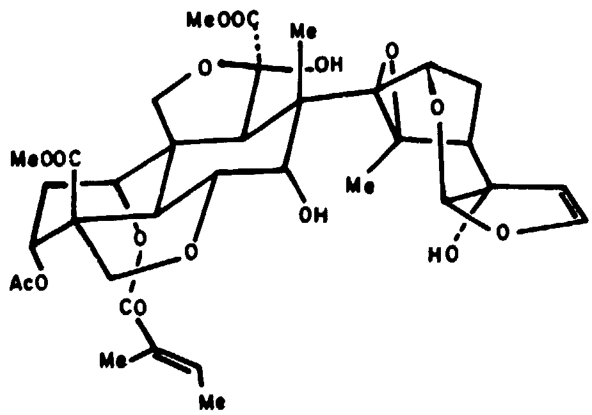

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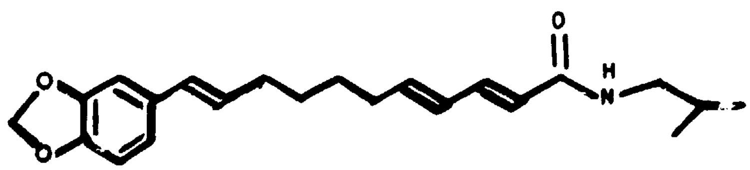

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PREDICTION AND AVOIDANCE OF RESISTANCE TO INSECTICIDES

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ABSTRACT

The development of resistance to insecticides is not always easy to predict but there are a number of key factors which are common to these recidivist pests: a short life cycle with multiple generations per year, often with no overwintering stage; a relatively limited host range, mostly on sprayed crops; high value host crops with low thresholds, usually requiring multiple sprays. Insecticide Resistance Managment (IRM) can be approached from two aspects; curative IRM (introduced in response to field failures) and preventative IRM (introduced before significant field problems occur). Successful IRM requires a working knowledge of many disciplines such as biochemistry, zoology, epidemiology, genetics, population biology, environmental and medical toxicology, botany, psychology, insect physiology, insect ecology, insecticide chemistry and toxicology, agronomy, plant physiology, extension entomology, sociology and, at times, politics. The first steps have now been taken to form an International Pesticide Resistance Management Organization (IOPERM) based on this concept of multidisciplinary teams from industry, government and academia.

INTRODUCTION

The insecticide resistance problem is increasing at an alarming rate while the introduction of new chemistry is slowing down. At the last census in 1986, there were at least 490 species of insects and mites resistant to insecticides [1]. In addition, an increasing number of these are developing multiple resistance to a number of insecticides. For example, by 1984, there were 17 species resistant to all 5 major insecticide groups (DDT, cyclodienes, organophosphates, carbamates and pyrethroids) [2]. Exacerbating this problem are the technical, toxicological and environmental constraints which are slowing up the introduction of new chemical groups. Screening success rates are now 1 in 20,000 [3] while the cost of developing a new insecticide is over $US50 million and $40-100 million extra if a manufacturing plant is required [4]. Thus, the price for new chemistry, if indeed it does become available, will most certainly be high and will increase rapidly. This, alone, is a strong enough incentive to preserve current cost effective compounds such as the pyrethroids. In agriculture, the impact of resistance is to reduce profitability and this has been well documented for the DDT resistance episode in the Ord River Irrigation Area of northern Australia (Fig 1, reworked from [5]). The National Academy of Science [6] suggested that "managing resistance will become a practical necessity for many farmers struggling to stay profitable in the face of growing international competition".

The development of resistance to insecticides is not always easy to predict. However, there are number of factors which predispose the insect and/or the insecticide to resistance development:

Insect

A short life cycle with multiple generations per year, often with no overwintering stage. eg. Sugar cane wireworm (with one generation every 2 years) took 20 years to develop dieldrin resistance. Root maggots (with 3-4 generations/year) took only 5 years [7].

A relatively limited host range, mostly on sprayed crops [8].

High value host crops with low thresholds, usually requiring multiple sprays [9, 10].
Method of reproduction (eg. parthenogenetic aphids or arrhenotokous whitefly and mites which have 1/3 greater resistance potential over fully diploid species) [11, 12].

More than one life stage (eg. moths & larvae) selected [13, 9].

Insecticide

Long residual activity eg. intermittent use of non persistent pyrethroids did not elicit pyrethroid resistance in houseflies whereas persistent pyrethroids did [14].

Single target site insecticides are at greatest risk to resistance development [6].

Low cost coupled with high efficacy (eg. pyrethroids) invite overuse.

Information on the above factors can aid in assessing the resistance risk of an insect/host/insecticide system. However, it must be stressed that each of these systems will have its own idiosyncracies and will most probably be unique [15]. For example, *Heliothis armigera* is a major resistance risk for cotton production in Australia, Thailand, India and Turkey but much less so in Africa.

Insecticide Resistance Management (IRM) can be approached from two aspects; curative IRM (introduced in response to field failures) and preventative IRM (introduced before field problems occur). Curative IRM strategies have been introduced in Australia, Thailand, Colombia and the USA in response to pyrethroid resistance problems in *Heliothis* spp. [16]. It is still too early to fully assess their impact but except for Thailand, it is generally agreed that these reactive strategies have been successful in at least prolonging the effective life of the pyrethroids (Figure 2). These apparent successes may indeed prove to be only increases in the calendar life of the pyrethroids, through temporal restriction on their use, rather than an extension of their absolute period of effectiveness [17]. Nevertheless, they will still have achieved their aim in delaying the problem and buying time for the delivery, development and implementation of new control methods (both chemical and non-chemical). There is no doubt that preventative IRM strategies are ideally the best option, as the chances of long term success are much better and they can be much less restrictive in relation to pesticide use periods [18]. Preventative IRM strategies have been introduced in Zimbabwe and Egypt and so far have been very successful [16]. However, their long term-viability is uncertain. The lengthy discussion in the literature on the relative merits of IRM by rotations, mixtures or mosaics etc., is mostly irrelevant to the needs of practical IRM. By necessity, IRM will involve integration of all these techniques along with standard pest management practices such as cultural control and resistant varieties.

Management of insecticide resistance is a problem which has been forced upon agricultural and public health scientists. As yet, the challenge has not been taken up. There has been much theoretical postulation but only a few groups have ever attempted IRM. Perhaps this is because of the complexity of the problem. Successful IRM requires a working knowledge of many disciplines such as biochemistry, zoology, epidemiology, genetics, population biology, environmental and medical toxicology, botany, psychology, insect physiology, insect ecology, insecticide chemistry and toxicology, agronomy, plant physiology, extension entomology, sociology and, at times, politics. Obviously, no single individual could be expected to possess all the necessary skills, so a co-operative team approach is essential. Over the next few decades these teams will evolve and the number of IRM programmes will escalate markedly as resistance develops to the currently cost effective groups such as the pyrethroids. Even now, the first steps have been taken to form an International Pesticide Management Organisation (IOPERM) based on this concept of multidisciplinary teams from industry, government and academia. The aim of this broad based organisation will be to provide an international forum to promote the concepts of pest resistance management within the context of Integrated Pest Management (IPM) and to facilitate the implementation of programmes in industrial and developing nations and the emerging democracies. Within the Insecticide/Acaricides sub group there are four Working Groups which have been chosen to cover the most pressing insecticide resistance problem areas: cotton, vegetables, mites on tree crops and public health pests. The aim of each of these groups will be to work up resistance management proposals for consideration at the inaugural International Pest Resistance Management Congress for Implementation to be held at the National Academy of Sciences in Washington DC in mid 1992. This meeting should provide a strong focus for the future development of IRM strategies.

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PREDICTION AND AVOIDANCE OF FUNGICIDE RESISTANCE PROBLEMS

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ABSTRACT

After twenty years' experience of fungicide resistance in many situations, it is now possible to assess in a general way (e.g. as low, medium, high) the risk of resistance arising against a particular fungicide treatment. The precise rate of build-up or ultimate degree of resistance cannot yet be determined. Four complementary approaches to prediction of resistance are described - genetic studies, multifactorial analysis, mathematical modelling and monitoring. Counter-measures include minimising use of the fungicide, application of a companion fungicide in a mixed formulation or treatment programme, and concurrent use of non-chemical control methods. The concept of integrated resistance management, involving essential co-operation of manufacturers and other organisations, is discussed.

INTRODUCTION

Fungicide resistance is essentially a phenomenon of the last 20 years. Before then, the build-up of resistant strains of target pathogens was a rare event, which took many years, and was local in occurrence. These isolated early examples, cited by Brent [1], are: in the USA the resistance of mould fungi (*Penicillium* spp.) that attack citrus fruit to both biphenyl fumigation and sodium orthophenylphenate dipping, which are common protectant treatments; in Australia the resistance of the wheat bunt pathogen (*Tilletia foetida*) to hexachlorobenzene seed treatments; in Scotland the resistance of the leaf-stripe pathogen of oats (*Pyrenophora avenae*) to organomercurial seed treatments; in the USA the resistance of the apple scab fungus (*Venturia inaequalis*) to sprays of dodine. The appearance of resistant strains of these fungi did cause practical difficulties in disease control, but only after at least 10 years and often much longer periods of continual use.

The advent of systemic fungicides in the 1970s was very soon followed by the appearance of much more rapid and widespread cases of build-up of resistance (Table 1). Efficacy of these fungicides declined rapidly as resistance intensified and spread. All the major groups of systemic fungicides were affected, with the notable exceptions of the morpholine fungicides and fosetyl-aluminium. All classes of fungal pathogens were involved, in many countries. Fungicide resistance problems have occurred most frequently in western Europe, presumably because most of the world fungicide usage takes place in that region. Warm-climate countries have fewer resistance problems, although the control of coffee berry disease (caused by *Colletotrichum coffeanum*) and banana leaf spot (caused by *Mycosphaerella fijiensis*) has been seriously affected by resistance to benzimidazole fungicides in East Africa and Central America respectively. No serious fungicide resistance problem has to my knowledge been reported yet in the literature from Asian countries, other than from Japan.

In this paper two important questions will be discussed. Firstly, can determining the risk of fungicide resistance be useful, and if so how can it be done? Secondly, to what extent can avoidance strategies be designed and implemented, and can their success be monitored?

THE PREDICTION OF FUNGICIDE RESISTANCE

This topic has been reviewed more fully by Brent, Hollomon and Shaw [2]. The ability to predict the likelihood of the build-up of resistant populations in target fungi is very important. Risk assessment can be used to guide the selection of candidate fungicides for further development towards those which are predicted to be more durable, to determine the need to monitor 'base line' sensitivity and the need to develop special strategies of use in order to ensure a long useful life for potential products.

Experience of fungicide resistance problems over two decades, and much experimental and survey data are now available. Using this information, several workers have addressed the problems of predicting the risk of resistance. Four main approaches can be distinguished. These are: genetic studies, multifactorial analysis, mathematical modelling and monitoring. It should be stressed that these approaches are not entirely separate, and in particular the multifactorial and modelling approaches utilise much data that are obtained from the genetic experiments and from monitoring in the field.

Genetic studies

The intrinsic capacity for mutation conferring resistance of a particular pathogen against a particular fungicide can be examined by mutagenesis experiments involving ultra-violet irradiation or treatment with chemical mutagenic agents. These speed up greatly the mutation rate, and are valuable because natural mutations occur much too rarely to be detected in small populations. The production of laboratory-induced resistant mutants which retain normal vigour and ability to infect ('fitness') gives a positive indication of the likely development of resistance. One good example is provided by laboratory studies on *Phytophthora megasperma* f.sp. *medicaginis*, in which metalaxyl-resistant mutants were readily produced by mutagen treatment [3]. This finding gave a

TABLE 1
Occurrence of fungicide resistance problems in crops*

Date (approx.)	Fungicide or fungicide class	Years of commercial use prior to resistance (approx.)	Main crops, diseases and pathogens affected
1960	Aromatic hydrocarbons	20	Citrus storage rots: *Penicillium* spp.
1964	Organo-mercurials	40	Cereal leaf-stripe: *Pyrenophora* spp.
1969	Dodine	10	Apple scab: *Venturia inaequalis*
1970	Benzimidazoles	2	Many target crop diseases and pathogens
1971	2-Amino-pyrimidines	2	Cucumber powdery mildew: *Sphaerotheca fuliginea*
1972	Kasugamycin	5	Rice blast: *Magnaporthe grisea*
1976	Phosphorothiolates	9	Rice blast: *Magnaporthe grisea*
1980	Phenylamides	2	Potato blight and grape-vine downy mildew: *Phytophthora infestans* and *Plasmopara viticola*
1982	Dicarboximides	5	Grape-vine grey mould: *Botrytis cinerea*
1982	Sterol demethylation inhibitors (DMI fungicides)	7	Cucurbit and barley powdery mildews: *Sphaerotheca fuliginea* and *Erysiphe graminis*
1985	Carboxin	15	Barley loose smut: *Ustilago nuda*

* Modified from Brent [1].

positive indication of the widespread practical resistance of target pathogens to metalaxyl and other phenylamide fungicides which has occurred subsequently. Resistant laboratory mutants cannot be induced against the older fungicides such as copper, dithiocarbamates and phthalimides, which have not encountered resistance problems [4]. However, failure to detect fungicide-resistant mutants in laboratory tests cannot be taken as an absolute indication of no risk. It is possible that a rare mutation could occur in large field populations and rapidly become dominant, and yet not be induced in the laboratory. Conversely, mutants resistant to morpholine fungicides, with normal pathogenicity, are readily produced in the laboratory and yet resistance problems have not emerged in practice [5].

Another important source of resistant variants in field populations is sexual recombination. Recombination experiments are less effective than monitoring for detecting rare single-gene mutations, since such mutations are unlikely to be represented in the small sample of parent strains used. However, when variation is controlled by many genetic factors, with mutations occurring in many isolates, progeny derived from crosses do reveal variation in sensitivity to the fungicides. In studies on barley powdery mildew, progeny from sexual reproduction yielded more variation in sensitivity to ethirimol and triadimenol than could be produced by mutagenesis experiments, or exposed by base line monitoring [6].

The initial low frequency of fungicide resistance alleles in field populations can be increased by selection, i.e. through repeated exposure to the fungicide. Thus, in growth room experiments on populations of *Phytophthora infestans* with an initial frequency of metalaxyl resistance of 1×10^{-4} [7], this frequency was increased one hundred-fold after exposure for three generations to metalaxyl sprays. However, initial frequencies in the field are likely to be well below 10^{-6}. In this case selection experiments need to utilise very large starting populations and results are likely to be erratic. Nevertheless, isolation of resistant mutants in a laboratory or field selection experiment does indicate a risk of resistance. Information on the fitness of the resistant variants is, of course, necessary. However, this can only be done in the laboratory or isolated glasshouse because it would be wrong to inoculate deliberately field crops with resistant forms if the pathogen were still effectively controlled in the field.

Multifactorial analysis

From the analysis of case histories (see [8] for examples) we can obtain some understanding of the many interacting factors that determine the rate and severity of resistance build-up. These factors have been discussed by many authors over the years. At least 15 of the factors were incorporated into a scheme prepared by Gisi and Staehle-Cseh [9]. These include inherent genetic and biochemical characteristics of the target pathogen, degree of cross-resistance to fungicides with a known resistance problem, the fecundity of the target pathogen and strategies of fungicide use. In this comprehensive approach, numerical scores of 1 - 3, indicating low, medium and high risk are allocated to each of the factors, judging by the best information available. Thus, evidence for cross-resistance, selection of resistant strains in mutagenesis tests or in heavily-treated field plots, evidence of loss of field performance, rapid rates of reproduction by the fungus, high frequency of fungicide application, large treated areas, and the use of the fungicide alone rather than in mixtures, are all factors favouring resistance and taken together would indicate a high risk. However, in practice not all these factors are easily measured nor will they be equally important. Consequently the total risk score obtained is not very reliable in terms of the time-scale of resistance or its ultimate severity. Nevertheless, this type of approach does seem to provide an indication of 'small', 'moderate' or 'large' levels of risk, and the accuracy does tend to improve as more knowledge accumulates about a particular fungicide/disease situation.

Mathematical modelling

Several models have been proposed to explain and predict the rate of build-up of resistance, and to indicate the effects of different strategies of fungicide use. Examples are given in references [10 - 14]. These models have concentrated on situations where there are two distinct groups of strains, with substantial differences in resistance which are controlled by a single gene. The general conclusions arising from the different models are broadly similar, and are in keeping with predictions arising from other approaches. They indicate that resistance develops most rapidly in pathogens which reproduce frequently and are exposed to highly effective, persistent fungicides. The lower the frequency of resistant mutants in the initial population, the longer that resistance will take to appear. Poor fitness of the mutant forms prevents the development of resistance.

Two forms of genetic control of fungicide resistance are now recognised. In one type, only a single gene is responsible, whereas in the second, many genes, each with a small but additive effect, are involved. Much less modelling research has been done in connection with the latter type of resistance. However, recent models proposed by Shaw [15] do address this problem by considering how fitness and growth rate change in relation to degree of fungicide sensitivity. Genetic information on the inheritance of resistance is also required through sexual crossing. It should be possible to validate Shaw's model by appropriate laboratory and field experimentation, but this remains to be done.

Monitoring

Monitoring for 'base line' sensitivity, at a very early stage in the use of a fungicide may reveal variation in sensitivity, especially with regard to sensitivity to the DMI and 2-aminopyrimidine fungicides, where resistance is considered to be polygenic. Subsequent changes in response to selection will be gradual, so that further monitoring should detect shifts in fungicide sensitivity before difficulties in practical disease control emerge. This has proved useful in the case of powdery mildews of cereals and their control by the above two fungicide groups [16]. However, in the case of single-gene mutations it will seldom be feasible to detect resistant pathogens until they reach high frequencies (> 1%) in the population. In these situations, positive results from monitoring may come too late to be a useful indication of risk. It will only take one or two treated generations from the time resistant forms are detected until the time of serious failure of disease control. Nevertheless, a valuable alert to risk may be given if the rate of reproduction of the fungus is only one or two generations per season, or where use of the fungicide has not started in other regions.

COUNTERMEASURES

The surest way of avoiding resistance is not to use the particular type of fungicide which is at risk. The likelihood of resistance occurring has caused manufacturers to decide not to develop and market certain experimental fungicides. Assuming, however, that the products will come into use then we must consider less stringent policies which are likely either to delay or avoid the appearance of resistance.

Minimising use

It may be possible to restrict the use of a product to times when its special properties are critically necessary for crop disease control. At other times either no fungicide or an alternative fungicide should be used. For example, ethirimol was used in the UK as a seed treatment for autumn sown and spring sown barley to control powdery mildew on the foliage. When the occurrence of resistant strains was first detected through monitoring, the manufacturers (ICI) recommended that its application to autumn-sown barley should cease [17]. It was considered that treated autumn-sown barley formed a selective bridge on which resistant forms would thrive and transfer to the spring-sown crop.

In the treatment of *Botrytis* disease of grape-vines the use of dicarboximide fungicides has been restricted to 2 - 3 sprays early in season. A similar strategy has been applied to the use of phenylamide fungicides against potato blight (*Phytophthora infestans*) and grape-vine downy mildew (*Plasmopara viticola*) in certain regions. In the case of phenylamides, however, mixtures with other fungicides (see below) also are used exclusively.

Altering fungicide dose could also affect selection of resistant strains. It remains an open question, however, as to whether it is more of a risk to lower or to raise the dose. Lowering the dose might decrease selection pressure that favours highly resistant forms. However, it might also encourage the spread of moderately or weakly resistant strains. Increasing the rate might encourage highly resistant forms to develop, but inhibit the more gradual build-up of resistance. However, experimental data regarding effects of dose on the risk of resistance are at present very few. In some experiments in the author's institute increasing the rates of application appeared to enhance shifts towards resistance to triadimefon in barley powdery mildew [18], but in other experiments on strawberry *Botrytis* [19] and on wheat eyespot (*Pseudocercosporella herpotrichoides*) (T. Hunter, V.W.L. Jordan and K.J. Brent, unpublished data) altering doses made little difference to the rate of build-up of resistance.

Combined use of different fungicides

Models have suggested that the combination of a high-risk fungicide with a companion fungicide of a different type will reduce selection pressure and delay resistance. The companion compound must control strains of fungi that are resistant to the at-risk fungicide, i.e. there must be no cross-resistance. Either multi-site or site-specific fungicides can be used as companion compounds, but suitable multi-site compounds are preferable if these are available. If two site-specific fungicides of different types are used there is some risk of double resistance eventually arising. Protectant fungicides such as mancozeb and copper have found renewed use as partners to the more recent systemic fungicides.

With present experience there appears little to choose between mixing and rotating the partner fungicides. However, in practice proprietary formulated mixtures are increasingly being marketed and used. Examples are mixtures of phenylamide fungicides with mancozeb or copper to control Oomycete diseases, and mixtures of sterol demethylation inhibitor (DMI) fungicides with chlorothalonil to control cereal diseases. If, as with phenylamide-containing sprays, these are the only products marketed which contain the at-risk fungicide, then the farmer has no option but to use the combined treatment and the mixture strategy is uniformly operated. Often the mixtures also have the advantage of increasing the target range and the effectiveness of the treatment.

Experimentally, it has been demonstrated in a few situations that the use of appropriate mixtures can delay the appearance of resistant populations ([7], [18], [20]). Success in practice is hard to judge, because strategies are operated over large regions with no equivalent 'non-strategy' area available for comparison. Practical experience to date suggests that the use of mixtures and/or rotations does stabilise polygenic resistance at an acceptable level, as for example in the case of resistance of barley powdery mildew to triazoles in the UK. Single-gene resistance is delayed, but tends to predominate eventually, as with the use of phenylamide-mancozeb against *Phytophthora infestans* in the UK.

Application of a combination of two fungicides showing negative cross-resistance could be particularly effective. The cereal seed treatment 'Ferrax' introduced by ICI [21] includes a 2-aminopyrimidine fungicide (ethirimol) and a triazole (flutriafol), and is designed to exploit the negative cross-resistance of powdery mildew which is known to exist between these two classes of fungicide. The fungicide diethofencarb [22] shows negative cross-resistance to benzimidazole fungicides. Thus it finds use as a mixture with a benzimidazole fungicide for control of *Botrytis cinerea* in grape-vines.

Integrated resistance management

It is important that the specific avoidance strategies involving fungicide use are combined with other activities. Monitoring is essential, to check that the use strategy is really working and to indicate the need to modify or strengthen the strategy if resistant forms are increasing. It is also wise to use complementary non-chemical methods of disease control wherever possible. For example, disease-resistant cultivars and hygienic cultural practices should be used, provided they are available and at least in part effective in controlling disease.

To establish integrated resistance management, co-operation between agrochemical companies, advisory bodies and growers is essential. Companies which supply fungicides of the same class (with regard to resistance) need to collaborate in designing and operating joint strategies to avoid resistance. Thus, the Fungicide Resistance Action Committee has been organised by GIFAP (International Association of Agrochemical Manufacturers) to ensure good inter-company collaboration and compatible policies with regard to fungicide recommendations.

Finally, it is very important that we maintain a good diversity of fungicides for crop disease control, since it is the repeated and exclusive use of particular fungicides which causes the major resistance problems. The discovery process must continue. No major new classes of fungicide have been announced since 1977, although it is encouraging that several experimental fungicides with novel structures and potent selective activity have been reported at recent conferences.

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RESISTANCE TO HERBICIDES: OCCURRENCE, PREDICTION AND AVOIDANCE

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ABSTRACT

The development of biotypes resistant to triazine and other herbicides is described, with examples. Methods for the determination of resistance are summarised. Mechanisms of action of herbicides and the modifications which may occur in resistant biotypes are described briefly. Lists are presented of factors which may predispose to the evolution of resistance, and of components of management strategies to prevent or alleviate resistance problems. International action on herbicide resistance issues is mentioned in conclusion.

INTRODUCTION

The majority of uses of herbicides in agriculture and horticulture are selective. They are based on major differences in susceptibility between the crop and its associated weeds. These differences derive from divergencies in morphological, physiological and biochemical characteristics of the species.

Differences between varieties in the level of resistance to herbicides by crops was observed over 40 years ago with the phenoxyacetic acid herbicides in linseed and maize. This led to early recognition by plant breeders of possibilities for developing more resistant varieties giving wider selectivity margins. However, breeding for yield and quality characteristics and for disease resistance took precedence.

There were also early perceptions that within a weed species loosely classified as susceptible, not only could different biotypes be distinguished on morphological grounds but also in their reaction to herbicides - generally by a small but nevertheless discernible factor.

Hence there were early signs that the potential existed for selection of herbicide-resistant biotypes within previously susceptible species. However, most weed scientists 3-4 decades ago thought major resistance problems, as seen with insecticides, were unlikely to occur with herbicides. Three principal reasons were given:

1) usually there is only one generation of weeds annually;

2) the buffering effect of the bank of weed seed in the soil, of which a large part may be derived from plants not exposed to the herbicide;

3) the enormous use of 2,4-D, MCPA and other phenoxyacid herbicides over a long period, particularly in temperate cereals, and often in mono-culture systems, without obvious development of resistant biotype problems.

In fact, early problems were due to selection between weed species, with more resistant weeds being released from competition of other weeds now controlled by herbicides. This occurred, for example, with *Avena* spp. in cereals in the United Kindom and *Setaria* spp. in maize in the United States of America.

However, from 1970 onwards there have been increasing numbers of reports of the evolution of resistant biotypes of previously susceptible weed species as shown by their ability to survive herbicide treatment at higher than normal doses. The number of species involved has now reached about 80. The majority are reported from North America and Europe but there are occurrences worldwide. In the Western Pacific area, Australia, Hawaii, Japan, New Zealand and the Philippines have encountered this type of problem.

BIOTYPES RESISTANT TO TRIAZINE HERBICIDES

The first reported case was of *Senecio vulgaris* resistant to simazine and atrazine in the northwestern United States in 1970. In the ensuing 10 years about 30 more species became involved and the area affected by triazine-resistant biotypes increased, outstripping occurrences with other classes of herbicide.

The importance of triazine-resistant biotypes has been maintained. A survey within the United States of America in 1989 reported their presence in 33 out of 50 States, involving nearly one million hectares. The most important species affected are *Amaranthus* spp, *Chenopodium album*, and *Kochia scoparia*. However, only a small proportion of these States reported that resistant biotypes were a serious weed problem requiring special effort.

Worldwide, 40 dicotyledonous species and 17 grass species now show resistance. In Europe the species reported most frequently as developing resistance to triazines are *Chenopodium album, Poa annua, Senecio vulgaris* and *Solanum nigrum*. This should not be interpreted as meaning that all infestations of these weeds have become resistant. That would be far from the truth. Nor is the evolution of resistance spread across all the major groups of annual weed species. For example, weeds from the Cruciferae are under-represented in the reports.

Most of the occurrences relate to the repeat usage of simazine and atrazine on the same site over a period of years. This happens where an annual crop resistant to triazine herbicides is grown as a monoculture system or where this type of herbicide can be used repeatedly and safely in a perennial crop. Major examples are:

Maize (corn in the Unites States of America)
Soft fruit
Orchard fruit
Vineyards

Nursery stock
Non-crop situations (e.g. railway tracks)
In many of these situations the use of triazine herbicides has continued despite observation of biotypes developing resistance. Often this has been due to absence of an economic alternative for the control of the susceptible weeds present.
Likely factors which have assisted the evolution of triazine resistant weeds are:

1. Efficiency as weedkillers, thereby exerting high selection pressure.

2. Cheapness, hence encouraging regular use.

3. Long persistence in soil, thereby restricting opportunity for escape by late germinators which would help maintain susceptible biotypes.

4. Mobility in soil in some cases (e.g. atrazine) and therefore being available to seedlings over the full range of germination depth.

5. Relevance to crop-weed situations where repeat application, sometimes within a season, seemed desirable.

Other factors may predispose against selection for resistance. Of particular importance is the 'fitness' of resistant biotypes. By this is meant the possession of characteristics which enable it to compete successfully with susceptible biotypes, other weed species, and the crop. Considerable research has indicated that biotypes resistant to atrazine or other triazines are inferior in vigour, possibly due to a less efficient photosynthetic system than the comparable susceptible types. In one investigation with biotypes of *Chenopodium album* evolved in France the resistant plants were generally taller and less branched, flowered later, and produced less seeds with a lower germination rate than susceptible plants.

RESISTANCE TO OTHER HERBICIDES

In more recent years there have been reports of evolution of biotypes resistant to herbicides of many other classes. In some cases these are photosynthetic inhibitors such as the substituted ureas, with a mode of action similar to triazines. In other cases the mechanism of action is very different. By 1989 there were reports of resistance development in 26 dicotyledonous species and 12 grass species. In many cases there is overlap with the list of species in which triazine resistance has evolved. These numbers continue to grow.

The classes of herbicides involved so far include:
Substituted ureas, e.g. diuron, chlorotoluron
Uracils, e.g. bromacil
Anilides, e.g. propanil
Sulphonylureas, e.g. chlorsulfuron
Dinitroanilines, e.g. trifuluralin
Triazoles, e.g. amitrole
Aryloxyalkanoic acids, e.g. MCPA, mecoprop

Esters of aryloxyphenoxyalkanoic acids, e.g. diclofop-methyl
Hydroxybenzonitriles, e.g. bromoxynil
Bipyridiniums, e.g. paraquat
Organoarsenicals, e.g. MSMA
These cover a considerable range of usage and modes of action.

Chlorotoluron

The evolution of biotypes of *Alopecurus myosuroides* resistant to chlorotoluron and other herbicides in the United Kindom illustrates a range of important aspects.

This species is an annual grass weed of cereals, primarily of winter wheat. It is winter germinating, very competitive, and a prolific producer of small seeds which are shallow germinators and can produce dense stands. It has become an increasing problem in Europe during the last two decades as a higher proportion of winter crops have been grown, cultivations (particularly ploughing) have been reduced, and competition from other weeds has been lowered by their effective control. This has led to the development of chemical control measures aimed particularly at this weed. Because of the long period of germination and establishment through the autumn and winter months a soil-acting herbicide with some persistence is advantageous. Thus, there has been widespread usage of the substituted urea herbicides chlorotoluron and isoproturon which have selectivity for this purpose in cereals.

After more than a decade of successful use, partial resistance was first detected at Faringdon, near Oxford, in 1982. Subsequently, more pronounced resistance was found at Peldon, Essex, about 175 km away, in 1984. By 1987, resistant or partially resistant biotypes had been found on 10 farms in England. By 1989 seed samples of the weed from over 250 fields had been tested. Resistance was detected in 33 fields on 20 farms in 6 Counties, with no evidence of their having spread from a common source. All fields had been in a rotation in which winter cereals predominated, as did cultivation regimes which did not include ploughing. Herbicides used were mainly chlorotoluron, isoproturon and diclofop-methyl, and on the fields concerned averaged 1.6 applications per year over the previous 10 years. At Peldon, the site where resistance was most severe, chlorotoluron was first used in 1975. There were then 13 applications of chlorotoluron or the closely related isoproturon between 1975 and 1984. At Faringdon there was a similar history.

At the latter site, where resistance was first discovered, there was seed available collected in 1976, only 2 years after chlorotoluron was first applied to the field. Subsequent seed collections were made in 1981, 1983 and 1985. In 1987 all four seed collections were germinated and the response of the seedlings to chlorotoluron tested together under identical conditions. Measurement of growth reduction showed a slow but steady increase in resistance with passage of time as represented by decreasing age of seed. In contrast, seed was collected in each of the years 1982, 1984 and 1986 from a site of Rothamsted which had not received any herbicide during its 140 years of recorded history. Simultaneous comparison of response of seedlings to chlorotoluron showed the same level of high susceptibility by each of the three batches.

The degree of resistance was very variable between sites where it was discovered, but in many of the cases it was sufficient to make effective control by chlorotoluron unattainable. However, the problem should not be overstated. A survey by the Advisory Service in 1988 on sites drawn at random showed the *Alopecurus myosuroides* at 86% of them to be still susceptible despite a high intensity of herbicide use at many of them. Only 5% of sites showed partial or major resistance. 9% were marginal, though such sites may offer a hint of potential for further development of resistance.

Other investigations show no major difference in fitness between resistant and susceptible biotypes. Nuclear inheritance of this trait is involved and hence resistance can be transferred by pollen. Nevertheless, there is no indication of spread over long distances.

Detection of Resistance

Many factors influence the performance of soil-acting herbicides such as chlorotoluron. Inferior performance in the field may be due to poor application; dry soil; rough soil surface; adsorptive soil (due either to organic matter or ash from straw burning); sub-optimal soil pH; slow action (particularly under dry conditions); expectations too high (it is difficult to achieve 100% control or maintain activity over a long period to control late germinators); or lastly resistant biotypes. Hence it is crucial to identify reliably whether a resistant biotype is present, and eliminate other factors.

In all cases comparison must be made with material from a known susceptible population which has been exposed to little or no herbicide. The most direct method is to collect mature seed from each site, sow in sandy loam soil in trays or pots, spray the soil surface with a range of doses, keep under standard conditions in a glasshouse and observe emergence and growth after 3-4 weeks. Phytotoxicity is compared with that shown by the susceptible standard. Containers with different seedstock - herbicide combinations may be buried to the rim at a suitable field site so that the assessment is made under field conditions. Some ureas and triazines may be formulated with oil and surfactant for post-emergence application to seedlings, thus giving a quick response assessable in 3-4 days. Other variations use herbicide in solution with seedlings from the various sources floated on rafts on the surface; alternatively the seed may be sown on filter paper moistened with solution in Petri dishes, kept out of direct sunlight at room temperature. Results may be assessable in up to 3 weeks, according to herbicide.

One very simple method can be used with many photosynthetic inhibitor herbicides. This involves taking leaf discs from plants of populations to be tested. These are floated on buffer + wetting agent + herbicide in a series of concentrations in specimen tubes. The tubes are then kept under vacuum for 20 minutes, shaken, the vacuum released and then reapplied. After 40 minutes all discs should have sunk. The solution is replaced by a new aliquot also containing sodium bicarbonate and the tubes kept under illumination. Discs from susceptible plants remain sunk. Discs from resistant plants resume photosynthesis and float. Results can be assessed after 1-2 h.

There are other more sophisticated variations on the above method of comparing interference with photosynthesis in susceptible and resistant biotypes. One uses infra-red gas analysis to measure carbon dioxide exchange in leaf discs maintained in an illuminated chamber after treatment with herbicide. With susceptible discs the rate steadily declines. With resistant discs the rate declines and then recovers. An answer is obtained within 3h but the equipment is expensive. Another method is applicable specifically to herbicides which inhibit photosystem 2 through binding to an active site in the chloroplast. This induces a fluorescence which can be measured, using either leaf discs or isolated chloroplast suspensions. Again the experimental period is short, but costly laboratory equipment is required. If chloroplast suspensions are used, it can demonstrate whether resistance is arising at the actual site of action of this type of herbicide.

Cross-resistance

Cross-resistance is a very important property of practical consequence which may occur with resistant biotypes. It is the term applied to resistance to herbicides other than the one which had exerted the original selection pressure leading to the emergence of the resistant biotype.

Many examples of cross-resistance are easily explained where the herbicides are closely related chemically or are known to have the same mode of action on plants. Thus there are many examples with the triazine and urea herbicides which interfere at a particular stage of photosynthesis. Selection pressure exerted by repeated use of one triazine herbicide leads to a biotype resistant to that herbicide and many other related herbicides.

Other instances are more complicated. Resistance patterns in biotypes of *Alopecurus myosuroides* resistant to chlorotoluron have been investigated using some of the detection techniques described above. The results may be summarised as follows.

Herbicides with similar mode of action to chlorotoluron and to which cross-resistance demonstrated: isoproturon, metoxuron, simazine, terbutryn.

Herbicides of other types, to which cross-resistance demonstrated:
chlorsulfuron, diclofop-methyl, imazamethabenz, pendimethalin

Herbicides to which susceptible:
ethofumesate, propyzamide, trifluralin (despite close chemical relationship to pendimethalin).

Resistance leads to a substantial reduction in herbicide efficacy when applied at field doses. This diversity of cross- resistance presents serious problems for the practical control of resistant biotypes.

One attempt to attack this problem involved the use of another herbicide, tridiphane, in mixture with isoproturon. Each herbicide, on its own has an effect on susceptible biotypes of *Alopecurus myosuroides*, both pre- and post-emergence. Both compounds had less effect on a resistant biotype. However, when both compounds were applied in mixture there appeared to be a synergistic effect with control even of the resistant biotype. The practical opportunities thus offered have yet to be verified or exploited.

Another interesting example of cross-resistance is provided by *Lolium rigidum*, a major annual grass weed of cereals in Southern Australia. The use of diclofop-methyl for selective control started in 1977 and became a widespread practice. In 1981 a resistant population was discovered at a site where the herbicide had been applied for 4 years. By 1989 more than 40 resistant populations had been found from widely spread areas, suggesting separate origins. There has been variation between populations in their level of resistance which is related to the amount of diclofop-methyl received in preceding years.

Cross-resistance studies with this weed have shown a complex situation. Resistance has been demonstrated to the following herbicides to which the population had not been exposed previously: fluazifop, haloxyfop, chlorazifop, quizalofop, alloxydim, sethoxydim, chlorsulfuron, metsulfuron, triasulfuron, trifluralin, metribuzin, isoproturon, propyzamide. These herbicides cover a range of modes of action. The resistant biotypes do, however, remain susceptible to the non-selective herbicides glyphosate and paraquat.

The same weed also infests railway rights-of-way in Australia, where it has been controlled by a mixture of amitrole and atrazine. After 10 years of annual treatment a resistant biotype was recognised which now affects 2000 km of track. Cross-resistance was investigated in 1988-9. The susceptible and resistant biotypes showed a tenfold difference in susceptibility to amitrole. In addition to atrazine a wide range of photosynthetic inhibitors in the triazine and substituted urea groups together with metribuzin and methazole failed to affect resistant biotypes. However they did show continuing susceptibility to a wide range of other herbicides with different modes of action, including diclofop-methyl and a number of others to which Australian biotypes of the same weed in cereals had become resistant.

MECHANISMS OF ACTION

The development of resistant biotypes has given considerable impetus to studies on the physiology and biochemistry of herbicide action and the mechanisms whereby susceptible and resistant biotypes differ in their response.

With a large number of herbicides which includes most triazines and substituted ureas, the effect is associated with photosystem 2 in the photosynthetic process. The site is a protein component of the chloroplast. The herbicide binds to this protein, blocking the electron flow, thereby inhibiting photosynthesis and exciting oxygen to the singlet state which induces cellular disorganisation. In resistant biotypes this chloroplast membrane protein has been altered, the gene responsible having mutated. This is thought to be a single gene, maternally inherited. The herbicide then no longer binds to the amended protein, photosystem 2 operates normally, and there is no herbicidal effect.

Paraquat also disrupts the photosynthetic mechanism but in this instance photosystem 1. The electron flow from water to the natural acceptor is diverted at the end of the system. This diversion starts a chain of events leading to generation of superoxide, hydrogen peroxide and hydroxyl free radicals. These then cause a rapid breakdown of organised cell structure. In resistant biotypes some reduction in herbicide uptake and mobility within the plant has been detected, possibly through binding to cell walls. However, greater interest attaches to there being enhanced levels of enzymes such as superoxide dismutase which detoxify the active oxygen species which damage the plant.

With chlorotoluron-resistant biotypes of *Alopecurus myosuroides* there is evidence of rapid detoxification of the herbicide by oxidation controlled by mixed-function oxidases. Their enhancement is a potent modification to the enzyme status, which may account for the variety of cross-resistance effects mentioned earlier.

Finally, another potentially serious resistance situation occurs with the relatively new sulphonylurea herbicides. These are potent herbicides many of which persist in soil, and which are effective selective weed killers in cereals. The first resistant biotype *Lactuca serriola* was discovered in 1987 in the United States of America, followed by a number of reports of resistant biotypes of *Kochia scoparia* from 1988 onwards. Resistant plants originating from sites where chlorsulfuron or metsulfuron have been used for 3 to 5 years to a total application over the period of 88 to 123g ai/ha have been investigated. These herbicides inhibit acetolactate synthase, which is an enzyme required for synthesis of branched-chain amino acids. The resistant plants did not show reduced uptake or movement of the herbicide. The resistance of wheat is due to rapid metabolism of chlorsulfuron but there is not increased breakdown in the resistant *Kochia* biotype. However, selection had given rise to a modified form of the acetolactate synthase which is less sensitive to the herbicide but still functions in producing precursors for branched-chain amino acid biosynthesis. There appears to be a cross-resistance to other amino acid biosynthesis inhibitor herbicides.

PREDICTION OF RESISTANCE

So far, the occurrence of herbicide-resistant biotypes of weeds has not, in general, given rise to crises in weed control over large areas. Nevertheless, complacency is an ever-present enemy. The first line of defence against this type of problem is to attempt to identify possible risk situations and to take early avoidance action wherever possible.

On the basis of experience to date, resistant biotype problems arise where several of the following factors coincide:

1. Repetitive use of a herbicide (or group of herbicides with the same mode of action) in annual crop monocultures, or in a perennial crop, or for total weed control in uncropped situations.

2. Long period of exposure to herbicide through persistence in soil.

3. Repeat applications of the same herbicide within a season.

4. Marked periodicity of weed germination, coinciding with time of maximum exposure to herbicide, so that few susceptible seedlings escape.

5. Weed species producing seed of fast-diminishing viability, so that there is no large seed bank in the soil.

6. Weed species showing large natural genetic variability.

7. Absence of control measures other than use of herbicides.

Attempts are being made to develop mathematical models to study the dynamics of populations of resistant and susceptible biotypes. These could then examine quantitatively the relevance of many of the above factors and variation within them. They could also examine the likely influence of various management strategies to contain the problem. As yet, much more detailed information is required on which to base such models.

MANAGEMENT STRATEGIES

There are many possible components to management strategies which might prevent or alleviate weed resistance problems:

1. Keep records of herbicide use (active ingredient, dose) field by field.

2. Be vigilant for development of resistant biotypes.

3. Rotate crops, maximising variety of methods of weed control.

4. Obtain greatest return from herbicide usage by concentrating at times when weed presence interferes most with crop culture and harvesting.
5. Use as low a dose of herbicide as possible, but try to avoid using successively increasing doses which raise selection pressure.
6. Avoid repetitive application of herbicides with long persistence in soil.
7. Follow cautious approach to use of 'packages' of broad- spectrum herbicide with genetically engineered crop variety resistant to the herbicide where this encourages continual use of the same herbicide.
8. Rotate herbicides, employing compounds with different mechanisms of action.
9. Use mixtures of different classes of herbicides.
10. Use synergists, if available.
11. Plan herbicide usage on knowledge of cross-resistance patterns.
12. Maintain availability of a wide choice of herbicides for major crops, retaining old ones as well as developing new.
13. Use mechanical or biological methods of control as alternatives.
14. Do not transfer seed of resistant biotypes to other fields and farms.
15. Integrate all methods of control into a cohesive and efficient planned programme.

ACTION ON HERBICIDE RESISTANCE ISSUES

There is need to increase awareness of the potential importance of weed resistance problems and measures which may need to be taken. One promising step has been the formation in 1989 of an industry-based Herbicide Resistance Action Committee under the auspices of GIFAP (International Group of National Associations of Manufacturers of Agricultural Products). This Committee has members from Europe, North America and Japan. The avowed aim is to make a concerted effort to prolong the effectiveness of herbicides liable to encounter resistance problems and to limit crop losses during emergence of resistance. It has set up technical Working Groups and is also tackling issues such as: 1) how to communicate and interact effectively with academic researchers, governments, regulatory bodies, extension workers and farmers; 2) how to play a major role in educating farmers and growers; 3) how to gain further understanding of herbicide resistance by commissioning fundamental research directly from selected institutions and universities.

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FURTHER READING

There is now a great volume of literature on weed resistance. The following sources provide gateways, and access to lengthy reference lists which include material incorporated into this paper.

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RESISTANCE PROBLEMS IN RICE CROPS IN THAILAND

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ABSTRACT

Thailand is one the major exporters of rice. Around 25 per cent of the rice production in Thailand is exported. As a foreign exchange earner rice growing is becoming more and more sophisticated. Both rice resistant varieties and the effectiveness of appropriate insecticides are studied in detail in Thailand. The paper discusses various rice varieties introduced into the country, the control of different insects, and resistance problems to insecticides used on rice.

GENERAL INFORMATION

Rice has been the staple food of Asia for centuries. The total rice growing area in Thailand is 9.36 million ha in the wet season and 0.73 million ha in the off season. The average production was 19.4 million tons in the crop year 1988/1989.

The highest export of rice from Thailand was 5.212 million tons in 1988. Approximately 11% of rice yield was estimated to be reduced annually by damage owing to pests including insects, diseases and rodents [1]. Insects were considered to be of most importance (Table 1). To solve the insect problem, insecticides [2] are widely used by rice farmers (Table 2). The farmers always use insecticides in the case of sudden outbreaks.

The large scale use of insecticides in Thailand started in 1967 when the outbreak of the yellow orange leaf virus occurred [3]. Carbaryl insecticide was later recommended for controlling the disease vector, *Nephotettix virescens* [4]. At least 17 insect species have been reported to be major pests in rice, but the important species are brown planthopper (BPH), stem borers, rice gall midge, leaf folder and leafhoppers.

After 1967 many other insecticides were introduced for farmers use including granular formulations of insecticides such as BHC which was banned later and replaced by carbofuran. In 1969, rice hybrid varieties RD1, RD2 and RD3 were released in order to solve the yellow orange leaf virus problem. From the three modern photo-non sensitive varieties, RD1 was the most popular because it produced high yield and was able to grow all year round.

Four years later, the first outbreak of the brown planthopper (BPH; *Nilaparvata lugens*) occurred in a large area in the central plain of Thailand where rice was intensively grown. Foliar sprays of carbaryl insecticide proved insufficient for BPH control. Then the

TABLE 1

Damage of rice fields by various pests in Thailand during 1984 - 1988[a]

Pest	Total damage area (ha)				
	1984	1985	1986	1987	1988
Insect	578,650	463,871	364,890	694,321	847,380
Disease	264,333	376,580	120,486	273,846	270,080
Rodents and other	478,019	670,596	792,851	367,716	172,987
Total	1,321,002	1,511,047	1,278,227	1,335,883	1,290,447

[a]Source = Data from Department of Agriculture Extension [1]. (DOAE)

new carbamate insecticides such as isoprocarb, fenobucarb and metolcarb were introduced and they very effectively controlled the insect. The use of motorized dusters with long plastic hoses was also introduced to control the BPH at the flowering stage of rice. The use of dusters was not only hazardous to the operators and beneficial insects but also increased residue problems. A few years later, the BPH problem was significantly decreased by the introduction of BPH resistant rice varieties, namely RD21, RD23 and RD25. However, these varieties were found later to be very susceptible to rice blast disease.

In 1987, the government released a new rice variety, namely Supan 60, and the variety was first believed to be moderately resistant to the brown planthopper. At the same time the price of rice has significantly increased due to world demand. Supan 60 variety was widely adopted by farmers because it produced high yield and good grain quality. In 1989 more than 70% of the rice growing area in the central plain was planted with Supan 60 variety. Then the big outbreak of the brown planthopper occurred from late 1989 to early 1990. The large scale outbreak of the insect was caused by planting the susceptible rice variety Supan 60 and overlapping cultivation of rice. Foliar spraying and dusting of insecticides was conducted on a large scale in order to control the insect. It was found this time that the serious outbreak of the insect occurred at all rice growing stages, from seedling through harvesting. Farmers had to spray many times to reduce the insect population and it was found that rice yield from the dry season 1990 was reduced about 70% in the severe infestation areas such as Phathumthani and Ayudhaya province.

PRESENT STATUS OF INSECTICIDE USE

In Thailand, most insecticides were locally formulated from the imported active ingredient to make the finished product. Importation of insecticides was increased during 1985-1988 (Table 2). In 1988 Thailand imported total insecticides which cost 45.48 million dollars. Organophosphorus and carbamate insecticides were mainly imported. The largest quantity of imported insecticides was used in rice fields (about 35%) and mainly contained these two groups.

TABLE 2
Imported Insecticides by Chemical Group, during 1985-1988[a]

Insecticide Chemical Group	Quantity/Year/tons (TG + FP)			
	1985	1986	1987	1988
Organophosphate	4,190	4,492	5,381	5,463
Organochlorine	662	510	835	624
Carbamate	917	1,060	998	1,550
Pyrethroid	132	161	133	226
Miscellaneous	280	314	262	83
Bio-insecticides	22	71	49	88
Fumigant	584	813	457	777
Total	6,747	7,421	8,115	8,811

[a]Source = Division of Agriculture Regulation, Department of Agriculture [2]
TG = Technical grade
FP = Finished product

The farmers usually use insecticides throughout the country, because they are well aware of yield losses caused by insects. Farmers in the central plain apply more insecticides due to more severe insect damage. More insecticides were used in the dry season than in the wet season. In general, severe infestations of insect pests occur in the irrigated area in the central region, and more so in the dry than in the wet season.

The largest agricultural land in Thailand is rice field. However, the average amount per hectare of insecticide used in rice is relatively low compared to vegetables. During 1974, when the first outbreak of brown planthopper occurred, isoprocarb and and fenobucarb are the most popular insecticides used to control this insect. Farmers applied insecticides when they found the damage but on average only 2-3 times per season and using only half of the officially recommended dosages. Other popular foliar insecticides were monocrotophos and methyl parathion which were being used against many insect species. Carbofuran, a granular formulation is also used in all regions. Isoprocarb and fenobucarb were popular only in the central region where severe outbreaks of BPH occurred.

RESISTANCE OF INSECTS TO INSECTICIDES

Since the first severe outbreak of the BPH in the central region of Thailand in 1974, isoprocarb was a well known insecticide for controlling the insect. During the last few years, however, farmers from the central plain claimed that it was less effective for controlling BPH. So the insecticide susceptibility level of BPH was first determined in 1975 [5], which data are shown in Table 3. In 1977, a BPH population collected from central Thailand was also studied in Japan [6].

TABLE 3
Insecticide susceptibilities of BPH from different trials

Insecticide	LD 50 ($\mu g/g$)		
	1975[a]	1977[b]	1984[c]
Carbofuran	0.0030		
Isoprocarb	0.0121	0.0009	0.2770
Monocrotophos	0.0200		0.0314
Metolcarb	0.0304	0.0140	
Carbaryl	0.0228	0.0015	0.2270
Fenobucarb	0.0335		

[a]Pimsaman and Budhasamai [5]

[b]Trial conducted in Japan by Nagata [6] from the population collected from central Thailand.

[c]Data obtained from male macropterous form collected from Chainat, Central Thailand

TABLE 4
Topical LD_{50} values of the Brown Planthopper as compared between different locations in Thailand in 1986-1987-1988 (LD_{50} : ug/g)[a]

	Central part[b]					Northern part[b]		Screen House		
Insecticide	Pathumthani			Chachoengsao		Pitsanulok Rice Research Center				
	1986	1987	1988	1986	1987	1986	1987	1986	1987	1988
carbofuran	0.379	0.507	0.6475	0.293	0.917	0.260	0.532	0.318	0.038	0.2931
carbaryl	2.749	2.076	2.8604	3.559	2.753	2.738	2.233	2.606	0.433	1.5396
fenobucarb	2.083	2.412		9.579	6.853	2.558	4.601	1.740	0.904	3.7730
isoprocarb	1.741	2.219	3.6792	5.846	5.546	2.353		1.461	1.251	2.9875
monocrotophos	1.822	1.798	2.2352	1.886	1.038	1.412	0.734	1.232	0.113	2.0362
malathion	32.853	18.992	82.2953	66.278		47.997	17.09	46.220	17.09	33.4381

[a]BPH were collected from the paddy fields in Thailand. They were reared on susceptible variety RD 7 rice seedling at 28 ± 1°C. The fourth generation (F 4) of macropterous females, 3-4 days of adult, were tested by a technique in the Recommendations of FAO/IRRI Workshop on Monitoring Susceptibility Levels of Rice Insects to Insecticides.

[b]In the Central area insecticides were applied around 2-3 times/season and in the northern part were only occasionally applied.

The population tested in Japan was more susceptible to insecticides, especially to isoprocarb and carbaryl. The same study was made again in 1984 and showed an increase in LD 50 value of all insecticides in the test, compared to the result of 1975.

In February 1983 an FAO/IRRI Workshop on Judicious and Efficient use of Insecticides on Rice was held. Thirty-eight scientists from 14 countries met at IRRI and discussed common problems of insecticide usage. In this workshop, the possibility of multiple insecticide resistance among major rice pests was indicated. Thus, FAO and IRRI held a second workshop in November 1984 to develop an International Network Project on Monitoring Susceptibility levels of Rice Pests to insecticides [7]. So a joint Thai - IRRI study on development of insecticide resistance was conducted following the method recommended by an FAO/IRRI workshop in 1985 . In the first experiment [8] the LD 50 values of insecticides were slightly different between two locations of the central plain.

In 1986-1988 the long-term experiment which used the recommended method by FAO/IRRI was performed (Table 4). BPH were collected from the two growing areas. The central part of the country (Pathumthani and Chachoengsao province) represented the high insecticide use area and the northern part (Pitsanulok Rice Research Center) represented a low insecticide use area. Populations of BPH from 2 locations were compared with the greenhouse population. The fourth generation (F4) of macropterous females, 3-4 day old adults, were used for testing. Six insecticides from the carbamate and phosphate groups were studied. It was found that LD 50 values in the brown planthopper of carbofuran insecticide both from the central and northern areas and the greenhouse were not much increased from 1986-1988 (Table 4). This indicated that the BPH was not resistant to this insecticide. However, the Chachoengsao strain (Central area) LD 50 values for carbofuran in 1987 were increased 3.13 times compared with 1986.

LD50 values for carbofuran, carbaryl, fenobucarb, isoprocarb, and monocrotophos were of a similar order across the three locations, whereas LD 50 values for malathion fluctuated between these sites. However, the LD 50s of the Chachoengsao strain for carbaryl, fenobucarb and isoprocarb were higher than at the other locations, which indicated that BPH were more resistant to those three insecticides in that area than at the others. Comparing the results from 1986-1988 with the experiments in 1975, 1977 and 1984 (Table 3), LD 50 values for strains from all locations for all insecticides had increased, indicating that the BPH had developed resistance to these insecticides.

RESISTANCE PROBLEMS

The first insect which showed the possibility of developing resistance to insectides was BPH, probably for the following reasons:

1. Too frequent use of insecticides.

2. Wrong application techniques.

3. Unsuitable timing of applications.

4. Use of too low a dosage.

5. Pyrethroid insecticides were also used which probably increased the population of insects (resurgence).

6. Tank mixing is a common practice by farmers, which sometimes decreased the efficiency of insecticides.

FUTURE NEED AND WORK PLAN

The International Network Project on monitoring susceptibility levels of rice pests to insecticides should be continued. Researchers and technicians are also needed, to be trained to use laboratory equipment which is necessary for conducting the LD 50 test; experimental error will be reduced by using experienced and well trained personnel. A meeting of collaborators involved in the monitoring activities in the network countries should be held regularly in order to discuss the progress of the work and associated problems.

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PESTICIDE - COTTON PEST RESISTANCE PROBLEMS IN PAKISTAN

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ABSTRACT

Cotton is the major contributor to foreign exchange earnings in Pakistan which ranks among the leading exporting countries of the world. In Pakistan cotton alone is attacked by more than 150 species of insects and mites. The paper describes the status of pesticide use and how organophosphorus (OP) and synthetic pyrethroid (SP) combinations dominate cotton treatment. Pest resistance to man-made chemicals is becoming a problem and priority should be given to scientifc analysis in order to solve this problem especially with regard to treatment of cotton.

BACKGROUND

Pakistan, a south Asian country, is located at 61-75°E longitude and 24-37°N latitude. This territory is a region of diversified relief, with mountains to the north and west; and arid and semi-arid expanses to the south and east. In the centre is a flat fertile plain, fed by the River Indus and its tributaries, covering approximately 120,000 sq.km. It has an alpine climate in the north-western mountain ranges and low irregular and extreme temperatures in the plains, with most of the rain in summer in the range of 120-250mm in the south, 300mm in the middle and 600-1000mm in the north of the country [1].

Agriculture is the mainstay of Pakistan's economy. It accounts for 26% of Gross Domestic Product (GDP), employs 54% of the total labour, supports directly and indirectly 70% of the population for their sustenance, contributes 80% of foreign exchange earnings (36% through export of agricultural primary products and 44% agro-based industrial commodities), and provides raw materials for major industries like cotton textiles, sugar and several medium/small scale industries [2].

Today Pakistan is the world's ninth most populous nation, with over 110 million people. Almost 75% of the population lives in about 45,000 farm villages. The literacy rate in Pakistan remains very low and was approximately 26 percent of the entire population in 1981. In the rural areas it was only 17 percent and in the urban areas 47 percent [2].

Pakistan has about 30 million hectares of culturable land ranking 32nd in the world. Out of 30 million hectares of cultivable land, about 20 million are under cultivation. At present it hardly produces 20% of its production potential of field crops. Cereals, sugarcane, oilseeds and cotton occupy 95% of cropped area [3].

Despite the impressive performance of agriculture, the sector has still to fulfil its promise. More particularly, yields per hectare of most of the crops are substantially below the perceived potential; yields of progressive farmers are also well below the average yields in more advanced economies of the world. The main limiting factors in food production in Pakistan are the high rate of population growth (3%), low yields, water logging/salinity, and passiveness in the adoption of technological advances particularly the use of inputs (seed, fertilizer, pesticides) and an inefficient pest management system.

COTTON AND COTTON PESTS

The cotton crop of Pakistan consists of both the *Gossypium arboreum*, and *G. hirsutum*, the latter being introduced in 1914 but now occupying 95% of the area grown. Cotton is our most important commercial crop and Pakistan usually ranks among the biggest producers of cotton in the world. The quality of the crop is good and it is usually regarded as the strongest cotton of its class. Pakistan has also a well established cotton textile industry which accounts for about 28% of the country's total industrial production [4].

Cotton also is a major contributor to foreign exchange earnings of Pakistan and ranks amongst the first three top cotton exporting countries of the world. In Pakistan cotton is grown on about 2.5 m ha with an annual production of about 9.0 million bales. However, per unit area output of cotton is very low. Insect pests and diseases particularly put a great pressure on the productivity of the crop [5].

Compared to any other crop, cotton is reported to host the maximum number of insects throughout the world; mainly because it is grown in warmer climates which are ideal both for the host (cotton) and the pest. Thus, insects have a maximum number of generations per season providing an excellent opportunity for build up of resistance to pesticides. The higher the number of generations, the higher will be the selection pressure. Compared to this situation the development of pest resistance takes longer under colder conditions.

Pakistan, with its warmer climate, is faced with a similar situation for build-up of pesticide resistance in the years to come. It is reported that over one hundred and fifty insect and mite species infest cotton in Pakistan [6]. The major insect species infesting cotton are *Pectinophora gossypiella* (Saunders), *Earias insulana* (Boisduval), *E. vitella* (F.) (*E. fabia* Stoll), *Sylepta derogata* (F.). *Heliothis armigera* (Hubner), *Amrasca (Empoasca) devastans* (Dist.), *Bemisia tabaci* (Genn.), *Gryllus bimaculatus* Deg. and *Tetranychus urticae* Koch (*T. telarius* L.) [7]. A detailed list of major, minor and potential insect pests of cotton is shown in Annex 1.

The extent of damage to cotton by insects is highly variable from year to year depending on seasonal variations and pest management efficiency, particularly the use of pesticides. Vaughan [8] conducted an experiment and showed that whitefly and jassid without control, reduced the yield of cotton by about 10% but bollworms by almost 57%, and both pests together reduced the yield by 83%. In recent years the status of the pest complex has changed because of extensive use of pesticides. Sucking insect (whitefly, jassid and aphids) have become major pests.

PESTICIDE USE STATUS

In Pakistan the use of pesticides for pest control started in 1954 with the import of 250 mt and the Government continued subsidising imports until 1980 when the marketing of pesticides was completely entrusted to the private sector. This major shift in policy paid dividends as evidenced from consumption of pesticides which has steadily increased over the past 9 years (Table 1). In Pakistan insect pests remain active during the greater part of the year owing to long summers, therefore, insecticides predominantly (up to 85% of pesticide usage) are used (Table 2). Of these insecticides, organophosphates (OPs) are by far the most popular group, owing to their high efficacy, wider spectrum of activity and lower costs. It is estimated that annually they share about 60% of local imports (Table 3). Monocrotophos, dimethoate, methamidophos, triazophos, phosphamidon, methyl parathion and formothion are some of the popular products belonging to the group. The first three are systemic in action, and provide very effective control of sucking pests of cotton and other crops.

Though synthetic pyrethroid pesticides (SPs) were introduced in Pakistan in 1981 for controlling the bollworm infestation, it was felt that for effective control of the two pests (sucking and bollworm species) which overlap in most cotton areas, mixing both OPs + SPs was necessary. Therefore, when a combination of OP + SP (Polytrin-C) was introduced in 1982, it caught public attention at once and sales steadily increased (Table 4). SPs are comparatively expensive products (2-3 times higher than OPs) but possess the advantage of being effective at very low dosages. Therefore, during 1989 as a single component they captured only 11% quantitative share of the local pesticide market whereas they apportioned 24% of the import bill. However, combinations of SP with OP's respectively captured 34 & 63% quantitative and value-wise share of the market depicting their wide acceptance by the local farming community. If the pattern of pesticide usage during the past 5 years is analysed it emerges that 40% of the market belongs to just 13 OP products and one organochlorine (OC) insecticide. At the same time combinations of SP's + OP's (mainly with cypermethrin) occupy 33% of the pesticide market.

PESTICIDES RESISTANCE PROBLEMS

In Pakistan, in addition to unethical marketing, the socio-economic factors favouring pesticide abuse are lack of education and awareness and ineffective implementation of pesticide regulations due to inappropriate institutional set-up of both regulatory/supervisory mechanisms and research/training resources. Generally usage of broad spectrum persistent insecticides has become a powerful selective force for any trait in arthropod populations that would allow survival. Not only did resistant strains of former pests begin to predominate but arthropods which had been of minor significance in the crops became prominent pests because of ecological disruptions. This led to insect pest resistance, outbreaks of secondary pests, resurgence, adverse effects on non-target organisms (natural enemies of pests) and human/animal health hazards. Resistance in various insect species or insect strains develops due to indiscriminate use of pesticides or constant use of the same pesticide in the field or selection pressure in the laboratory. These factors greatly increase the level of tolerance in the particular pest strain concerned. The phenomenon is bio-chemical and genetical.

Resistance to pesticides and cross resistance together with its rapid development are the most alarming features. Resistance was originally demonstrated in 1914 by Melande in sanjose scale to lime sulphur. Some 70 years later in 1984 the recorded resistant species numbered 428 representing 14 genera and 83 families of insects and mites of which 61 are of agricultural importance. Among mosquitoes, 96 species have been reported resistant to one or more groups of pesticides [9]. Among these, 36 were resistant to one group, 32 to two groups, 19 to three groups, 8 to four groups and only one to all five groups of pesticides. One of the earliest reports is that of Chattoraji and Brown [10]. Of the 23 species of agricultural pests known to resist insecticides in China, 4 are cotton pests, 4 rice pests and 5 are pests of brassicae [11].

Very little work has been done on pesticide resistance in Pakistan and this relates to the health sector. Several workers from Pakistan have reported resistance of house flies, mosquitoes and *Drosophila* [12].

Bishara [13] initiated studies on pesticide resistance to insect pests of cotton using several bio-assay techniques. The sensitivity of *E. vitella* moths to topical application of ten insecticides was tested in the laboratory. The results showed that four pyrethroids stood as a distinct group compared to the three conventional groups of insecticides used during the previous two decades. The toxicity ratio of pyrethroids to OP-compound dicrotophos varied between 70-271 fold in the case of fenvalerate and 198-412 fold in the case of permethrin. The weakest pyrethroid was 11 fold more toxic than carbaryl and 55 fold more potent than monocrotophos. Both OP compounds were most commonly used for controlling bollworm infestation in Pakistan.

Bishara [13] further tested the sensitivity of pink bollworm, *P. gossypiella* Saund, a major cotton pest in Pakistan, against six insecticides applied topically to full grown larvae. Based on comparing LD_{50} values, the pyrethroid cypermethrin exhibited 10 fold more toxicity then fenvalerate of the same group, 135 fold more than the OP-compound monocrotophos and 568 fold more than the chlorohydrocarbon, endrin. The tolerance to monocrotophos can safely be attributed to the fact that Nuvacron and Azodrin were the most common compounds used by progressive farmers in the region. Exposure of the insect to sublethal doses and improper application of insecticides can be the major reason for development of such high levels of resistance to these potent chemicals. A possible explanation of the high tolerance to endrin (134.2 μg/g.b.wt.) is the biochemical changes occurring in the fat content of the pink bollworm larvae late in the cotton season and early in diapause. It has been shown that the increase in the level of resistance to endrin coincided with a remarkable increase of 58% in the unsaturated fatty acid content of the insect lipid. Bishara [13] reported high resistance levels to endrin and toxaphene in pink bollworm larvae late in diapause.

Similar sensitivity studies of different groups of insecticides on armyworm *Spodoptera litura* (F.) showed that three tested pyrethroids and the carbamate methomyl were much more toxic than the three organophosphates. Among the pyrethroid group, cypermethrin, based on LD_{50} values, was respectively 6.43 and 21.15 fold more potent than permethrin and fenvalerate. Toxicity ratio of cypermethrin to the OP compound monocrotophos was

477 fold. Such a remarkable level of tolerance of *S. litura* larvae to monocrophos might be attributed to the extensive use of Nuvacron and Azadrin in the past. The ability of closely related *Spodoptera* spp. to develop resistance to monocrotophos has been reported. Vaughan [8] also reported the appearance of mites on cotton due to use of carbaryl. This phenomenon was also reported in the rest of the world because of the ineffectiveness of carbaryl against mites in general. He also observed that aldicarb, disulfoton and a mixture of disulfoton + DDT also lost their efficacy against cotton pests, which was interpreted as resistance of the cotton insects to these pesticides.

Earlier pesticide resistance indications were also reported by Baloch [14], where the use of endrin and malathion completely failed to kill army worm (*Spodoptera* spp.) on wheat because of the prolonged and continuous use of these insecticides in Pakistan.

By measuring higher levels of esterases in the body of the insect, Jabbar [15] reported that cotton aphids have developed resistance to OP compounds. Baloch (unpublished) has also interpreted increases in the dosage of dimethoate as an indication of the incidence of resistance in thrips and whitefly on cotton in Pakistan.

CONCLUSIONS

The above alarming indicators of pesticide resistance in the various insect species in Pakistan, which are mainly due to inappropriate application of pesticides, need priority attention of the Government of Pakistan in order to start systematic planning and studies to follow up the situation. If due attention is not given at this stage, Pakistan is going to face a disaster in the world cotton market. Similar situations have been faced in Sudan and other African countries where 20 to 30 sprays of insecticides could not achieve effective control of cotton pests because of the build-up of resistance and cross resistance. The Government of Pakistan has to take major steps to slow down the build-up of pest resistance to pesticides by regulating the application of appropriate chemicals (rotate the type/groups of pesticides), creating awareness among farmers and establishing institutional set-up for research and training.

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TABLE 1
Quantity (m/t a.i) and Values (m/rs.) of Pesticide Imports during 1981-1989

	1981	1982	1983	1984	1985	1986	1987	1988	1989
Quantity	905	1320	1557	2517	3489	4112	4428	3759	4460
Annual growth %		46	33	45	39	18	8	-15	19
Growth from 1981 %		46	94	178	286	354	389	315	393
Value	204	339	626	1255	2278	2791	3290	2657	3642
Annual growth %		66	85	100	82	23	18	-19	37
Growth from from 1981 %		66	207	515	1017	1268	1513	1203	1685

TABLE 2
Consumption of Pesticides in Pakistan during 1981-1989 (m/tons a.i.)

Pesticides	1981	1982	1983	1984	1985	1986	1987	1988	1989
Insecticides	724	932	1431	2172	3083	3642	3881	3198	3735
Fungicides	132	161	172	212	224	273	251	242	326
Herbicides	34	94	119	90	114	165	250	317	380
Acaricides	2	3	6	31	60	15	6	-	-
Nematicides	9	1	-	-	-	-	-	-	-
Rodenticides	1	1	1	1	2	5	3	2	3
Fumigants	3	68	28	11	6	12	36	-	-
Others	-	-	-	-	-	-	-	-	15
Total	905	1320	1757	2517	3489	4112	4428	3759	4460

TABLE 3
Consumption of Synthetic Pyrethroids & their OP Combinations
(Quantity in m/t formulation and value in m/rs)

Year	Singles		Combinations		Total			
					Quantity		Value	
	Qty	Value	Qty	Value	Total	Annual Growth %	Total	Annual Growth %
1981*	50	8	-	-	50	-	8	-
1982	202	78	52	13	254	407	91	1040
1983	336	161	532	212	868	242	374	2579
1984	458	290	628	203	1086	25	493	32
1985	759	1127	1175	362	1934	78	1489	202
1986	1856	1138	1546	551	3402	76	1689	13
1987	2026	1046	2467	901	4493	32	1747	15
1988**	1197	641	3146	1320	4361	-	1961	1
1989	1573	861	3463	1458	5036	16	2319	18

*Figures for single for 1981 approximate

**The trade generally discouraged sale on credit

TABLE 4
Comparison of Consumption of certain Pesticides Groups during 1985-1989 (M/t. a.i.)

Name of product	1985	1986	1987	1988	1989
Total pesticides	3489	4112	4428	3759	4460
Insecticides					
Dimethoate	406	543	512	409	520
Monocrotophos	246	383	654	601	744
Methamidophos	72	118	97	30	129
Phosphamidon	48	35	19	21	33
Me. parathion	114	99	75	37	60
Fenitrothion	108	82	54	20	8
Triazophos	151	275	202	95	67
Acephate	52	29	74	36	-
Disulfoton	46	57	41	18	23
Formothion	27	57	65	44	49
Pirimiphos methyl	47	84	108	10	18
Endosulfan	-	246	147	103	98
Trichlorfon	15	24	-	4	9
Dichlorvos	18	0.4	41	20	25
	1350 (38.7%)	1842.4 (44.6%)	2088 (47.16%)	1448 (38.5%)	1783 (39.96%)
Single SPs					
Fluvalinate	5	0.4	-	-	42
Cypermethrin	60	50	31	20	31
Fenvalerate	91	41	27	17	18
Fenpropathrin	70	66	76	12	47
	226 (6.48%)	157 (3.8%)	134 (3.02%)	49 (1.30%)	138 (3.09%)
Combination of SP + OPs					
Cypermethrin	-	669	947	941	1156
Cyfluthrin	-	-	108	65	137
Deltamethrin	-	-	-	76	93
Fenvalerate	-	-	31	27	52
Fluvalinate	-	-	-	-	40
	-	669 (16.3%)	1086 (24.53%)	1109 (29.50%)	1478 (33.13%)
Fungicides	226 (6.47%)	273 (6.62%)	251 (5.67%)	306 (18.14%)	320 (7.17%)
Herbicides	114 (3.3%)	165 (4%)	250 (5.64%)	337 (8.96%)	379 (8.49%)

NB: Groupwise percentage against total pesticides consumed is in parenthesis

ANNEX 1

INSECT PESTS OF COTTON IN PAKISTAN

Status	Scientific Name	Common Name
Major Pests	*Pectinophora gossypiella* (Saund)	Pink bollworm
	Earias insulana Boisd.	Spotted bollworm
	Earias vittella (F.)	Spotted bollworm
	Heliothis armigera (Hubner)	American bollworm
	Bemisia tabaci (Genn.)	Cotton whitefly
	Sylepta derogata (F.)	Cotton leaf roller
	Prodenia litura (F.)	Army worm
	Amrasca devastans Dist.	Cotton jassid
	Aphis gossypii Glov.	Cotton aphid
Minor pests	*Sphenoptera gossypii* Kerr.	Cotton stem borer
	Myllocerus balandus Fst.	Cotton grey-weevil
	M. maculosus Desbr.	Cotton weevil
	Nazara viridula L.	Green bug
	Chrotogonus spp.	Surface grass hopper
	Aiolopus sp.	Surface grass hopper
	Dysdercus koenigii (F.)	Red cotton bug
	Agrotis flammatra Schiff	Cutworm
	Amsacta moorie Butl.	Hairy caterpillars
	Euproctis spp.	Hairy caterpillars
Potential Pests	*Thrips tabaci* Lind	Onion thrips
	Tetranychus spp.	Red spider mites
	Oxycarenus laetus Kby.	Dusky cotton bug
	Gryllus bimaculatus DeG.	Field cricket
	Tarache spp.	Cotton semi looper

FIELD WEEDS AND THEIR CHEMICAL CONTROL IN CHINA

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ABSTRACT

The diversity of environmental conditions and farming systems leads to a great variety of weed problems, with more than 700 species from over 70 families and 240 genera represented. More than 500 species are found as upland weeds and more than 100 species as weeds in paddy fields. It is estimated than 41.6×10^6 ha are weed infested and that serious damage is caused on 9.3×10^6 ha. Loss of grain yield during the 1981-5 period was assessed at 1.75×10^7 t per year, with over 50 billion working days per year spent on controlling weeds. The history of the chemical control of weeds in China is summarised and the herbicides now produced are listed. Some problems in the use of herbicides are explained briefly.

NATURAL CONDITIONS AND WEEDS IN CHINA

China is a vast country, with a total area of about 9.6 million square kilometres. It extends 5,500km from south to north, and 5,000km from east to west. Tropical, subtropical, temperate and cool temperate zones are included. The topography is complicated, with a variety of hills, mountains, rivers and plains. Annual rainfall varies greatly: for example, the rainfall is 1,000-1,300mm in the area to the south of the Yangtze River, but below 50mm in the northwest region.

The consequent differences in ecological environment lead to variation in the species composition of communities and the distribution of weeds. Thus the major weeds in wheat fields are as follows.

In the Northeastern and Inner Mongolian spring wheat zone annual weeds are of most importance. The dominant species are wild oat, black bindweed, lambsquarter, willowleaf knotweed, crested elsholtzia, hemp-nettle, common sowthistle, barnyardgrass. (A full list of Latin names of weeds mentioned in this paper is given in an Appendix, arranged alphabetically by common name.)

In the northern winter wheat zone (from the Huai River to the Great Wall) overwintering weeds are the most important, together with some annual weeds, such as case weed, flixweed, beggar-weed, nettle-leaf goosefoot and barnyardgrass.

In the southern winter wheat zone (to the south of the Huai River) the main weeds are those which thrive in moist and warm environments, such as blackgrass, giant chickweed, catch-weed, common vetch, hairy bittercress, bog starwort, polypogon and heartweed.

In the same regions, due to the variation in terrain and altitude, different climates and ecological environments are formed, which cause changes in the weed flora. For example, on the Yunnan-Guizhou Plateau, in an area of low altitude the main weeds are crowfoot-grass, hilograss, garden euphorbia and other tropical weeds; in the area of middle altitude (1,800-2,000m) the main weeds are sprangletop, blackgrass and other subtropical weeds; in the area of high altitude (above 2,400m) there exist wild oat, catch-weed, common groundsel; typical cool temperate zone weeds are found in the area of 2,700-3,000m altitude, such as crested elsholtzia, winged knotgrass and tartary buckwheat.

The following four points are concluded;

(1) There are very many kinds of farmland weeds in China;

(2) Weed species vary with change of longitude, latitude and altitude;

(3) Weeds grow over a long period, especially in the southern regions where weeds germinate and emerge throughout the seasons, with consequent serious damage;

(4) Weed distribution is closely related to temperature and especially moisture; in the region to the south of the Yangtze River the most important weeds are hygrophilous and thermophilous but in the north, northeast, northwest and Inner Mongolia drought-tolerant weeds are dominant.

CHINESE TILLAGE AND WEEDS

China is a large traditional agricultural country, which has 109.35 million ha of farmland. The majority of people work in agricultural production, with careful and intensive cultivation adopted everywhere.

With the change in the degree of latitude, the number of crops, type of rotation and cropping systems vary greatly throughout the country. In the northern and northeastern rain-fed agricultural zone of China, the main cropping systems involve one or two crops per annum, or a three-crop two-year system and drought-tolerant weeds are dominant. In the southern region, where three or more crops are harvested every year, moisture-tolerant weeds spread widely, such as purple nutsedge and cogongrass. In the continuously cropped spring wheat fields of Qinghai, Inner Mongolia and Heilongjiang, wild oat is the dominant weed, causing great damage.

In the northern spring soybean zone, where one crop per annum is grown, barnyardgrass, dayflower, willowleaf knotweed, lambsquarter, redroot pigweed, cocklebur, black nightshade give a mixed weed community. Weeds germinate over a long period in this region.

In the multiple cropping soybean zone of the Yellow River and Huai River Valleys, summer soybean is grown. It is planted after harvesting wheat every year when the weather is hot and rainy. Weeds germinate almost at the same time, and cause great damage to soybean seedlings. The main weeds at this time are common crabgrass, bullgrass, golden foxtail, green foxtail, false daisy and mercury-weed.

In the southern soybean zone, where various multiple cropping systems are adopted, weed species and their time of occurrence vary greatly, due to differences in soybean planting date and previous crop and tillage measures. The main weeds are barnyardgrass, Chinese sprangletop, umbrellasedge, bullgrass, false daisy, purple nutsedge and common crabgrass.

In different parts of China, the area cultivated by a single farmer varies greatly. In the Yangtze River Valley, a farmer only cultivates 200-500m^2 of farmland, so careful and intensive culture is practised and weed damage is minimal. In northeast China and Inner Mongolia, a farmer cultivates more than 1.0 ha of farmland, the cultivation is extensive and weeds do great damage. On state farms, cultivation is mechanized, a farmer can cultivate 10-100 ha of farmland, and damage from weeds is even more serious.

In general, four points are clear:

(1) In the region where three or more crops are harvested every year, intensive cultivation is practised, and many kinds of weed species grow and reproduce;

(2) In continuous cropping, weed damage is very serious;

(3) Weed damage is more serious on state farms than on small farm holdings;

(4) In the remote provinces, such as Heilongjiang, Inner Mongolia, Quinghai, Xinjiang, Yunnan and Hainan, weed damage is serious.

EXTENT OF DAMAGE FROM WEEDS IN CHINA

China is a vast country, with various climates, soils and crops, and much variety in crop frequency, rotation, and cropping systems. Therefore, there are many kinds of weeds, which spread widely and do great damage. Farmland weeds total more than 700 species in China, belonging to over 70 families and more than 240 genera. Among them, more than 500 species are upland field weeds, belonging to more than 50 families and about 160 genera; the most important belong to the Gramineae, Compositae, Polygonaceae and Labiatae. There are more than 100 species of paddy-field weeds, belonging to 43 families and 80 genera; most of them are Cyperaceae and Gramineae.

According to the statistical data of 1981-1985, about 41.637 million ha crop land suffered from weeds, of which serious damage occurred in about 9.266 million ha (Table 1). The loss of grain each year was 175.15 billion kg, and of cotton 5.0 million quintal (100kg); 50-60 billion working days were spent on weed control. Moreover, foreign weeds entered China continously: e.g. from 1953-1980, more than 600 weed species were found in imported grain, averaging 0.2%. Based on these data, probably 0.5-0.6 million tons of weed seeds have been imported into China in grain between 1961-1981. This indicates the importance of spread by trade.

Later, with the transition of agricultural production from a traditional natural economy to a commercial market economy, the evolution of agriculture from traditional to modern, the further reform of agricultural management structure, and the reduction in number of agricultural labourers, weed damage will become of greater concern. In this situation chemical control of weeds becomes more important.

TABLE 1
The area damaged by weeds and the losses incurred

Crop	Area damaged by weeds (10^4 ha)	Area damaged seriously by weeds (10^4 ha)	Loss of yield ($x10^{10}$kg)	Rate of Loss (%)
Rice	1,550	380	1.0300	13.4
Wheat	1,000	267	0.4000	15.0
Cotton	220	13.3	-	14.8
Soybean	200	66.7	0.0500	19.4
Corn, Sorghum etc	667	133	0.2500	10.4
Rape	120	33.3	0.0100	7.1
Peanut	66.7	13.3	0.0100	9.0
Cane, Beet	60	20	0.0015	8.2
Vegetables	280	-	-	-
Total	4,163.7	926.6	1.7515	13.4

CHEMICAL CONTROL OF WEEDS IN CHINA

The Development of Types and Production of Herbicides

The pesticide industry began late in China. For a long time insecticides were the main products and herbicides accounted only for a small part (Table 2).

About 50 herbicides were introduced into China from other countries. Trifluralin was imported in largest quantity, and played an important role in promoting the development of the herbicide industry and the chemical control of farmland weeds. At the same time, herbicide production in China began to develop. By 1987, herbicide production increased remarkably, the total (a.i.) reaching nearly 30,000 ton. The main products are butachlor (2,230 ton), nitrofen (2,350 ton), atrazine (5,220 ton), chlorotoluron (13,480 ton), 2,4-D (990 ton), MCPA (640 ton), glyphosate, propanil, simetryn, acetochlor and bentazone. Further highly effective and ultrahighly effective herbicides are in experimentation or under development.

TABLE 2
Changes in total amount of pesticides produced in China

Pesticides	1970 Production 10,000 t	1970 %	1980 Production 10,000 t	1980 %	1984 Production 10,000 t	1984 %
Herbicide	0.89	9.6	1.66	9.6	0.87	4.8
Insecticide	7.85	84.6	16.36	84.8	13.61	74.9
Fungicide	0.38	4.1	1.24	6.4	3.06	16.8
Others	0.16	1.7	0.04	0.2	0.63	3.5
Total	9.28	100.0	19.30	100.0	18.17	100.0

The Development of Chemical Control of Weeds

The development of chemical control of farmland weeds in China is closely related to the development of the herbicide industry and the kinds and quantity of imported herbicides. In 1956, 2,4,5-T was used for the first time in experiments in Heilongjiang Province to control broadleaf weeds in paddy fields. This was the beginning of chemical control of farmland weeds in China; in 1959 more than 2,000 ha of paddy fields were sprayed with 2,4,5-T by airplane to control weeds in Yanshou County, Heilongjiang Province. In 1963, 2,4-D was used to control weeds by aerial spraying on more than 6,600 ha of wheat fields. Later, chemical control of farmland weeds was practised throughout the country. By 1967, the total area on which weeds had been controlled chemically reached 326,700 ha. From the beginning of the 1980s, chemical control of weeds developed quickly and the area treated with herbicides increased at a rate of 10% every year (Table 3). Provinces with very large areas where weeds are controlled chemically are Heilongjiang, Jiansu, Guangdong, and Yunnan. As to crops, paddy fields are the biggest area, followed by wheat and soybean.

Topics requiring further study are:

(1) the chemical control of weeds in bast-fibre crops, rape, sesame, peanut and other cash crops;

(2) the chemical control of weeds in cotton, maize and crops grown under plastic cover;

(3) weed control in irrigation/nutrition furrows of cotton and vegetables; weed control in beet planted with seedlings in paper pots; weed control in tobacco seedling cultivation;

(4) the chemical control of weeds in vegetable and melon fields;

(5) setting up systems of chemical control of weeds in no-tillage culture;

(6) the chemical control of weeds in forest seedling nurseries, city lawns, football grounds and golf courses.

TABLE 3
The change in area of cropped land treated with herbicides in China

Year	1967	1974	1979	1983	1984	1985	1987	1989
Area (1,000 ha)	327	1,667	3,638	4,667	6,667	10,000	13,333	13,340

PROBLEMS IN CHEMICAL CONTROL OF FARMLAND WEEDS

Droplet Drift of Herbicide Spray
An early problem when herbicides were first used in China was that 2,4-D droplet evaporation and drift from wheat fields damaged sensitive crops and trees. In aerial spraying, 2,4-D droplet drift reached 4,000m, causing serious damage to soybean, sunflower, vegetables and trees.

Production of Herbicides
At present, because of the weak basis of the chemical industry in China, the development and production of herbicides are affected. Some herbicides which are needed in agriculture cannot be produced while others are over-produced. For example, the supply of butachlor surpassed the need of the domestic market, but post-emergence herbicides to control broadleaf weeds in broadleaf crop fields are lacking. Only simple formulations may be available which do not always satisfy the need of agriculture.

Toxicity and Pollution
Herbicides have been used in China for more than 30 years. Although they play an important role in increasing crop yields, their effects as artificial chemicals on ecological environments have not been fully studied. It is an obstacle to pisciculture in paddy fields that thiobencarb and molinate damage aquatic animal species. Another problem is that thiobencarb produces dichloro-thiobencarb in poorly-drained paddy fields.

Change of Weeds Flora under the Selection Pressure of Herbicides
Because of the use of 2,4-D in wheat fields over a long period of time most broadleaf weeds have decreased in number enormously but graminaceous weeds and 2,4-D-resistant weeds, such as crested elsholtizia, hemp-nettle and black bindweeds, have increased in great quantities, causing serious damage. On state farms in Heilongjiang, trifluralin is used year by year in soybean fields. This reduces graminaceous weeds but broadleaf weeds, especially dayflower, black nightshade, and bur beggarticks, have become urgent problems in production.

APPENDIX
Common and Latin Names of Weeds

Barnyardgrass [*Echinochloa crus-galli* (L.) Medic.]
Beggar-weed (*Polygonum aviculare* L.)
Black bindweed (*Polygonum convolvulus* L.)
Black grass (*Alopecurus aequalis* Sobol.)
Black nightshade (*Solanum nigram* L.)
Bog starwort (*Stellaria alsine* Grimm.)
Bullgrass [*Eleusine indica* (L.) Gaertn.]
Bur beggarticks (*Bidens tripartita* L.)
Case weed [*Capsella bursa-pastoris* (L.) Medic.]
Catch-weed (*Galium aparine* L.)
Chinese sprangletop [*Leptochloa chinensis* (L.) Nees]
Cocklebur (*Xanthium strumarium* L.)
Cogongrass [*Imperata cylindrica* (L.) Beauv.]
Common crabgrass [*Digitaria sanguinalis* (L.) Scop.]
Common elsholtzia [*Elsholtzia ciliata* (Thunb.) Hyland]
Common groundsel (*Senecio vulgaris* L.)
Common sowthistle (*Sonchus oleraceus* L.)
Common vetch (*Vicia sativa* L.)
Crowfoot-grass [*Dactyloctenium aegyptium* (L.) Richter]
Dayflower (*Commelina communis* L.)
False daisy (*Eclipta prostrata* L.)
Flixweed [*Descurainia sophia* (L.) Webb.]
Garden euphorbia (*Euphorbia hirta* L.)
Giant chickweed [*Stellaria aquatica* (L.) Scop.]
Golden foxtail [*Setaria glauca* (L.) Beauv.]
Green foxtail [*Setaria viridis* (L.) Beauv.]
Hairy bittercress (*Cardamine hirsuta* L.)
Heartweed (*Polygonum persicaria* L.)
Hemp nettle (*Galeopsis bifida* Boenn.)
Hilograss (*Paspalum conjugatum* Bergius.)
Lambsquarter (*Chenopodium album* L.)
Mercury weed (*Acalypha australis* L.)
Polypogon (*Polypogon higegaweri* Steud.)
Purple nutsedge (*Cyperus rotundus* L.)
Redroot pigweed (*Amaranthus retroflexus* L.)
Small goosefoot (*Chenopodium serotinum* L.)
Tartary buckwheat [*Fagopyrum tataricum* (L.) Gaertn.]
Umbrella sedge (*Cyperus iria* L.)
Wild oat (*Avena fatua* L.)
Willowleaf knotweed (*Polygonum bungeanum* Turcz.)
Winged knotgrass (*Polygonum nepalense* Meisn)

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION'S (UNIDO) ACTIVITIES ON PESTICIDES

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ABSTRACT

United Nations Industrial Development Organization's technical assistance to developing countries in the area of pesticides is based on the status of development in the developing countries in terms of market size, capability of existing pesticide industry in active ingredient manufacture and formulation, research and development activities in newer and safer formulations, in development of non-conventional pesticides, in biological and toxicological evaluation etc. On a broad basis the developing countries are classified into four different categories and as an example, establishment of a pesticide formulation plant in Myanmar (Burma) is discussed in detail.

INTRODUCTION

Most of the criticisms attributed to pesticides emanate from their misuse, mismanagement or misjudgement. Despite the controversy on the use of pesticides, it should be borne in mind that pesticide inputs are of vital importance to agriculture to safeguard food and fibre from pests, if we are to feed and clothe the world's evergrowing population which is likely to reach six billion by the turn of the century. More than two thirds of this population will be inhabitating the developing countries (Figure 1).

Over the years, the use of pesticides, among other inputs, has increased the average yield of major crops worldwide (Table 1) and this is also reflected in an enormous increase in the value of pesticides at the user level during the last 30 years from $1 billion in 1960 to more than $20 billion in 1989 (source: Wood MacKenzie).

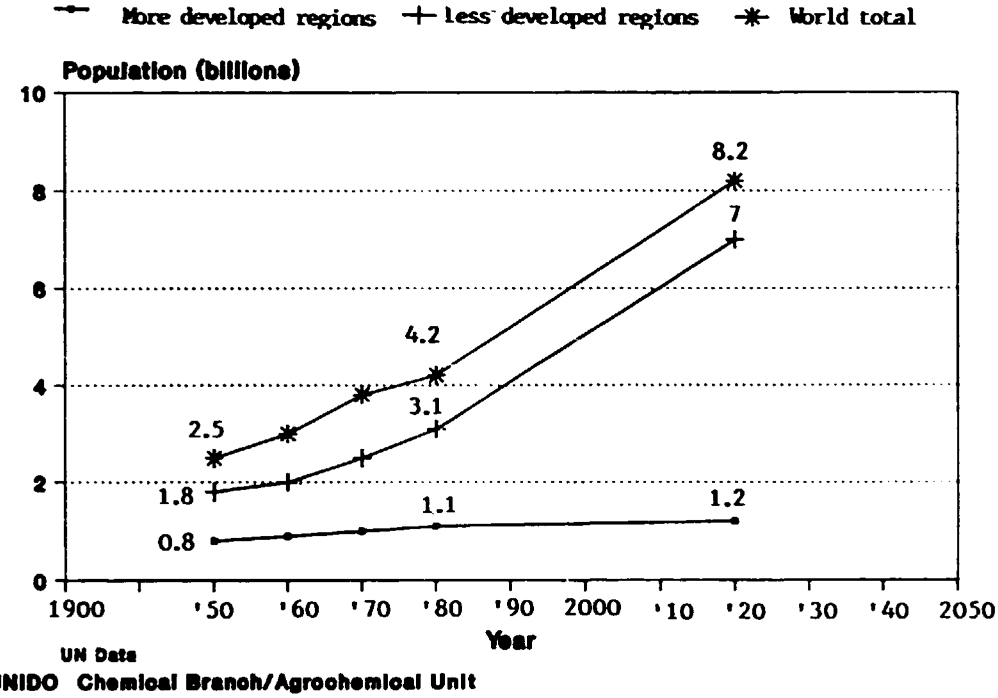

Figure 1 Population projection in developed and developing regions according to UN data

TABLE 1
Average yields of major crops (1980-1987)

Crop	1980 yield kg ha^{-1}	1987 yield kg ha^{-1}	Increase %
Wheat	1,877	2,289	+22
Barley	2,030	2,305	+14
Maize	3,060	3,566	+17
Rice	2,770	3,110	+12
Soya beans	1,561	1,901	+22
Rape seed	996	1,360	+37
Sugar beet	29,284	36,640	+25
Potatoes	12,800	15,857	+24

Source: AGROW

While the majority of the developed countries have almost reached the peak in terms of usage of pesticides and yield per unit area, a greater proportion of the projected increase in the use of pesticides will be in the developing countries, due to their aspirations to become self-sufficient in agriculture.

CLASSIFICATION OF DEVELOPING COUNTRIES

During the last ten years, there has been an increasing number of requests and enquiries to UNIDO from developing countries for technical assistance in the area of pesticides. In order to provide technical assistance to developing countries, UNIDO has broadly classified them into four categories.

Category 1	Countries with no manufacture and inadequate usage of pesticides
Category 2	Countries with substantial pesticide den and and some distribution system but no local production
Category 3	Countries with sizeable pesticide markets and local formulation plants but no production of basic pesticides
Category 4	Countries with capabilities of manufacture of pesticides with potential for export and also capable of doing R & D work in exploitation of local raw materials

NATURE OF UNIDO'S TECHNICAL ASSISTANCE

Based on the level of development in the country or the region concerned, UNIDO's technical assistance ranges from simple market surveys, opportunity studies, surveys of raw materials and quality control to research and development in pesticide formulation, toxicological evaluation, finding new environment friendly pesticides, industrial safety, effluent control etc. Technical assistance is provided in the form of advisory services, on the job training, workshops, expert group discussions, procuring equipment and know-how, testing locally available raw materials for pesticide formulation, installation of pilot plants leading to investments and private industry participation.

Category 1
To this category belong the majority of the African countries, a few Asian and Latin American countries, where the market is small or agriculture is not well organized. Most of the pesticides are imported as finished products; supply is uncertain and non-dependable. UNIDO's assistance in these countries is mainly market surveys and opportunity studies. In future these countries will go for small scale repackaging/formulation units, share market with other countries and put more emphasis on application technology to get maximum benefits from the meagre amount of pesticides used.

Category 2
This category is very important in that there are many developing countries with a good pesticide market wanting to develop their pesticide formulation ca[illegible] make use of locally available raw materials and importing mainly active ingr[illegible]ctants and adjuvants. The biggest advantage is the flexibility in buying differe[illegible]edients and formulating, when needed, and the introduction of new technology in making safer formulations.

Category 3
This category is rather complicated due to complexities involved in active ingredient production and UNIDO's assistance is confined mainly to a few countries where the basic infrastructure exists and to those who are planning product diversification. The tendency is to go for flexible multi purpose pilot plants where a group of active ingredients having common toxophores could be produced.

Category 4
Countries in this category belong mainly to Asia, Latin America and Eastern Europe who in the next 10 - 15 years will become important contributors. Three later papers (J.K. Roh, S.P. Dhua and G. Matolcsy) represent this category. One additional project worth mentioning is the establishment of a 'centre of excellence' in India to carry out R & D in pesticide formulation to introduce wettable powders, water dispersible granules, biocide formulations and above all to train personnel from small/medium scale local formulations in aspects related to quality control, use of locally available raw materials and in industrial safety. The centre is established near New Delhi and is already used as a training centre for the Asia region in formulation technology.

ASSISTANCE TO MYANMAR (BURMA)

As a case history, I want to give UNIDO's assistance in the establishment of a pesticide formulation plant in Myanmar (Burma). Myanmar by definition belongs to category 2 and during the pre-and post-war era Myanmar remained the rice bowl of Asia as a major exporter of rice. Unfortunately from the '60s onwards agriculture suffered a set back and the country is now just barely able to support itself in food production. Inputs into agriculture became almost negligible and use of fertilizer/pesticides varied and were non-dependable due to reliance on foreign aid to import such commodities.

In the late 1970's, the Government of Myanmar requested UNDP/UNIDO to provide assistance in establishing a pesticide formulation complex for the production of emulsifiable concentrates/granules/dust/ultra-low-volume formulations.

Based on the consumption of pesticides, mainly in the form of e.c. ranging from 600,000 litres to 1,000,000 litres, and also lack of expertise in the country in pesticide formulation, it was decided to establish, as a first step, an e.c. plant with a scope for future expansion to cover granules and other solid formulations.

In 1986/87 Myanmar imported 336,905 litres of e.c. at a cost of $2,699,426 (Table 2), mainly in 0.5 litre, 1 litre and 2 litre tin containers and distributed to the farmers through cooperatives. The real demand was around 600,000 litres but due to lack of foreign exchange supply could not meet the demand. Major crops on which pesticides were used are cotton (60%), rice (30%) and others (10%).

Basic Economic Analysis
In a developing country which imports all its pesticides the following factors influence decision making

- savings in foreign exchange
- production of cheaper pesticides

- development of national industry and expertise
- availability of pesticides during seasonal and emergency needs
- flexibility to use different pesticides

In a typical pesticide formulation plant the sale price, broadly speaking, would be determined by:

- variable costs
- fixed costs
- margins

Variable costs are mainly the cost of ingredients that go into formulation and the labour cost. Table 3 gives typical figures for a pesticide formulation plant in Western Europe and its adaptation to Myanmar.

TABLE 2
Pesticide formulations imported into Myanmar (1986-87)

Product	Volume litres	Imported cost US$
Phenthoate 50 e.c	50,848	N.A
Diazinon 40 e.c	56,033	393,912
EPN 45 e.c	80,712	N.A
Fenitrothion 50 e.c.	80,712	651,345
Fenvalerate 5 e.c	56,500	610,200
Fenvalerate 2.5 ulv	10,000	105,040
Kasugamycin	2,000	N.A
Total	336,805	2,699,426

Fixed costs are covered by:

- Utilities
- Waste disposal
- Maintenance and safety
- Depreciation

Margins are made up of

- Taxes
- Duties
- Interest on investment
- Licence fee

- Registration costs if any
- Middle agents
- Profit
- Transport cost

Except a few items under variable costs most of the other items could be borne by local currency. In Myanmar, as an example, fenitrothion (50 e.c) was imported at a cost of $8.07/litre.

TABLE 3
Formulation cost breakdown in percentage in foreign currency (f.c) and local currency (l.c)

Components	Endosulphan	Fenitrothion	Cypermethrin
Active ingredients (f.c)	70	68	84
Emulsifiers (f.c)	6	10	3
Stabilizers (f.c)	2	2	-
Solvents (l.c)	8	6	5
Raw materials	86	86	92
Labels + container tin or aluminium (volume (l.c)	10(3lit)	10(5lit)	6(lit)
Labour costs (l.c)	2	2	1
Quality control and storage (l.c)	2	2	1
Total	100	100	100

Producing fenitrothion (50 e.c) in Myanmar was calculated as:

Fenitrothion	US$3.12 (f.c)
Emulsifiers	US$0.30 (f.c)
Solvent	US$0.20 (l.c)
Raw materials	US$3.62
Packaging	US$0.70 (l.c)
Labour cost	US$0.50 (l.c)
Total cost	US$4.82

Direct foreign cost currency savings 57.6%

Total price of imported fenitrothion (50 e.c)	US$651,345
Price of locally formulated materials	US$274,561
Difference	US$376,784

For other pesticides the figures are given in Table 4. From these figures one should discount margins and fixed costs for profits.

TABLE 4
Direct savings by formulating pesticides in Myanmar

Formulation	Savings US$	% savings in foreign currency
Fenvalerate (5 e.c)	320,920	67.6
Diazinon (40 e.c)	119,351	51.0
Fenvalerate (2.5 ulv)	66,660	78.7

Based on this it was decided to approach the project in the following two ways:

1. Initially to make standard emulsifiable concentrates in Myanmar by importing all ingredients so that they could be directly used by the farmers.

2. Carry out tests on locally available solvents for their suitability for pesticide formulation so that imported solvents could be slowly replaced by local solvents.

While the construction of plant started, in parallel five different solvents available in Myanmar were tested under a sub-contract arrangement. Table 5 gives comparison of the physical properties of these solvents compared to that of xylene.

From the physical properties superior kerosene is the only solvent that could be used. Mann-Reformate which has a high aromatic content unfortunately has a low flash point.
The following tests were carried out on superior kerosene to ascertain suitability:

- Solubility at required concentration on its own and in combination with xylene and other standard solvents
- Formulations that could be produced in Myanmar
- Accelerated storage tests
- Corrosion tests with spraying equipment used in Myanmar
- Choice of packaging materials
- Phytotoxicity tests

Solubility
Diazinon (40%), cypermethrin (10%), fenvalerate (5%) are readily soluble in superior kerosene. Other pesticides needed cyclohexanone or xylene as co-solvents.

Emulsification
Emulsification was tested by CIPAC method 36.11 with an exception that the temperature was kept at 20±1 °C. The emulsification tests were repeated by storing formulations for

40 days at +20 °C and +40°C. The following formulations were selected as possible choices for Myanmar.

Fenitrothion - 50 e.c		**Endosulphan - 35 e.c**	
Xylene	16.9	Xylene	46.3
Superior kerosene	16.9	Superior kerosene	12.7
Non-ionic surfactants	10.9	Epichlorhydrin	1.0
Epoxidized soybean oil	5.3	Anionic/non ionic surfactants	5.0

Diazinon - 40 e.c		**Cypermethrin - 10 e.c**	
Superior kerosene	53	Superior kerosene	42.0
Anionic/non-ionic surfactants	5	Xylene	40.0
Epichlorhydrin	2	Anionic/non-ionic surfactants	8

Corrosion on sprayer equipment and packaging materials

In Myanmar almost all liquid formulations are sprayed with hand held sprayers. Therefore, it was necessary to carry out corrosion tests with different parts exposed to pesticide formulations in the sprayers. Some of the leather/rubber gaskets, drain plugs, piston bowl and other packing materials were tested by storing them at 40°C for 40 days in various formulations produced. The changes in colour, elasticity and weights were noted. Except for fenitrothion 50 e.c and dichlorvos 25 e.c the various parts of the sprayer withstood the formulations.

Among the packaging materials PET, tin and lacquered tin were tested for corrosion with various solvents and formulations at 40°C and tested for weight changes after one month and two months. PET bottles proved to be the best for all solvents and formulations while dichlorvos affected tin and lacquered tin plates.

Stability tests

The stability of different formulations were tested by means of accelerated storage for 40 days at +20°C, +40°C and in some cases +70°C. Development of layers during storage was a sign of decomposition of emulsifiers and precipitation or darkening of the liquid was a sign of decomposition of either emulsifiers or active ingredients. Based on the accelerated storage tests and checking active ingredient content, appearance and emulsification tests the following formulations were selected as suitable choice for Myanmar with local solvents.

Endosulphan 35 e.c		**Cypermethrin 10 e.c**	
Endosulphan (96.3%)	36.34%	Cypermethrin (94.4%)	10.59%
Xylene	46.30%	Superior kerosene	41.14%
Superior kerosene	11.36%	Anionic/non-ionic surfactants	8.00%
Anionic/non-ionic surfactants	5.00%	Xylene	40.27%
Epichlorhydrin	1.00%		

Diazinon 40 e.c		Phenthoate 50 ulv	
Diazinon (97.9%)	40.86%	Phenthoate (91%)	54.95%
Superior kerosene	55.14%	Xylene	12.52%
Anionic/non-ionic		Superior kerosene	12.53%
surfactants	4.00%	Raw rape seed oil	20.00%

Phytotoxicity

So far only limited tests have been carried out in the glasshouse. Diazinon 40 e.c's in xylene and/or superior kerosene were tested on beans and cucumber as test plants.

Plants were sprayed with 0.6% diluted solutions until wet and kept at 20-21°C in the glasshouse. No visible phytotoxicity was noted after 5 days.

Further tests are to be carried out in Myanmar under field conditions.

While carrying out the solvent tests, UNIDO assisted Myanmar in establishing a plant at a green field site at Hwambi about 50 km from Yangon (Rangoon) on the famous road to Mandeley. UNIDO has provided a small 200 litre capacity mixer for pilot scale studies to prepare new formulations. The plant has now been established under a subcontract and test runs have been completed using mainly imported solvents. A laboratory has been set up in which further tests will be caried out under Myanmar conditions.

Other selected projects

Under category 2, UNIDO also provided technical assistance to Cuba to establish a demonstration plant for the production of wettable powders by jet milling technology. Under category 3, UNIDO assisted Egypt in establishing a pilot plant for the production of dimethoate and malathion. Prior to commissioning of the plant UNIDO provided a complete safety check list for the plant covering:

- Process safety
- Engineering control of hazard
- Employee safety
- Fire safety
- Waste disposal
- Medical care/monitoring
- Storage material handling

CONCLUSION

UNIDO is putting greater emphasis on quality and safety in chemical production in developing countries. The two self-adhesive stickers shown here have proved popular in Asia and with the help of The Government of Finland are in the process of developing international safety guidelines for pesticide formulation in developing countries.

UNIDO

QUALITY

is assurance
is confidence
pays

PDPI

Do not compromise on QUALITY

UNIDO

SAFETY

is common sense
is awareness
is responsibility

PDPI

Give SAFETY a chance

UNDP/UNIDO PROJECT - ESTABLISHMENT OF TOXICOLOGY RESEARCH CENTRE 4, DAEJEON, REPUBLIC OF KOREA

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ABSTRACT

The Ministry of Science and Technology (MOST) of the Republic of Korea initiated a toxicological testing programme as a national project in recognition of the needs of industry as well as the nation. The Government established the Toxicological Research Centre (TRC) at the Korea Research Institute of Chemical Technology (KRICT) located at the Deaduk Science Town of Daejeon in 1984 with the co-operation of UNDP/UNIDO. The Government on behalf of the project has provided physical facilities, equipment and personnel for the Toxicology Research Centre. UNDP/UNIDO has provided indispensable technical assistance from the project concept formulation to the training of staff which began in 1985. The project was successfully completed in 1988. After satisfying good laboratory practice (GLP) regulations the Centre acquired GLP clearance from the Japanese Ministry of Agriculture and Fisheries. The Centre has 55 trained staff and occupies 6,000 m^2 of floor space and has become the leading Centre in toxicity testing in the Republic of Korea.

INTRODUCTION

Evalulation of chemical products and pollutants to ascertain their effects on humans as well as the environment has become an important subject in modern society. The study of toxicology as well as chemical control regulations were mainly initiated by industrialized countries. The scope and requirements of testing had been broadened since the 1960s and as a result, the cost of new product development increased several times. In the Repulic of Korea, toxicology and toxicity testing had lagged behind even though the country has achieved remarkable progress in its economy and in science and technology.

The country's chemical industry, especially, the fine chemical industry, has achieved some progress in the last two decades from the stage of importing final products from abroad, to the simple process of intermediate production, and then to the stage of producing a few final products and also researching for new compounds. It has also been possible for the country to export some final products and at the same time supply products to meet the domestic market at low cost.

However, unlike the petroleum industry, the chemical industry is small with moderate size capital investment. Therefore the industry cannot afford the capacity to check the safety of chemicals produced which is essential for registration and international trading. Moreover, with the adaptation of new patent policies by the Government of the Republic of Korea in 1987 the industry has had to make an effort toward the research and development of new chemicals.

The Ministry of Science and Technology (MOST) of the Republic of Korea initiated a national project for the development of new chemicals (agro chemicals and pharmaceuticals). A toxicological testing programme was selected as one of the essential components.

The Korea Research Institute of Chemical Technology (KRICT) established the Toxicology Research Centre with Government funds and with assistance from the UNDP in 1984. The Government provided the facilities, the equipment and the personnel.

The UNDP has also provided indispensable technical assistance from concept formulation to training of staff through the executing agency, UNIDO. The UNDP/UNIDO assistance began in 1985 with a budget of about half a million dollars. It was terminated by the end of 1988. During that period, many short term international experts provided advice and a number of staff was trained abroad in reputable laboratories in various aspects of toxicology.

As a result of the efforts of the MOST, UNDP, and UNIDO the Toxicology research Centre has become the first GLP institution in toxicity testing of pharmaceuticals in the Republic of Korea. The Centre is now about to reach an international level of expertise and recognition. The KRICT was established in 1977 by the Government to support the chemical industry through research and development activities and it is similar to the Shenyang Research Institute of Chemistry. There are seven different divisions and one Toxicology Research Centre.

II. DESIGN OF THE NEW ORGANIZATION

1) Assessment of Type and Function of the New Organization

It was very important to define the scope of the new organization to be established to ensure an effective and successful operation. In examining the status of toxicology testing in highly developed countries it was found essential to discuss the precise identification of the function of a toxicology laboratory with government officials, industrialists, laboratory designers and academics. Each has a specific role to play, e.g. the Government serves to enforce the law, to strengthen regulations and to provide methodology guidelines. Industrialists on the other hand, are actively engaged in meeting the requirements of the regulations as well as minimizing the side effects of the compounds they develop. However, toxicity testing requires various resources of personnel and the ability to maintain special facilities. There are only a few large multinational chemical manufacturers currently operating comprehensive testing facilities for industrial toxicology. These in-house laboratories are generally designed to accommodate a consistent quantity and type of testing for the company.

Increase in the demand for testing due to new regulations may necessitate that the company contact an external commercial laboratory to undertake the additional tests. Smaller companies with only limited testing facilities must resort to the services of external laboratories. Therefore, currently there are many large scale privately owned contract organizations which are in the business of supporting industrial needs. There are about 50 in the United States of America, 20 in Europe and 30 in Japan; examples are Hazleton, Huntingdon and Pana Pharm. In addition, there are laboratories supported financially by groups of industries. Examples of these laboratories are the Chemical Industry Institute of Toxicology in the Unites States of America, the British Industrial Biological Research Association in the United Kingdom and the Institute of Environmental Toxicology in Japan. Finally academics are more interested in basic research which involves the mechanism of toxicity than in routine testing.

Therefore the scope of the Toxicology Research Centre was devised so as to follow the contract laboratories in support of the country's industries as well as Government needs.

2) Assessment of Personnel

A comprehensive assessment programme requires substantial resources for training and experienced personnel. The personnel must be qualified in a wide range of disciplines to cover the biological, chemical and physical aspects of the effects of chemicals on man and the environment. Their disciplines may include pharmacology, physiology, pathology, biochemistry, analytical chemistry, laboratory animals maintenance etc. Of particular importance is the role of the toxicologist whose expertise should be acquired from a combination of training and experience. Concern has been expressed at the current shortage of these types of scientists, as well as pathologists, even in advanced countries.

In the Republic of Korea there has been no experience in toxicity testing so that staff recruited were graduates of pharmacy, veterinary medicine and biology schools. The selected graduates were then sent abroad for training. Also foreign experts were mobilized to train the national staff in-house in toxicity testing. Fortunately there was an adequate number of key personnel available at universities. Currently there are 20 pharmacy, 10 veterinary medicine and 30 medical schools in the country.

3. Laboratory Facilities

The laboratory facility necessary for detailed testing is complex and expensive. For toxicology testing, there must be facilities available in which to house and handle properly the test animals and in addition the instruments for analyses. Also it requires good environmental control of animal rooms, constant temperatures and humidity and biologically clean room concepts, particularly for long term studies. The kind of animals required for laboratory purposes will influence the design facility.

For the operation of all these pieces of equipment sufficient space must be provided. This is in addition to the necessary office space for the laboratory staff, and space for data storage and library facilities. For a fully equipped toxicology laboratory, it is suggested that a building of 5000m^2 is necessary for a staff of 50 professionals, 50 technicians and assistants.

4. Equipment and Laboratory Instruments

This area presents no difficulties in the establishmentof the toxicity testing operation. For example, one could simply purchase the same type of instruments which are used by other laboratories . However, it is desirable to select within the budget limitations, the most essential instruments ensuring also that small parts suitable to increase productivity are also available.

III. EXECUTION OF THE PROJECT

The main objective of the project was to establish a capacity to carry out the systematic toxicity testing of chemicals at the international level of expertise within the facility in the Republic of Korea. Therefore it involved:

1. Preparation of the facility.
2. Recruitment and training of key personnel.
3. Sending the staff abroad for training.
4. Recruitment of foreign experts.
5. Procurement of the necessary laboratory equipment.
6. Carrying out the toxicity testing.
7. Setting up the operations system.

After 6 years of active execution of the project, we have been given international recognition for the facility and for the expertise and experience gained. However, we had to overcome the following problems:

First: It was hard to synchronize the numerous functions at the beginning of the project; construction of the new facility, recruitment of national staff and the training, utilization of foreign experts, etc. These problems became easier with the increase of the national staff and support of the institute.

Second: It was necessary to establish a system for managing research projects. The standardization consisted of : (1) the establishment of a standard protocol (experimental plan) for each type of experiment (2) the establishment of standard operating procedures for each experimental operation and (3) the standardization of an operations schedule.

Third: We developed a comprehensive experiment management system so that we could efficiently assign our human resources, facilities and equipment to diversified research projects. Even if a research organization has a capacity to carry out a certain research project, an incorrect assignment of researchers would bring about unsatisfactory results. Should a research organization be unable to undertake any research project, this might result in the poor utilization of personnel and facilities or a failure in management efficiency.

We discussed experimental schedules with our clients, paying attention to the adjustment of assignments of human resources and facilities to respective research projects. This gave rise to the necessity of a comprehensive experiment management system which enabled us to find out promptly how all projects, including plans, were progressing.

Fourth: In order to raise output quality and research management efficiency, it is indispensable to systemize various factors of research projects for attaining a rationalization comparable with industrial manufacturing process control. Should this not be done, even a large research market would not be profitable.

Computerization of data is essential for the accuracy and efficiency of toxicity testing. Accordingly, we have been successfully operating an on-line computer system after two years of training and preparation.

In conclusion a toxicological testing programme needs properly trained personnel, good facilities, and an operational system.

Our growth in the past was so rapid that we were compelled to build up personnel and the facilities through the "patchwork" method. However, we now have a full set of necessary testing facilities and an organizational system composed of several units. UNDP/UNIDO has played a major role in bringing the TRC to its present capability.

REGIONAL NETWORK ON PESTICIDES FOR ASIA AND THE PACIFIC (RENPAP) - AN OVERVIEW -

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ABSTRACT

The objectives and activities of the Regional Network on Pesticides for Asia and the Pacific (RENPAP) and its linkage with the Pesticide Development Centre (India) are described. The role of various countries as Technical Coordination Units is explained.

BACKGROUND

RENPAP stands for the Regional Network on Pesticides for Asia and the Pacific, a programme funded by the United Nations Development Programme (UNDP) and executed by the UNIDO in association with the Food and Agriculture Organization of the United Nations (FAO), the World Bank, the World Health Organization (WHO) and the Economic and Social Council for Asia and the Pacific (ESCAP). This multi-sectoral project is based on an innovative concept of UNDP supporting a regional, inter-Governmental cooperative programme.

The basic objective of the programme is to bring together a group of Asia-Pacific countries having identical problems relating to pesticides production, usage and control with the sole purpose of solving these through clear identification of the individual country problems and by sharing each others experiences. The countries participating in the programme are Afghanistan, Bangladesh, China, India, Indonesia, Iran (Islamic Republic of), Malaysia, the Philippines, Pakistan, Republic of Korea, Sri Lanka, and Thailand. Iran (Islamic Republic of) and Malaysia have joined recently.

PHASES I AND II OF RENPAP

During the first two phases (Phase I from 1982-85 and Phase II from 1986-89), the project succeeded in creating a spirit of regional cooperation in promoting an intimate understanding on the various aspects detailed earlier and also setting up of an organisational structure tc implement and monitor the activities of the project. Both the phases witnessed increasing contribution of the member countries and at the end of the second phase, the contribution by member countries amounted to about US $894,000 as against the UNDP contribution of US $848,644.

The new innovative approach adopted in this Network project, resulted in development of intimate technical cooperation between the participating countries for strengthening the pesticide industry through upgrading of knowledge and skill in the targeted areas. The linkage with the country programme, namely, the Pesticide Development Centre (formerly known as Pesticide Development Programme India) with the Regional Network programme has greatly benefited the participating countries in upgrading knowledge and skill in the sphere of pesticide formulation technology and quality control.

The major project activities included appointment of regional consultants, holding of workshops, arranging expert group meetings etc. on the following specialised areas:

- Pesticide data collection system (UNIDO/ESCAP)
- Formulation of pesticides (UNIDO)
- Quality control of pesticides (UNIDO/FAO/World Bank)
- Harmonisation of pesticide registration requirements (FAO)
- Trade and tariff considerations (UNIDO)
- Pesticides residue analysis (UNIDO/FAO/World Bank)
- Toxicology forum (UNIDO/WHO)
- Environmental aspects of pesticide production and use (UNIDO).

CURRENT PHASE

The success of the Phases I and II of the project was duly recognised by the joint UNDP/UNIDO evaluation mission, which also recommended an extension of the project for another 3 years, with funding at a level higher than the current level of funding. The Tripartite Review Meeting attended by National Coordinators from the member countries, representatives from UNDP/UNIDO and other UN agencies including FAO, WHO, ESCAP and The World Bank, after reviewing the progress made, endorsed the recommendations of the Evaluation Mission justifying extension of the project and continued UNDP supports to the Network programme.

UNDP/UNIDO duly approved entension of the project with the aim to augment the regional capability to promote safe development of pesticides in the region by making use of the existing institutional set-up available in the member countries in the field of pesticide formulation, quality control, bio/botanical pesticides, application technology, industrial safety, hazard analysis, effluent control measures and data collections and dissemination of information. The developmental objectives of the current phase of RENPAP are:

- Promote regional cooperation and agricultural output through safe use of pesticides
- Establish technical coordination and development centres for exchange of expertise available within the region and assist countries having no facilities
- Documentation and dissemination of information on development of safe agrochemicals
- Promote active participation of member countries in safe development and use of pesticides

PRIORITY OBJECTIVES

The immediate objectives defined for achieving the developmental goals of the project are:

- Consolidation of achievements in:
  - market survey and data collection
  - survey of raw materials available within the region
  - pesticide formulation technology
  - quality control
- Harmonised approach for industrial safety, hazard management and effluent control and promotion of bio/botanical pesticide usage and application technology
- Coordination with FAO project (Japanese funded)on FAO code of conduct on pesticide distribution and use
- Self sustainability of the project

The current phase of the programme has, thus, an orientation towards strengthening the pesticide industry as a whole through a harmonised approach on industrial safety, hazard management, effluent treatment, pollution control and promotion of bio/botanical pesticides usage as well as adoption of safer and more effective application technologies. At the same time the project is busy consolidating achievements of the previous phase encompassing the areas of market survey and data collection, survey of raw materials available within the region, pesticides formulation technology, quality control and residue analysis.

ACTIVITIES

To put the project on a more sound footing, the Project Management Committee at its meeting held in Islamabad from 18-20 November, 1989 decided to set up Technical Coordination Units in countries who have offered to host by virtue of the availability of infrastructural facilities and expertise. The Technical Coordination Units to be hosted by the member countries are as follows:

- Pesticide Formulation Technology/Quality Control - *India*
- Pesticide Specification and Impurities in Active Ingredients at the Manufacturing Level - *Republic of Korea*
- Residue Analysis/Bio-Botanical Pesticides - *Thailand*
- Industrial Safety - *Philippines*
- Eco Toxicology - *Pakistan*
- Effluent Control/Waste Disposal - *Indonesia*

With the setting up of these six Technical Coordination Units, the project would be providing training and consultancy services in the much needed specialised areas to meet the urgent requirements of the region adopting the concept of technical co-operation among developing countries.. These coordinating units are designed to meet the following requirements of the region:

- Consultants in,specialised fields
- Organisation of workshops in identified areas
- Organisation of indepth training facilties
- Trouble shooting

The Regional Coordinating Unit would be maintaining a roster of experts to meet the needs of the member countries encompassing the entire spectrum of pesticides production, marketing and control. To make the programme more result-oriented for the greater benefit of the participating countries, the Project Management Committee also decided to suitably strengthen the Regional Coordinating Unit.

The Meeting also recommended that appropriate measures be taken to persuade the Governments of the Network countries to pledge funds on an annual basis to run the various scheduled activities in the important field of pesticide manufacturing, use, hazard management and environment protection. Also the meeting discussed the proposal for development and use of computer software for pesticides market data input and retrieval received from Centre de Cooperation Internationale de Recherche Agronomique pour le Developpement (CIRAD), France and expressed its appreciation for the support offered by the Government of France. The meeting also discussed the urgent need for steps to make RENPAP self sustaining after the present phase of the project.

The programme for the year 1990 as approved by Third Project Management Committee meeting of the RENPAP held in Islamabad from 18-20 November, 1989 was as follows:

- Workshop on R & D in Formulation Technology of Newer Formulations and Quality Control, April, 1990

- Participation in the Collaborative International Pesticides Analytical Council (CIPAC) meeting (Tunisia) May, 1990

- Workshop on Industrial Safety and Protection on Environment/Effluent Control (Indonesia) Dec., 1990

- Recruitment of experts for member countries

  - Instrumentation/handling/packaging/storage - *Afghanistan*
  - Consultants in handling/packaging/storage of pesticides and environmental toxicology- *Bangladesh*
  - Preparation of standard pesticides sample - *China*
  - Effluent control and waste disposal - *Indonesia*
  - Use of locally available formulation raw materials - *India*
  - Controlled release pesticide formulation - *Republic of Korea*
  - Eco-toxicology - *Pakistan*
  - Industrial safety and environmental protection - *Philippines*
  - Insecticides efficacy - *Sri Lanka*
  - Botanical pesticides development - *Thailand*

- Fellowship Training of officials

  - Biological screening - *Bangladesh*
  - Instrumentation analysis - *China*
  - Development of bio-botanical pesticides - *India*
  - Controlled release formulation - *Republic of Korea*
  - Treatment and disposal of waste - *Indonesia*
  - Application technology - *Pakistan*
  - Formulation technology - *Philippines*
  - Disposal of out-dated pesticides - *Sri Lanka*
  - Botanical pesticides development - *Thailand*

Recruitment of consultants/experts and the fellowship placements of candidates were arranged by UNIDO/UNDP, based on the job description and nominations from the member countries and the activities have progressed as per schedule.

RENPAP AND PESTICIDE DEVELOPMENT CENTRE

Linkage of RENPAP with The Pesticide Development Centre (PDC), a UNDP/UNIDO assisted country project of the Government of India, has greatly helped the participating countries in upgrading knowledge and skill in the sphere of pesticide formulation technology and quality control. The Centre, which is a technical coordinating unit of RENPAP, has made significant strides in the development of technologies for several new types of formulations which are more efficient, less toxic and safer to the users and environment compared to the conventional types of pesticide formulations being widely used in the region. Newer technologies which have been developed by PDC include:

- Suspension concentrates (Carboxin 40 SC)
- Water dispersible granules (Isoproturon 75 DG & Mancozeb 75 DG)
- Concentrated and micro emulsions (Butachlor 50 EW & 15 ME)
- Controlled release granules (Fluchloralin 3G)

In addition to these, a novel self spreading formulation has also been developed by the centre, which is tailor-made for controlling various pests that feed/inhabit at the water surface. Products formulated in this manner include:

- Microbials *Bacillus thuringiensis* and *B. sphaericus* formulations for the control of *anopheline* larvae of mosquitoes which are the vectors of malarial disease
- Lindane and BHC formulations for the control of brown plant hopper infestation in paddy rice.

The Centre is supported by a well equipped analytical developmental laboratory which caters to the needs of the pesticide industry and plays an active role in CIPAC collaborative testings. These testings include:

- Methamidophos (HPLC)
- Edifenphos (GLC)
- p,p'-DDT (GLC) - for WHO
- Ethiofencarb (HPLC)
- Tolylfluanid (HPLC)
- Amitraz (GLC)

Another major impact made by the centre has been through its uniquely designed training programmes on pesticide formulation technology and quality control. So far a total of 260 personnel, including 50 from the member countries of RENPAP other than India, have benefited from these practically orientated training courses tailor-made to suit the needs of the industry.

The Pesticide Development Centre serves as a good example of a country project flowing into a Regional Network Programme for the overall benefit of Asia-Pacific Region. It is strongly felt that such models of cooperation may be repeated in other vital areas for effecting fruitful interaction in the technical field between the countries of the Region.

CIPAC MEETING IN TUNISIA

As the Regional Coordinator, RENPAP, the author attended the 34th CIPAC meeting in Tunisia during May 28 to June 2, 1990 and presented a paper on Contribution of the Regional Network on Pesticides for Asia and the Pacific and its active participation with CIPAC. Arrangements made by RENPAP for the active participation of member countries were emphasised in this presentation, which was well received by the representatives of WHO, FAO, GIFAP (Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques) and other participants from various countries.

WORKSHOP ON PESTICIDE FORMULATION TECHNOLOGY AND QUALITY CONTROL

RENPAP organised a Regional Workshop on R&D in Pesticides Formulation Technology of Newer Formulations and Quality Control from 9-21 April 1990. The programme was hosted by the Pesticide Development Centre (India). The Workshop was attended by nominees of 10 participant countries viz. Afghanistan, Bangladesh, China, Indonesia, India, Republic of Korea, Pakistan, Philippines, Sri Lanka and Thailand. Out of the 12 nominees from the participating countries, five were women holding senior Government positions in their respective countries making thereby 42% participation by women in this Workshop.

The Workshop laid special emphasis on adopting newer formulations of pesticides which are environment friendly and in the long run reduce overall load on the environment and are safe to handle by the farmers. The newer technologies also would help in moving away from the use of petroleum products needed in the present day formulations which cause major pollution to the environment.

In order to inculcate self-confidence in developing new formulations and also undertaking effective quality control measures, the participants were given "hands on" training during the programme. The faculty comprised of internationally reputed experts and the programme was held in the Pesticides Development Centre in India. The Workshop has enabled the participants from the network countries to appreciate better the area of concern with regard to safe and effective use of pesticides and will be helpful to them in spreading the knowledge and skill in their respective countries. The Workshop is considered to be a model for regional cooperation as in this programme all the 10 countries of the region are intimately involved.

RENPAP GAZETTE

RENPAP has just commenced to publish a quarterly journal "RENPAP Gazette" containing scientific papers and technical articles on selected current topics by eminent scientists, technologists and experts in the field of pesticide production technology and usage, environmental protection, hazard control, eco-toxicology etc., besides data collection on pesticide production, import, export and usage. The advertisements collected by National Coordinators will be published in the journal and the earnings from this will form a part of project funding additional to the sale proceeds of the journal. The journal is priced at 40 US dollars for annual subscription and the first issue of the "RENPAP Gazette" focuses on safety.

CONCLUSION

In the words of Dr Erling Dessau, Resident Representative of UNDP in India, RENPAP is a good example of a country project, namely, the Pesticide Development Centre, flowing into the Regional Network Programme for the overall benefit of Asia and the Pacific Region and this would be a good model for regional cooperation which could be repeated in other vital areas for effecting cooperation and interaction in the technological field between the countries of the region.

PESTICIDE REGULATION : AN OVERVIEW

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ABSTRACT

The registration of pesticides as a pre-requisite to marketing a new crop protection product, or the continuation of existing products, is an essential part of agriculture and is becoming increasingly difficult in the light of 'political' pressures and environmental considerations. Regulatory systems throughout the world have tended towards a degree of uniformity in their requirements for toxicological and residues data but environmental data requirements continue to increase and to vary considerably between different countries. Attempts to harmonise data requirements and data interpretation have met with little real success although recent initiative within the European Community would appear to offer the opportunity of achieving such a goal at least within western Europe. Increasing pressures to reduce the overall use of pesticides must be viewed with considerable caution in the light of the need to feed an ever-increasing world population.

INTRODUCTION

It is of paramount importance to ensure that crop protection products are allowed to be marketed only when any potential hazards have been fully evaluated and when the benefits of the proposed uses have been considered. In order to achieve such a pre-marketing assessment Regulatory Authorities have been established throughout the world. These have traditionally undertaken the necessary risk/benefit analysis before authorizing the use of the product. Additionally authorities have frequently supported these authorizations by post-marketing monitoring exercises aimed at assessing any consequences arising from the use of the pesticide in terms of consumer, operator and environmental risks.

Over recent years however, and particularly in western

Europe, United States, Australia and Japan, the benefits of crop protection products have assumed less importance at the expense of a greater concern with the perceived risk. The use of pesticides in these countries has therefore increasingly become a 'political' issue with the consequential result that the registration of a new pesticide has become more difficult. Additionally, greater regulatory attention has been focused on the continued use of products already marketed and extensive re-registration programmes have been initiated, notably in the United States, the United Kingdom, Denmark and Germany. As a consequence of these regulatory activities fewer new pesticides are registered and an increasing number of existing pesticides are being withdrawn or their uses restricted. Furthermore the objective of reducing overall pesticide usage has, in some countries such as Sweden, Denmark and the Netherlands, become official Government policy with targets being established for the desired reduction (Table 1).

TABLE 1
Reduction in pesticide usage : European targets

Country	Reduction Target
Sweden	50% by 1990 Further 50% by 1995
Denmark	25% by 1990 Further 25% by 1997
Netherlands	50% by 1990 70% by 2000
European Community	50%

These general regulatory trends and some of the more important consequences of these trends are considered in more detail below.

REGULATORY DATA REQUIREMENTS

General

The purpose of providing Regulatory Authorities with data on a crop protection product is to enable the Authorities to assess the potential hazards posed by the proposed use of the product to those applying the product (operators), to those consuming foodstuffs which may have been treated with the product (human consumers or domestic animals), to those who may be inadvertently contaminated during application (bystanders), to non-target species such as birds, fish, soil fauna, beneficial insects (ecotoxicological effects) and to soil and water (environmental fate). The generation of these data is both costly (current estimates are in excess of $10 million) and time consuming (at least five years).

Toxicological data

There is broad international agreement regarding toxicological data requirements which are summarised in Table 2.

It should of course not be overlooked that in many cases additional studies will be required to clarify any significant observations made in some of these tests or to investigate specific properties of some particular compounds (e.g. neurotoxicity studies for organophosphorus compounds).

TABLE 2
Summary of major requirements for toxicological data

Type of study	Details
Acute toxicity*	Oral, dermal, inhalation (rat)
Irritancy*	Skin, eye (rabbit)
Sensitization*	Dermal (guinea-pig)
Sub-acute toxicity	28-day studies in rat, mouse, dog
Sub-chronic toxicity	90 day studies in rat, mouse, dog
Chronic toxicity	2-year chronic toxicity/oncogenicity rat 18 months oncogenicity mouse 12 months chronic toxicity dog
Reproductive toxicity	Teratology studies in rat, rabbit Multigeneration study in rat
Mutagenicity	Ames Test, Unscheduled DNA Repair, In vitro chromosome analysis, In vivo chromosome damage
Metabolism	Absorption/Excretion and Metabolite Identification in rat and dog. Enzyme induction studies. Cattle, pigs, poultry residue identification

* These studies are required on both the active ingredient and the formulated products(s).

These toxicological requirements, which have been developed over a period of years, have now reached a fairly stable plateau although there are indications that additional requirements relating to neurotoxicity and immunotoxicity may be forthcoming in the future. Whereas the type of data required is generally common between different Regulatory Authorities the interpretation of these data can differ significantly and to the extent that some authorities may register a pesticide whereas others may not. Areas of particular difficulties include the significance of liver tumours in rodents (particularly the mouse), the significance of thyroid tumours in the rat, and the interpretation of 'positive' mutagenicity studies. Associated with these difficulties in interpretation are the problems arising from the application of mathematical models to animal data in an attempt to predict carcinogenic risks to man. Whereas such models may have a role to play in the assessment process, sole reliance on their use in arriving at a regulatory decision implies a degree of credibility and scientific reliability which is not warranted and which ignores the 'weight of evidence' approach to the overall toxicological data package.

Mathematical models are also being increasingly used in estimating risks to operators and a variety of models, based on different estimates of exposure and of dermal absorption, are currently in use. Here again such models must be used cautiously and perhaps are best employed in indicating the need for field studies of actual operator exposure and/or the need for experimentally derived estimates of dermal absorption.

Residues and Plant Metabolism Data

Requirements for residues and plant metabolism data which are summarised in Table 3 have always assumed a very high importance. In this respect little has changed except that technological advances in analytical chemistry have resulted in dramatic improvements in methodology and sensitivity. In contrast however, the requirements for plant metabolism data have increased to the point where some Regulatory Authorities now require the identification of almost 100% of the plant metabolites. It might therefore be argued that these particular studies have assumed the level of academic research projects rather than studies aimed at providing data to support a risk assessment.

Environmental Data

In contrast to the data requirements in the residues and toxicological areas, those in the ecotoxicological (see Table 4) and environmental fate (see Table 5) have increased dramatically over the past few years. It should be noted that many of these studies may need to be supplemented by field studies, e.g.

TABLE 3
Summary of major requirements for residues and plant metabolism data

Type of study	Details
Analytical Methodology	Residue methods for crops, animal tissues and by-products, diets for toxicology studies, soil, water, etc.
Residue studies	Measurement of residues in crops (at harvest and decline studies), processed foods
Animal feeding studies	Measurement of residues in animal tissues (cattle, pigs, poultry) and by-products (milk, eggs).
Metabolism studies	Identification of metabolites in typical crops

TABLE 4
Summary of major requirements for ecotoxicological data

Type of study	Details
Avian toxicity	Acute oral (2 species) 8-day dietary toxicity (2 species) Reproductive effects
Fish toxicity	Acute toxicity (3 species) Early life stage toxicity Bioaccumulation
Toxicity to other aquatic species	Daphnia acute and reproduction shrimp and algae acute
Non-target organisms	Bees, beneficial insects, earthworms, soil fauna, soil micro-organisms

TABLE 5
Summary of major requirements for environmental fate data

Type of study	Details
Soil studies	Adsorption/desorption, leaching, lysimeters, photodegradation, metabolism
Water studies	Metabolism, photolysis, hydrolysis
Soil/water studies	Sediment, biodegradation

effects on bees, soil dissipation, mesocosms, avian field studies. Furthermore many of the studies, particularly in the area of aquatic toxicity must be undertaken on both the active ingredient and the formulated product(s).

Clearly the assessment of the potential effect of pesticides on the environment is one of great importance but I would suggest that much knowledge and experience has been gained by all concerned since the ecological effects caused by the use of persistent organochlorine insecticides were seen in the 1950s and 1960s. Nevertheless, whereas the legacy of these effects remain with us, available evidence indicates that the modern use of pesticides is not having any serious effects on wildlife populations even if occasional members of that population are affected. For example, a very extensive monitoring exercise undertaken in the United Kingdom [1] and involving working farmland systems over a period of 4 years indicated that there was no clear chemically related impact on field margin flora, birds and most small mammals. Nevertheless the use of pesticide is still perceived as causing serious ecological effects and in this context it is worth noting that the estimated death of 20-70 million birds and 0.7-1.3 million hedgehogs killed on United Kingdom roads every year [2] goes largely unnoticed.

More recently the attention of Regulatory Authorities has focused on environmental fate and in particular soil persistence, leachability and the potential contamination of groundwater.

Other Data Requirements

In addition to the data requirements described above the regulatory data package must also include extensive information on the chemical properties of the active ingredient and formulated product, the stability of the product under extremes of different storage conditions and, of course, comprehensive biological field data on the performance of the product under a variety of climatic, agricultural, environmental and pest-infestation conditions.

HARMONISATION OF DATA REQUIREMENTS

A number of attempts have, over the years, been made to harmonize regulatory data requirements and procedures, most notably the Council of Europe [3] and FAO [4, 5, 6]. These attempts have met with little success, due primarily to two major reasons. Firstly, pesticides are used throughout the world under a variety of different climatic, environmental and agronomic conditions and consequently the risk/benefit analysis of any proposed use of a pesticide must be considered in the light of the particular conditions pertaining in that country where this use is to take place. Data requirements can thus be expected to differ to some extent between different countries but not, I would suggest to the degree to which they actually do. Secondly, National Regulatory Authorities have traditionally taken a somewhat 'parochial' view of pesticide registration and, in many cases and perhaps understandably, have been reluctant to accept the evaluation of other Regulatory Authorities.

A notable exception has been the general (although not universal) acceptance of the evaluations undertaken by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) and its consequent recommendations for Acceptable Daily Intakes (ADI) and Maximum Residue Limits (MRLs). It is perhaps unfortunate that the JMPR concerns itself with only potential hazards to consumers and that there is no equivalent international body which considers environmental data on pesticides to the extent that JMPR considers toxicological and residues data.

Despite the relative lack of success in achieving harmonisation in the past, recent initiatives within the European Community however have presented the Registration Authorities in Western Europe with an opportunity to make considerable progress in this area. The Community is currently considering a Commission Proposal to harmonize the registration of plant protection products [7]. This Proposal has been considered in detail elsewhere [8] but basically it involves a two-tier approach whereby active ingredients would be evaluated by a Community procedure, i.e. by an Expert Committee comprising representatives of all 12 Member States of the Community. A consensus agreement by this Committee to approve' the active ingredient would result in that active ingredient being included on a so-called 'Positive List'. Registration of products containing those approved active ingredients would then be left to individual Member States having due regard to the particular environmental, agronomic and climatic conditions of the particular Member States. Data requirements for both the active ingredient and the formulated product have been defined in the Proposal and Uniform Principles aimed at establishing when these data will be needed and how they should be interpreted are to be drafted in the near future.

As might be expected discussion on this Proposal has been extensive and agreement has yet to be reached. There would however seem to be a considerable 'political' will towards reaching agreement although it is difficult to predict how long this will take. Given that a wide range of different rules, regulations and procedures have previously been harmonized within the Community, the delay in achieving the harmonization of pesticide registration reflects the difficulties involved. Furthermore these European difficulties are an indication of the even greater difficulties involved in extending the harmonization of pesticide registration to other parts of the world.

FUTURE DEVELOPMENTS

The comments above have highlighted the increasing pressures on the use of pesticides and the increasing regulatory requirements which must be met in order to achieve new registrations or maintain existing registrations. In other words the introduction of new pesticides on to the market is becoming more and more difficult. This is regrettable as, by and large, the new pesticides are 'safer' than their predecessors, i.e. they are generally of lower toxicity and are applied at significantly lower rates thus leading to a significantly lower environmental burden.

It is apparent that these 'negative' attitudes towards pesticides are most acute in Western Europe and the United States of America - countries which, I would suggest, are in the fortunate position to be able to 'afford' this position.

Let us consider a few relevant facts:

1. As an indication of world food supplies, world cereal stocks, as shown in Table 6, are predicted by the FAO [9] to fall to just 17% of annual consumption which is equivalent to less than 2 months' supply.

TABLE 6
World cereal production and stocks (million tonnes)

	1986/87	1987/88	1988/89 (estimated)	1989/90 (Forecast)
Production	1863	1803	1758	1867
Stocks	455	401	307	296
Stocks as % of annual consumption	27	24	18	17

2. Natural catastrophes such as drought in the United States, floods in Bangladesh and locusts in Africa have occurred and will continue to occur on a regular basis. Emergency response to famine, such as that in Ethiopia, can only be undertaken where stocks are available.

3. 950 million people are hungry and undernourished today [10] whereas in the western world millions of people are dieting to lose weight.

4. Even with the use of pesticides the FAO has estimated that 20-40% of food production is lost annually to pests and diseases [11].

5. The world population continues to increase at a rate of 200,000/day and is expected to reach 6 billion by the year 2000. It is estimated that world food supply must increase by 75% to meet this increase in population [12].

6. 40,000 people die from starvation every day.

These facts clearly support the continued need for pesticides in food production and an equally convincing argument can be made to support their continued use in the production of non-food crops such as cotton, rubber, etc., and in the public health area for the control of insect-borne diseases and of pests such as cockroaches, fleas, etc.

Thus any short-term measures for increasing the regulatory control of pesticides to the point at which they inhibit the development of new, more effective, more environmentally acceptable and safer pesticides, must be viewed with considerable caution against the longer-term needs to ensure efficient world-wide food production.

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PESTICIDE USE IN SRI LANKA AND SOME SUCCESSFUL CASES OF PEST MANAGEMENT WITH DUE REGARD TO ECOLOGICAL PRINCIPLES

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ABSTRACT

Crop protection depends heavily upon the use of chemical pesticides. The farmer usually aims for pest control rather than pest management. The excessive use of chemical pesticides has led to problems in pest management as well as adversely affecting the environment. Recommendations for pesticide use in agriculture are made by the various research institutions dealing with specific crops. Pest problems in the three major plantation crops, namely tea, rubber and coconut, and in the minor export crops and sugar cane are covered by the respective research institutions dealing with those crops. Sri Lanka's problems with the use of BHC dust and the problems for the control of brown plant hopper (BPH) in rice and how these problems were overcome is described. Successful biological control of some pests in onion and coconut crops are given. A number of non-conventional approaches giving promise in Sri Lanka is given.

AGRO-ECOLOGY

Sri Lanka is located between 6^0 and 10^0 north of the equator at the southern tip of the Indian sub continent. The island has a total area of 6.6 million (m) hectares (ha), which is divided into 3 climatic zones: a wet zone of 1.54m ha in the south west quadrant, a dry zone of 4.17m ha in the north, north east, north west, north east and south east and an intermediate zone of 0.85m ha sandwiched between the two other zones.

The three climatic zones are sub divided into eight major agro-ecological regions by altitude, rainfall and land form. These eight zones are further divided into twenty four well defined agro-ecological regions each with its unique combination of rainfall pattern, elevation, land form, temperature range and soil types. [1].

Rainfall in Sri Lanka follows a distinctive bimodal pattern. Consequently there are two cultivation seasons: the **Maha** season from October to January which is influenced by convectional rains and the north east monsoon and the **Yala** season from May to September, when the south west monsoon is in force. Rainfall in the wet zone is adequate for year round crop growth. In the intermediate and dry zones the rainfall is adequate only during the Maha season. Temperature within the country shows a marginal variation. Maximum and minimum air temperature vary from 20°C to 10°C in the up country dry zone. Sri Lanka's wide variation in precipitation, topography and soil make it possible to grow a wide range of crops.

ECOSYSTEM AND AGRO-ECOSYSTEMS

The word ecology is derived from the Greek word "oikos" meaning "house" and so literally ecology is the study of "houses" or more broadly "environments". The living communities and the non-living environment function together as ecological systems or ecosystems. A natural ecosystem is self-perpetuating and the vegetation is a product of natural selection.

Agricultural systems are special types of man-made ecosystems called agro-ecosystems which are different from the undisturbed naturally occurring systems like forests and range lands. In an agro-ecosystem its sustained existence depends upon manipulation of energy flows directed by man. The biotic environment is drastically reduced in complexity and through the conventional farm operations a few selected energy paths are maximized to produce the greatest output from a single species of cultigen. Agro-ecosystems are not self-perpetuating and so they vary in duration from orchards and plantations of coconut or other perennial crops that last about 40 - 50 years to arable crops of a few months duration. In an agro-ecosystem the vegetation is selected by man, the diversity of species is reduced and the levels of nutrients in their foliage is higher than those found in the plants of a natural ecosystem. Therefore, pest and diseases are a regular feature of agro-ecosystems necessitating crop protection.

PESTICIDE USE

Crop protection depends heavily upon the use of chemical pesticides and the farmer aims for pest control rather than pest management. By pest control one gets the unrealistic idea of pest elimination rather than management of pest populations at tolerable levels. The excessive use of chemical pesticides has led to problems in pest management as well as to the environment. Nevertheless, pesticides cannot be completely dispensed with, even in pest management systems and therefore, based on needs, appropriate formulations have to be recommended.

Growth in pesticide consumption in Sri Lanka was synonymous with increased adoption of new high yielding varieties of crops and expansion of irrigation systems. Recommendations for pesticide use in agriculture are made by the various research institutions dealing with specific crops. The Department of Agriculture makes recommendations for the control of pests and diseases of rice, other field crops, fruit crops and vegetables. Pest problems in the three major plantation crops namely tea, rubber and coconut and in the minor export crops and sugar cane are covered by the respective research institutions dealing with those crops.

Some important insect pests requiring frequent chemical control and for which standard recommendations are made available by the Department of Agriculture of Sri Lanka have been listed in Table 1.

Total imports of WHO Class I insecticides into Sri Lanka between 1986 and 1989 is shown in Table 2.

Some Special cases of our experience in pest management are as follows:

Rice is a crop of major importance to Sri Lanka. The area under cultivation annually is around 780,000 ha with about 50,000 ha under continuous cultivation. This caused a major outbreak of the brown plant hopper (BPH), (*Nilaparvata lugens*), in the mid-seventies in eastern Sri Lanka in which 16,200 ha were affected and 2000 ha destroyed. A build-up of about three generations of this pest is sufficient to result in patches of "hopper burn" in infested fields.

Analysis of this problem showed that the factors listed below were contributory towards the appearance of this pest in epidemic proportions:

Cultivation of long maturing susceptible varieties

Staggered planting of the rice crop throughout the year

- at no time of the year was there less than 8,000 ha of field carrying a rice crop.

Use of very high seed rate at broadcast planting.

- 260 - 360 kg ha^{-1} of seed is broadcast while the recommended rate is 100 - 125 kg ha^{-1}.

Extensive dusting of BHC, an organochlorine compound, on the crop canopy while the insect pests thrived at the base of the crop.

Staggered planting of the susceptible variety provided a continuous food supply and protected the pest from the hazards of dispersal. Also the cultivation of a long maturing variety allowed the development of several generations of the plant hopper. The high seed rate resulted in a dense crop which provided abundant shade and food supply, a high relative humidity and temperature, which all together provided conducive micro climate for BPH development. Extensive dusting of BHC powder on the crop canopy destroyed natural enemies like *Cyrtorhinus*, coccinellid beetles, spiders and damsel flies, while the pest sheltered and thrived at the base of the crop. As a result the pest built up in epidemic proportions.

Remedial measures which helped recover the rice crop in affected areas were in line with ecological principles.

BPH resistance was bred into new improved varieties from local traditional varieties and mainly from the Indian variety Ptb 33. (The improved resistant variety at present is Bg 379-2).

Lower seed rate for broadcast planting was recommended.

Arrangements were made with irrigation authorities to supply water for synchronous planting in the entire range instead of staggered planting, so that a crop free period between two cropping seasons would be allowed.

Along with reduced seed rate, the new varieties also had short stiff leaves from IR8 parentage, so that the crop base was not shaded.

Economic threshold was established and chemical control was need based. Emphasis was placed on pest surveillance and treatment was recommended only if pest numbers exceeded the economic threshold level (ETL).

Use of BHC dust was banned and soil treatment with a granular carbamate was recommended so that the existing abundant natural enemies could be conserved.

All these factors contributed towards tilting the microclimate against the pest and offered good control.

Onion is a high value cash crop grown throughout the year in the northern area of Sri Lanka. A consistent outbreak of the lesser armyworm, *Spodoptera exigua* (Hubner) in epidemic proportions was observed in these areas on the onion crop. The pest had developed resistance to several insecticides and was therefore referred to as the "tough skin caterpillar". At such a critical phase a pyrethroid insecticide came in effectively useful with its quick knock down effect. In Sri Lanka pyrethroids are reserved for use as a last line of defence against local pests and restricted for use on onion caterpillar and cotton pests only [2]. Now areas in which this pest is endemic are advised to use granular formulations of carbofuran during the first week of planting and thereafter monitor the pest population very closely for judicious and optimal use of recommended insecticides. Subsequently, the Department of Agriculture of Sri Lanka noticed that the Nuclear Polyhedrosis Virus (NPV) was an important natural enemy of this pest. The virus was propagated quite easily and sprayed on the crop on a small scale. This control method was found to be highly economical, safe to man and other animals and also compatible with the environment. Although extensive use of NPV is not yet reported this pest can be contained to a great extent by this strategy.

Coconut is one of our commercial crops which is cultivated in about 400,000 ha or 25% of the total cultivated area in Sri Lanka.

The coconut leaf miner, *Promecotheaca cumingi* came to Sri Lanka as a foreign invader during the early seventies. It is a beetle pest which in the absence of its natural enemies appeared in epidemic proportions, threatening the coconut plantations with destruction. In its own natural environment in countries like the Philippines, Indonesian and Malaysian islands this beetle is reported to be kept well under control by its natural enemies, *Dimmockia javanica* and *Pediobius parvulus*. These parasites were imported into Sri Lanka, mass reared and released. Control was achieved within a short period of time. Several years later an outbreak of this pest appeared in a patch of coconut land and no control measures were taken, since, the natural enemies were already within our shores. The parasites did take control of the situation on their own, showing that a balance or equilibrium exists between the pest and the parasites. It is evident that successful biological control is a stable process in this case.

The Coconut Research Institute of Sri Lanka has an active biological control laboratory in which larval and pupal parasites of important pests like the coconut caterpillar are mass-reared and released [3].

The trend in Sri Lanka today is initially to use resistant varieties, wherever feasible, minimize and optimize applications of insecticides, use granular formulations wherever appropriate and treat seed and plant material prior to planting rather than spray a standing crop. Further, *Bacillus thuringiensis* has now been registered for use. Other safer pesticides like growth regulators, biological control agents and botanicals with insecticidal properties are tested experimentally for future use.

Some promising botanicals with pesticidal properties have been listed in Table 3.

Other pest management tactics which are being tested include the cultivations of mixed cropping systems or agro-forestry systems rather than vast extents of monocultures. [4]. These systems are slowly but steadily gaining popularity, especially in coconut, and various types of crops such as horticultural and minor export crops along with arables, are being intercropped under coconut. However, the pest management effects from such intercropping systems and the appropriate combinations of crops that would produce optimal crop protection effects need further study.

TABLE 1
Some important pests requiring frequent chemical control and for which standard recommendations are available

On Rice	
Brown plant hopper	*Nilaparvata lugens*
Gall-midge	*Orseolia oryzae*
Thrips	*Stenchaetothrips biformis*
Stemborer	*Scirpophaga incertulas*
Leaf folder	*Cnaphalocrocis medinalis*
On other food crops and vegetables	
White flies	*Aleurodicus disperus* *Bemisia tabaci*
Aphids, scales and mealy bugs	
Bean fly	*Ophiomyia phaseoli*
Bean pod borers	
Cucurbit fruit fly	*Dacus cucurbitae*
Cutworms and army worms	
Brinjal shoot borer	*Leucinodes orbonalis*
Cabbage caterpillar complex	
Nematodes	*Meloidigyne* spp.
On fruit crops	
Pineapple mealy bug	*Dysmicoccus brevipes*
Banana weevils	*Cosmopolites sordidus* *Odoiporus longicollis*
Fruit fly	*Dacus* spp.

TABLE 2

Total imports of Class I Insecticides into Sri Lanka from 1986 - 1989

Year	Amount in litres	
1986	521, 866	
1988	391,400	25% reduction approximately
1989	348,523	10% reduction approximately

Note there is a phased restriction on the import of WHO Class I insecticides.

TABLE 3
Some botanicals tested for pesticidal properties in Sri Lanka

Botanical	Effective on
Acorus calamus	Bean aphid - *Aphis craccivora*
Azadirachta indica	Bean aphids
Azadirachta indica	Cabbage caterpillars
Azadirachta indica	Root knot nematoae - *Meloidogyne incognita*
Azadirachta indica	Rice storage pest - *Sitotroga cerealella*
Ageratum conyzoides	Bean aphids (as repellant)
Tricodenia zeylanica	Bean aphids
Calatropis gigantea (flowers)	Rice leaf older - *Cnaphalocrocis medinalis*
Eryngium foetidium	Bean aphid - *Aphis fabae*
Pavetta indica	Bean aphid - *Aphis fabae*
Lantana camara	Potato tuber moth - *Phthorimaea operculella* (duringstorage)
Chenopodium ambrosioides	Potato tuber moth (during storage)

*Some botanicals have had pesticidal effects when used as green manures

Botanical	Green manure on
Croton laccifer	Betel
Pongamia pinnata	Cucurbits
Cassia auriculata	Onion
Indifogera aspalathoides	Manioc
Tephrosia purpuria	Tobacco

Clausena indica	Tobacco
Cullen corylifolium	Tobacco
Pavetta indica	Tobacco

*Effect of botanical extracts on soil-borne pathogens (Laboratory tests)

Botanical	Effective on
Adhatoda vasica	*Phytophthora* sp.
Adhatoda vasica	*Pythium* sp.
Adhatoda vasica	*Sclerotium rolfsii*
Cullen corylifolium	*Sclerotium rolfsii*
Azadirachta indica	*Rhizoctonia solani*

*None was effective on *Fusarium solani*

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ENVIRONMENT-FRIENDLY PESTICIDES

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ABSTRACT

While decreased application rates serve as the major purpose of research in pursuit of environmentally acceptable herbicides and fungicides, in the insecticide field the development of compounds acting selectively on insect-specific biochemical or behavioural functions is the most promising approach to environmental safety.

By making use of the pro-drug approach, a new group of juvenile hormone mimics was developed within the framework of the UNDP/UNIDO supported project "Development of non-toxic insecticides". The long term theoretical research programme of the project was aimed at new leads and new anti-insect activities serving as potential starting points in search for selective insecticides. The main results of these efforts were the discovery of the anti-spiracular effect, a tissue specific activity disrupting larval respiration, the development of a new type of egg-laying deterrent and the synthesis of compounds inhibiting the ecdysone-20-monooxygenase enzyme which regulates moulting hormone biosynthesis.

TRENDS IN RESEARCH ON NON-CONVENTIONAL PESTICIDES

The early fifties marked the end of a period of enthusiasm and false sense of security brought about by the spectacular success of DDT and other chlorinated insecticides in the aftermath of World War II. The environmental damage caused by them and other conventional pesticides made themselves felt and the search for related type derivatives with improved environmental properties brought only partial success. It became evident that elimination of environmental, ecological and toxicological hazards can be brought about only by pesticides with novel and specific action.

Research which followed this goal resulted in significant successes throughout the last two decades. The results manifested themselves in various ways in different pesticide classes.

In the field of fungicides and herbicides high application rates created one of the most serious environmental problems. Research was therefore concentrated on the development of chemicals which permit application in low dosages due to their increased biological potency.

Table 1 shows how the development of more and more active herbicides enabled the gradual reduction of dosages during seventy years, starting from 20kg ha^{-1} dose of sulphuric acid and ending with 5 g/ha of chlorsulfuron.

TABLE 1
Herbicide dosages

	Year	Dosage (kg ha^{-1})
Sulphuric acid	1909	20
Trichloroacetic acid	1947	6 - 8
2,4-D	1949	2.5 - 4
Atrazine	1957	2.5 - 3
Trifluralin	1960	0.8 - 1.5
Metribuzin	1970	0.6 - 1
Chlorsulfuron	1978	0.005 - 0.01

The same decrease of dosages could be observed in the field of fungicides (Table 2). Triadimefon, reaching the market in the mid seventies, with application rates as low as 100g ha^{-1} creates slight chemical contamination as compared with the 3 kg ha^{-1} rates of copper oxychloride at the turn of the century.

Selective insect control creates much more serious problems, as the similarity between the biochemical functions of humans and those of insects offers limited scope for research on compounds acting selectively against insects without affecting non-target organisms.

The hormonal regulation of insect development proves to be just such an insect-specific biochemical function which falls into this narrow margin, offering possibilities for research on safe and selective insect control. A finely tuned regulatory system, composed of the juvenile hormone and ecdysterone (moulting hormone) controls this balanced regulatory cycle [1-7].

TABLE 2
Fungicide dosages

	Year	Dosage (kg ha^{-1})
Copper oxychloride	1900	2.5 - 4
Zineb	1943	2 - 3
Captan	1949	1.2 - 2
Benomyl	1968	0.4 - 0.5
Triadimefon	1975	0.1 - 0.25

Of these two regulatory hormones, the juvenile hormone was the first to become a starting point for research aimed at developing compounds which either mimic the natural hormone and disrupt the hormonal balance by imitating an overdosage or false presence of the natural hormone, or conversely, block its biosynthesis, acting as anti-juvenile hormones.

Figure 1 shows the chemical structure of one of the four closely related natural juvenile hormones, JH-II, and some typical representatives of the several hundred synthetic juvenile hormone mimics prepared by different authors. Those which were prepared in the late sixties were closely related to the natural hormone, but with time, compounds increasingly remote from the natural juvenile hormone were discovered as highly active juvenile hormone mimics.

Methoprene and fenoxycarb (Figure 1) received formal regulatory status in plant protection, but the use of these two products became limited to special applications, in spite of the fact that they are harmless to mammals, fish and birds. The main limiting factors in their application are the narrow range of activity on different insects and their action only in the critical development stage which requires absence of natural juvenile hormones.

The opposite, anti-juvenile hormone, approach aims to disrupt rather than mimic juvenile hormone function. Compounds acting as anti-juvenile hormones exert their activity by various mechanisms, such as acting as metabolic analogues of biointermediates in juvenile hormone synthesis [8, 9] or through a specific cytotoxic action on the *corpus allatum*, the insect organ responsible for juvenile hormone production [10].

Though none of the anti-juvenile hormones have reached practical utilization, their practical potential is higher than that of the juvenile hormone mimics.

Research on mimics and antagonists of the moulting hormone (ecdysterone), the other key member of the insect development regulatory system, was impeded by the complicated chemical structure and high cost of this hormone. Recently, however, an insecticide derived from hydrazine (RH-5849) was described which acts as an ecydysterone mimic [11]. In contrast to juvenile hormone mimics, where structural similarities between the natural juvenile hormones and their synthetic analogues might explain their similar activity, the ecydysterone mimicking action of RH-5849 cannot be explained on the basis of structural similarities. Chemical formulae of ecdysterone and of RH-5849 are shown in Figure 2.

The discovery of the ecdysone agonist activity of mimicking RH-5849 will give strong impetus to research on compounds interfering with moulting hormone function and biosynthesis.

The insect hormonal approach is only one part of non-conventional, selective insect control strategies. Compounds affecting biosyntheis and sclerotization of the insect cuticle, insect-specific neuropeptides and chemicals affecting insect behaviour, such as pheromones, antifeedants and egglaying deterrents may serve as further promising targets in the search for selective anti-insect agents. Yet experience of the past two or three decades has dashed early enthusiastic expectations that these new approaches can take over the role of the conventional insecticides. A more realistic viewpoint suggests that the presently known non-conventional alternative anti-insect agents can complement rather than replace the traditional insecticides used in today's agricultural practice.

Research in this field has to face therefore a dilemma. If the search for new compounds remains within the limits of the non-coventional anti-insect agents which are already known, then accumulated knowledge provides a relatively good chance of success but one has to cope with all predictable drawbacks associated with the given groups. Escape

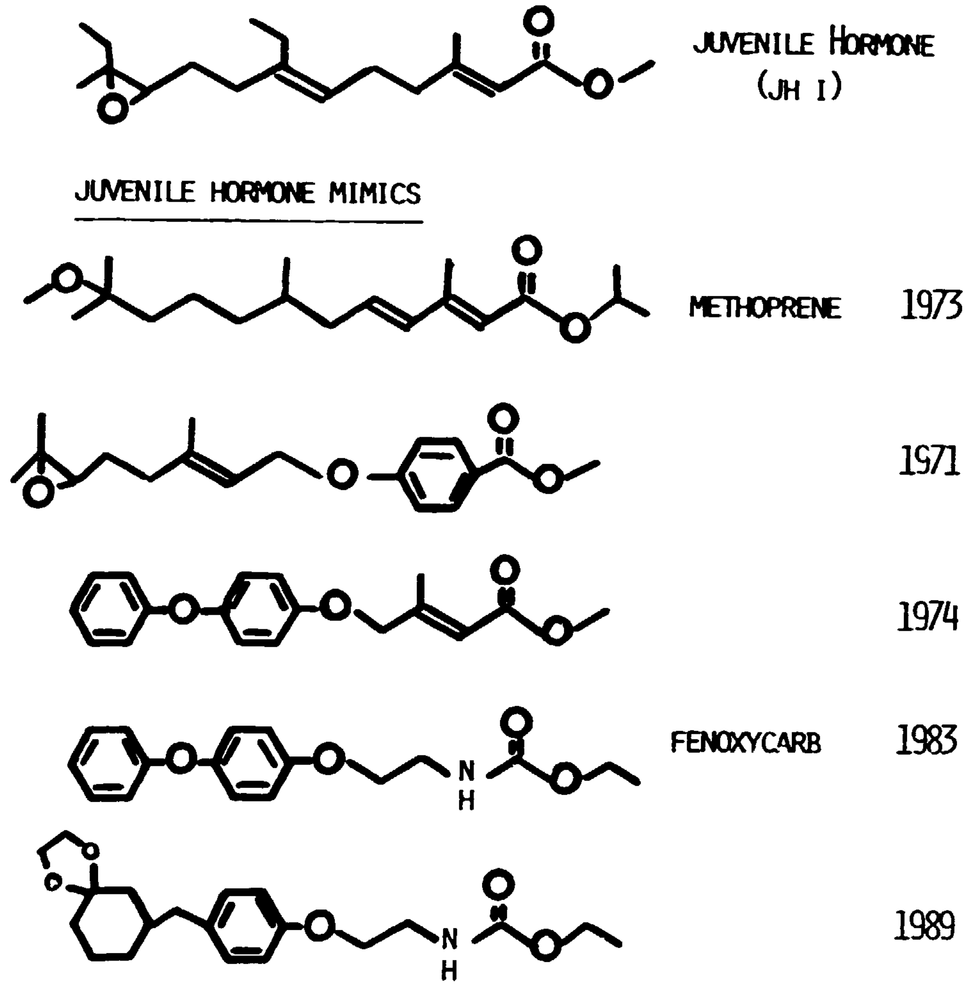


FIGURE 1. NATURAL JUVENILE HORMONE AND SOME SYNTHETIC MIMICS.

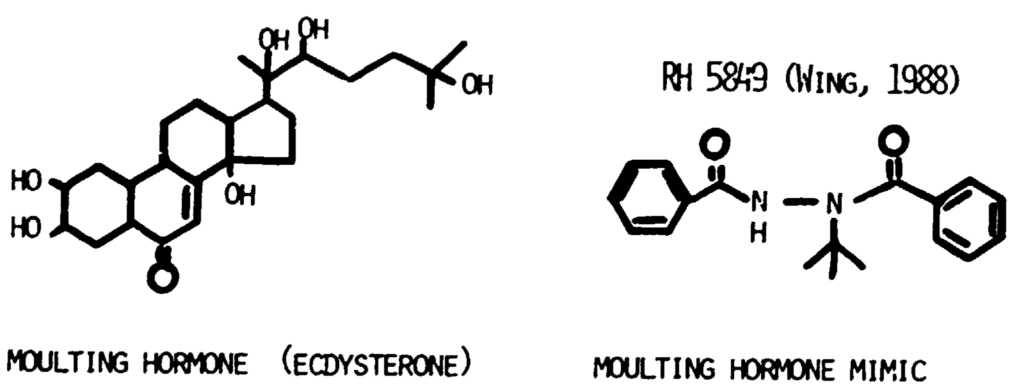


FIGURE 2. NATURAL MOULTING HORMONE AND A SYNTHETIC MIMIC.

from these limitations requires leads representing hitherto unknown insect-specific activities, but research pursuing this aim has to face a lower probability of finding active substances.

RESEARCH PROGRAMMES WITHIN THE UNDP/UNIDO SUPPORTED PROJECT DEVELOPMENT OF NON-TOXIC INSECTICIDES

When planning our UNDP/UNIDO supported project "Development of non-toxic insecticides" we started research programmes representing both long term objectives aimed at finding new leads with hitherto unknown or scarcely investigated insect-specific activities and a more closely practice-oriented programme focused on the development of novel juvenile hormone mimics.

Discovery of Anti-spiracular Effect

A programme launched in cooperation with the Zoology Department of the University of Washington, Seattle, Washington, United States of America, was focused originally on the development of compounds which could selectively inhibit the biochemical mechanisms regulating sclerotization and thus hardening of the insect cuticle. Some of the compounds designed and synthesized by us on the basis of rational considerations showed a hitherto unknown physiological activity: following treatment of third instar larvae some of the larvae died during molt to fourth instar; those which survived were lacking most of their abdominal spiracles, openings needed for respiration, and the crochets, prolongation of the legs needed for the larvae to hold themselves on the plant. This response repeated itself in the fourth to the fifth larval transformation. Some of the compounds showing this activity [12, 13] are presented in Figure 3.

Further research in this field is in progress to elucidate structural requirements and mechanism of this activity, as well as to reveal its possible significance in regard to selective insect control.

Insect Egglaying Deterrents

A further cooperative programme within our UNDP/UNIDO supported project was performed jointly with the Pesticide Research Center of Michigan State University, East Lansing, Michigan, United States of America. The programme was focused on compounds disrupting the developmental cycle of insects by preventing egglaying.

The starting point of this work was the previous finding of Hollingworth *et al.* [14], our cooperation partners, that cinnamaldehyde acts as a strong inhibitor of egglaying of the onion fly. In our subsequent cooperation we regarded cinnamaldehyde as a lead compound and synthesized an array of related substances, out of which the compounds shown in Figure 3 revealed highest deterrent activity, surpassing that of cinnamaldehyde [15].

Inhibitors of Moulting Hormone Biosynthesis

We synthesized the imidazole and triazole-containing compounds PIM and sPTM shown in Table 3, as well as their "soft alkyl derivates" by using the soft drug approach developed by Bodor and co-workers [16, 17] in rational drug research. PIM and sPTM are imidazole- and triazole-analogues, respectively, of metyrapone, which is a potent inhibitor of a

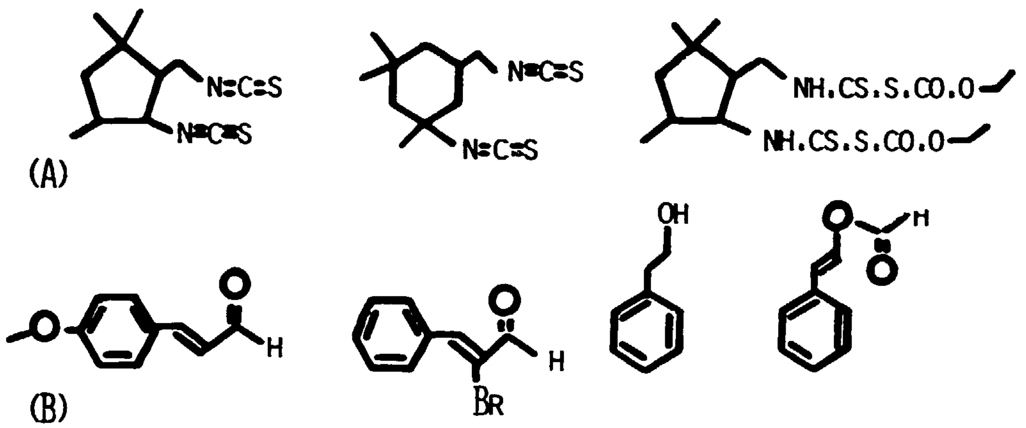
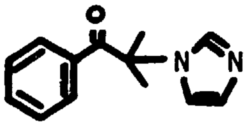
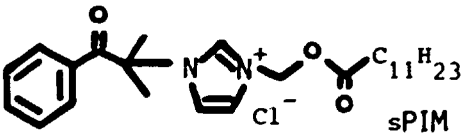
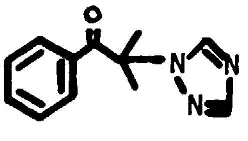
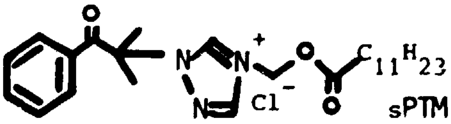


FIGURE 3. COMPOUNDS SHOWING (A) ANTI-SPIRACULAR ACTIVITY; (B) INSECT EGG-LAYING DETERRENT ACTIVITY

TABLE 3
INHIBITION OF ECDYSONE-20-MONOOXYGENASE ISOLATED FROM THE FAT BODY OF NEOBELLARIA BULLATA LARVAE

	E-20-M ACTIVITY (PMOL/H/MG PROTEIN)			
CONCENTRATION (M)	10^{-4}	10^{-5}	10^{-6}	10^{-7}
 (PIM)	0.86	1.11	6.19	12.34
 sPIM	5.52	2.16*		
 (PTM)	10.52			
 sPTM	5.92	9.72*		
METYRAPONE	0.18	0.92	4.38	11.66

CONTROL VALUE = 14.33

*SPONTANEOUS HYDROLYSIS WITHIN 1 DAY

cytochrome P-450-dependent monooxygenase enzyme involved in moulting hormone biosynthesis.

Table 3 presents the structure of the compounds and their *in vitro* activity on ecydysone-20-monooxygenase. Though the two compounds did not surpass metyrapone in regard to this *in vitro* enzyme inhibitory activity, under *in vivo* conditions sPTM strongly inhibited pupariation, while metyrapone revealed slight activity in this respect [18].

Development of New Juvenile Hormone Mimics

The practice oriented programme of our project pursued the aim of developing new selective anti-insect agents as juvenile hormone mimics.

We approached this goal by making use of the pro-drug principles, research strategies which led to significant results in drug research, to find anti-insect agents acting as juvenile hormone mimics.

A pro-drug is a biologically active compound which is inactive in its original form and is transformed into its active state by the organism. Due to their improved physicochemical properties, pro-drugs often possess enhanced capacity to move through biological membranes and to reach the site of action where the active form is released to perform its activity. This concept has been known for half a century. An early example of a pro-drug is prontosil used for the treatment of streptococcal and pneumococcal infections [19]. It is metabolically converted into *p*-aminobenzenesulfonamide responsible for the therapeutic action [20, 21].

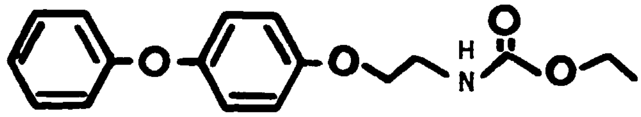
Fukuto and co-workers [22, 23, 24] in the United States and independently Drabek and associates [25] in Switzerland adopted the pro-drug principle for insecticide research. They prepared sulfenylated and sulfinylated derivates of known carbamate type insecticides. The rationale for the design of these derivates was based on the premise of introducing a "delay factor" into methylcarbamates, resulting in reduced mammalian toxicity along with retention of insecticidal activity.

Fenoxycarb, a highly active juvenile hormone mimic developed by Fischer, Masner and co-workers [26, 27] served as the lead compound in our investigations. We attempted to subject this compound to different structural modifications applied in pro-drug and pro-pesticide research. Most of these attempts failed for chemical reasons, but we succeeded in synthesizing its sulfenylated and sulfinylated derivatives. Out of 12 compounds prepared the four compounds depicted in Figure 4 showed the highest activity and were selected for more detailed tests. Compounds 1-3 are unsymmetrical sulfenylated derivatives. Sapogenat-T-130, a surfactant having excellent translocation characteristics in mammalian organisms, was used as a building block in synthesizing Compound 3, aimed to facilitate movement through biological membranes in the insect organism. Compound 4 is a symmetrical sulfinylated derivative.

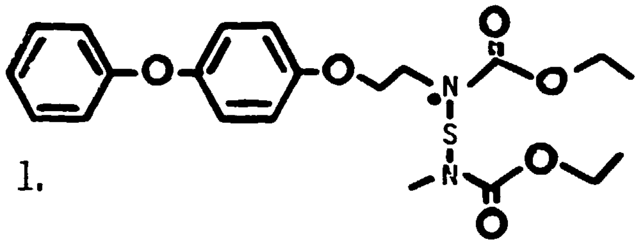
Data in Table 4 indicate that the biological activity of Compund 4, marked with the code number NKI-35120, surpasses the activity of the lead compound fenoxycarb against various insects. The most probable explanation for this increased activity is that the sulfinylated derivative possesses improved translocation characteristics in the insect organisms, thus facilitating its movement to the site of action.

Patents have been granted for these compounds in a number of countries and some of them are under extended glasshouse and field evaluation in Hungary and other countries against various insect pests.

Existing pesticides applied in huge tonnages cannot fulfil the growing demands of environmental safety. Growing awareness of the public towards toxic substances in the



FENOXYCARB



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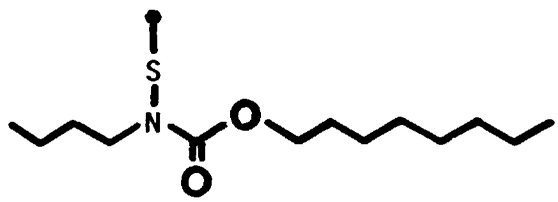

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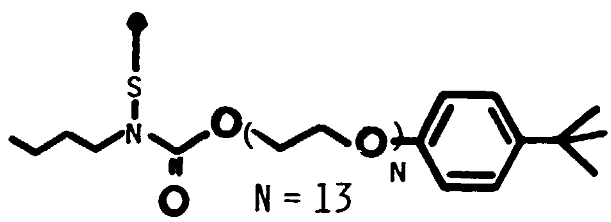

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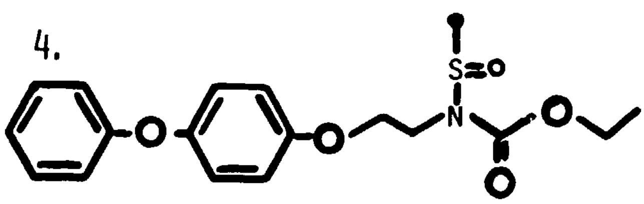

FIGURE 4. FENOXYCARB AND SOME PRO-INSECTICIDE DERIVATIVES

environment may bring even greater restrictions on pesticide usage, creating an urgent need to intensify the search for alternative pesticides usable in reduced dosages and possessing a high degree of selectivity to the target organism.

TABLE 4
Insecticidal activity of NKI-35120

Mussel purple scale, *Lepidosaphes beckii*; orange plantation field test (Egypt)

	Activity [%]	Egg production [eggs/female]
NKI-35120 0.1%	90.8	9.7
Fenoxycarb 0.1%	65.1	13.7
Untreated	-	29.7

Larvae of the cabbage moth, *Pieris brassicae*; topical treatment

	ED50 (ng/larva]
NKI-35120	2.6
Fenoxycarb	21.0

Larvae of the fleshfly, *Sarcophaga bullata;* topical treatment

	Mortality [%]
NKI-35120 0.25 μg/larva	100
NKI-35120 0.10 μg/larva	50
Fenoxycarb 0.25 μg/larva	87
Fenoxycarb 0.10 μg/larva	27

This work has been performed by the following members of the project team of chemists and biologists:

Krisztina Bauer, Ivan Belai, Bela Darvas, Adrien Fonagy, Peter Kulcsar, Andras Szekacs, Ferenc Szurdoki, Mohamed Taha Abdel-Aal, Istvan Ujvary and Laszlo Varjas.

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PESTICIDES AND GROUNDWATER CONTAMINATION

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ABSTRACT

Groundwater contamination may arise as a consequence of the agricultural application of pesticides. Surveys of drinking water and groundwater in the United States indicate that the problems occur over widely distributed areas. Concentrations in most cases are well below the health advisory guideline levels published by the U.S. Environmental Protection Agency (USEPA). The U.S. Department of Agriculture and the U.S. Geological Survey have also mounted large-scale programs to discover the extent of the problem.

Point sources of contamination may be important in some instances and the likelihood of contamination at the well head may be reduced by modifying farm practices.

Contamination of groundwater as a result of agricultural use of pesticides depends on a number of factors including: the properties of the chemical used, the nature of the soil and the site of application, agricultural practices employed, and climatic factors. A considerable research effort initiated by the USDA involves several approaches: recognition of situations that are vulnerable, predictive modelling of movement of pesticides through soil, investigation of management practices to remedy the problem, novel technology, such as the use of controlled release pesticides, band application, pesticide combinations, and combinations of chemical and non-chemical measures.

Similar problems of groundwater contamination may be anticipated in the developing countries. Whether or not they occur will depend on the factors indicated previously. It is important to avoid such contamination. This will require that pesticides be used judiciously and that vulnerability for potential degradation of groundwater quality be recognized. It is necessary that pesticide users be made aware of the situation and that educational and regulatory programs address the issue.

INTRODUCTION

In the United States, groundwater is an important source of drinking water supplies - about 50% in 1983 - and it also supplies about 80% of rural and livestock needs and 40% of irrigation needs, according to the US Geological Survey. Estimates prepared in 1984 suggested that 2% of the nation's groundwater contained contaminants from a variety of sources including agricultural chemicals and an Office of Technology analysis reported that over 200 substances had been detected in groundwater [1]. The report summarized the numbers of sources and amounts of material flowing through or stored in sources. Among potential sources of groundwater contamination were pesticide and fertilizer applications. Active ingredients of pesticides were applied at an estimated 260 thousand tons per year as 280 million acre treatments. Fertilizers were applied at an estimated 42 million tons per year as 29 million acre treatments [1].

The problem of nitrate contamination must be included to provide a complete view of water quality problems that face agricultural management. Public concern over water quality issues increased during the 1980s. Monitoring programs were intensified and pressures for legislative action increased [2]. In 1986, the United States Environmental Protection Agency reported that 17 pesticides had been detected in the ground water of 23 states in concentrations that ranged from trace amounts to several hundred parts per billion [3].

A recent bibliography containing 7800 citations selected from the international literature on agricultural aspects of the pollution of ground and surface waters indicated the scope of the problems and the issues raised [4].

Concern arosen over the presence of these contaminants, even in the absence of demonstrable adverse effects. Because groundwater is the primary source of drinking water for many rural and urban communities in the Cornbelt, knowledge of the extent of contamination has stimulated public demand for changes in agricultural practices to eliminate potential contamination.

IMPACT OF PESTICIDES AND FERTILIZERS

In the United States, increases in agricultural production were accompanied by increased use of chemical fertilizers, pesticides and other chemicals by the farmer. Particularly noteworthy is the increase in herbicide use in the past twenty years. Persistent insecticides, such as DDT, were replaced by less persistent compounds such as the organophosphates. At the same time, alternative techniques for insect control were introduced and the adoption of "integrated pest management" was effective in reducing insecticide use.

Nevertheless several insecticides have been detected in groundwater and their occurrence is dependent or [illegible] class of compound, usage patterns, and hydrogeological and climatic factors in the area in which they were used.

In August, 1988 the USEPA began a National Pesticide

Survey to measure the content of more than 100 commonly used pesticides in community and private drinking-water wells. An interim report was released in September 1989 giving findings based on 295 water samples. Six of the 180 community wells and 9 of the private wells tested showed some level of pesticide residues. Three of the 15 wells contained pesticides at concentrations above the health advisory levels. Of the community wells, 79 contained nitrate/nitrite residues, as did 66 of the private wells [5]. The drinking-water standard for nitrate of 10 parts per million was exceeded in 8 of these 145 wells. The completed survey will include data from about 1350 wells.

An earlier USEPA report summarizing the available data on pesticides in groundwater [6] included data from about 150 monitoring studies and stated that normal agricultural use had led to residues of 46 different pesticides in the groundwater of 26 states. A total of 74 pesticides were detected in the groundwater of 38 states from all sources, including normal agricultural use, spills, and residues from mixing, loading and disposal of pesticides. Other sources included back-siphoning into wells during irrigation. Most concentrations measured fell below USEPA's health advisory levels.

The U.S. Geological Survey has also initiated national programs to monitor public water supplies.

The contamination of groundwater by herbicides and nitrates is of particular concern in the north-central and eastern regions of the United States where most N, K, and P fertilizers are used and pesticide application to corn and soybeans is considerable [7]. Agricultural chemicals can be found in many of Iowa's groundwater aquifers and these commonly exhibit nitrate concentrations above the maximum contaminant limit of 10 mg/l NO_3-N (45mg/l as NO_3)[8].

Other States have reported similar problems. A study of the Columbia aquifer in the Central Delmarva peninsula, Maryland, showed that nitrates were the most common contaminants in water samples [9]. Although the aquifer serves as a major water source, many wells have been abandoned because of high nitrate concentrations. Analyses of water from 604 wells for nitrogen species (nitrate, nitrite, ammonia, and organic nitrogen) showed that over half the samples collected contained nitrate concentrations greater than 3 mg/l as nitrogen. The water quality standard of 10 mg/l nitrate was exceeded in 15% of the samples included in the study. Hydrogeologic factors are also of major importance and the Columbia aquifer in the study area lies under shallow, well-drained, unconfined flow systems where contaminant sources such as chickenhouses, fertilized fields, septic tanks, and sanitary landfills can be identified.

Specific chemical findings were summarized in 1987 in a report by the International Union of Pure and Applied Chemistry (IUPAC) Commission on Pesticide Chemistry [10]. In 1985, a report of USEPA studies [11] stated that 17 different pesticides had been detected in the ground water of 23 states. The IUPAC report stated that roughly 6500 wells of the 13 million wells in the United States contained pesticide residues. Recent surveys indicate that the problem of pesticide contamination may not be as extensive as was originally feared, although certain areas of the country are more vulnerable as a result of geological and hydrological factors, and agricultural systems.

A report from the Monsanto Agricultural Company of the National Alachlor Well Water Survey [12] contains similar data. From a total of 6 million rural, domestic wells in the areas where alachlor was used, a total of 1430 wells in 89 counties in 26 states was selected at random and water samples from these wells were analyzed over a one-year period beginning in June 1988. Five herbicides were included in the analysis: alachlor, metolachlor, atrazine, cyanazine, and simazine. Gas chromatography/mass spectrometry was used for the analysis and the detection limit was 2 parts per 100 billion. Nitrate levels were also measured in water from these wells.

Nitrate was expected to be detectable in 52.3% of the wells and approximately 5% were projected to contain nitrate in excess of the USEPA Maximum Contaminant Level of 10 parts per million (ppm). The majority were expected to contain nitrate levels generally less than 3 ppm. No herbicides were detectable in 87% of the wells tested. In 0.1% of the tested wells, herbicides were present at levels exceeding the USEPA Health Advisory Level. Atrazine was the most commonly detected herbicide and was found in 12% of the wells, generally at levels less than 0.5 ppb. Less than 0.1% of the wells were estimated to contain levels in excess of the Health Advisory Level of 3 ppb. In the case of alachlor, detectable levels were projected for 0.78% of the 6 million wells surveyed and only 0.02% were expected to contain levels in excess of the Health Advisory Guideline of 2 ppb. Similar findings were reported for metolachlor.

The European Community Drinking Water Directive (80/778/EEC) requires that no single pesticide shall exceed 0.1μg/L and the total pesticide concentration shall not exceed 0.5μg/L. The World Health Organization has proposed that a fraction of the Acceptable Daily Intake (ADI) should be allocated to drinking water. A similar approach has been proposed by GIFAP (International Group of National Associations of Manufacturers of Agrochemical Products).

A recent position paper from GIFAP [13] summarizes recent monitoring surveys and concludes that monitoring results indicated that in the majority of water samples analyzed pesticides were not detected. The report cites a study in the Federal Republic of Germany in 1986. In this study 13,000 water analyses were conducted on samples from 206 wells. Less than 0.5% contained pesticides above 0.1μg/L. The report also states that broadly similar results were obtained in surveys of both ground and surface water in France, the USA and Switzerland, with some local variations.

Typical levels of chemicals detected in these surveys are in the low or fractional parts per billion range (μg/L). In some instances, the detection of higher levels suggests that contamination originates in point sources and that in these cases the well may have been contaminated by chemical spillage, cleaning application or mixing equipment near the wellhead, or some other faulty practice.

HEALTH ADVISORIES

When the presence of pesticides and nitrates in groundwater became a major public issue, the USEPA issued drinking-water health advisories for 55 pesticides selected because of their potential for leaching to groundwater, high sales volume and potential health impacts. The Health Advisories contained information on health risks and treatment technologies [14] and specified levels of chemical concentrations in water acceptable for drinking. Examples of levels are: alachlor 0.4 μg/L; atrazine 3 μg/L; aldicarb 10 μg/L; 2,4-D 70 μg/L; diazinon 0.6 μg/L; 1,2-dichloropropane 0.6 μg/L; dieldrin 0.002 μg/L; nitrite 1 mg/L; nitrate 10 mg/L ; and ethylene dibromide 0.0004 μg/L.

Excessive amounts of nitrate in water may cause methemoglobinemia in infants [15]. This condition occurs most often at nitrate levels > 100 mg NO_3/L, but is rarely observed at 50 mg/L. In addition, the potential harmful effects of nitrite lie in its ability to react with biological nitrogenous compounds to form potentially carcinogenic N-nitrosamines and since nitrite concentration is directly correlated with nitrate content, it has been suggested that reduction of the 50 mg/L nitrate level as an upper acceptable figure would be a meaningful prophylactic measure [16]. The presence of nitrate may also indicate that other forms of contamination are present.

VULNERABILITY

Major factors in determining leaching potential are the chemistry of the active ingredient and the type of formulation, but whether leaching will actually occur will depend on the time of application, soil type, climatic factors, cultural system, etc.

A system has been described of evaluating the water pollution potential for any area in the United States. The system incorporates hydrogeological settings upon which are superimposed relative ranking factors. The concept of hydrogeologic settings is used to describe mappable units that possess common major geological and hydrological features controlling groundwater movement. The ranking system is known as the "Drastic" system and the factors included as a basis for ranking are: the depth to the water table; net recharge to the aquifer; soil media; topography of the land surface; impact of the vadose zone; and the hydraulic conductivity of the aquifer. The vadose zone is the unsaturated zone below the soil surface above the water table. The acronym "Drastic" is derived from the initial letters of the system components:

DEPTH to ground water
RECHARGE of ground water by rainfall and irrigation
AQUIFER MEDIA
SOIL MEDIA
TOPOGRAPHY (slope of land surface)
IMPACT of vadose zone
CONDUCTIVITY (hydraulic conductivity of the aquifer)

Each component is allotted a numerical rating from 1 to 10 and addition of ratings multiplied by weighting factors gives a total score that can be used to identify areas vulnerable to groundwater pollution. The higher the score, the greater the vulnerability of the area [17].

IMPACT OF SPECIFIC CHEMICALS

A number of chemical and physical criteria are used by regulatory authorities in assessing potential for leaching, including: water solubility greater than 30 parts per million: a hydrolysis half-life greater than about 25 weeks; a soil half-life that is more than 2-3 weeks; and a soil partition coefficient (k_d) value less than 5. Any one of these criteria may be reason for the categorization of the material by the USEPA as having the potential to reach groundwater [18].

PERSISTENCE OF CHEMICALS AND TRANSPORT

Pesticides are transported by water that percolates through the soil layers. The potential for chemicals to reach ground water requires an understanding of the processes influencing the water flux and the transport of chemicals through soil i.e. the physical and chemical processes that occur in the various soil zones. The root zone is the zone in which biological and chemical processes are important. Below this lies the vadose or unsaturated zone and this overlays the saturated zone. Water flow is dependent on soil structure. The relative pore sizes are important and the flow through macropores or channels formed by plant roots, soil animals or insects are mechanisms by which pesticides may be transported to depths below those at which the bulk of the applied pesticide is found.

The interaction between a chemical and the soil is dependent on the structure and reactivity of the chemical and the composition of the soil. The organic matter content of soils is important because the binding ability of soils containing considerable amounts of clay and organic matter may substantially reduce the mobility of some pesticides as compared with their movement in well-drained sandy soils.

The routes by which pesticides or fertilizers may enter surface waters are: runoff; leaching to ground water and subsequent transport to surface water; drift; volatilization during or after application; and erosion by wind or water. Volatility is a function of the vapor pressure of the pesticide. However, rates of loss by this route depend not only on temperature but also on the nature of the environmental surface. Volatilization and drift may be important routes by which pesticides are lost during application, but the extent of deposition of pesticides in rainfall, fog etc. is not known. There are few measurements but these indicate that in rainfall events a significant amount of material may be washed out [19].

Runoff is a source of loss and chemicals may be transported directly to surface water by this route. The loss due to runoff may be as much as 5% from fields of moderate slope or 2% from fields of low slope [20]. Higher losses may occur if there is heavy rainfall producing substantial runoff during the first two weeks after application.

Consideration of physical properties may indicate that a compound may have potential for leaching. However, it is also necessary to consider its susceptibility to degradation in the root zone. Diazinon, for example, is quite water soluble (40 ppm at 40°C) but it is rapidly hydrolyzed at environmental pHs. The half-life is 561 hours at pH 7 and 30°C, and at 50°C this is reduced to 76 hours. A decrease in pH of 2 units reduces the half-life to 42 hours at 30°C. Therefore it is unlikely to reach ground water because it will be readily degraded [21].

MODELS

A recent workshop report [22] lists about 60 models and data bases pertaining to water quality with brief descriptions, applicability, type, and availability. The models serve many different purposes. The Agrichemical Leaching Loss Algorithm being developed by the Economic Research Service of the USDA estimates potential pesticide loss by leaching that may result from the geographic distribution and production of major US crops. It will predict effects of changes in use of specific pesticides; regional shifts in crop production; and the effects of removing certain types of land groups from production. The CREAMS model (Chemicals, Runoff, and Erosion of Agricultural Management Systems) is a simulation model for field-size areas that will permit evaluation of alternative management practices. The Exposure Analysis Modeling System (EXAMS) is an EPA model that can be used to evaluate the fate of chemicals in a wide range of aquatic environments. The Nitrate Leaching and Economic Analysis Package (NLEAP) is designed to assess water and nitrate-N budgets for crop root zone and shallow aquifers from inputs of farm practices, soil, climate, aquifer data and economic information. It will estimate potential leaching of nitrate-N from agricultural lands and potential impacts on the quality of ground water.

The Drastic system was developed by the USEPA as a predictive tool to assess groundwater pollution potential on the basis of known factors that are readily available for most parts of the United States. Other models have been developed and applied such as the Pesticide Root Zone Model (PRZM) used to evaluate the potential of pesticides to leach through to groundwater [23]. This is a one-dimensional model that includes interactions of pesticides in surface runoff (in water and on eroded sediment), advection in percolating water, molecular diffusion, uptake by plants, sorption to soil, and chemical and biological degradation. The model was tested for aldicarb using data that had been obtained at sites in New York state, Florida, and Wisconsin [24].

Modelling depends on assumptions concerning flow processes, and requires data inputs that include the physical properties of chemicals, their interactions with soil components, their rates of degradation, etc and describes flow processes by combining the laws of conservation of mass with solute and water flux equations.

Deterministic models are limited in value by their failure to take into account flow mechanisms that serve to transport chemicals to ground water by preferential flow mechanisms (macropore flow, complexation with soil components, etc.). These pathways are randomly distributed in space and must be considered by inclusion of a stochastic component within the model [25]. A field experiment was conducted in which leaching of chemicals by sprinkler irrigation was investigated. Analysis of soil core samples showed that a fraction (20%) of the chemicals, napropamide and prometryn, did not appear to be adsorbed and was found at depths lower than any predicted by a pesticide simulation model. It was suggested that a mobile organic complex or attachment to fine colloidal particles may be responsible.

RESPONSES TO THE PROBLEM IN THE USA

In the United States, the response to the question of water quality was enunciated at the national level by President Bush's announcement of his Initiative to Enhance Water Quality. The US Department of Agriculture (USDA) and the US Geological Survey (USGS) were given specific assignments under the initiative and their research efforts were closely coordinated.

To approach the problems of contamination of ground water by pesticides and nitrogen fertilizers, the research agencies of the USDA in cooperation with other Federal and State institutions undertook a broad-ranging program to provide needed information and technology. The objectives were to improve the understanding of processes that determine agricultural productivity, and the fate and transport of agricultural chemicals. An important component of this program was the Midwest Initiative to assess the severity and extent of the ground water problem in selected corn and soybean production areas of several Midwestern States. A systems approach will then be used to determine the combinations of production practices that best satisfy the economic, environmental, and social needs of the region.

The goal of the national plan formulated by the Agricultural Research Service (ARS) of the USDA is to provide an adequate quantity of ground water of high quality in the presence of sustained agricultural activities [26]. This entails an assessment of the severity and extent of agriculture's impact on water quality and the development of new and improved agricultural systems that are cost effective and enhance ground water quality. A number of objectives have been defined:

"1) Document sources and amounts of potentially hazardous contaminants in water which are attributable to current agricultural and forestry practices, and identify the basic processes involved in their movement through soil and into groundwater.

2) Develop new field and laboratory methods for rapidly,

reliably, and inexpensively analyzing pesticide residues and for determining the rates at which water and chemicals move through soils to ground water.

3) Develop new and modified conservation-production systems that substantially decrease the movement of potentially hazardous chemicals into groundwater, and determine the effects of these new systems on farm costs, changes in farm inputs, and production choices.

4) Develop simple, inexpensive, onfarm methods for disposing of pesticide containers and wastes without contaminating groundwater.

5) Develop decision-aid systems that may be used by technical and farm management specialists, Extension agents ,and farm consultants to help individual farmers select, apply and manage profitable and environmentally sound crop production practices.

6) Evaluate the economic, social, and political impacts of alternative production systems, policies, and institutional strategies to control groundwater contamination."

The USDA announced its Midwest Research Initiative in May 1990 and stated that 5 areas overlying aquifers in 9 midwestern states had been selected. This effort will be combined with the US Geological Survey's Mid-Continent Initiative. USDA and State research institutions will focus on the upper, unsaturated part of the soil and USGS will emphasize the underlying saturated soil and the saturated groundwater system.

IMPLICATIONS

The results of surveys in Europe and the USA indicate the potential problems of ground water contamination by pesticides. Fortunately, the impact of pesticides on water quality appears to be limited to specific areas. However, the question of nitrates remains to be resolved.

In the framework of developing agricultural systems, the increased use of chemical pest control methods may offer many advantages through substantial increases in yield and reduction in labor costs. Pesticide chemicals also play an important role in improved land management, as in their use in conservation tillage systems to prevent soil erosion, weed control on railway tracks and other rights of way, rodent control, and public health programs.

However, there must be an awareness of the implications of their use for humans, animals, and the environment. Both legal and educational aspects are essential components of sound management of pesticide use. It is important to provide strong enforcement capabilities to ensure that regulations and guidelines are followed. The United States, through the Land Grant University system possesses regional extension systems whose personnel are familiar with local farming communities and practices. These contacts have created working cooperation between farmers and experienced extension workers who can recommend practices suited to local cultivation and soil systems that are not only profitable but also avoid adverse environmental impacts. Thus, the USEPA and State environmental protection authorities remain free to operate independently in their concern over environmental impacts. This reduces internal policy conflicts and actions in environmental matters can be determined after consultation with agricultural officials or other groups.

This relationship among the agricultural community and the organizations involved in environmental protection is important in serving the needs of the whole population. The question of water quality is a major issue because in most countries water is a critically important but limited resource. The success of China's agriculture has throughout history depended on effective management and allocation of water resources.

If the expansion of chemical use is not to endanger water resources, careful consideration must be given during the process of official approval of each chemical as to its potential to contaminate water, based on knowledge of its chemical structure, proposed types of formulation and application, the agricultural system in which it will be used, patterns of use, local geological, hydrological, climatic, topographical, and other factors that affect this potential.

Research in the field or laboratory may be important in establishing whether the potential for contamination is substantial and, if the chemical is to be developed for large-scale use, what techniques can be used to remedy or avoid problems. Integrated pest management programs offer promise of reduction in pesticide use. Rotational cropping systems or other cultural practices may be introduced or continued to avoid over-reliance on chemical methods of pest control. Methods of application should seek to minimize off-target loads and losses to water, soil, and the atmosphere. There should also be adequate data on dissipation of pesticides in soils according to locality, soil type, and climate. The most important factor in avoiding the potential contamination of community water supplies is the understanding of pathways of water flow and aquifer or surface water recharge pathways. This entails sound knowledge of the geological and hydrological features and a program of analysis of water from various sources. Improvements in formulation may improve efficacy and decrease mobility. Controlled-release formulations, possibly those based on locally-available raw materials (e.g. natural biodegradable polymers such as latex, starch, etc.) may be valuable in reducing mobility or improving effective use of chemicals. Above all, the chemistry of new pest control agents must be compatible with environmental as well as agricultural goals.

Fertilizers, whether of chemical or animal origin, must be managed in a conservative and rational manner. The addition of nitrogenous fertilizers will often increase crop yields in nitrogen deficient soils, but excess nitrogen that is not taken up by plants may enter ground water and contaminate wells or be lost by runoff to surface water. Erosion of soil from agricultural lands deposits sediment carrying a burden of nutrients that may affect the quality of surface waters and reduce their economic value by reducing their ability to support fish populations, or to serve as sources for irrigation or community water supplies. The issue of nitrate content of ground water is taking on greater dimensions with increased demands for water and growth in human population. Agricultural sources of nitrogen are supplemented by biological waste treatment plants, septic tanks, animal waste, etc. and these sources must be included in a management scheme that is to be effective in fertilizer management.

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THE FATE OF PESTICIDES IN PLANTATIONS AND THE DESIGN OF PARAMETERS FOR SELECTING SUITABLE PESTICIDES

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ABSTRACT

Studies on the loss or degradation of pesticides applied to the tea plant demonstrate the roles of dilution through subsequent growth, photolysis, volatilisation, elution by rainfall and thermodegradation during processing of the shoots. Infusion may extract some of the remaining residues into the beverage for consumption. Parameters for judging suitability of pesticides for use in tea plantations are embodied in an equation to provide a numerical basis for selection.

INTRODUCTION

As with other crops, control of pests by chemicals is widely used in tea plantations. Tea is an unusual crop for the following reasons. Firstly, the product of economic importance from the tea plant is the portion which is sprayed directly with the pesticide. The shoots of the tea plant are thin and tender, and the surface area per unit weight of leaf is relatively larger than with other crops (Table 1). Secondly, the tea bush is harvested several times per year. Thirdly, the interval period between the spraying date and the plucking date is shorter than with other crops, and the plucked shoots are processed directly without washing. So, in comparison with other crops, the residue level of pesticide on tea shoots is higher under the same applied dosage. Fourthly, as a beverage, the pesticide residue in the processed tea may be extracted into the infusion during the brewing process.

TABLE 1
Area-to-weight ratio of tea leaves and various vegetables

Plant	Area-to-weight ratio (cm^2g^{-1})
Cabbage leaves	18.7
Cabbage	0.8
Cucumber	0.7
Tomato	0.6
Spinach	27.7
Celery	38.2
Edible amaranth	53.9
Tea: tender leaf	41.7
Tea: mature leaf	15.9

DEGRADATIVE DYNAMICS OF PESTICIDE ON THE TEA PLANT

After pesticides are sprayed on the canopy of the tea plant, almost ail of them are degraded in two stages [1 - 8]. The first stage is the rapid degradative process dominated by the mechanism of evaporation, then followed by a slower degradative process. It can be expressed by a first-order kinetic equation: $C_t = C_o e^{rt}$, where C_t is the pesticide residue at time t (mg/kg), C_o is the initial pesticide deposit (mg/kg), r is the degradation rate constant of the pesticide (sec^{-1} or day^{-1}) and t is the time after the pesticide application (sec or day). Table 2 presents the degradation rate constant of pesticides in the tea garden and the half-life (HL_{50}) of pesticides on tea leaves. The r values of organophosphate pesticides are generally within the range of 5×10^{-6} sec^{-1} to 40×10^{-6} sec^{-1}, while those of pyrethroids are mostly lower than 4×10^{-6} sec^{-1}. The factors inducing the degradation of pesticides on the tea plant include growth dilution, photolysis, evaporation and elution by rainfall.

Growth dilution plays an important role in the degradation of pesticides in the tea garden. This is because the tea shoot has a rapid rate of growth thereby producing a diluting effect on the residual pesticide attached to the tissue of the tea shoots. According to the results of an investigation on the degradation rate of cypermethrin on shoots at different developmental stages, the degradation rate of pesticide is proportional to the growth rate of tea shoots (r = 0.98) (Table 3). The younger the shoots, the faster the growth rate and the larger the contribution of growth dilution to the pesticide degradation on the shoots. Investigation showed that growth dilution played a most significant role in the degradation of those persistent pesticides such as pyrethroids and organochlorine pesticides, where dilution contributes around 40-50% of reduction in concentration.

Sunlight is also an important environmental factor influencing the degradation of pesticides in the tea garden. According to the investigation, the photolysis rate of pesticide on the tea plant is dependent upon three factors: photo-quantum yield (ϕ) of pesticide in

TABLE 2
Degradation rate constant and half-lives of pesticides on fresh leaves

Pesticide	Degradation rate constant ($x10^{-6}$ sec^{-1})	Half-life (days)
Dichlorvos	40.1	0.20
Phoxim	33.3	0.24
Trichlorfon	23.6	0.34
Malathion	21.6	0.37
Fenitrothion	16.0	0.50
Dimethoate	8.50	0.95
Phosmet	6.90	1.15
Quinalphos	5.78	1.39
Cypermethrin	3.20	2.50
Permethrin	2.98	2.70
cis-Cypermethrin	2.77	2.90
Fenvalerate	2.59	3.10
Deltamethrin	2.48	3.20
Bifenthrin	2.54	3.20
Cyhalothrin	2.36	3.40
Dicofol	2.08	3.85

TABLE 3
Degradation rate constant of cypermethrin on tea shoots at different developmental stages

Growth stage	Growth rate constant of tea shoot (day^{-1})	Degradation rate constant of cypermethrin on tea shoots (day^{-1})
Bud	0.159	0.292
Bud and 1 leaf	0.131	0.214
Bud and 2 leaves	0.084	0.202
Bud and 3 leaves	0.070	0.142

solid state, extinction coefficient of pesticide ($A\lambda$) and irradiance intensity of sunlight($Eo\lambda$). The former two factors are physical properties of a pesticide, and the last factor is an external environmental factor. The quantum yield represents the fraction of photons absorbed that result in photoreaction and can be estimated in the laboratory [9]. The extinction coefficient reflects the adsorptivity of pesticide to various wavelengths of the light source and can be estimated by spectrophotometer. The irradiance intensity of sunlight is variable at different latitudes and seasons; it may be obtained from Bener's information (1972) [10]. Table 4 lists the φ value of 8 pesticides in solid state. The photolysis rate constant (kp) can then be obtained by the following equation:

$$K_p = 2.303 \cdot \varphi_{313} \frac{M}{J \cdot W} E_{o\lambda} A_\lambda$$

where M is the molecular weight of pesticide, J is the Einstein constant (6.023×10^{-23} photon $Einstein^{-1}$), $E_{o\lambda}$ is the irradiance intensity of sunlight (photon cm^{-1} wavelength $distance^{-1}$) and W is the mass of pesticide used in the estimation of extinction coefficient (g cm^{-2}).

TABLE 4

Photolysis rate constant and quantum yield for photolysis of solid-phase pesticides under 313nm monochromatic light

Pesticide	Photolysis rate constant (hr^{-1})	Photo-quantum yield (φ_{313})
Fenvalerate	0.20100	0.09390
Dimethoate	0.00153	0.05020
Dicofol	0.01324	0.04510
Buprofezin	0.00286	0.03820
Cypermethrin	0.60230	0.03010
Malathion	0.00415	0.01980
Quinalphos	0.04500	0.00091
Parathion-methyl	0.04500	0.00075

Volatilisation is another important factor causing the loss of pesticides, especially those which possess a higher vapour pressure (v.p.). Under the environmental condition of high air temperature, the rate of evaporation can be expressed by the following equation: $K_E = C.VP.\sqrt{M}$ where K_E is the rate of evaporation, C is the constant which depends on the mobile state of the atmosphere in the system, VP is the vapour pressure of pesticide and M is the molecular weight of pesticide. So, in the same system, for pesticides which have a similar molecular weight, the rate of evaporation depends mainly on the vapour pressure. Table 5 presents results from an investigation on the evaporation rate constant of different pesticides in a phytotron. These show that the larger the vapour pressure, the more pesticide is evaporated.

Rainfall elution is important during the first few days after application, for those pesticides which have a high water solubility. An experiment with simulated rainfall on various pesticides with different water solubilities proved that the rate of rainfall elution is closely related to the water solubility of pesticides. In addition, the rate of elution is negatively correlated with the interval between the time of spraying and onset of rain [11].

TABLE 5
Relationship between vapour pressure of pesticides and evaporation rate constant

Pesticide	Vapour pressure (mbar)		Evaporation rate constant (hr^{-1})	
			30°C	40°C
Dichlorvos	1.2×10^{-2}	(20°C)	3.8340	10.4450
Fenitrothion	1.6×10^{-4}	(25°C)	0.1230	0.2034
Malathion	3.2×10^{-4}	(25°C)	0.0314	0.1387
Quinalphos	3.0×10^{-4}	(25°C)	0.0304	0.1306
Dimethoate	3.0×10^{-5}	(25°C)	0.0180	0.0995
Bifenthrin	1.8×10^{-7}	(25°C)	0.0019	0.0133
Fenvalerate	2.8×10^{-7}	(25°C)	0.0004	0.0006
Cypermethrin	3.2×10^{-8}	(25°C)	0.0002	0.0007

DEGRADATION OF PESTICIDE RESIDUES DURING THE MANUFACTURING PROCESS

Tea shoots are the harvested portion of the tea plant. After plucking, the fresh shoots must pass through a manufacturing process. According to the investigation on more than 30 pesticides, the residual pesticides in or on the fresh tea leaves are mainly degraded via evaporation and thermodegradation during the manufacturing process. Those pesticides with high vapour pressure have a higher degradation rate [5, 6, 8]. For example, the VP value of dichlorvos, naled, fenitrothion, malathion, phoxim and quinalphos are within the range of 10^{-2} to 10^{-4} mbar, and the degradation rates of these pesticides are as high as 60-80%. Pesticides such as phosmet and parathion are intermediate (10^{-5} mbar), so their degradation rate is decreased to the range of 40-60%. With those pesticides such as DDT, permethrin, dicofol, deltamethrin, alpha-cypermethrin, bifenthrin, fenvalerate and cypermethrin which have a low VP value (10^{-6} - 10^{-8} mbar), the degradation rates are only around 20-30% (Table 6).

EXTRACTIVE CAPACITY OF PESTICIDE DURING TEA INFUSION PROCESS

When infused with boiling water, pesticide residues contained in processed tea are partly degraded by the high temperature of the water and partly dissolved in the infusion which is to be drunk by humans. The amount of pesticide extracted into the tea infusion depends on the water solubility of the pesticide. The extractive percentage of pesticides with higher water solubilities (such as dimethoate and malathion) reached as high as 80-90%. Pesticides with lower water solubility (such as pyrethroid insecticides and DDT) have a relatively low percentage extracted (Table 7).

TABLE 6

Percentage degradation of pesticides on fresh tea leaves during processing (data derived from several experiments)

Pesticide	Degradation (%)	Standard deviation	Number of replicates
Cyhalothrin	12.1	7.1	11
Deltamethrin	20.3	12.2	38
Fenvalerate	22.8	9.4	36
Cypermethrin	22.8	16.9	19
Bifenthrin	24.6	8.3	16
Permethrin	26.2	9.7	17
DDT	29.0	9.4	15
Dicofol	35.3	9.2	5
Quinalphos	52.6	12.0	22
Phoxim	53.8	12.1	9
Dimethoate	61.1	12.8	14
Fenitrothion	65.8	4.7	8
Omethoate	67.0	12.9	11
Malathion	67.9	11.6	8
Chlordimeform	71.1	18.9	7

TABLE 7

Relation between percentage extraction of pesticides in tea infusion from processed tea and water solubility of pesticides

Pesticide	Water solubility (mg l^{-1})	Extractability of pesticide during infusion process (%)
pp - DDT	0.001	1
Cyhalothrin	0.005	2.9
Permethrin	0.040	2.9
Cypermethrin	0.041	1.8
Deltamethrin	0.1	1.2
Dicofol	0.1	2.2
gamma-BHC	7.0	6.5
Quinalphos	22.0	40.4
Fenitrothion	30.0	70.9
Malathion	150	86.3
Dimethoate	25000	98.3

DESIGN OF PARAMETERS FOR SELECTING SUITABLE PESTICIDES FOR TEA PLANTATION USE

Principles of Suitability Assessment

The results presented above show that from being applied on the tea plant to being taken up by the human, pesticide degradation mainly occurred in three stages: growth of the tea plant, tea processing and tea infusion. The amounts of pesticide residue in fresh tea leaves at a specified time can be expressed as

$$C = C_0 . e^{-0.69(t\frac{1}{2})^{-1}.t} \quad (1)$$

where C is the concentration of pesticide residue (mg kg^{-1}) in fresh tea leaves at time t (days) after spraying, C_0 is the original pesticide concentration and $t_{1/2}$ (days) is the half-life of pesticide on the tea plant. When fresh tea leaves are processed, 20-80% of pesticide on tea leaves can be lost. When the processed tea is infused with boiling water, only a part of the residue in processed tea can be dissolved in the infusion, which is the very part to be taken in by the human. The amount of pesticide taken by the human through tea drinking (C') can be expressed as:

$$C' = C.f_1.f_2.W \quad (2)$$

where f_1 is % of residue left on tea after processing, f_2 is the % of residue entering the tea infusion from the manufactured tea and W is the consumption of tea (kg) per capita per day.

The principle for assessing pesticide suitability for tea plantation use from the viewpoint of safety to the consumer is that the amounts of pesticide taken by the human through tea drinking should be less than the acceptable daily intake value (ADI), i.e.

$$C' < ADI.W'.f_3 \quad (3)$$

where W' is the average human body weight (kg) and f_3 is the % of tea in the total diet.

Model Development

Combining equations (1), (2) and (3), and taking W,W' and f_3 as 0.01kg, 60kg, and 0.5% respectively, then the equation for pesticide suitability assessment is obtained:

$$\ln C_0 + (-0.69.t\frac{1}{2}).T + \ln f_1 + \ln f_2 + (\ln ADI) < 3.4 \quad (4)$$

The minimum interval between pesticide application and harvest (T) can be calculated according to equation (4), provided all the five variables in the equation are known. Ordinarily, the interval period should not be longer than 10-14 days in the tea garden. In other words, all pesticides with T value larger than 10-14 are not suitable for tea plantation use. According to the results of research already performed, C, f_1 and f_2 can be predicted by pesticide application dosage, vapour pressure and water solubility of pesticide respectively. For the purpose of simplifying the pesticide suitability assessment, five parameters are suggested based on the research results and equation (4):

TABLE 8

Quantitative relation between suggested parameters and corresponding items in equation (4)

D ($g\ ha^{-1}$)	lnC_o	t1/2 (day)	$-6.9t1/2^{-1}$	VP (mbar)	lnf_1	SW ($mg\ L^{-1}$)	lnf_2	ADI ($mg\ kg^{-1}$ day)	ln ADI
5	0.5	0.5	-14	10^{-7}	-0.1	1	-4.5	0.1	2.5
50	2.5	1.5	-4.5	10^{-6}	-0.5	5	-3.0	0.01	4.5
500	4.0	3.0	-2.5	10^{-5}	-0.7	20	-1.5	0.005	5.5
5000	4.5	5.0	-1.5	10^{-4}	-1.2	100	-0.5	0.001	7.0

ln = natural logarithm

D - dosage of pesticide used in tea garden (g ha^{-1})
$t_{1/2}$ - half-life of pesticide on growing tea plant (day)
VP - vapour pressure of pesticide at room temperature (mbar)
SW- water solubility of pesticide at room temperature (mgL^{-1})
ADI - acceptable daily intake value of pesticide (mg kg^{-1} day)

Table 8 gives a quantitative relationship between the values of the five parameters and the value of the corresponding terms in equation (4). Suitable pesticides for tea plantation use should be those with low application dosage, low to medium persistence, high vapour pressure, low water solubility and high acceptable daily intake. Among the five parameters, $t_{1/2}$ plays the most important role in deciding pesticide suitability, for its value range from -1.5 to -14, is much larger than the range of the other four parameters.

Among the five parameters, four of these can be obtained from a handbook [10] or literature; only $t_{1/2}$ needs experimental work. When all the five parameters are known, the value of corresponding terms in equation (4) can be obtained from Table 8. If the accumulated value of the five terms is larger than 3.4, the pesticide is not suitable for tea plantation use. As mentioned above $t_{1/2}$ is the only unknown parameter. However, a prediction on $t_{1/2}$ can be made which is that no pesticide can have a $t_{1/2}$ on the growing tea plant longer than 7 days, because the volume and weight of the tea shoot will double within 5-7 days. This is useful for assessing the suitability of pesticides whose $t_{1/2}$ is unknown. For example, in the case of carbaryl whose $t_{1/2}$ on the tea plant is unknown, the value of the five parameters is as follows:

$$D = 500, t_{1/2} = 5, VP = 10, SW = 1, ADI = 0.01$$

In accordance with Table 8, the calculated value of the assessment is 1.3, smaller than the value of 3.4. Thus, the suitability of carbaryl for tea plantation use, from the view point of safety to the consumer, should not be in doubt.

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COMPARATIVE STUDIES ON PESTICIDE RESIDUES IN SOILS, WATER AND VEGETABLES IN INDONESIA AND JAPAN

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ABSTRACT

As an aspect of the cooperation on Crop Protection Studies in the Framework of Agroecosystem between Indonesia and Japan, residue levels of two major groups of insecticides, organochlorine and organophosphorus insecticides, in soils, river water and vegetables in Indonesia and Japan were compared. Since many data of pesticide residues in crops and the environment in Japan have already been published, the pesticide analysis was focused on materials from Indonesia. Soil samples were collected from fields of rice, soybean, potato and several kinds of vegetables and from forests and ruins in South Sumatra, Central Java and Bali Island. River water samples were collected from a stream over its whole length between mountain and sea. Vegetables (cabbage, tomato and cucumber) were obtained from a market in Yogyakarta. Diazinon, fenitrothion, BHC isomers, DDT isomers, aldrin, dieldrin and endrin in these samples were analyzed at ppb to ppt levels using simplified methods. DDT and other organochlorine insecticides were found at high concentration in vegetables and in some soils, compared to those in Japan. Diazinon was also detected at considerable levels in all vegetable samples and in soils.

INTRODUCTION

Pests have been recognised as one of the most important constraints in food crop production. Even though many pest control methods have been developed and applied for the last two decades, pest control has been largely dependent on organic pesticides.

In Indonesia, the use of pesticides has been increasing very rapidly. In the last 10 years the total amount of pesticides distributed to farmers for the intensification program has increased six times. In the 1980/81 and 1981 crop season about 9,000 tons of insecticides, 2,500 t of fungicides and 75 t of rodenticides were distributed for crop protection [1]. Also, though DDT is approved only for malaria vector control, a great deal is distributed to the agriculture sector. At present about 430 pesticide formulations are allowed for commercial use. Insecticides represent the major portion of pesticides, with organophosphorus and carbamate compounds much utilized for control of pest insects, particularly those of rice. In Indonesia fungicide use is still limited to vegetables and some estate crops. Though less in quantity, herbicides are increasingly used, mainly for estate crops in some places where labour shortage is critical. The amount of pesticides applied is expected to increase rapidly in the near future.

In Japan, about 350 compounds and 5,300 formulations are registered as agricultural pesticides at present. About 90,000 t of active ingredients and 600,000 t of formulations were produced in 1983 [2] and approximately the same amount of pesticides was applied to 5 million ha of arable land in Japan. Thus Japan is one of the countries where the largest quantity of pesticides is sprayed per unit area of arable land.

In Indonesia, although the national average use of pesticides per farmer or per ha is low, the use of pesticides creates some alarming situations in some locations ;and with some crops. A number of cases of pesticide poisoning have occurred among users and workers. Other side effects, e.g., poisoning of people from accidental contamination of foodstuffs; environmental pollution, particularly reduction of inland fish; development of pest resistance to pesticides (though not serious at present); and resurgence of pests, also occurred.

Pesticide residue analysis in water, soils, crops and foods is the first step in monitoring the impact of pesticides on human safety and the environment and for providing guidance for appropriate pesticide use in an overall strategy of integrated pest management. However, the techniques and instrumentation for pesticide residue analysis require much sophistication, and incorrect data will endanger our safety when underestimated, or cause over-regulation of pesticide use when overestimated, resulting in loss of social benefit. The state of the art of residue analysis in Indonesia is insufficient at the moment.

In these present situations, our team from Indonesia and Japan on Crop Protection Studies in the Framework of Agroecosystem took up the residue problems of pesticides in crops and the environment, as one of our cooperative studies. Most of our analytical research has have been carried out with material from Indonesia, since much data on pesticide residues in Japan have already been accumulated.

A part of our study was carried out to develop a simplified and economical analytical method for pesticide residues, because the supply of analytical instruments and other materials such as gas chromatographs, glassware, organic solvents and other reagents is not fully sufficient in some institutions in some areas in Indonesia as well as in many developing countries.

MATERIALS AND METHODS

Research in 1982 (Preliminary research)

To ascertain approximate levels of pesticide residues in the environment in Indonesia, preliminary research was carried out in 1982.

Soil samples were collected from soybean fields in Lampung, rice fields mainly in Bali, and other fields and forest in Bali and Central Java. Sampling methods were the same as in the main research in 1984 described below.

Soil samples were partially air-dried, brought to Japan and analyzed one to two months after sampling, because the analytical equipment was not yet established in our cooperative institutes in Indonesia.

The method of pesticide - residue analysis was approximately the same as that of the main research in 1984 described below.

Research in 1984 (Major part of the research)

Sampling. In Central Java soil samples were collected from Dieng Plateau, Wonosobo in Central Java and from a teak forest nearby, from a depth of 0-5cm and 5-10cm as follows:

A: Upland field soils collected from "UPP Intensifikasi Tembakau Rakyat" Kledung, Parakan, Temmanggung. The crop rotation pattern was tobacco-corn-potato. Pesticide used was formothion ('Anthio' 1l/ha), 15 days after planting and every 15 days thereafter. All pesticide application was stopped 30 days before harvesting.

B: Peat soil collected from Ardjuna Temple Plateau, north of Wonosobo. Soil in a potato field was also sampled. The pesticides used were 'Xantilin', permethrin ('Ambush'), 'DDT Super', and all pesticide application was stopped 3 months before harvest.

C: Upland field soils collected from Kejajar, in front of SD Patak, Banteng, north of Wonosobo. The crops were cabbage and potato and the pesticides used were propineb ('Antracol'), and mancozeb (manzeb) and DDT.

D: Teak forest soil collected from Simpen, south-west of Wonosobo.

The vegetable samples were randomly collected from the Yogyakarta city market. Cabbage, tomato and cucumber were analyzed.

On Bali Island soil samples were collected from Candi Kuning and the Botanical Garden in the mountain area of Bali. Water samples were collected from the Yehho river.

E: Soil collected from a botanical garden near a summit.

F: Pine forest soil collected near a botanical garden.

G: River water samples were collected from river near Penabel, Tabanan village and near Denpasar.

Analysis

1) Reagents: The standards of pp'-DDT, op'-DDT, pp'-DDD (TDE), pp'-DDE, α, β, γ-BHC, aldrin, dieldrin, endrin, heptachlor-epoxide, fenitrothion and diazinon were purchased from Gaschromato Kogyo Inc.

2) GC analysis: for organochlorine pesticides a GC-7A equipped with ECD (63Ni) was used, with a glass column (2m x 3mm id) packed with mixture of 1.25% OV 17/1.5% DC QF-1 on chromosorb W(AW-DMCS). Column temperature was 230°C. Carrier gas was helium 40ml/min. For organophosphorus pesticides a GC-7AG equipped with FPD was used, with a glass column (1m x 3mm id) packed with 5% OV 17 on chromosorb W(AW-DMCS), column temperature 215°C

3) Extraction and purification:

a) Soil: Fifty g of wet soil were weighed, put into a glass bottle, and acetone (100 ml x 2) added. The mixture was shaken for 30 min. and then filtered through a glass filter by suction. The filtrate was evaporated in a rotary evaporator and the residue transferred quantitatively with 8ml of n-hexane to a glass stoppered reaction tube, to which sodium sulfate was added. After keeping overnight the n-hexane solution was transferred quantitatively to a 10ml volumetric flask and the volume was made up with n-hexane. The n-hexane solution was subjected to a glass chromatograph.

b) Water: Five l of water sample were filtered through a SEP-PAK C18 cartridge (Waters LTD), and the cartridge then washed with 5ml of acetone. The eluate was analyzed by a gas chromatograph equipped with EFD or FPD directly.

c) Vegetables: About 125g of cabbage, 250g of cucumber and tomato were weighed. 200ml of acetone was added to each sample and blended for 2-3 min. The mixture was filtered through a glass filter with suction. The residue was blended once again with 150 ml of acetone and filtered, then washed with 50ml of acetone. The combined filtrate was quantitatively transferred to a separatory funnel and 25g of sodium chloride was added. The mixture was extracted three times with 40ml of benzene. The benzene layer was evaporated and the residue was dissolved with 10 ml of n-hexane. The n-hexane solution was then cleaned up in a Florisil column topped with anhydrous sodium sulfate. The clean-up was carried out with a mixture of n-hexane and ether (10:1) until about 125ml eluate was collected.

The eluate was evaporated in vacuo, and the residue was dissolved in n-hexane and transferred quantitatively into a 10ml volumetric flask. The n-hexane solution was subjected to a gas chromatograph with ECD.

RESULTS

The results of the main research in 1984 for the residue analysis of DDT, its related compounds and other organochlorine compounds in soils and vegetables of Central Java are presented in Table 1.

Residue levels of DDT together with its related compounds in potato and cabbage field soils of Ardjuna Temple Plateau were detected to levels of 0.6 and 1.6ppm respectively. In a potato field of Kejajar, a level of 2.04ppm at 0-5cm and 0.76ppm at 5-10cm were detected in the soil. The residual amount in forest soil was at a low level of 0.6 ppb. Residual amounts of BHC and its related compounds in soil were also detected at low levels. At the UPP Intensifikasi Tembakau of Kledung, 0.067 ppm of α - BHC and 0.036 ppm of γ - BHC were detected. Dieldrin was detected at a level of 0.22 ppm in soil of a potato field at Kejajar and heptachlor-epoxide at 0.04 ppm in soil after harvest of cabbage at Kledung. As an example, the gas chromatogram of organochlorine insecticides in soil of a potato field at Kejajar is shown in Figure 1.

DDT and its related compounds and organochlorine insecticides were detected at levels of 1 ppb to 50 ppb in cabbage, tomato and cucumber from the central market 'Sriwedani' in Yogyakarta. Amongst these, DDT and its related compounds were detected at a level of 0.028 ppm in cabbage. 0.03 ppm of heptachlor-epoxide was found in cucumber.

Residual amounts of DDT, its related compounds and other organochlorine insecticides in soils and water in Bali Island are listed in Table 2.

Heptachlor-epoxide, dieldrin, β-BHC and γ-BHC were detected at levels of 9, 0.3, 11 and 5 ppb respectively in the Botanical Garden. Forest soil was contaminated by heptachlor-epoxide at 11 to 17 ppb. op'-DDT, pp'-DDT, γ-BHC, BHC were detected at 0.4 ppb or less in the soil samples analyzed.

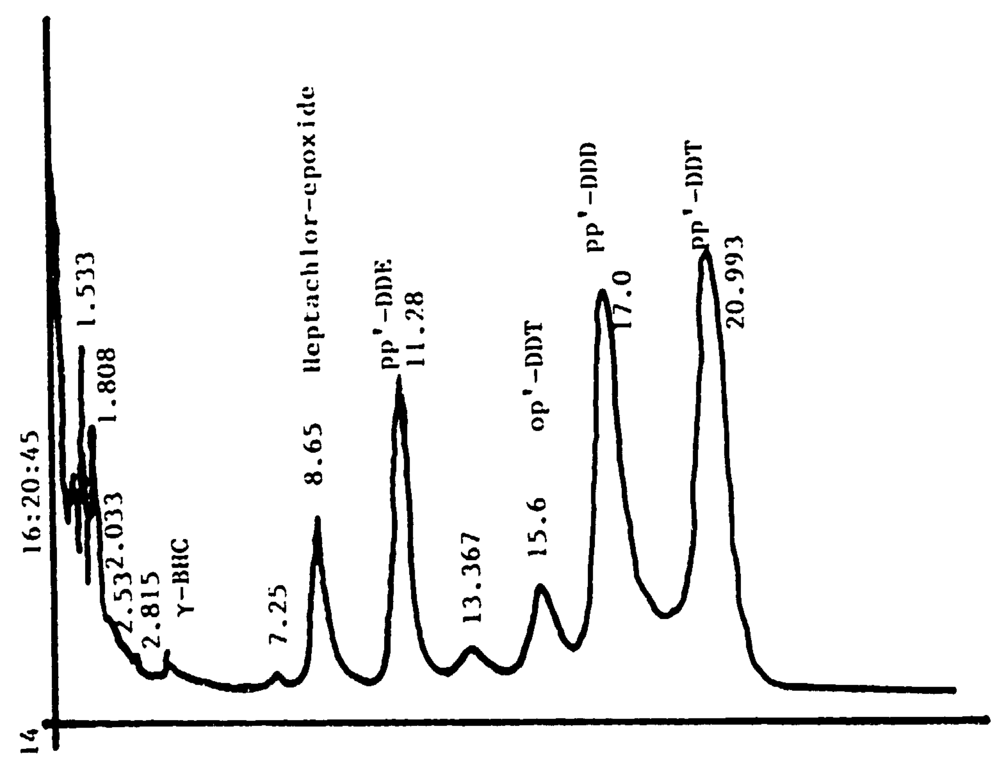

Figure 1. Gas chromatogram of chlorinated compounds in soil of a potato field at Kejajar.

TABLE 1
Pesticides in soil and vegetables in Central Java

Central Java, Jogjakarta-Wonosobo area: Unit: ppb

	α-BHC	β-BHC	γ-BHC	Aldrin	Dieldrin	Hept-E†	Endrin	pp'-DDT	pp'-DDE	op'-DDT
[A] Tobacco field soil										
After harvest	67.0		36.0			40.0		34.0	26.0	9.0
Cabbage growing	0.9		2.0	0.04	0.07	6.0	1.0	11.0	5.0	3.0
[B] Dieng plateau										
Ardjuna Temple:										
Ruin field peat soil		0.66	0.06						0.69	
Ruin field peat soil			4.0	3.0		26.0	0.37*		0.001	0.8*
Potato field soil	6.0	4.0	2.0	0.85*	5.0	4.0	3.0	365	131	104
Cabbage field		4.0	4.0	0.41	25.0	9.0	2.0	1041	214	366
[C] Potato field soil										
At harvest 0-5cm	30.0		3.0		218	10.0	2.5	1336	183	523
5-10cm			2.0		2.0	19.0		534	77	144
[D] Teak forest soil		0.06	0.008		0.02	0.005		0.002	0.001	0.001
Yogyakarta city market										
Cabbage	5.6	0.5	0.5		1.0			11.9	7	9
Tomato	5.0	14.0	7.0	3.0	0.11*	1.0		11.9	6.0	2.0
Cucumber	3.0		51.0	0.1		27.0		3.0	3.0	

*ppt †Heptachlor-epoxide

TABLE 2
Pesticides in soil and riverwater in Bali Island

Bali Island, from mountain top to coast:			Unit: ppb
[E] Botanical garden soil near summit:	0 - 5 cm	heptachlor-epoxide	9
		dieldrin	0.3
	5 - 10 cm	α-BHC	11
		γ-BHC	5
[F] Forest soil near botanical garden:	0 - 5 cm	heptachlor-epoxide	17
	5 - 10 cm	γ-BHC	0.06
		heptachlor-epoxide	11
		dieldrin	0.4
		endrin	0.453
		op'-DDT	0.4
		pp'-DDT	0.117
[G] In water:			
Location 1 (stream near Penabel village, before entering paddy)		γ-BHC	0.004
		β-BHC	0.009
Location 1 (before entering paddy)		aldrin	0.007
Location 1 (before entering paddy)		pp'-DDE	0.009
Location 2 (stream near Penabel from paddy)		γ-BHC	0.044
		β-BHC	0.046
Location 3 (stream near Tabanan village)		γ-BHC	0.055
		aldrin	0.006
		pp'-DDE	0.003
Location 4 (stream near Denpasar)		γ-BHC	0.034
		β-BHC	0.094
		aldrin	0.015

In water, pp'-DDE, aldrin, β-BHC and γ-BHC were detected in the Yehho river in Penabel and Tabanan village. The highest residual amount of BHC-related compounds in river water was 0.09 ppb of β-BHC detected in the sample taken near Denpasar. Aldrin and op'-DDT were found at 0.015 ppb or less.

Residual amounts of diazinon and fenitrothion in soil and river water in Central Java and Bali island are listed in Table 3. Diazinon was detected at around 1ppb in soil at UPP Intensifikasi Tembakau, Kledung, Ardjuna Temple Plateau and Kejajar in Central Java. Fenitrothion was detected at 3 ppb only in field soil at Kejajar. In cabbage, tomato and cucumber only about 0.4 ppb of diazinon was found. In Bali, diazinon was detected at a level of only about 0.2 ppb in Yehho river from Penabel village to Denpasar.

The results of the preliminary study in 1982 are shown in Table 4. Organophosphorus and organochlorine insecticides other than those shown in Table 4 were not detected at 0.05 ppb level. The values of the residue levels of the insecticides shown in the table, especially organophosphorus insecticides, may indicate smaller values than the real residue levels, because the soil samples collected were dried to be taken to Japan and analyzed several months later. Most of the soil samples contained BHC-isomers and DDT and its related compounds although the residue levels were not so high. DDT contents were relatively high in some particular fields of soybean and vegetable. This may mean than DDT is still being applied to some arable fields. Even in a natural forest in the Botanical Garden in Bali, DDT was detected in the surface soil.

DISCUSSION

Organochlorine insecticides are very persistent, particularly in upland soil. The orde[illegible] persistence of organochlorine insecticides in upland fields is dieldrin > DDT > BHC > chlordane > heptachlor-epoxide > aldrin. Residual amounts of DDT and its related compounds in soils of vegetable fields were relatively high in Central Java.

BHC analogues left much more residue in crop field soils than in forest soil, and the other organochlorine insecticides were also detected in vegetable field soils. In central Java, the Wonosobo area was still using DDT and organochlorine insecticides to control vegetable insects, and farmers used crude organochlorine insecticides intensively. The vegetables collected from the central market 'Sriwedani' Yogyakarta mostly came from the Wonosobo area.

As for Bali Island, the organochlorine insecticides were detected at low levels in soils rather than in river water. BHC-related compounds were more often detected than DDT and its related compounds, endrin and aldrin.

The organophosphorus insecticides, diazinon and fenitrothion, were detected mainly in Central Java. Diazinon was detected in many places in Central-Java but fenitrothion was only found in potato field soils. In Bali Island, diazinon was only detected in river water. The organophosphorus insecticides were found to decompose rapidly in tropical and sub-tropical areas.

In Japan, the use of the persistent pesticides such as DDT, BHC, dieldrin, aldrin and endrin as well as toxic pesticides such as organomercury fungicides and several organophosphorus insecticides and the water-polluting pesticides such as pentachlorophenol, endosulfan and others, were prohibited or limited by regulation after 1971 by the pesticide regulation la[illegible]. After 1970, the residue levels of the persistent organochlorine insecticides in crops, water and soil have been monitored in many places. In the same way, the

TABLE 3

Residual amounts of diazinon and fenitrothion in Indonesian soils and waters

Central Java, Jogjakarta -Wonosobo area

	Diazinon	Fenitrothion
Dieng plateu		
Ruin field peat soil	1.1	ND
Potato field soil (5-10cm)	1.6	ND
Cabbage field (0-5cm)	1.1	ND
Tobacco field soil		
After harvest	0.4	ND
Cabbage growing	0.7	ND
Potato field soil		
At harvest 0-5cm	0.9	3.3
0-10cm	1.0	1.1
Teak forest soil	ND	ND
Jogjakarta city market		
Cabbage	0.5	ND
Tomato	0.3	ND
Cucumber	0.4	ND

Bali Island — Unit: ppb

	Diazinon	Fenitrothion
Botanical garden		
0-5cm	ND	ND
5-10cm	ND	ND
Forest soil (near botanical garden)		
0-5cm	ND	ND
5-10cm	ND	ND
In water:		
Stream near Penabel village, before entering paddy		
Location 1	ND	ND
Stream near Penabel village, from paddy		
Location 2	0.1	ND
Stream near Tabanan village		
Location 3	0.3	ND
Stream Near Denpasar		
Location 4	0.2	ND

TABLE 4
Residual amounts of pesticides in Indonesian soils (unit: ppb)

	Diazinon	Fenitrothion	α-BHC	β-BHC	γ-BHC	δ-BHC	pp'-DDT	op'-DDT	pp'-DDE
Lampung-Soybean fields (0-10cm deep)									
1	1.0	1.2	0.6	2.3	0.9	1.8	20.6	1.6	9.4
2	-	-	0.4	2.6	1.2	2.4	11.7	0.6	4.9
3	-	-	2.1	2.7	1.1	2.1	22.0	1.2	8.3
4	-	-	0.3	0.8	-	-	-	-	1.9
5	-	-	0.7	0.6	-	-	-	-	1.0
6	-	-	0.2	1.4	0.5	1.8	0.3	-	0.7
7	-	-	0.4	0.7	0.4	0.9	-	-	0.6
Jogjakarta-No.11 (sugar cane), No.12 (rice), No.13 (peanut field), No.14 (ruin, 0-10cm deep)									
11	0.5	-	0.1	0.5	0.1	1.1	8.3	0.6	9.4
12	-	-	0.2	0.3	0.1	0.2	3.7	0.3	3.5
13	-	-	0.1	0.6	0.3	1.9	3.4	-	1.5
14	-	-	0.2	0.5	-	1.6	1.1	-	0.4
Bali-Rice fields, except No.22 (bamboo forest), No.23 (natural forest) and No.24 (carrot field)									
21 (0-10)	1.2	-	0.3	0.2	-	-	-	-	-
22 (0-10)	-	-	0.4	1.8	0.8	1.4	-	-	0.7
23 (0- 5)	-	-	-	-	-	-	6.0	-	4.6
(5-10)	-	-	0.4	3.1	1.2	2.6	0.6	-	0.9
(10-15)	-	-	0.6	8.0	0.7	1.3	-	-	1.1
24 (0- 5)	-	-	0.5	0.1	-	0.6	14.0	-	8.7
(5-10)	-	-	0.3	0.9	1.1	0.8	18.3	0.8	4.4
(10-15)	-	-	0.4	1.4	0.7	1.3	6.6	0.6	2.5
25 (0- 5)	2.2	-	0.9	0.6	0.1	-	-	-	0.7
(5-10)	0.7	-	1.2	3.0	0.5	1.3	-	-	0.9
26 (0- 5)	1.6	-	1.5	3.2	1.3	1.8	0.6	-	1.3
(5-10)	1.3	-	1.5	3.3	0.1	2.7	0.6	-	1.2
27 (0- 5)	2.0	-	1.6	3.5	1.8	3.2	0.3	-	1.5
(5-10)	1.5	-	3.5	3.9	1.3	11.6	0.6	-	1.4
28 (5-10)	0.5	-	2.5	11.5	1.2	2.4	-	-	1.0
(5-10)	-	-	2.2	2.7	1.0	2.4	-	-	0.9
- less than	0.5	0.5	0.09	0.09	0.09	0.09	0.1	0.1	0.09

persistence of all pesticide chemicals in crops and soil must be made clear for registration, and persistent pesticides could not be registered after 1971.

In 1974, the residual amounts of DDT and BHC ranged from 1 to 100 ppb level and from 1 to 1000 level, respectively, in paddy field soils, and 0.001 - 0.01 ppb and 0.01 to 1 ppb, respectively in river water [4, 5]. The average BHC residue in rice grains was about 0.15 ppm as total BHC at the end of the 1970s [6]. Aldrin is transformed to dieldrin in the environment. The residue tolerance level of dieldrin expressed as the sum of aldrin and dieldrin in crops is very low at 0.02 ppm because of its high toxicity. In 1969, the levels were defined for 12 crops [6]. The residual amounts of the sum of dieldrin and aldrin in soil of upland fields were about 0.5 ppm on an average.

After the use of these persistent insecticides was stopped in 1971, the residual amounts in the environment have decreased gradually. The half life of these insecticides is estimated to be about one month in soil of upland fields. BHC and DDT are degraded more rapidly in paddy fields than in upland fields.

In 1980, dieldrin was not detected at more than the detectable level (0.5 ppb) in most arable soils [7]. In our research in 1981, the amount of dieldrin was detected at less than 0.1 ppb in upland soils and from 0.2 to 3.5 ppb in sediments in river and sea, and at 0.008 ppb in rain water. The results indicated that the diversion of dieldrin into the environment seemed to have been almost completed by the present time. The residual amounts of DDT and BHC in the environment are thought to be less than that of dieldrin, because most of the data have shown that these were in undetectable amounts.

Many studies have reported that pesticides in soil are degraded more rapidly at higher temperature and that pesticides in field soil disappear faster in warmer areas. However, it is very difficult to find data on the rate of decrease of pesticides in field soil in tropical countries, although we can easily find a huge number of such data from research in temperate areas. Study of the fate and behaviour of pesticides in the environment in tropical countries is thought to be an urgent problem. Finally, it may be added that the amounts of DDT and BHC in the air and sea water near the countries of Indonesia, Philippines and Thailand are several times higher than those near Japan in these years [8].

CONCLUSION

In Indonesia, residue levels of DDT and other organochlorine insecticides were found to be quite high in vegetables and soils, some being beyond the level of tolerance. Low levels or no residual amounts of organophosphorus insecticides were detected in the same samples. It is clear from these results that use of organochlorine insecticides should be minimized or avoided. However, studies on the fate and behaviour of such compounds in tropical areas are not yet adequate. It is also important to carry out comparative studies on the residue problems of pesticides in both tropical and temperate areas.

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INTEGRATED PEST MANAGEMENT IN COTTON WITH SPECIAL REFERENCE TO HELIOTHIS AND BEMISIA CONTROL

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ABSTRACT

Among the cotton growing countries in the world, India has the largest acreage under cultivation (7.9 million hectares) but the yields are lowest (276 kg ha^{-1}) when compared to countries like Israel and Egypt. One of the major constraints in increasing the yields is the damage and losses caused by insect pests. In the late 1980s whitefly, (*Bemisia tabaci* Genn.) and the American bollworm (*Heliothis armigera* Hubner) occurred in pest proportions and devastated the crop. Farmers, in spite of plant protection measures, could not harvest more than 2 to 3 quintals/acre even though they cultivated high yielding varieties and adopted essential agronomic practices.

Both these insects survived all insecticides used extensively not only on cotton but also on other cash crops like chillies and tobacco. Farmers in their anxiety to increase their returns have misused or over used insecticides which has led to problems like insecticide-resistance in bollworms, resurgence of cotton whitefly and outbreaks of secondary pests. Bioassay studies conducted on third instar larvae of *H. armigera* and tobacco cutworm, (*Spodoptera litura* Fab.) revealed the development of several fold levels of resistance to commonly used insecticides in both insects. The Gunter strain of *H. armigera* developed 18.7, 9.2, 8.8, 7.8, 7.5, 3.9, 3.7, 3.7, and 3.4 fold levels of resistance to cypermethrin, fenvalerate, DDT, deltamethrin, monocrotophos, quinalphos, chlorpyrifos, acephate and carbaryl respectively. The Gunter strain *S. litura* exhibited 20.5, 14.2, 12.5, 9.4, 8.1, 6.8, 6.0, 4.4, 4.1, 3.8 and 2.6 fold levels of resistance to deltamethrin, endosulfan, carbaryl, monocrotophos, BHC, DDT, cypermethrin, malathion, fenitrothion, methyl parathion and fenvalerate respectively.

Important features on the biology and damage by major pests and factors contributing to the outbreak of *Heliothis* and *Bemisia* species are reported. Integration of pest management strategies including that of cultural practices, physical methods, mechanical approaches, varietal resistance, seed treatment practices, biological control methods and chemical control practices are discussed. The guidelines for undertaking chemical control measures and insecticide management are highlighted keeping in view the safety of the

environment. Other aspects such as the need for cooperation on the part of industry in maintaining quality of insecticides and social issues concerning sale of products are discussed.

INTRODUCTION

Among the cotton growing countries in the world, India has the largest acreage under its cultivation (7.9 million hectares) but the yields are lowest (276 kg ha^{-1}) when compared to countries like Israel (1405 kg ha^{-1}), Egypt (972 kg ha^{-1}) and China (871 kg ha^{-1}). It produces 10.8 million bales (1970 kg each bale) of cotton against 15.4 million bales by United States of America with only 4.2 million hectares under cultivation.

The various reasons that are attributed to low yields may be due to the:

(1) Existence of still sizeable area under desi cotton i.e. *Gossypium arboreum* and *G. herbaceum* which are poor yielders with short staple length.

(b) Inadequate availability of quality seed of intra (*G. hirsutum*), inter-specific (*G. hirsutum* x *G. barbadense*) hybrids with high potentiality and quality.

(c) Lack of irrigation facility for major cotton growing area.

(d) Losses due to pests and diseases.

The insect pest problems on *G. hirsutum*, *G. barbadense*, their intra and inter specific hybrids steadily increased from year to year and now its very cultivation is threatened by the American bollworm (*Heliothis armigera* Hubner) and the whitefly, (*Bemisia tabaci* Genn.). For instance the incidence of whitefly on cotton in Andhra Pradesh during 1984-85 was as high as 100 adults/leaf and that of *H. armigera* during 1986-89 was 50 or more larvae per plant.

Cotton is attacked by insect pests from seeding to final picking. Before the crop enters the reproductive phase, it is the sucking pest complex comprising of jassids, thrips and aphids while later both sucking pests (whitefly, mealybugs, mites and pod sucking bugs) and bollworms (American bollworm, spotted bollworm, pink bollworm, and tobacco caterpillar) infest the cotton crop (Reddy and Murthy, 1989). Estimated yield losses were found to vary from 16.8 - 34.7 per cent due to sucking pests and about 44.5 - 61.7 per cent due to bollworms (Hussain and Trehan, 1942). With the gradual replacement of desi cottons by *G. hirsutum* and *G. barbadense* and their intra and inter-specific hybrids both under irrigated and non-irrigated conditions, mono-culturing, high doses of nitrogen fertilizers, non-adoption of suggested pest management practices coupled with favourable weather conditions for pest build up, pest problems have worsened. The bollworm, *H. armigera* and whitefly, *B. tabaci* have become regular and key pests, crippling the cotton yields and economy of the farmer.

BIOLOGY OF MAJOR PESTS ON COTTON

American bollworm, (*H. armigera*)
This is a polyphagous pest which feeds on more than 200 species of host plant. It lays eggs singly on tender leaves, squares, buds and flowers. Eggs are spherical and light yellow in colour which may turn brownish later on. Parasitized eggs appear black in colour. Larvae are variable in colour and undergo 6 moults to reach the pupal stage. A single caterpillar can damage up to 10 bolls. Pupation takes place in the soil. Adults are medium sized with yellowish brown forewings having a chain of black markings and pale white hindwings with a broad smoky margin. The insect passes through 8-10 overlapping generations in one year. There is no diapause in South Indian conditions, whereas the species undergoes facultative diapause during the pupal stage in winter for a period of 2-3 months in North India.

Spotted bollworm, (*Earias vittella Fab.* **and** *Earias insulana Boisduval*)
Adults of *E. vittella* possess pale white fore-wings with a green central band and *E. insulana* has uniformly green fore-wings. Adults lay 60-80 spherical and sculptured bluish eggs on tender leaves, flower buds and squares. Larvae bore into young shoots, floral parts, buds and bolls. Affected shoots droop and dry up. Infested buds and bolls are shed in large numbers. The spotted bollworm spends 2-3 weeks in the larval stage and pupates on the surface of bolls, bracts, in soil or other crop refuse. Pupae are boat shaped pale brown cocoons.

Pink bollworm, (*Pectinophora gossypiella Saunders*)
Hirsutums are highly susceptible to this insect. Adults are small with numerous black spots on dark brown wings. Eggs are flat, scalelike and white, laid singly on young shoots and half developed bolls. Larvae when fully grown attain a pink colour. Pupation takes place inside the boll, often inside the seed hollowed out by the larva. It is a specific pest of cotton confining its damage to immature bolls. Moderate temperatures with cloudiness and high humidity favour pest build up.

Tobacco cutworm, (*Spodoptera litura Fab.*)
This is a polyphagous noctuid pest feeding on foliage as well as on the floral parts of cotto n. Moths are medium sized and stout bodied with pale brown fore-wings having white markings and white hind wings. Female moths lay up to 300 eggs which hatch within 3-5 days. Larvae pass through 6 moults in 2-4 weeks to enter into pupal stage. Pupation takes place in the soil. The insect passes through 8 overlapping generations in a year.

White fly, (*Bemisia tabaci Genn.*)
This insect infests about 420 species of plants from 18 families (Mound and Hasley, 1978). Eggs are stalked, laid singly on the top and middle order of leaves. A female can lay up to 70 light yellow eggs which hatch in 3-6 days. They become adults in 12-15 days by passing through 3 larval moults, prepupal and pupal stages (Sankarappa et al., 1976). Both nymphs and adults suck sap from leaves and tender bolls. Yellow chlorotic spots appear on infested leaves, which turn reddish. Affected leaves fade away and drop off prematurely. Flowers, buds and bolls are shed in large numbers. The size of bolls becomes reduced and the quality of lint deteriorates. Plants become stunted. Honey dew is also excreted on which sooty mould develops affecting photosynthesis. Whitefly also act as vectors in the transmission

of virus diseases such as tobacco leaf curl, cotton leaf curl and mosaic diseases (Costa, 1969; Murugesan et al., 1977 and Shankarappa et al., 1976)

Leaf hopper, (*Amrasca biguttula biguttula Ishida*)
This is also a polyphagous pest changing its colour through the season from green to greenish yellow. Each female lays up to 15 eggs by puncturing the parenchymatous tissue of the leaf. After a week the nymphs hatch out, sucking sap from leaves and becoming adults in 2-3 weeks, passing through 5 larval moults. There are 4-5 generations in a year As a result of sap drain by the hopper the plants become stunted, leaf margins initially turn yellow and later reddish and fade away. Affected leaves curl downwards and exhibit hopper burn symptoms. Necrotic spots develop at the places of oviposition sites. High temperatures coupled with high humidity favour pest multiplication.

In recent years, *Heliothis* and *Bemisia* have become a menace in cotton production. A critical analysis of factors that contribute to their outbreak enable us to formulate strategies to combat the pests effectively.

REASONS FOR THE OUTBREAK OF H. ARMIGERA

(a) Monocropping with susceptible varieties.

(b) Excessive irrigation, heavy precipitation.

(c) Non-synchronous sowings and high plant density.

(d) Presence of alternate hosts in the vicinity. For instance, during a visit to Kakumanu village, Gunter district, the authors noticed the occurrence of *Heliothis* on tobacco, pigeonpea, chickpea, tomatoes, maize, sorghum, chillies, coriander, sunflower, blackgram and greengram in addition to cotton.

(e) Excessive nitrogen fertilization. Farmers apply more than the required nitrogen fertilizer (150 to 200 $kg^{-1}ha$) as against the recommended dose of 80 kg ha^{-1} This leads to excessive vegetative growth making the plants more susceptible to pest attack.

(f) Over-use of insecticides at sub-lethal dose and inadequate coverage. Farmers while conversing with the author boast of controlling the shoot and fruit borer of egg plant, *Leucinodes orbonalis* by repeated applications of deltamethrin (8-10) times, but are unaware of the development of several fold resistance in *Spodoptera* and *Heliothis* against the same insecticide. Farmers should understand that *Heliothis* problem is their own making by over-dependence on chemical control.

(g) Elimination of natural enemies through indiscriminate use of insecticides.

(h) Development of resistance in insects to the commonly used insecticide.

Detailed studies carried out on *H. armigera* and *S. litura* indicated the development of varied levels of resistance to commonly used pesticides (Tables 1 and 2). Farmers are unhappy with the use of pesticides because they are not getting the satisfactory control of major pests. This is partly due to the occurrence of overlapping generations of insect pests and also due to development of insecticide resistance. Field populations of Srikakulam (SKL) and Guntur (GNT) zones each characterized by the lowest and highest rates of consumption of pesticides were collected and maintained on artificial diet (Reddy et al., 1976). Third instar larvae were subjected to graded levels of insecticides. Mortality counts were recorded 48 hours after treatment. LC_{50} values were calculated after treatment for susceptible and resistant strains. Probit regressions were estimated and resistance ratios determined by dividing LC_{50}'s obtained from resistant Guntur strain by those of susceptible Srikakulam strain. The data showed both the bollworms developed multiple resistance to the different groups of insecticides. Both species, being polyphagous insects, have high levels of detoxifying oxidases which protect them from deleterious effects of insecticides.

(i) Marketing of substandard/spurious chemicals.

(j) Application of adulterated and time-barred chemicals.

(k) Wrong pesticide delivery system

(l) Ideal winter weather.

CAUSES FOR THE OUTBREAK OF WHITEFLY

(a) Prevalence of continuous dry spell drought conditions during November-December.

(b) High temperature 28-33°C.

(c) Low rainfall.

(d) Relative humidity 60-90 per cent.

(e) Excessive use of nitrogen fertilizer.

(f) Use of insecticides at sub-lethal doses and improper coverage.

(g) Defective delivery system.

(h) Indiscriminate use of synthetic pyrethroid and insecticides with broad spectrum action.

(i) Elimination of natural enemies may perhaps be the main reason for the whitefly.

There are several instances of sucking pests i.e. mealy bugs on grapevines, scales on sugarcane, aphids and mites on chillies, which were originally considered to be minor pests but which turned into major problems. The main reason for these transformations was the elimination of natural enemies by over use of insecticides having broad spectrum action. These sucking pests problems, including whitefly on cotton, are man made situations, created by the indiscriminate use of insecticides by farmers.

(j) Lack of rainfall during vegetative phase.

Chemical control of *Bemisia* and *Heliothis* populations failed in the late 1980s and it was a man made situation. Farmers had been over-dependent on chemical control and had over-used insecticides, initially on tobacco and chillies and later on cotton and chillies. This led to the development of insecticide resistance in the bollworms. Under these circumstances integrated pest management (IPM) is the only remedy which has been advocated (Reddy and Reddy, 1984). This strategy integrates all the available methods of control including cultural, mechanical, physical, legal, biological and chemical, so as to arrive at an environmentally safe and economically viable programme for cotton pest management.

MANAGEMENT PRACTICES TO BE ADOPTED FOR CONTAINING THE PESTS

Cultural Method

	Practice	Against the pest
(a)	Summer ploughing to expose the pupa, to destroy weeds and alternate hosts	*Heliothis* and *Spodoptera*
(b)	Cultivate early maturing varieties Lam hybrid 1, NA 1280 Adopt whitefly tolerant varieties LPS 141, LK 861, JGL 14515. Desi varieties are less prone to *Heliothis*	*Bemisia* (Natarajan and Sundaramurthy, 1987)
(c)	Undertake early sowings	Bollworms
(d)	Observe synchronous sowings	White flies
(e)	Practice crop rotation with non-host plants bajra, sorghum, ragi, groundnut, gingelly, mustard and grams	*Heliothis* and *Bemisia*

Crop rotation, an important farm practice, helps in reducing the selection pressure of insecticides on pests because rotated fields are sprayed less often than non-rotated fields.

(f) Maintain optimum plant density. Often farmers use excessive seed rate instead of the recommended populations of 44,000 plants ha^{-1}. Higher seed rate leads to a dense canopy resulting in difficulty of access to the field and poor spray penetration of the crops.

(g)	Discourage ratoon crops and destroy the crop remnants	*Heliothis* and *Bemisia*

Ratoon crops act as sources of pests and diseases (white flies and bollworms). Even in sugarcane, control of scale insects is a big problem when ratoons are grown. Pest problems including that of whitefly increase and infestation spreads to neighbouring fields.

(h) Avoid extending the duration of crop period to prevent carry over of pests to next season.

(i) Provide wide rows and sufficient space between rows to enable parasites and predators easy access to the pest populations.

(j)	Use recommended dose of nitrogen fertilizers - apply potash fertilizers in split doses - apply neem cake	All pests
(k)	Practice clean cultivation	Bollworms and leaf rollers
(l)	Removal of alternate hosts and weeds	Polyphagous pests

(*Solanum nigrum, Acalypha indica, Abutilon indicum, Hibiscus ficeleneus, Acheranthes aspera, Datura stramonium, Acanthosperum* sp., *Cynodon dactylon, Gynadropsis pentaphila, Cyperus* sp.)

(m)	Intercropping with cereal crops like sorghum, wheat and maize	White flies & *Spodoptera*
	Inter-cropping with greengram	Leaf hoppers
	Inter-cropping with onions, chillies, gingelly, castor, cowpea, coriander, grams	*Heliothis*
(n)	Raise barrier crops of sorghum and maize	White flies

Wheat grown as a border crop acts as a mine of natural enemies (parasites and predators) of pests. Inter-cropping with rape during spring and corn during summer facilitated multiplication and migration of parasites and predators into the cotton crop.

(o) Grow trap crops around cotton such as -

Corn and redgram	*Heliothis*
Bhendi	*Earias*
Brinjal	Whiteflies
Castor, sunflower and blackgram	*Spodoptera* (Jayaraj, 1986)
(p) Frequent irrigation and light dose of N fertilization	Whiteflies

Thus, every agronomic practice must be attempted to exploit maximum advantage of cultural control methods.

Physical Methods

Yellow sticky traps	*Bemisia* (Gerling and Horowitz, 1984)
Pheromone traps - Hexadecenol	*Heliothis*
- Litlure	*Spodoptera*
- Gossyplure	*Pectinophora*
Light traps	Leaf hoppers

By setting up light trap/pheromone traps the period of adult emergence can be determined. In the majority of cases adults emerge after the onset of rains. From this the time of oviposition and egg hatch can be predicted. First instar larvae are the most vulnerable stage in the life cycle of any insect and this is the stage against which insecticidal spray should be aimed. By undertaking timely control measures it is possible to bring down populations to below threshold levels and also to reduce the number of applications. Pests controlled in the early stages are less likely to cause economic damage.

Mechanical Methods

Hand picking and destruction of egg masses and skeletonized leaves	*Spodoptera*
Collection and destruction of growing larvae	*Heliothis* and *Spodoptera*
Digging trenches around fields	*Spodoptera*
Seed treatment with hot air at 65^{0}C for 10 minutes	Pink bollworm

Erect bird perches to attract drongo and mynah which predate upon *Heliothis*.

Varietal Resistance

(a)	Evolve glabrous, nectarless varieties with high gossypol content	*Heliothis* and *Earias*
(b)	Evolve glabrous varieties with open canopy and thick lamina	Whitefly

Reddy and Rao (1989) reported that the varieties LK 861, LPS 141, D 53, A 102, JK 286, JK-97-FBRN and NHV 1 are tolerant to whitefly compared to the check MCU-5. They found that higher concentration of phenols, tannins, P, Mg, Mn and low N and Fe are associated with whitefly resistance.

Seed Treatment

Soaking of seed in 0.1% monocrotophos for 1 hr 0.1% dimethoate for 4 hr and 0.1% phosphamidon for 6 hr	Pink bollworms and jassids

The seed may be delinted by treating with concentrated sulphuric acid or subjected to fumigation with aluminium phosphide to kill pink bollworms prior to sowing.

Biological Control

Parasites and Predators. A number of parasites and predators are recorded on all major pests of cotton. Quite a few exotic parasites i.e. egg parasites, *Trichogramma brasiliensis* Ashmi, *T. australicum* Girault, egg-larval parasite, *Chelonus blackburni* Cam and larval parasite *Bracon kirkpatricki* Wilk are mass bred and released against *H. armigera.* They are found to be established in several parts of the country and further periodic releases are made to augment the value of biological control (Singh, 1985). Other parasites and predators recorded on *H. armigera* are:

Egg parasites	*Telenomus*
Larval parasites	*Campoletis chloridae* *Bracon hebetor* *Chelonus heliopae* *Eriborus trochanteratus* *Eucelatoria bryni* *Carcelia illota*
Pupal parasites	*Trichospilus pupivora* *Tetrastichus israeli*
Predators	*Menochilous and Chrysopa* (Achan et al., 1968)

Efforts are being made to mass multiply the predator lacewing, *Chrysopa* spp. and utilise it in *Heliothis* control. A pilot project on the integrated control of *Heliothis* has been planned and is being implemented with the following components.

(a) Utilization of egg parasites *T. brasiliensis, T. australicum*

(b) Egg-larval parasite *C. blackburni*

(c) Larval parasite *B. kirkpatricki*

(d) Exploitation of the predator *Chrysopa*

(e) Utilization of moult inhibitors (diflubenzuron) and growth regulators (neem oil emulsion and neem seed kernal suspension)

(f) Application of selective insecticides endosulfan and phosalone along with microbials such as Bt endotoxin and nuclear polyhedrosis virus (NPV).

The occurrence of parasites *Encarsia* spp. and *Eretmocerus mundus* on nymphs and pupae of *Bemisia* was reported earlier (Shankarappa et al., 1976). Natarajan et al. (1987) recorded the predatory lacewing bug *Chrysopa* spp. and the Coccinellids *Brumus* and *Scymnus* feeding on nymphs and adults of *Bemisia*.

Entomopathogens. Species of *Heliothis* and *Spodoptera* were reported to be susceptible to almost all groups of entomopathogens viz. viruses, fungi, bacteria, protozoans and nematodes. Though some of these pathogens have been exploited in the west in the control of insect pests, their use is rather restricted in India. The failure of chemical insecticides to contain these pests at reasonable doses and the problems associated with indiscriminate use of insecticides necessitated studies on the alternatives, particularly microbials.

In the recent past, extensive studies have been made on the utility of *H. armigera* NPV on various pulses and *S. litura* NPV on cotton, tobacco, cole crops, banana and blackgram. The success of NPV against *Heliothis* on cotton was limited because of some factors concerning high leaf pH, leaf exudates, plant phenology and host feeding behaviour. Earlier attempts were made to formulate *H. armigera* NPV into wettable power and dust formulations and their efficacy was evaluated in the laboratory against the host larvae (Table 3). The results showed that talc-based wettable powder formulations of NPV were more effective than dust formulations and as effective as unformulated virus. In a field study, efficacy of NPV with certain adjuvants for the control of *H. armigera* on cotton was investigated (Table 4). The results revealed that NPV + endosulfan 350 a.i.ha^{-1} + adjuvants such as larval extracts 4% and crude sugar 15% was as effective as endosulfan 700 g a.i. ha^{-1} in reducing larval population, damage to flowers, squares and bolls and increasing the seed cotton yield. Combination of NPV with half the recommended dose of test insecticides (endosulfan, fenvalerate or chlorpyriphos) not only controlled *S. litura* on groundnut effectively but also realized higher yields over untreated control (Reddy et al., 1985).

If NPV is to be used for the control of caterpillar pe[illegible] a need to establish production units either within the government setup or [illegible] vate organizations. Until such laboratories are established and start functioni[illegible] progress in the biological control will be made. This is equally true for the use of parasites where India has been a pioneer in establishing mass production units in Bangalore to supply parasites and predators on a commercial basis.

Seasonal outbreaks of diseases caused by entomogenous fungi such as *Aspergillus, Beauveria, Metarhizium* and *Nomuraea* spp. have been reported in *H. armigera* and *S. litura* populations on several crops in India. Field efficacy of these entomogenous fungi has not been tested against these pests, but attempts have been made to identify several virulent strains, of *Beauveria bassiana* (Bals.) Vuill (Table 5). The results indicated that all the fungal isolates tested against *H. armigera* and *S. litura* proved pathogenic to both species exhibiting varying degrees of virulence. One isolate of *B. bassiana* (BPT) showed the highest virulence to both pest species.

Bacterial insecticides can be applied either alone or integrated with other methods of pest control to achieve either short or long term control. The commercial preparation of *Bacillus thuringiensis* (B.t.) was effective against *H. armigera* and *S. litura* in laboratory tests and some field trials on cole crops and vegetables, but its field efficacy is not well documented on crops like cotton.

H. armigera has been shown to be susceptible to protozoan diseases in addition to NPV, fungi and bacteria. A microsporidian (*Vairimorpha* sp.) was isolated from a few dead caterpillars in a natural population of *H. armigera* on field beans in Bangalore, India. A study on this pathogen showed that first three instars of *H. armigera* recorded 100 per cent mortality and late instars were comparatively less susceptible (Table 6).

Chemical Control

Chemical control should only be used when the pest exceeds economic threshold levels. In a crop like cotton,which is highly prone to pests and diseases, there is a need to undertake weekly population counts to know the levels of pest population. In the absence of these checks, the representative of the Agriculture Department at the village level should be made responsible to inform the farmers on pest incidence data. The presence of technical staff at village level is essential for proper surveillance and reliable forecasting. IPM will work effectively only when economic threshold levels are utilized properly and this is possible only when staff are set apart for collection and onwards transmission of surveillance data.

Economic thresholds (ET) worked out for the major pests of cotton are as follows:

Pest	**ET level**
Spodoptera	One egg mass/10 plants
Heliothis	4-15 larvae/100 plants or more than 10 moths/trap daily
Spotted bollworms	1 larvae/10 plants or 10 per cent infested bolls
White fly	20 nymphs/pupae/leaf or 6-8 adults/leaf
Jassids and Thrips	5 adults or nymphs/10 leaves

Aphids and Mites	15 per cent affected plants

Guidelines for taking up Chemical Control Measures

1. Effective use of pest surveillance information through the installation of yellow sticky traps, light traps, pheromone traps and visual observation of the pest in the field.

2. Use selective insecticides i.e. endosulfan, phosalone, demeton-s-methyl and trichlorfon, which are less toxic to natural enemies and fit into IPM programmes.

3. Avoid broad spectrum insecticides which are harmful to parasites and predators. Adopt recommended doses and applications. Farmers apply insecticides more than 30 times during a crop season as against University's recommendation of 10 times. There is need to reduce selection pressure of insecticides to bring down the levels of insecticide resistance.

4. Avoid chemicals which are persistent in nature or formulations which release the chemical for longer duration than the required period. By applying persistent chemicals insecticidal pressure continues to work not only on immature stages but also on adults, which should be avoided, lest the insecticide resistance problem becomes aggravated and unmanageable.

5. Discourage use of slide pump and spinning disc sprayers to prevent
   (a) evaporation and drift losses and
   (b) health hazards to operator.

6. Use either hand compression sprayers or mist blowers.

7. Avoid repetition of the same insecticide.

8. Use potable water for mixing insecticides. It is the experience of the authors to come across farmers using muddy water for spray purposes. The insecticides may lose their toxic properties by being adsorbed onto clay particles or even be affected by saline conditions.

9. Monitor the population levels of parasites and predators and occurrence of natural epizootics in pest population and time the insecticidal sprays. Adopt control measures only when benefit risk ratios are tilted in favour of insecticides. Insecticides to be used up to flowering for containing sucking pests which cross the ETL are:

Oxydemeton-methyl 0.05%	
Dimethoate 0.05%	
Monocrotophos 0.1%	Need based sprays
Ethion 0.1%	
Quinalphos 0.075%	

The following insecticides are recommended for the control of bollworms.

Monocrotophos 0.1%Chlorpyriphos 0.05%
Acephate 0.1%Endosulfan 0.07%
Carbaryl 0.15%Quinalphos 0.07%
Triazophos 0.1%Fenvalerate 0.005%
Deltamethrin 0.002%Cypermethrin 0.004%

The above insecticide sprays may be used sequentially and not repeatedly. The use of synthetic pyrethroids may be restricted to one or two sprays only.

The following chemicals are found to be effective against whiteflies:

Triazophos 0.1%Acephate 0.1%
Monocrotophos 0.1%Methyl-S-demeton 0.05%
Phosalone 0.05%Amitraz 0.1% (Vidyasekar et al., 1989)

Against aphids, reduced dose of oxydemeton-methyl is recommended to allow survival of some aphids which support ladybird beetles.

The compound dicofol @ 3ml l^{-1} is recommended against mites.

Where water become a constraint especially on rainfed cotton, dusting of carbaryl 5 or 10%, endosulfan 4%, quinalphos 1.5%, phosalone 4%, methyl parathion 2% can be undertaken alternately at 20 to 25 kg ha^{-1} against sucking pests and bollworms.

Nonconventional insecticides like chitin inhibitors i.e. diflubenzuron and antifeedants i.e. neem oil emulsion 0.05% and neem kernel suspension 5% have been found to be effective against bollworms and whiteflies. Both the groups have ovicidal advantages and also interfere with growth and development. They are biodegradable and fit into IPM programmes (Malleswar et al., 1987). Rao and Reddy (1984) reported the usefulness of chitin inhibitor diflubenzuron against *S. litura*. The compound exhibited ovicidal action as well as moult inhibition effects when tested at concentrations of 100 ppm and above. Mayuravalli et al. (1987) tested graded levels of growth regulators SIR-8514 and diflubenzuron against larvae of *S. litura* and found the former compound twice as toxic as the latter in affecting the development of *S. litura* larvae. Incorporation of diflubenzuron as one of the treatments into IPM programmes on the groundnut pest complex worked effectively in preventing damage done to the foliage by *S. litura* and also resulted in increased yields (Malleswar et al., 1987).

LEGISLATIVE MEASURES

When the population increased to alarming numbers (100 or more whiteflies/leaf, 50 or more *Heliothis* larvae/plant) the Government should enforce legislative measures compelling every farmer to adopt chemical control measures at the right time in the right way with proper dosage to prevent damage by such established pests.

Social Issues

Farmers receive insecticides on credit and become indebted to business or dealers. They listen to the advice of salesmen on the choice of insecticide to be purchased and apply insecticides as they like, some times repeatedly. It is an irony that salesmen become the advisors rather than technical or qualified staff in recommending insecticides. Farmers should take the recommendations from qualified staff of the Agriculture Department or the University. There is a need to impart training to insecticide dealers or salesmen in identifying pest problems and in prescribing appropriate insecticides. Pesticides should be sold under prescription as in the case of human medicines. Farmers should not purchase insecticides without a bill. Industry should co-operate and help maintain quality of compounds.

There is a need to alert staff of the plant protection wing of the State Department of Agriculture as well as the Centre and advise them to be in readiness to meet any eventuality of pest outbreak by keeping the machinery in order always. Finally the co-operation of cotton growers is very much needed in tackling pest problems in cotton.

TABLE 1
Resistance levels in third instar larvae of *H. armigera* (GNT Strain) to certain insecticides

Insecticide	LC_{50} of resistant strain (GNT) / LC_{50} of susceptible strain (SKL)	Resistance index
DDT	0.0821/0.0093	8.83
Endosulfan	0.0359/0.0087	4.13
Monocrotophos	0.0526/0.0070	7.51
Quinalphos	0.0118/0.0030	3.93
Chlorpyriphos	0.0241/0.0065	3.71
Acephate	0.0241/0.0065	3.71
Carbaryl	0.0208/0.0062	3.36
Cypermethrin	0.0131/0.0007	18.71
Deltamethrin	0.0047/0.0006	7.83
Fenvalerate	0.0046/0.0005	9.2

TABLE 2

Resistance levels in third instar larvae of *S. litura* (GNT Strain) to certain insecticides

Insecticide	LC_{50} of resistant strain (GNT) / LC_{50} of susceptible strain (SKL)	Resistance Ratio
Endosulfan	0.0541/0.0038	14.24
Monocrotophos	0.0581/0.0062	9.37
Carbaryl	0.0739/0.0059	12.53
Cypermethrin	0.0043/0.0072	5.97
Deltamethrin	0.0041/0.0002	20.5
Fenvalerate	0.0037/0.0014	2.64

TABLE 3
Laboratory evaluation of efficacy of NPV formulations (involving water) against second instar larvae of *Heliothis armigera*
(After Ethiraju *et al.*, 1988)

Treatment		% mortality (1)
NPV (unformulated)	(1 x 10^6 POBa/ml)	71.9b
NPV WP (Dedenol)	"	77.0ab
NPV WP (Lissapol)	"	62.5b
NPV dust (Talc)	(6 x 10^7 POBs/g)	50.0bc
NPV dust (Kaolin)	"	50.5bc
NPV dust (Lilite)		46.3c
Endosulfan 0.035%		93.3a
Control		-

(1) Numbers followed by the same letter are not significantly different at 5% level using Duncan's multiple range test.

TABLE 4

Larval populations of *Heliothis armigera* in different treatments seven days after each application in DCH 32 cotton

	Treatment	Larvae/5 plants 7 days after spray		% Damage		Seed cotton yield kg ha^{-1}
			Flower	Squares	Bolls	
1.	NPV + cotton seed kernal powder 2.5% + crude sugar 17.5% + endosulfan 350 g a.i./ha.ULV	3.30a	9.14ab	10.53ab	7.67a	2490a
2.	NPV + crude sugar 20% + endosulfan 350 g a.i./ha - ULV	5.05ab	10.94b	14.71b	9.86a	2420a
3.	NPV + *H. armigera* larval extract 4% + crude sugar + 15% + endosulfan 350 g a.i./ha - ULV	3.00a	7.51a	9.11a	6.67a	2520a
4.	NPV + whole milk 10% + crude sugar 15% + endosulfan 350 g a.i./ha -ULV	3.33ab	7.59a	10.47ab	7.63a	2500a
5.	Endosulfan 700 g a.i./ha - ULV	6.15ab	9.08ab	9.47a	6.78a	2518a
6.	Endosulfan 700 g a.i./ha - HV	7.00ab	8.12a	9.11a	6.51a	2521a
7.	NPV - ULV	9.00b	19.84c	19.35c	12.11b	1810b
8.	Control	16.09c	27.73d	27.73d	21.08c	1560b

* NPV @ 450 LE/ha; ULV - Ultra Low Volume, HV - High Volume. After Dhandapani et al. (1987)
Numbers followed by the same letter are not significantly different at 5% level using Duncan's multiple range test.

TABLE 5
Susceptibility of *H. armigera* and *S. litura* to certain fungal isolates
(After Deva Prasad, 1989)

Fungal isolate	Strain	LC_{50} (X 10^5 Conidia/ml) *H. armigera*	*S. litura*
B. bassiana	New Delhi	5007	7571
	Bangalore	4188	5554
	Bapatla	2	20
Paecilomyces fumosoroseus	Kerala	6691	9412
P. farinosus	Kerala	52208	55788

TABLE 6
Effect of *Vairimorpha* sp. on different larval instars of *H. armigera*
(After Narayanan, 1987)

Larval Instar	Mortality (%)	Incubation period (Days)
I	100	5 - 7
II	100	6 - 8
III	100	6 - 10
IV	87	8 - 12
V	10	9 - 35

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INTEGRATED PEST MANAGEMENT IN JUTE AND ALLIED FIBRE CROPS

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ABSTRACT

In the integrated pest management research programme at Bangladesh Jute Research Institute several alternative approaches to crop protection and pest control in respect of jute and allied fibre crops have been developed with varying degrees of success. The information will contribute to better understanding and hopefully, better management of pests.

Integrated pest management in jute and allied fibre crops in Bangladesh is a multi-tactical approach that encourages the fullest use of mechanical control, natural mortality factors, and indigenous plant materials. Pesticides are used only where economic damage threshold levels would otherwise be exceeded. Pesticides which will cause less residual and environmental hazards and will fit in best with established agricultural and retting practices of jute are used.

Research work on the development of pest resistant varieties has received increased attention particularly with the availability of exotic germplasm collected through IJO germplasm project activities. In these remarks, attempts have been made to outline the views on some of the most important aspects of integrated pest management in jute and allied fibre crops.

INTRODUCTION

For an efficient production of food and fibre crops to support the rapidly expanding world population, it appears very likely that the use of pesticides will keep on increasing in the foreseeable future. The reason is that the pesticides have now become an important agricultural input into our national life, mainly to save crops from pest attacks. However, our aim is to minimise the undesirable environmental consequences of the use of pesticides including the health hazards for human beings and toxicity to fish. The other problem that demands our immediate attention is reducing the cost of production of jute and improving the quality of fibre.

Against this background pest control research programmes at Bangladesh Jute Research Institute (BJRI) are designed to show how pest species on jute and allied fibre crops occur in relation to growth stages of the crops and when pest management is applied at a particular location and how research results will impact on jute agriculture. Tolerable levels of key pests have been differentiated from intolerable levels and we have reasonably transferred that information to the extension or farmers level. In doing so, we have also recognised and incorporated into research and development activities the following tenets of integrated pest management (IPM) and application of those data to impact on jute production: (1) the ecosystem is the management unit; (2) natural mortality factors of key pests are relied on to a maximum extent (parasites, predators, pathogens, heavy rainfall, drought and flooding etc.); (3) multiple control strategies are developed and used against target pests; (4) an interdisciplinary system approach to pest control is essential so as to achieve the goal of optimum production of high quality fibre at a minimum cost.

Therefore, IPM practice requires a thorough understanding of the pest, the agricultural ecosystem, biological control factors, development of several alternative approaches to crop protection and the ability to coordinate this approach with jute crop protection and production disciplines.

It has been estimated that in Bangladesh the overall production losses of jute and allied fibre crops due to insect and mite pests is about 12 per cent. Chemical control gives satisfactory results but is costly and causes environmental pollution besides other associated problems [1]. On the other hand, single factor control does not provide a permanent solution to any pest problem. Our aim is to reduce the cost of production of jute and to avoid residues of pesticides on jute that can be termed as hazardous to man or to the environment. Hence there is the necessity for the development and application of integrated pest management.

It has been recognised that major insect and mite pest infestations are a constraint on achieving increases in fibre yields and improving the quality of fibre. The pests attack all parts of the jute plant including flower and seed pods [2]. It has been demonstrated that adoption of pest control measures recommended by BJRI may prevent yield losses of from 72.7 to 181.8 Kg per acre depending on the intensity of infestation.

ECONOMIC IMPORTANCE OF THE DIFFERENT PEST SPECIES

As many as 40 different species of insect and mite pests have so far been recorded on jute, kenaf and mesta in Bangladesh. However, about eight major pest species have serious economic consequences for jute and allied fibre cultivation in the country. The key pests are: field cricket (*Brachytrypes portentosus*), jute hairy caterpillar (*Spilosoma obliqua*), jute semilooper (*Anomis sabulifera*), Indigo caterpillar (*Spodoptera exigua*), jute stem weevil (*Apion corchori*), yellow mite (*Polyphagotarsonemus latus*), mealy bug (*Pseudococcus virgatus*) on mesta (*Hibiscus sabdariffa*) and spiral borer (*Agrilus acutus*) attacking kenaf (*Hibiscus cannabinus*). Of these, the field cricket, hairy caterpillar and indigo caterpillar normally reduce yields; jute stem weevil and kenaf spiral borer cause the deterioration of fibre quality; while jute semilooper, yellow mite and mealy bug cause both reduction in yield and fibre quality.

PEST CONTROL APPROACHES AND TECHNIQUES DEVELOPED

In our research activities on integrated pest management for jute pests emphasis is given on cultural and mechanical control methods, protection of natural enemies, chemical control practices and use of local plant materials. Researches are in progress of developing pest resistant varieties especially against yellow mite (*P. latus*), jute stem weevil (*A. corchori*) and spiral borer (*A. acutus*). Both local and exotic germplasm materials are being sereened and some promising lines have been identified. With this background, current knowledge of integrated control approaches of jute pests and the recommendations so far released to the resource poor farmers are now discussed.

1. Field cricket (*B. portentosus*) causes damage to seedling jute plants and reduces the plant population which ultimately leads to reduction in per acre yield of fibre. The recommendations for its control are the following:

   (i) Infested fields may be flooded with irrigation water as and when initial infestation is detected. (ii) For localities where field histories of its attack suggest that damage occurs year after year, high seeding rates are recommended with a view to increasing the initial plant population to offset losses. Thinning operation is advised 4 to 5 weeks after planting. (iii) Operating fires will attract field crickets to the fires and will ultimately reduce cricket populations. (iv) Mixing soil insecticides (Heptachlor 40%, Dieldrin 40% WP) in water as recommended and using about 250ml of the preparation per insect hole; or using strip treatment, mix one ounce of the recommended insecticide in as much water as is required then treat $95m^2$ of infested area with sufficient solution poured into fresh burrows.

2. Jute hairy caterpillar (*S. obliqua*) usually the larvae feed on mature leaves but in case of heavy infestation, the plants are totally defoliated. Infested plants become stunted in growth and yield is reduced. The young caterpillars remain gregarious for about 6 days on the lower surface of the leaves and skeletonize them. Control measures so far developed are:

   (i) Hand picking of early instar larvae when they are in the gregarious state and kiiling them either by burning or dipping in kerosinized water. Control measures against hairy caterpillar are most effective when applied to the pest at the time of maximum concentration and minimum mobility. (ii) A Brachonid parasite, *Apanteles obliquae* and Tachinid complex *Blepharella* sp, *Cercilia* sp. and *Palexorista* sp. give good control of *Spilosoma obliqua* under favourable situation. A considerable number of pest larvae suffer natural mortalities due to virus and a fungal (*Erynia neopyralidarum*) infection. Protection of these natural enemies is advocated. (iii) Once the caterpillars have swarmed in the field, the growers become concerned. Under such circumstances insecticides like diazinon 60% EC; fenitrothion (Sumithion 50% EC), bromophos (Nexion 25% EC), monocrotophos (Nuvacron 40% EC) and quinalphos (Ekalux 25% EC) are recommended for control.

3. Jute Semilooper (*A. subulifera*) feeds on apical leaves/top shoot of jute plant causing stunted growth and side branching. The following control measures are recommended:

(i) If perches are provided in the infested jute field for encouraging insectivorous birds, they will eat the semilooper larvae and help considerably in controlling the pest. (ii) Semilooper feeding on apical leaves can be prevented by dragging a rope soaked in kerosene oil across the infested field so as to dislodge the pest. (ii) A nuclear polyhedrosis virus caused natural mortalities of jute semilooper. The diseased larvae become sluggish and gradually turn yellowish in colour. Before death, infected larvae stop feeding and migrate to the top of the jute plant where they hang with head downwards [3]. After death, the body contents become dispersed over the jute plant in the form of light yellowish or whitish fluid heavily charged with nuclear polyhedra, resulting in natural dissemination. The virus is highly infectious and virulent, so that 6-8 fully grown larvae in an advanced stage of the disease are sufficient to make one gallon of spray. To produce effective mortality, it is important that the virus preparation should be applied soon after the time of egg hatching. (iv) A Tachinid parasite *Tricholyga sorbilans* and *Eurytoma* sp. (Eurytomidae) are important parasites of jute semilooper. (v) Spraying with any one of the insecticides; Ekalux 25% EC, Nexion 25% EC and malathion 57% EC using recommended doses gives very good control of jute semilooper. Only the top leaves are subjected to insecticidal pressure.

4. Jute stem weevil (*A. corchori*) is one of the very serious pests of jute which affects the quality of fibre. The damage is mainly caused by the larva which feeds inside the bark damaging the fibre bundles. Recommendations for its control are the following:

(i) Removal of the top shoots from infested seedling plants at the time of the weeding and thinning process and their destruction. (ii) The parasites, *Entedon* sp. and *Bracon greeni* cause high mortalities of the pest under field conditions. Consequently, in our present pest management programme preventive spraying is not encouraged, a modification of earlier practice. (iii) Destruction of alternate host plant *Triumfeta rhomboidea* and other shrubs harbouring the adult weevils during off-jute season offers a method of reducing the stem weevil field populations. (iv) Of the two cultivated species of jute (*Corchorus capsularis, Corchorus olitorius*), *C. capsularis* suffers serious damage due to stem weevil infestation. Therefore, insecticides are usually applied on capsularis jute against the pest. The recommended insecticides are diazinon 60% EC and oxydemeton-methyl (Metasystox 50% EC).

5. Jute yellow mite (*P. latus*) at present is the most serious pest of jute in Bangladesh. It is responsible not only for yield losses but also for the reduction of fibre quality. Current control measures include:

(i) Chemical control using a miticide, namely sulphur (Thiovit 80% WP), dicofol (Kelthane 42.5% EC), fenbutatin oxide (Torque 55% WSC) or Uniflow

52.4% EC, is suggested at the time of initial attack and it is advised that only the top leaves (up to 11th leaf) need to be sprayed [4, 5]. This will greatly reduce the cost of production of fibre. Timing of application must be optimal. (ii) Use of local plant materials, mainly neem (*Azadirachta indica*) leaf extract in hot water and neem seed oil have been recommended for the control of jute yellow mite. At the village level, the extract can easily be prepared by using green neem leaf at the ratio of 1:10 in hot water kept for 2-5 minutes and by crushing neem seed in simple machinery which can be easily fabricated to produce neem oil. Neem seed oil is used at the concentration of 2 ml per 100 ml water, adding 1 gram of soap per litre of preparation. The materials are applied to standing jute crop to control the pest. Usually a second spray within 48 hours following the first spraying gives adequate control. The method is safe, convenient and effective. However, neem seed oil at higher dosage rates will cause phytotoxicity of jute plants.

6. Mealy bug (*P. virgatus*). The infested leaves gradually shrivel up and curl over. The infestation caused swelling of the terminal shoot and induces side branches giving rise to witches-broom. The apical part of the plant is subjected to insecticide spray using any one of the recommended chemicals such as diazinon 60% EC, malathion 57% EC and Nuvacron 40% EC.

7. Spiral borer (*A. acutus*) causes damage to *Hibiscus cannabinus* (kenaf) and reduces the quality of the fibre. About 92 per cent of attacks are concentrated within the lower 2 metres of plants above soil level [6]. Application of insecticide covering the lower 2 metres of the plants gives adequate control of the pest.

RESEARCH ON BOTANICALS HAVING INSECTICIDAL PROPERTIES

A few local plant materials having insecticidal properties have been identified and their efficacies are being investigated for possible use against the pests of jute and allied fibre crops. The botanicals so far selected and tested are Neem, *Azadirachta indica* (leaf & fruit); Nishinda, *Vitex negundo* (leaf); Bankalmi, *Ipomoea sepiara* (leaf), Biskatali, *Polygonum hydropiper* (leaf) and jute seed, *Corchorus capsularis* (seed). Laboratory and field tests are being carried out for assessing mortality effect, repellency and antifeedant actions of some of the promising botanicals. On the basis of test results obtained so far, provisional recommendations have been released to the jute farmers for using neem leaf extracts and neem seed oil for field use as safe and inexpensive control agents against the insect and mite pests of a jute and mesta.

Arrangements have also been made for conducting field trials against jute pests using azadirachtol/azadirachnol, nimolinone and nimbocinone [7, 8] for evaluating their effectiveness (toxicity, antifeedant, growth regulating properties and other biological effects).

PLANT RESISTANCE

The use of crop varieties resistant to damage or attack by insects has been practised for many decades [9, 10]. Efforts are being made at BJRI to develop resistant varieties especially against jute stem weevil (*A. corchori*), yellow mite (*P. latus*) and spiral borer (*A. acutus*). A major constraint to the development of pest resistant varieties of jute and allied fibre crops has been the lack of sufficient diversity in the germplasm. In efforts to overcome this problem, The International Jute Organization (IJO) Germplasm Project involves the collection of diverse germplasm from different sources world-wide. Samples of IJO seed material (germplasm) are stored at the Gene Bank of BJRI which has been designated as the Centralized Germplasm Repository (CGR).

Screening of germplasm lines against sucking pests, particularly yellow mite has yielded encouraging results. Hopefully, incorporation of yellow mite resistance into improved varieties will be possible within a reasonably short time.

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PESTICIDES IN THE 21ST CENTURY

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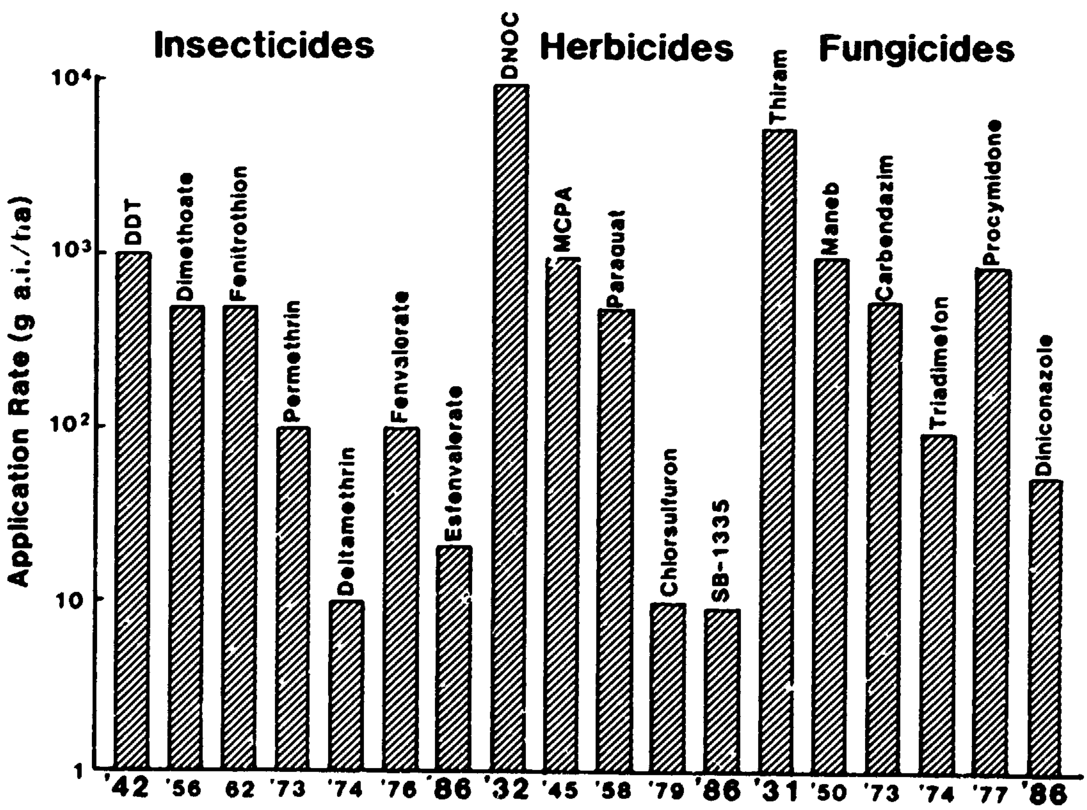
It is unanimously agreed that pesticides have played a significant role in increased agricultural production during the past half century. At the early period just after the Second World War, however, those compounds with longer persistency and wider pesticidal spectra were well accepted, resulting occasionally in certain adverse environmental effects. In contrast, more recently owing to the advances in numerous disciplines of science related to research on pesticides, much more efficacious, and at the same time, more selective and biodegradable compounds have been introduced, as illustrated in Figure 1. It is well recognised that chemical pesticides will remain predominant in the total strategy of plant

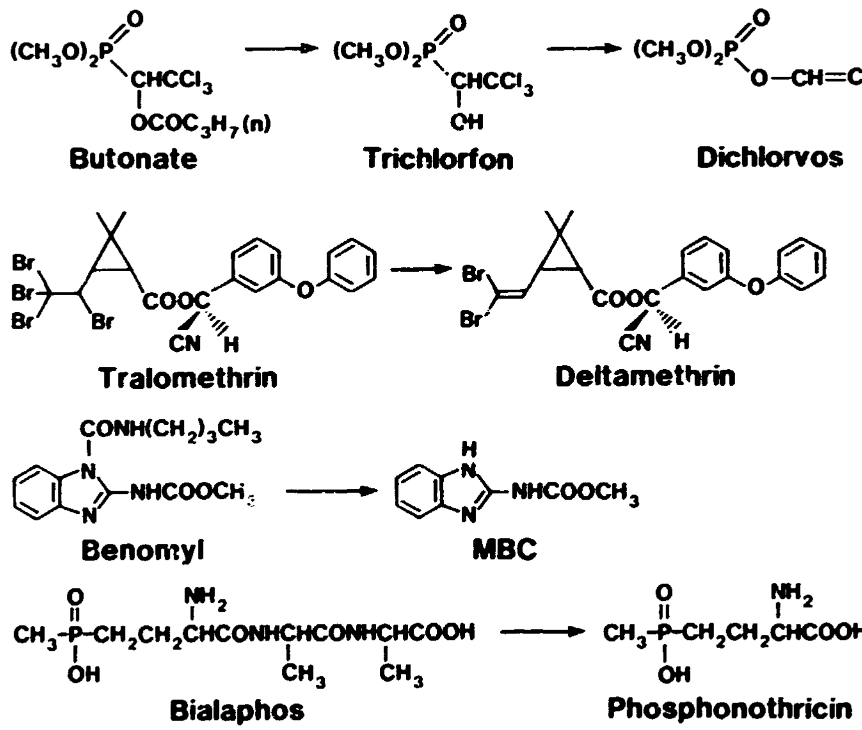
Figure 1. Year of marketing and efficacy of pesticides



protection in the foreseeable future to cope with a tremendous population increase on the earth. It is obvious that the endeavour to seek better pesticides has to be strengthened world-wide through collaboration with all those concerned, including academia and industry.

Elucidation of the mode of action of pesticides, coupled with differential metabolism for bioactive metabolites, has been, and is even more significantly today, one of the essential components of rational approaches to modern pesticides. Actual knowledge on metabolism of pesticides in living organisms leads to the concept of bioactivation of xenobiotics (e.g. butonate to dichlorvos, benomyl to MBC, tralomethrin to deltamethrin, bialaphos to phosphonothricin, Figure 2), thus permitting modification of chemical structure in more appropriate manners, including construction of propesticides. It is well known that in

Figure 2. Bioactivation of propesticides



certain cases selective toxicity of pesticides stems from their differential metabolism in susceptible and resistant organisms. The site of action of pesticides has been gradually elucidated in biochemical terms, as shown in Table 1. Thus, the effort to find out additional targets which are preferably specific to pest organisms should be encouraged, since it will lead to novel frontiers of plant protection.

The recent advances in computer-aided quantum chemical calculation including computer graphics, in combination with elucidation of molecular structure of receptor site by means of gene engineering and related techniques, have contributed much to a more precise understanding on how bioactive xenobiotic molecules interact with the respective machinery of living organisms. One of the representative examples of three dimensional

TABLE 1
Biochemical and molecular site of action of pesticides

Site of action	Example
Nervous system	
sodium channel	Pyrethroids
Acetylcholine receptor	Nicotine, Cartap
Acetylcholinesterase	Organophosphates, Carbamates
Chitin synthesis	Diflubenzuron, Buprofesin
Egosterol synthesis	Triazoles
Mitosis (β-tubulin)	Benomyl, Diethofencarb
Phospholipid synthesis	IBP, Edifenphos
Melanin synthesis	Fthalide, Tricyclazole, Pyroquilon
Photosynthesis	
Photosystem II	Triazines, DCMU
Chlorophyll synthesis	Diphenylethers, Tetrahydrophthalimides
Aminoacid synthesis	
EPSPS	Glyphosate
Acetolactate synthase	Sulfonylureas, Imazapyr
Glutaminesynthase	Phosphonothricin, Bialaphos
Gibberellin synthesis	Uniconazole, Paclobutrazol, Inabenfide
Electron transport/phosphorylation	Rotenone, Ioxynil, Phosphine, Carboxin, Paraquat

structure elucidation is nicotinic and muscarinic acetylcholine receptors with active conformation of acetylcholine bound with the respective receptors. More direct evidence of herbicide terbutryn bound with photosystem II of the purple bacterium *Rhodopseudomonas viridis* is visualized with computer graphics, as reproduced in Figures 3 and 4. Furthermore, the primary structure of *Torpedo* acetylcholinesterase, bacterial glutamine synthase, as well as several microsomal P450's has been elucidated. One additional interesting example is the interaction of benzimidazole fungicides with microbial β–tubulin (Figure 5), which is their known mode of action as fungicides. Among the 447 amino acid sequence of a benzimidazole-sensitive strain of *Neurospora crassa*, phenylalanine at No167 or glutamic acid at No198 is modified to tyrosine, or to glycine, respectively, to become resistant to benzimidazoles and/or to diethofencarb, although the detailed mechanisms of how the modified β-tubulin proteins interact with different fungicides is yet to be clarified

Figure 3. Photosynthetic reaction center (*Rhodopseudomonas viridis*)

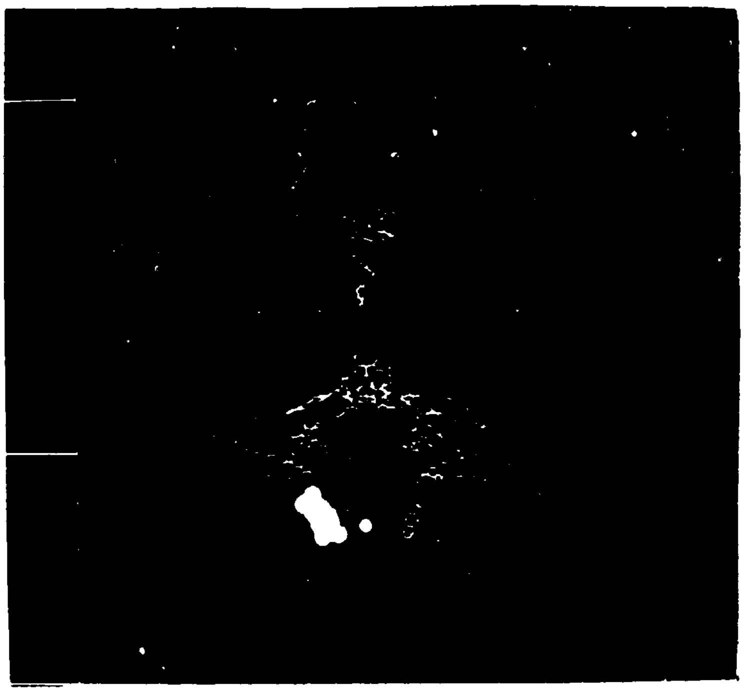
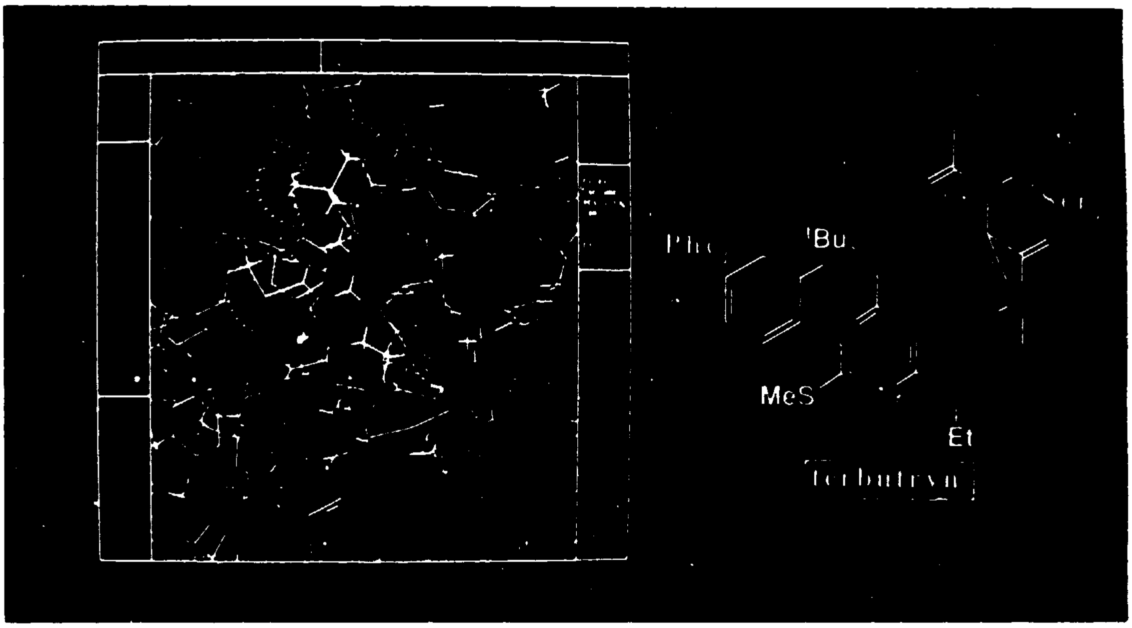
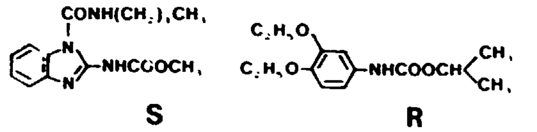


Figure 4. Binding of triazine type herbicide



This cumulative knowledge on structural detail of receptors as well as interaction of xenobiotic molecules accelerates the approach to more efficacious pesticides by modernizing the rational synthesis of candidate compounds in ways not previously possible. Also, the knowledge will help to elucidate certain resistance mechanisms, especially resistance due to so-called target insensitivity.

Figure 5. Binding of fungicides with microbial β-tubulin (*Neurospora crassa*)
N.B. S: susceptible. R: resistant



Fungicide		Amino acid	
Benomyl	Diethofencarb	No. 167	No. 198
S	R	Phe (F)	Glu (E)
R	S	Phe	Gly
R	R	Tyr	Glu

```
        10         20         30         40         50         60         70
MREIVHLOTG OCGNOIGAAF WOTISGEHGL DASGVYNGTS ELOLERMNVY FNEASGNKYV PRAVLVDLEP
        80         90        100        110        120        130        140
GTMDAVRAGP FGOLFRPDNF VFGOSGAGNN WAKGHYTEGA ELVDOVLDVV RREAEGCDCL OGFOITHSLG
       150        160        170        180        190        200        210
GGTGAGMGTL LISKIREEFP DRMMATFSVV PSPKVSDTVV EPYNATLSVH OLVENSDETF CIDNEALYDI
       220        230        240        250        260        270        280
CMRTLKLSNP SYGDLNHLVS AVMSGVTVSL RFPGOLNSDL RKLAVNMVPF PRLHFFMVGF APLTSRGAHH
       290        300        310        320        330        340        350
FRAVSVPELT OOMFDPKNMM AASDFRNGRY LTCSAIFRGK VSMKEVEDOM RNVONKNSSY FVEWIINNVO
       360        370        380        390        400        410        420
TALCSIPPRG LKMSSTFVGN STAIOELFKR IGEOFTAMFR RKAFLHWYTG EGMDEMEFTE AESNMNDLVS
       430        440
EYOOYODAGV DEEEEEYEEE APLEGEE
```

Although direct use of naturally occurring bioactive products including insect and plant hormones and a variety of semio- chemicals for plant protection purposes is generally considered to be difficult except under certain circumstances because of several reasons such as intrinsic low activity, complex chemical nature, unfavourable physicochemical properties and ecological difficulty, they nevertheless serve either as a lead for chemical synthesis or as a tool to explore mode of action. Therefore, studies ought to be encouraged for potential plant protectants. Since much information is available on these, just a couple of examples are cited here, Figures 6 and 7, including those discussed in the last 7th International Congress of Pesticide Chemistry, Hamburg, 1990. The structure of some of them in Figure 6 (pyrrolnitrin, strobilurin) has been modified for use in plant protection. Since the chemical structure of these natural products in relation to their mode of action is little understood at present, more academic efforts are needed before they can be incorporated into plant protection strategies.

In conjunction with what has been mentioned, structural modification of juvenile hormones (JH) has been attempted yielding several synthetic analogs which, beginning with methoprene, have proved now to be successful in insect pest control. Methoprene is more stable than natural JHs and has been used for control of mosquito and house-fly larvae, but is seldom used in agriculture. Other JH analogs such as phenoxycarb, and especially pyriproxyfen sterically very similar to JH III, are demonstrated to be intrinsically more active, with unexpectedly, additional biological activity as exemplified by the ovicidal activity of pyriproxyfen (Figure 8).

Figure 6. Several examples of naturally occurring bioactive products

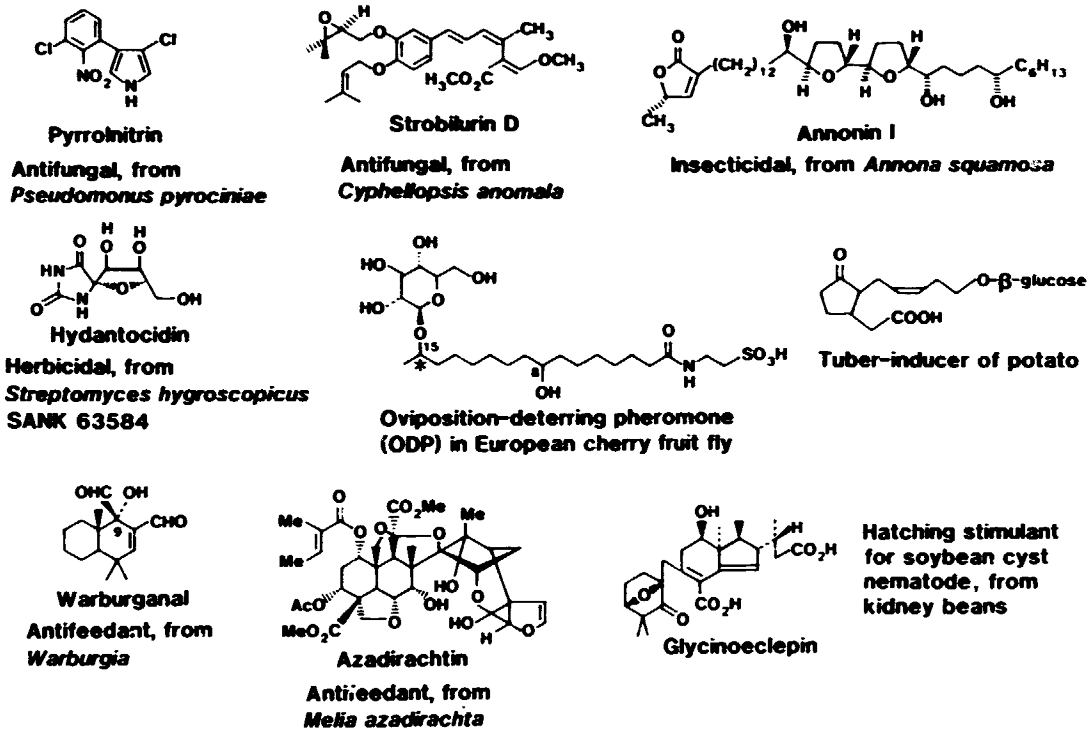


Figure 7. Polypeptides and polyamines as insect hormones or toxins

PBAN (Pheromone Biosynthesis Activating Neuropeptide)

(a) *Heliothis zea*

Leu-Ser-Asp-Met-Pro-Ala-Thr-Pro-Ala-Asp-Gln-Glu-Met-Tyr-Arg-Gln-Asp-Pro-Glu-Gln-Ile-Asp-Ser-Arg-Thr-Lys-Tyr-Phe-Ser-Pro-Arg-Leu-NH_2

(b) *Bombyx mori*

H-Leu-Ser-Glu-Asp-Met-Pro-Ala-Thr-Pro-Ala-Asp-Gln-Glu-Met-Tyr-Gln-Pro-Asp-Pro-Glu-Glu-Met-Glu-Ser-Arg-Thr-Arg-Tyr-Phe-Ser-Pro-Arg-Leu-NH_2

Bombyxin II, PTTH (Prothoracicotropic Hormone) from *Bombyx mori*

```
1                              ┌──────10──┐                                       20
H-Gly-Ile-Val-Asp-Glu-Cys-Cys-Leu-Arg-Pro-Cys-Ser-Val-Asp-Val-Leu-Leu-Ser-Tyr-Cys-OH
                        \                                                  /
1                        \       10                              20       /
pGlu-Gln-Pro-Gln-Ala-Val-His-Thr-Tyr-Cys-Gly-Arg-His-Leu-Ala-Arg-Thr-Leu-Ala-Asp-Leu-Cys-Trp-Glu-

-Ala-Gly-Val-Asp-OH
```

Adipokinetic hormone
from *Schistocerca gregaria*

Glu-Leu-Asn-Phe-Thr-Pro-Asn-Trp-Gly-Thr-NH_2

Venom of ponerine ant (*parapouera clauata*)

Phe-Leu-Pro-Leu-Leu-Ile-Leu-Gly-Ser-Leu-Leu-Met-Thr-Pro-Pro-Val-Ile-Gln-Ala-Ile-His-Asp-Ala-Gln-Arg-NH_2.

δ-Philanthotoxin, Venom of wasp *Philanthus triangulum*

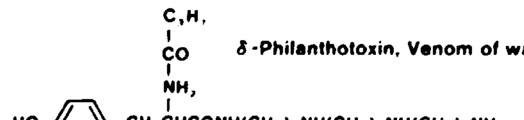
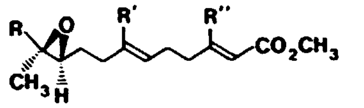
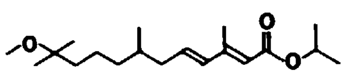


Figure 8. Efficacy of pyriproxyfen (JHA) on insect pests

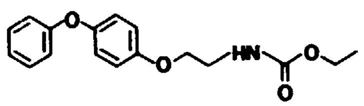


Juvenile Hormone (JH)

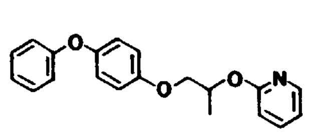
	R	R'	R''
JH III	Me	Me	Me
JH II	Et	Me	Me
JH I	Et	Et	Me
JH 0	Et	Et	Et



Methoprene (1973)



Phenoxycarb (1979)



Pyriproxyfen (1984)

1. Efficacy to Mosquito, *Aedes Aegypti*, (Last Instar Larvae)

	IC_{50}, ppb
Pyriproxyfen	0.0060
Methoprene	2.1

2. Viability of Whitefly Eggs (*Bemisia Tabaci*)/Cotton

Concentration (ppm, a.i.)	Days After Treatment	Egg Mortality, %
1) Preventive		
Untreated	1	12.3
1	1	100
Untreated	13	11.9
5	13	88.3
1	13	46.3
2) Curative		
Untreated	0	23.7
50	0	100

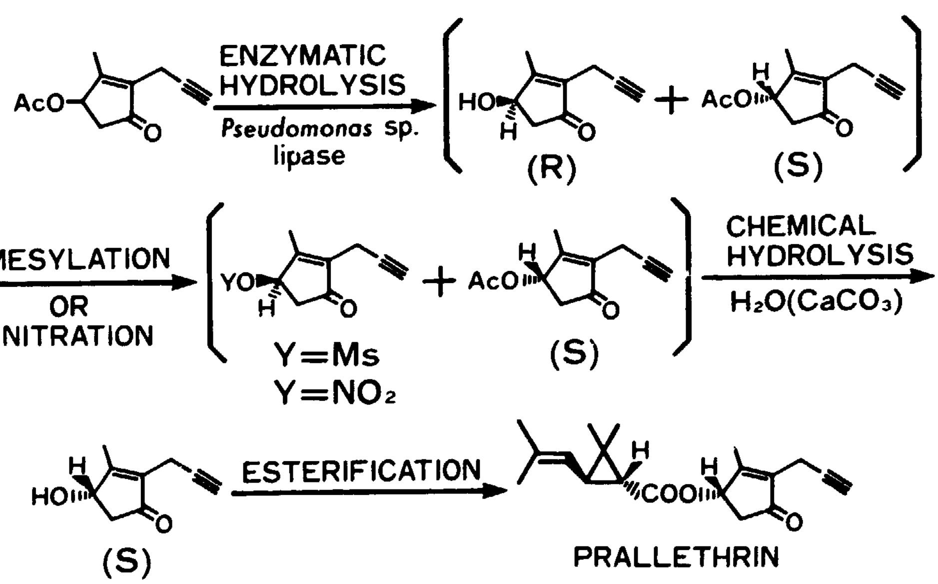
The presence of chiral centres in the molecule generates stereoisomers, one of which may possess different biological activity. A typical example has been seen in synthetic pyrethroids, e.g. esfenvalerate and deltamethrin, already commercially available nowadays. Figure 9 shows another example, where PGR activity of uniconazole can be separated structurally from its fungicidal activity. The progress of stereoselective synthesis will enable to manufacture one specific chiral isomer in a large scale, as shown in Figure 10, in which one optical, insecticidally most active prallethrin isomer can be prepared by combined chemico-enzymatic processes. Such attempts at synthesizing desired isomers should be encouraged, since, if commercialised they will result in release of smaller amounts of necessary aliquot of pesticide into the environment. Thus, in short, thorough chemical understanding on behaviour of living organisms, comparative metabolism, biochemical and molecular studies on mode of action of xenobiotics, coupled with computer chemistry approaches, should be integrated for creating innovative, and rationally designed pesticides, with higher biological activity.

Figure 9. Fungicidal and PRG activities of optical isomers of uniconazole

	Fungicidal Activity(rust inhibition)*			PGR Activity(barnyard grass)
	50	12.5	3.1(ppm)	I_{50}(g/a)
E-R	4	4	4	30
E-S	1	0	0	1.0

*0=49 %, 1 : 50~74%, 2=75~89%, 3=90~99%, 4=100 % control

Figure 10. Chemico-enzymatic synthesis of optically active prallethrin



The principle for generation of genetically engineered plant varieties has been well established and several transgenic plant varieties conferred with insect resistance or herbicide resistance have been available as shown in Table 2. In addition, introduction into plants of viral coat protein genes or anti-sense RNA sequence to viral genome renders them disease- resistant. Diagnostic reagents of various kinds for plant disease are now being prepared. Thus, in future these new plant varieties as well as related novel techniques can be practically used, at least to some extent, for plant protection, and therefore, these and related studies should be expanded and accelerated as much as possible. However, the eventual outcome of genetic engineering research including safety of these plant varieties should be carefully examined and verified for their general acceptance in society.

Just a brief mention should be made regarding formulation chemistry and application technology, which should be improved taking into account the following viewpoints.

- minimum hazard to applicator
- uniform distribution and effective absorption of active ingredient to plants
- least contamination of the surrounding environment
- safe handling of container and waste disposals

To meet these requirements, solventless, and/or driftless formulations have been elaborated, including microcapsules, wettable dispersible granules, and water soluble packet as well. These considerations are particularly important for workers under tropical and subtropical conditions and also for untrained applicators. The use of appropriate adjuvants and surfactants should be recommended to increase adsorption and absorption of active ingredients, as well as electrostatics and anti-drift additives to minimize contamination of surrounding environment. Where appropriate, automatic rinsing devices, and returnable and recyclable pack programmes will be used to avoid excess waste disposal.

TABLE 2
Genetic engineering in plant protection

I. Transgenic plants	
Insect resistance	
Tobacco	Protease inhibitor gene
Cotton, Tomato, Potato, Tobacco	BT-toxin gene
Disease resistance	
Tobacco	TMV coat protein gene
	TMV mild strain
	CMV satellite RNA
	CMV anti-sense RNA
	Tabtoxin acetylase gene
Potato	PVX, PYX coat protein gene
Herbicide resistance	
Soybean, Cotton, Tomato, Rape	Glyphosate
Maize	
Tobacco, Wheat	Sulfonylurea
II. Diagnostic reagents for plant disease	
Monoclonal antibody	
Soybean	*Rhizoctonia*
Rice	RSV
Beet	BNYVV
Kiwi	*Pseudomonas syringae*
DNA/RNA probe	
Potato	PXV (DNA probe)
	PSTV (RNA probe)
Plum	Plum pox virus (RNA probe)

Clearly mammalian toxicology studies are intended to clarify the toxicological features of respective pesticides, based on which NOAEL (No Observed Adverse Effect Level) is established, to be extrapolated to determine Acceptable Daily Intake for Man (ADI). At this moment a number of detailed guideline studies have been required by national regulatory agencies, and the procedures to set up ADI (and VSD - Virtually Safe Dose for tumorigenic compound adopted in the United States of America) have been commonly accepted internationally. However, the cumulative evidence indicates that there exist species differences in response to xenobiotics which sometimes are not yet well correlated with each other, and by which the extrapolation is made with little sound scientific agreement. In other words the relevance to man is remote or non existent in such cases. For typical examples, the rat testicular interstitial cell tumor observed in many strains, hepatocellular tumor by peroxisome proliferators, thyroid follicular cell tumor by thiouracils, renal tumor by branched hydrocarbons, and the mouse hepatocellular tumor by urethanes are often questioned with respect to their relevance to man. Thus, comparative studies in experimental animals and man in every aspect of toxicology, especially those based on molecular understanding, will be undertaken much more extensively to bridge such gaps, including pharmacokinetics (low dose extrapolation) of bioreactive metabolites which produce the toxicological changes. These regulationally less constrained but more in-depth studies help enlighten the true nature of the toxicity.

Another demanding task in toxicology is how to rationalize and refine existing testing protocols based on the numerous new findings, which is also related to social acceptance of animal experiments. Actually a variety of so-called alternative test procedures have been proposed, as listed in Table 3, and several of them are actually used either for confirmatory

TABLE 3

Alternative methods in toxicology

I. Acute toxicity
   1. Fixed dose procedure, by
      British Toxicology Society, Bundesgesundheitsamt, or OECD Method
   2. *In vitro* cytotoxicity assays;
      Morphological changes of cell component
      Inhibition of cell proliferation
      Rate of DNA or protein synthesis

II. Eye irritation
   1. Morphology; Enucleated superfused rabbit eye system
   2. Cell toxicity; Adhesion/Cell proliferation
   3. Cell and tissue physiology; Bovine cornea/Corneal opacity
   4. Inflammation/Immunity; Rat peritoneal cells/Histamine release
   5. Recovery/Repair; Rabbit corneal epithelia (cells/wound healing)

III Skin irritation
   1. Morphology; Test skin (hybrid organism) assay system, Enucleated animal or human skin system
   2. Cell toxicity; Keratinocyte/Proteinase inhibition

IV. Carcinogenicity
   1. Mutagenesis; Gene mutation, Chromosomal abbreviation, DNA damage and repair
   2. Promotor assay; Cell-cell communication, Ornithine decarboxylase induction

TABLE 3 Continued

	3.	*In vivo* short (medium) assay:
		Rapid bioassay
		Multiorgan bioassay for hepato-carcinogenesis.
	4.	Cell transformation assay
V.	Teratogenicity	
	1.	Mouse ovarian tumour cells/cell adhesiveness
	2.	Mouse limb bud/histological differentiation, synthesis of proteoglycans
	3.	Rat neural tube and limb bud/histological differentiation
	4.	Rat whole embryo culture/malformation, death, growth retardation

purposes or for predictive screening testing apart from the required guideline studies. When considering how to minimize false-positive and false-negative findings, how to incorporate human systems, how to reduce the number of animals used, and especially how to acquire scientifically acceptable and significant findings, well simplified, alternative, cost/effective procedures including those *in vitro* using cultured tissue systems will be developed. It is hoped that ultimately some of these will be utilized, replacing the present guideline studies.

Similarly to other structure-activity relationship studies, computer-based structure toxicity relationships (QSAR) have been examined, based on which several programmes have been elaborated as supplements, if pertinent, for predicting toxicity of compounds.

Including all the above, the respective national guidelines and protocols for mammalian toxicity testing should be harmonized internationally to avoid mere repetition of testing, thereby reducing meaningless expenditure of social resources.

No pesticides are completely selective, acting only onto target pest organisms. Depending on their physico-chemical properties, and also on the environmental conditions, they behave in quite a variety of ways, either to translocate to other ecocompartments, or to undergo metabolic alterations yielding more reactive (toxic) molecular species. Thus, to safeguard environmental quality and safety by avoiding as many of the possible environmental issues associated with use of pesticides shown in Table 4, a wide range of environmental studies are needed including 1) crop metabolism and residue determination, 2) abiotic and biotic degradation, as well as bioconcentration and 3) short-term and long-term toxicity in non-target organisms.

TABLE 4
Major environmental issues related to pesticide use

Soil persistency (Build up, Rotational crops)
Ground water contamination
Bioaccumulation in the environment
Undue residues in agricultural commodity
Adverse effects (acute and long-term) on non-target organisms

However, the mere accumulation of numerous experimental trials is insufficient for the discovery of general principles on the environmental behaviour of pesticides: they should be conducted systematically, so as to generate forecasts of the fate of xenobiotics, even under different environmental conditions. It is well known that several physico-chemical properties of pesticides as shown below are particularly useful to predict their mobility within and between environmental compartments as well as alterations therein, and should be utilized as extensively as possible:

- physical state at ambient temperature (mp and bp)
- solubility in water, Sw
- vapour pressure (at 20 ~ 25°C)
- partition coefficient (n-octanol/water), Pow
- adsorption/desorption (preferably Koc - based on organic carbon content of soil or sediment)
- dissociation constant, pK
- relative molecular mass (volume), M

Table 5 shows one example of how these parameters are used to forecast environmental behaviour of pesticides.

TABLE 5

Criteria of pesticide characteristics on groundwater contamination potentiality

Water solubility	:	> 30 ppm
Adsorption coefficient (K)	:	< 5 (usually < 1 ~ 2)
(Koc)	:	< 300 ~ 500
Henry's law constant	:	< 10^{-2} atm. m^3/mol
Charge	:	Negatively charged at ambient pH
Hydrolysis half-life	:	> 25 weeks
Photolysis half-life	:	> 1 week
Field dissipation half-life	:	> 2 ~ 3 weeks

The theoretical approach by using computer modelling and simulation, although premature at present, should be encouraged to enable the data obtained case-by-case to be generalised to establish more predictable principle for environmental behaviour of pesticide.

Since there are vast numbers of non-target organisms in the environment, it is imperative to choose certain limited number of appropriate species for ecotoxicology testing, and also to carefully construct total testing systems including necessary criteria for triggering. The testing conditions should reflect actual environmental conditions where these non-target organisms are to be exposed to pesticides. The environmental monitoring, when deemed necessary, should be conducted in cost/effective ways so as to acquire significant information.

In some countries general public concern about food safety and the safety of minute amounts of pesticide residues which remain in agricultural commodities is questioned, and it appears that legislation and regulation of pesticides are in serious doubt because people think these can never guarantee food safety. However, the fact is that pesticide residues in food never endanger public health: pesticide residues are not the only contaminants in food with toxicological concern, and the total toxicants including those of natural origin should be assessed on the same basis. The consumers have insufficient sound knowledge on pesticides - their importance in food production, and their toxicological properties as well as the regulatory procedures for minimizing risks. Since they can neither avoid exposure to pesticide residues, nor visualize the attendant hazards, they will inevitably be suspicious of pesticide use. So every necessary step should be taken to assist general public through appropriate "risk communication" to form a balanced view on the possible risks of pesticides as compared, e.g., with natural toxic contaminants.

It is unanimously agreed that international collaboration is highly necessary to harmonize national regulations on pesticides, and to solve the problems associated with pesticide residues in agricultural commodities entering world trade. Already the framework for the purpose has been formed, e.g. through the Joint Meeting on Pesticide Residues, the Codex Committee on Pesticide Residues and the International Programme on Chemical Safety activities, and endeavours to strengthen such international ties should be increased. In fact, the difficulty with which developing countries are confronted in urgently increasing agricultural production, can be overcome more easily through closer collaboration of developed countries, including smooth technology transfer. In this context especially "The International Code of Conduct on the Distribution and Use of Pesticides" established by FAO in 1985 should be substantiated as early and as firmly as possible. In tropical and subtropical areas additional considerations and precautions are needed owing to the climatic conditions there which significantly impact on the use of pesticides, e.g., complexity in agricultural pests, altered environmental behaviour of pesticides, easier deterioration during storage of technical products and formulations, more hazards for applicator due to unfavourable working conditions. Thus, mutual understanding and collaboration among every individual and every nation concerned will contribute a great deal to the betterment of mankind in the 21st century, which certainly accords with the sovereign aim of the United Nations Industrial Development Organization.

POSTER PRESENTATIONS

PRESENT STATUS AND COUNTERMEASURES OF INSECTICIDE RESISTANCE IN RICE AND VEGETABLE PESTS IN CHINA

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Of the 26 species of agricultural pest reported to resist insecticide in China, 6 are rice pests and 8 are vegetable pests. Their occurrence is summarised in Tables 1 and 2.

In the green rice leafhopper *Nephotettix cincticeps*, malathion resistance is caused by increased carboxylesterase activity, which plays a more important role in the resistance to dimethoate than the mixed function oxidases. The *in vitro* and *in vivo* results are in agreement with studies of synergism of malathion and dimethoate by triphenyl phosphate (TPP) and S-benzyl O,O-diethylphosphorothioate (EBP). These synergists delay the development of resistance, and EBP when added to malathion has limited the development of resistance to malathion in the green rice leafhopper.

The diamondback moth (*Plutella xylostella*) from Shanghai and Gongchu has developed resistance to organophosphates, carbamates, pyrethroids and DDT. Among them the resistance levels are particularly high for pyrethroids, such as deltamethrin (more than x 10414), fenvalerate (x 2102 and more than x 3569) and permethrin (x 245 and x 1533) by topical application. *In vivo* and *in vitro* studies show that insecticide resistance of the diamond back moth involves several factors: acetylcholinesterase insensitivity, high mixed-function oxidase activity, slight (x 2.4) increase in glutathione S-transferase as well as probable nerve insensitivity. Carboxylesterase might be involved, but does not play an important role in the diamondback moth.

Synthetic population experiments in which the mosquito *Culex pipiens pallens* was used as the standard model pest indicated that insecticide mixtures, alternation or rotation can delay buildup of resistance; resistance to malathion and trichlorfon was delayed when the two insecticides were used together. Used singly each insecticide selected for high resistance within 25 generations. The simulation of mosaic control of malathion and fenvalerate delayed the onset of resistance to malathion but not to fenvalerate within 10 generations. Field experiments showed that mosaic rotation of dimethoate and fenvalerate delayed the onset of insecticide resistance in *Lipaphis erysimi pseudobrassicae* and *Cavariella salicicola.*

TABLE 1

Cases and levels of resistance of rice pests to insecticide in China up to 1989
(Sources: references 1-12)

Species	Insecticide and resistance level	Method of testing	Areas and years occured
1. Rice stem borer *(Chilo suppressalis)*	BHC (x2-4) Parathion (x5) Trichlorfon (x4) Malathion (x3) Dimethypo (x4-15) Methamidophos (x4-13) Methyl parathion (x4-12)	Topical application	Jiangsu, Shanghai, Zhejiang (1986) Shanghai (1987) Jiangxi (1987, 1988)
2. Paddy stem borer *(Scirpophaga incertulas)*	BHC (x5-14) Parathion (x3-6) Fenitrothion (x4)	Impregnated rice seedlings and poisoned breeding medium	Shanghai, Zhejiang and Jianhsu (1975)
	Trichlorfon (x4) Methamidophos (x3) Methyl parathion (x15) Fenitrothion (x3)	Topical application	Shanghai (1988), Guangxi (1988), Guangdong (1988, 1989) Jiangsu (1988)
3. Green rice leafhopper *(Nephotettix cincticeps)*	Malathion (x4) Parathion (x3) Dimethoate (x6) DDT (x3) Metolcarb (MTMC) (x2) Carbaryl (x2)	Topical	Zhejiang (1976)
4. Brown planthopper *(Nilaparvata lugens)*	BHC (x4-6.6) Malathion (x3-10) Fenitrothion (x7-10) Methyl parathion (x3) Isoprocarb (x5-10) Metolcarb (MTMC) (x5-10)	Topical	Zhejiang and Jiangsu (1975, 1986)
5. White backed plant-hopper *(Sogatella furcifera)*	BHC (x3) Methyl parathion (x78) Malathion (x80) Fenitrothion (x97) Carbaryl (x73) Isoprocarb (x8)	Topical	Hunan (1983) (Compared with the LD_{50}'s of the colony from Kyushu, Japan in 1963)
6. Rice leaf roller *(Cnaphalocrocis medinalis)*	Trichlorfon (x3) Methyl parathion (x11) Dimethypo (x16)	Topical	Jiangsu (1986-1987)

TABLE 2

Cases and levels of resistance of vegetable pests to insecticide in China up to 1989
(Sources: references 13-22)

Species	Insecticide and resistance level	Method of testing	Areas and years occurred
1. Melon-cotton aphid *(Aphid gossypii)*	Fenvalerate (x223) Deltamethrin (x520) Dimethoate (x18) Omethoate (x13) Pirimicarb (x81)	Dipping	Beijing, Hebei (1983-1986)
2. Willow aphid *(Cavariella salicicola)*	Malathion (x35) Deltamethrin (x300) Fenvalerate (x230)	Topical application	Shanghai (1986)
3. Mustard aphid *(Lipaphis erysimi pseudobrassicae)*	Sumethrin (x10) Fenvalerate (x8) Dimethoate (x5)	Topical application	Shanghai (1986)
4. Cabbage flea-beetle *(Phyllotreta cittata)*	DDT (x3)	Spray	Zhejiang (1964)
5. Greenhouse whitefly *(Trialeurodes vaporariorum)*	Deltamethrin (x6290) Fenvalerate (x1942) Malathion (x10)	Dipping	Beijing (1987-88)
6. Green peach aphid *(Myzus persicae)*	Dimethoate (x4) Dimethoate (x56) Omethoate (x217) Fenvalerate (x1088) Deltamethrin (x929)	Topical application	Jiangxi (1988) Beijing (1983-88)
7. Cabbage worm *(Pieris rapae)*	DDT (x5-55) Trichlorfon (x100) Acephate (x6) Deltamethrin (x5-28) Fenvalerate (x6) Trichlorfon (>x100)	Topical application	Shandong, Hubei, Heilonjiang, Sichuan, Jiangsu and Shanxi (1981) Shanghai (1988)
8. Diamondback moth *(Plutella xylostella)*	Deltamethrin (x287) Fenvalerate (x435) Cypermethrin (x411) Flucythrinate (x925) Acephate (x4)	Immersion	Shanghai (1986)
	DDT (>x3.1) Carbaryl (>x3.1) Deltamethrin (>x10414) Fenvalerate (x2102->3569) Permethrin (x245-1533) Malathion (x27-144)	Topical application	Shanghai, Guangzhou (1988)

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EFFECTS OF DELTAMETHRIN ON PHOSPHORYLATION OF MOUSE BRAIN PROTEIN *IN VITRO*

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Protein phosphorylation may play an important role in neuronal function, with involvement in regulating processes, such as neurotransmitter biosynthesis or release, generation of postsynaptic potential, and ion channel conductance [1]. Some neuroactive agents produce diverse responses in the nervous system by affecting the phosphorylation status of specific neuronal proteins, which may be implicated in the mechanism of neurotoxicity of neurotoxic agents [2, 3]. Pyrethroids are well known neurotoxic insecticides, but their effect on protein phosphorylation in the nervous system is relatively unexplored. The present paper deals with the effect of deltamethrin on endogenous protein phosphorylation of mouse brain in vitro, which may be helpful in understanding the mechanism of deltamethrin action on the nervous system.

The phosphorylation assay of brain proteins was carried out by incubation of brain preparations with (γ - 32P) ATP as phosphate donor to phosphorylate the protein receptor, two-dimensional electrophoresis to separate the phosphoproteins, and autoradiography to examine the phosphorylation pattern.

RESULTS AND DISCUSSION

Addition of deltamethrin to the mixture for brain slice phosphorylation resulted in increased labelling of three proteins (named proteins 1, 2 and 3 respectively) and decreased labelling of three other proteins (named proteins 4, 5 and 6) (Fig. 1.).

These six proteins were probably phosphorylated by cAMP-dependent protein kinase, since cAMP stimulated their labelling.

Proteins 1-3 with molecular weight 55KD and isoelectric point at pH 7.0-7.5 seem to be "protein III b" which has been identified and proved to be heterogenous on isoelectric focusing [4] but the physiological function of "protein III b" remains unknown.

Figure 1. The effects of deltamethrin on protein phosphorylation of mouse brain fragments with (γ - 32P) ATP. (a) Protein phosphorylation of mouse brain fragments with (γ - 32P) ATP. (b) Proteins 1 to 6 were phosphorylated by cAMP protein kinase, depending on the cAMP stimulation of the labelling of these proteins. (c) Addition of deltamethrin into the mixture for mouse brain fragment phosphorylation resulted in increased labelling of three proteins (1, 2 and 3) and decreased labelling of three other proteins (4, 5 and 6).

Fractions C, D and S were prepared from mouse brain [5], the dominant components of which are nerve endings and synaptic vesicles for C, nerve endings and synaptic membranes for D, and microscomes for S separately. In tests with these three fractions, stimulative effects of deltamethrin on the phosphorylation of proteins 1, 2 and 3 were detected which were similar to those with brain slices, but the amount and labelling intensity of phosphorylated proteins in C and D was larger than in S, respectively (Fig. 2, 3, 4), suggesting that C and D were likely the vital sites for protein phosphorylation, and therefore important sites of deltamethrin effects.

In the experiments with synaptic membrane from mouse brain, phosphoproteins 1-3 can be visualized that seem to be "protein IIIb" which were stimulated by cAMP. Protein 4-6 were hardly detected. A 48 KD protein (named protein 7), however, appeared to be intensively labelled, with isoelectric point of approximately 4.5 pH unit. Moreover, cAMP had no effect on the phosphorylation (Fig. 5). Based on its behaviour on two dimensional electrophoresis and cAMP-independent phosphorylation, it might be the brain specific "B-50 protein", which plays a role in regulation of (poly)phosphoinositide metabolism [6]. The important phenomenon was that the phosphorylation of this protein could be strongly increased by the addition of deltamethrin.

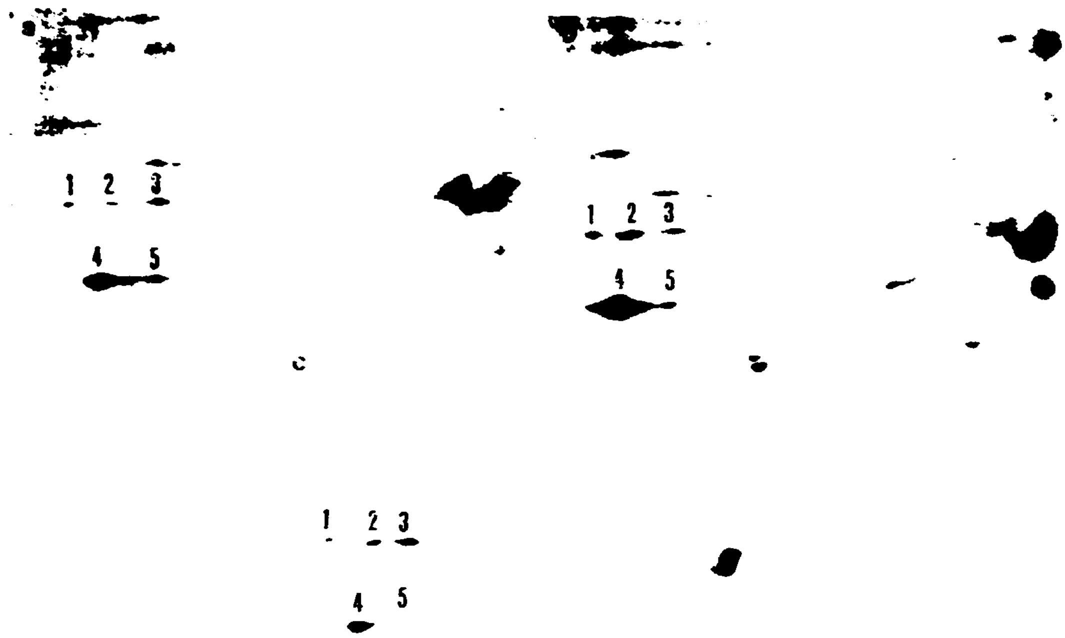

Figure 2. The effects of deltamethrin on protein phosphorylation of fraction C from mouse brain (a), (b) and (c). The phosphorylation pattern of proteins 1 to 5 was similar to that with mouse brain fragments (Fig. 1).

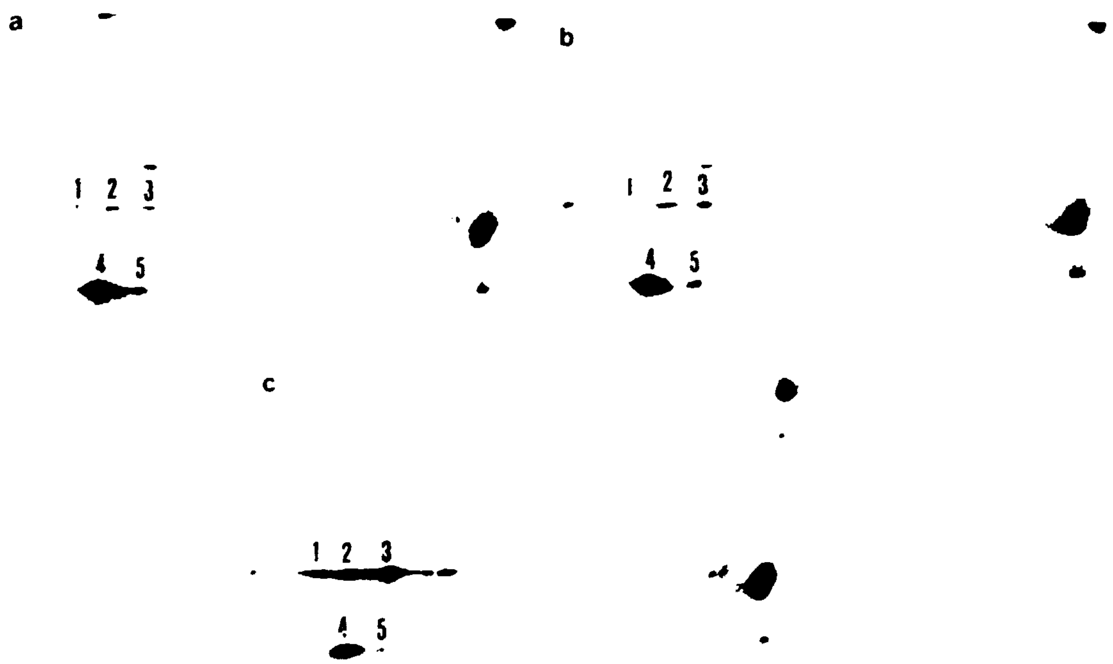

Figure 3. The effects of deltamethrin on protein phosphorylation of fraction D from mouse brain (a), (b) and (c). The phosphorylation pattern of proteins 1 to 5 was similar to that with fraction D (as Fig 2).

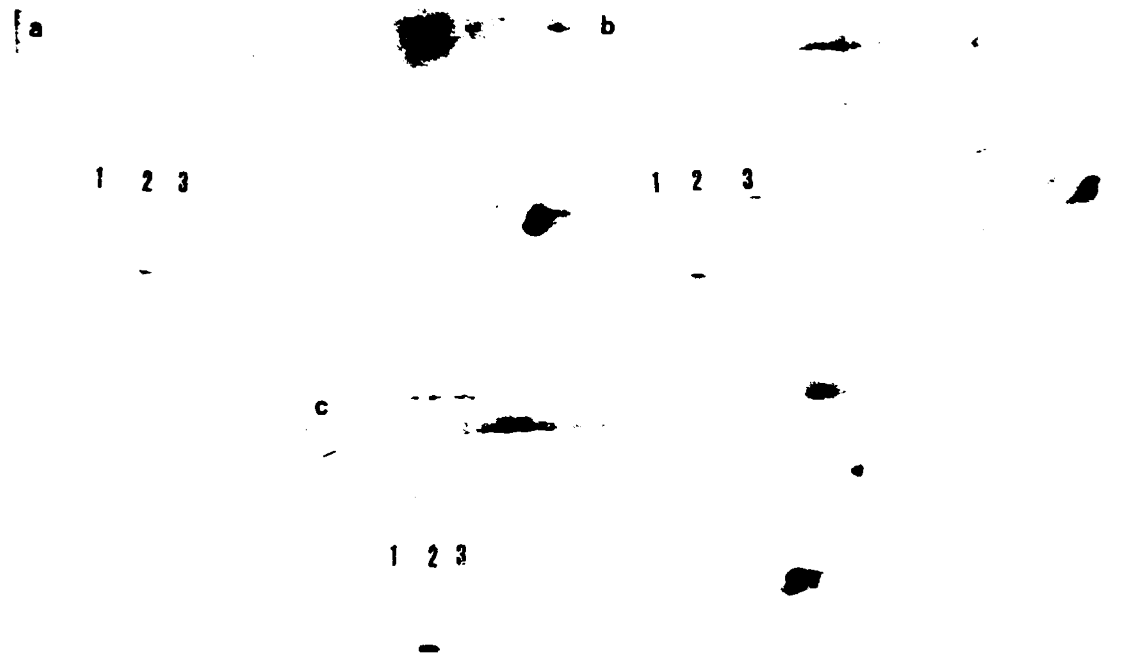

Figure 4. The effects of deltamethrin on protein phosphorylation of fraction S from mouse brain. (a) protein phosphorylation of fraction S with (γ - 32P) ATP as control. (b) stimulative effect of cAMP on the phosphorylation of protein 1, 2 and 3. (c) no effect of deltamethrin.

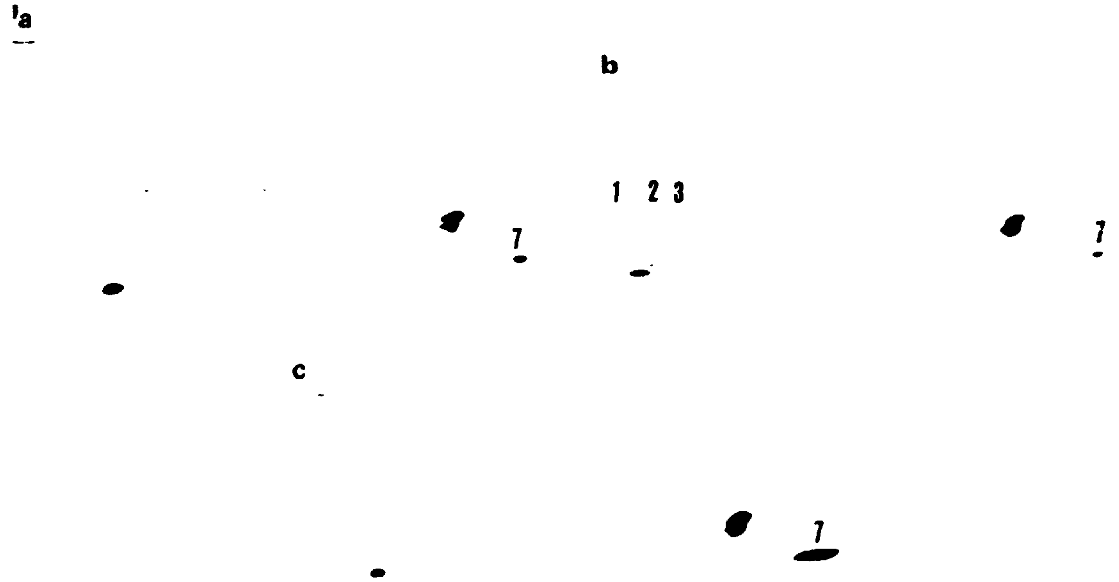

Figure 5. The effects of deltamethrin on protein phosphorylation of synaptic membrane from mouse brain (a) protein phosphorylation of synaptic membrane as control (b) stimulative effort of cAMP on the phosphorylation of proteins 1, 2 and 3, (c) phosphorylation of protein 7 was intensified by deltamethrin, independent of cAMP.

CONCLUSIONS

In an examination of the effect of deltamethrin on phosphorylation of mouse brain fragments or synaptic membranes by *in vitro* incubation with (γ - 32P) ATP, the results showed that addition of deltamethrin into the reaction mixture for phosphorylation of proteins caused increased labelling of proteins (1, 2 and 3) and decreased labelling of proteins (4, 5 and 6). The proteins 1-3 with molecular weight around 55 KD and isoelectric point at pH 7.0-7.5 seem to be "Protein IIIb" which had been identified and proved to be heterogenous on isoelectric focusing. The phosphorylation pattern of fraction C, D and S from mouse brain was similar to that of brain fragments, but the amount and labelling intensity of phosphorylated proteins appearing in C and D were greater than in S respectively. Thus, C and D were more likely to be vital sites for phosphorylation, and possible targets for deltamethrin action.

A 48 KD protein (named Protein 7) with isoelectric point approximately 4.5 pH unit appeared to be intensely labelled in the experiment with synaptic membranes. Based on its behaviour on two dimensional electrophoresis it may be the brain specific "B-50 protein", involved in the regulation of (Poly) phosphoinositide metabolism.

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INSECTICIDE RESISTANCE IN *APHIS GOSSYPII* AND THE POSSIBLE COUNTERMEASURES

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The cotton aphid (*Aphis gossypii* Glover) is one of the most important cotton pests in China. Owing to its short life cycle and great capability in parthenogenetic reproduction, the populationwill increase enormously and break out in a very short time when the environment is suitable. Thus, it is an important target pest for control by chemicals. Because of long-term application of different kinds of insecticides and the special biological characteristics of this pest-insect, it became one of the most resistant species to various conventional insecticides used in North China. This species has been found to be resistant to eleven kinds of insecticides belonging to 3 different types (organophosphates: demeton, parathion, dimethoate, omethoate and phosphamidon; carbamates: carbaryl and carbofuran; pyrethroids: deltamethrin, fenvalerate, lambda-cyhalothrin, and cypermethrin). This has been reported in various areas and at different times.

Studies have been carried out with laboratory and field strains to search for countermeasures to the development of insecticide resistance in this species. The results obtained in recent years are summarized as follows: 1) The cotton aphid exhibits differing ability to develop resistance to various insecticides. Resistance to pyrethroids is developed rapidly because of high frequency of the resistance gene in the natural population of cotton aphids (10^{-}[illegible]) ; 2) Insecticides with long persistency can speed up resistance development, owing to their continuous selection pressure on the immigrant aphids during the period for which the insecticide residues are effective; 3) Destruction of natural enemies by use of insecticides may be the main reason for aphid resurgence, leading to increase of the application frequency and the concentration of insecticide in spraying liquids, thereby speeding up resistance development. 4) Rotational use of different insecticides at rational intervals is likely to be an effective method to restrict resistance development. Continuous use of one kind or one type of insecticide mixture may result in resistance.

Based on the data available at present, suggestions for insecticide resistance control are proposed. Firstly, for resistance management, it is necessary to exploit more insecticides with the following properties : without cross resistance; with low resistance gene frequency in the natural population of pests; low toxicity to natural enemies; short persistence period; efficient in controlling pests; ability to induce only low resistance and to give full control including resistant individuals. Secondly, cross-resistance should be studied in detail and clarified for those insecticides in use. Thirdly, manufacture, supply and rotational use of insecticides not showing cross-resistance should be controlled by government. Lastly, natural enemies should be protected as far as possible by use of suitable insecticides so that they may eliminate pest resurgence, and hence allowing the frequency of insecticide application to be reduced.

USE OF THE SPORE GERMINATION METHOD TO SELECT FUNGICIDES WITH POTENTIAL AGAINST *CERCOSPORELLA BRASSICAE*

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In recent years Cıinese cabbage (*Brassica pekinensis*) grown in Northeast China has been seriously affected by the fungal pathogen *Cercosporella brassicae* Hoehnel. It is now considered to be the second most important disease of this crop after turnip mosaic virus. No resistant varieties to this pathogen have been found. Although 18 varieties have been evaluated they all showed different degrees of susceptibility with disease indices varying from 10 to 51. Four fungicides were examined using a spore germination technique to determine their potential for controlling the disease. Fresh spores were suspended in a 0.125% solution of the formulated product and incubated for 72 hours at 25°C. Effectiveness of each treatment was determined by comparison to an untreated control.

Fungicide	Formulation	% Inhibition
Fenaminosulf + tricyclazole	37.5/37.5% WP	95
Carbendazim	50% WP	94
Mancozeb	70% WP	90
Chlorothalonil	75% WP	78

These data suggest that all these fungicides could be useful for the control of *C. brassicae* in the field.

COMMENTARY ON THE RESISTANCE OF COTTON INSECTS TO PYRETHROID INSECTICIDES AND MONOCROTOPHOS AND THEIR RESPONSE TO METHOMYL

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Resistance to pyrethroid insecticides and monocrotophos has developed rapidly in the cotton aphid (*Aphis gossypii* Glover) and the cotton bollworm (*Heliothis armigera*). Monocrotophos has been used extensively from 1982 for control of cotton aphid and this has led to the development of aphids with 781 fold resistance over susceptible populations. Pyrethroids have been used since 1984 and so frequent was their application that by 1989 aphids with 10,300 fold resistance were present. This meant that neither insecticide gave effective insect control even at rates double those that are recommended. Methomyl on the other hand has been used successfully for 5 years and still gives effective control of cotton aphids at its recommended application rate.

A similar situation has occured with control of cotton bollworm. Application rates of monocrotophos have doubled from 1984 but the level of insect control has fallen with 10 fold resistance being noted. The situation for pyrethroids against cotton bollworm is even worse as the frequent and high use rate against cotton aphid has led to high levels of resistance rendering these compounds virtually ineffective. In 1985 recommended use rates of pyrethroids gave complete control of this insect but by 1988 this had reduced to 65%. Once again methomyl has been shown to maintain its level of control over a 5 year period with no loss of effectiveness.

Earlier work in this laboratory has suggested that there is negatively correlated cross resistance between methomyl and both pyrethroids and monocrotophos against aphids. These data suggest that a similar relationship exists between methomyl and these compounds thereby providing a tool to combat the development of resistance of two major pests in cotton and to allow cost-effective insect control in the most important insecticide market in China.

STUDY ON WATER-BASE ULV SPRAY TECHNIQUE

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The formulations, which were composed of water soluble evaporation inhibitors (molasses, paper industrial black liquor and sodium carboxymethyl cellulose), technical materials or formulations of pesticides for spray application, and water, have been developed for water-based ultra-low-volume spraying. They can be used in ULV spraying by airplane or by ground sprayer due to the inhibition of water evaporation of drops in the course of falling to the target and retention of adequate diameter by drops until they reach the ground.

Between 1980 and 1990, 14 pesticides (methamidophos, acephate, phosphamidon, trichlorfon, dichlorvos, phenthoate, malathion, dimethoate, phoxim, fenitrothion, isofenphos-methyl, lindane, shachong-shuang and sulphur) in three formulations (solution, suspension and emulsion) were tested in total area of 93,333 hectares to control 11 targets: pine caterpillar (*Dendroliumus* spp.), rice leaf-tier (*Parnara guttata*), rice case worm (*Cnaphalocrocis medinalis*), aphids (*Aphis* spp.), cabbage butterfly (*Pieris rapae*), locusts (*Locusta* spp.) on pasture, mosquitoes, flies, midges, buffalo gnats, and powder mildew (*Oidium heveae*) of rubber trees. This technique can also be used in dry areas of Xinjiang with a relative humidity of 20-40%. As a new method of pesticide application in China, this technique possesses originality, advantage and practicability which has led the ULV spray technique to be adopted and welcomed widely.

FURTHER STUDIES ON THE INSECTICIDAL PLANT CHINESE BITTERSWEET, *CELASTRUS ANGULATUS*

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The Chinese bittersweet, *Celastrus angulatus* Max., which is widely distributed in China, is a potential botanical insecticide. The root bark contains much more bioactive material compared with the other parts of the plant and is suited to formulations of dustable powder or emulsifiable concentrate for insect pest control. The results of field plot experiments showed that the damage of *Pieris rapue, Parnara guttata, Athalia flacca, Semiothisa cinereuria* and *Aulacophora femoralis* etc. could be controlled effectively by application of the preparations. The extracts from the plant possess at least 4 types of action, i.e. antifeeding action, insecticidal action, narcotic action and fungicidal action. An ethyl ether extract of the root bark was found to be rather stable to sunlight, heat and alkaline condition as compared with many other natural products. A novel insect antifeedant, celangulin, has been isolated from the root bark. Celangulin is a sesquiterpenoid compound. Its structure was determined by NMR and mass spectrometry. Three compounds that have strong narcotic action against armyworm (*Spodoptera frugiperda*) have been isolated under the guidance of the bioassay, but the determination of the structures has not been finished. The symptoms of the narcotic action are similar to the symptoms caused by an analogue of the insecticide nereistoxin (NTX). The fraction possessing narcotic action acts on the nerve - muscle junction suppressing the excitatory junction potential (EJP), while NTX and its analogues act on the nerve synapses, suppressing the excitatory postsynaptic potential (EPSP). The Chinese bittersweet preparations have been found safe for mammals and other nontarget organisms and the environment, effective for controlling insect pests and available in large quantity. These characteristics meet the requirements of the criteria that plant species for pest control and use in rural development should possess.

PRELIMINARY STUDIES ON THE PROPERTIES OF A VIRUS INACTIVATING SUBSTANCE FROM SPINACH LEAVES

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Sap from spinach leaves was treated with 50% ammonium sulphate and the precipitate resuspended in 0.01M neutral phosphate buffer. This was then filtered through a Sephadex G-100 column and the active fractions were combined. Further purification was achieved by pouring the combined fractions through DEAE-cellulose and CM-cellulose ion exchange columns. The purified inhibitor gave a positive reaction with both biuret and Coomassie brilliant blue.

The ultraviolet absorbance spectrum showed a typical protein curve with a maximum absorbance value at 280nm. The molecular weight was about 42,000 D. If stored at 4°C for 100 days the leaf extract lost its inhibitory activity.

In whole plant studies it was shown that the inhibitor prevented TMV infection on *Nicotiana glutinosa* but had little effect on *Chenopodium amaranticolor*. If the purified leaf extract was sprayed onto tobacco leaves and then rinsed with tap water prior to inoculation with TMV good protection from viral infection was still achieved. Indeed the protective effect of the extract exerted its effect for a long period after application.

The observations suggest that the proteinaceous inhibitor is either binding to the leaf or cell surface or it is inducing an antiviral response in the host plant cell. Further studies are in progress.

FENVALERATE, MALATHION AND THEIR MIXTURE AS AN APPROACH TO THE DEVELOPMENT OF RESISTANCE IN CABBAGE APHID (*LIPAPHIS CRYSIMI* (KALTENBASCH))

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During 1986 - 1987 the susceptibility of the cabbage aphid (*Lipaphis crysimi*) to fenvalerate was tested in the area of Beijing. This indicated that the aphid population from Hai Dien district had 11.8 - 388.52 fold resistance as compared with that from two remote districts, Hui Rou and Yen Chin. For this reason, cabbage aphids were used as one testing insect to study the development of resistance to fenvalerate, malathion and their mixtures.

1. Cabbage aphid (*Lipaphis crysimi*) was collected from a village in Hai-Dien district, Beijing and then reared on turnip leaves in the greenhouse for two weeks. They were then treated topically with fenvalerate (Fe), malathion (Ma) or a mixture (FM) to determine an LD50 value. Subsequently the aphids were reared as 4 separate strains (Fe, Ma, FM and the check), in 4 insectaries. Each strain was treated every 20 days with either fenvalerate, malathion, the mixture or untreated control. A rate giving 80% control was used.

After the 13th treatment considerable changes in susceptibility had resulted. The concentration of fenvalerate applied rose from 50ppm to 800ppm, whilst the aphid mortality fell from 86.2% to 58.3%. Resistance rose to 163.2 fold over the initial level but if compared with Hui Rou relative susceptible strain, the resistance reached 938.9 fold. The concentration for malathion treatment rose from 50ppm to 125ppm. The mortality rate dropped from 76.2% to 74.3%. Resistance was 15.5 fold. The concentration of the fenvalerate/malathion mixture was still 50ppm, while the aphid mortality rate was always above 85%. The FM strain showed 4.1 fold resistance to the mixture.

This result indicated that as compared with the two single compounds, fenvalerate/malathion mixtures would definitely delay the development of resistance in cabbage aphid (*Lipaphis crysimi*).

2. Enzyme *in vitro* activity evaluation showed the carboxyl-esterase activity value in Fe strain was 568 μM-naphthol/mg protein/15 minutes which was 2.7 fold that of FM population (211 μM-naphthol/mg protein/15 minutes). When triphenyl phosphate (TPP)

was added, the susceptibility of Fe strain was restored to its previous level. This result showed that the increase of carboxylesterase activity was one of the major causes of the development of resistance to fenvalerate.

It is also indicated that the resistance to malathion was also positively related to the intensified activity of acetycholinesterase. However, the function of phosphatase and glutathion transferases is not clear and further investigation is needed.

3. Mathematical statistics and computer analogical curve were adopted to forecast the life of FM EC. In terms of the analogical curve we inferred that resistance rose by 10 fold and 100 fold when fenvalerate was sprayed 5 times and 11 times and malathion 12 times and 24 times, but FM EC could be sprayed 28 and 60 times. If insecticides were applied twice per year on average, fenvalerate could be used for 2-5 years, malathion could be used for 6-12 years, while FM EC could be used for 14-30 years. This indicated that compared with single fenvalerate, FM EC would prolong its life by 6-7 fold.

BEHAVIOUR OF DIMEHYPO IN SOILS

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Dimehypo [2-(N,N-dimethylamino)-1, 3-(dithiosulfonate sodium) propane] is a novel pesticide developed in China. There is little research work about physicochemical behaviour and environmental effect of the pesticide. For its proper use and management we have investigated the degradation, adsorption and leaching of dimehypo and its primary degradation product, namely nereistoxin [4-(N,N-dimethylamino)-1, 2-dithiolane].

1. The hydrolysis rate of dimehypo is less than 10% at 50°C in buffer solution of pH 3, 7 and 9. Under strong alkaline condition, dimehypo can be easily changed to nereistoxin. The degradation of dimehypo in red soil, black soil, yellow brown soil and meadow soil indicates that degradation rate slows down with the decrease of soil pH. Furthermore, the disappearance of dimehypo in soil is mainly by microorganism-related processes. Dimehypo and nereistoxin are sensitive to sunlight, and the $t_{1/2}$ of photodecomposition is 3.75 hours for dimehypo (average luminous intensity 80,000 Lx) and 21 minutes for nereistoxin (average luminous intensity 54,000 Lx).

2. Adsorption of dimehypo by soils is negligible, whereas nereistoxin can be sorbed in soils to a large extent. On the basis of the molecular structures and the experimental results, we propose that metal-ion-bridged (especially Mn2 +,4 +) mechanism be the dominant interaction mechanism for dimehypo, and soil organic matter be the main adsorption site for nereistoxin.

3. Considering the characteristics of dimehypo (high water solubility, resistance to hydrolysis, little adsorption in soils, low degradation rate under normal soil pH value) and weak microbial activity in subsoil, we should pay particular attention to leaching of dimehypo and threats of groundwater contamination. A field experiment in a suburb of Nanjing has proved the considerable potential of dimehypo and nereistoxin to leach down the soil profile in paddy fields.

TOPICS FOR GROUP DISCUSSIONS

Each day during the Seminar work group discussions were held on the following topics:

Can the developing world afford rational pesticide design and do they have the technology to manufacture complex molecules?

Chairman, L.G. Copping (United Kingdom) — Rapporteur, A.K.M.F. Kabir (Bangladesh)

What new or different pesticide targets are there in developing countries? Are they different from those in Europe, the United States and Japan? Can pesticide discovery be regional?

Chairman, B. Sugavanam (UNIDO) — Rapporteur, R.C. Saxena (Philippines)

What special properties are needed for pesticides targeted for agriculture in developing countries? (Mobility, persistence, spectrum, activity level, mode of action, etc).

Chairman, K. Holly (United Kingdom) — Rapporteur, B. Thomas (United Kingdom)

Will population/economic factors lead to an increased dependence on crop protection agents? Will there be a population shift from the farm to urban/industrial life styles?

Chairman, K.J. Brent (United Kingdom) — Rapporteur, G.A. Matthews (United Kingdom)

What formulation types are preferred for developing countries? Should they be crop specific?

Chairman, K.J. Brent (United Kingdom) — Rapporteur, A.K.M.F. Kabir (Bangladesh)

Will application techniques render crop protection more efficient? Do we have the correct formulations for new application equipment?

Chairman, L.G. Copping (United Kingdom) — Rapporteur, K.H. Kuck (Germany)

Should we concentrate on improved cultural/agronomic practice rather than chemical crop protection?

Chairman, B. Sugavanam (UNIDO) — Rapporteur, B. Thomas (United Kingdom)

What can we learn from experience with natural products? Is there really a "gold mine" waiting to be discovered?

Chairman, K. Holly (United Kingdom) | Rapporteur, D. Mangold (Germany)

What strategies should be adopted to avoid the onset of insect resistance? What species and crops are particularly at risk?

Chairman, K. Holly (United Kingdom) | Rapporteur, S.P. Dhua (India)

What approaches should be taken to prevent the development of disease resistance? Where is there likely to be a major problem?

Chairman, L.G. Copping (United Kingdom) | Rapporteur, B. Thomas (United Kingdom)

Is the possibility of herbicide resistant weeds a cause for concern? If so, how can it be avoided?

Chairman, K.J. Brent (United Kingdom) | Rapporteur, C.E. Price (United Kingdom)

How can UNDP/UNIDO improve the efficiency of its aid/education programmes?

Chairman, B. Sugavanam (UNIDO) | Rapporteur, N.W. Forrester (Australia)

All groups - What single take-home message is there for developing countries from this meeting?

Chairman, B. Sugavanam (UNIDO).

RECOMMENDATIONS

Based on the recommendations of the various discussion groups the meeting concluded that such international seminars on pesticides covering high level technology are rarely organized in developing countries, and that organizations like UNIDO should assist in conducting such seminars once in 3 or 4 years in an advanced developing country.

The following recommendations were made by the Working Groups and adopted by participants of the Seminar.

Recommendation 1

i) Having discussed the capability available in some developing countries to design compounds from basics, and considering the fact that no major pesticides have been developed in developing countries, the group recommended that:

developing countries with capabilities should adopt a broad-based approach to discovering new pesticides founded on natural products, synthesizing novel compounds and collaborating with major companies for development.

ii) Having realized the manufacturing potential of many developing countries, the group recommended that:

collaboration should take place with major manufacturing countries to ensure cost-effective and safe production and, above all, collaboration should be fostered among developing countries as a way forward, particularly with respect to the manufacture of pesticides.

Recommendation 2

Having considered in detail various bacterial diseases, virus diseases, insecticide-resistance strains, pest with resurgent potential, and nematodes and having seen similarity in some of the requirements between developed and developing countries, the group recommended that:

ways and means be developed to find pesticides based on natural products, good aphicides, oviposition inhibitors, nematicides and soil fungicides.

Recommendation 3

i) Having considered the crucial need for the safety and cost-effectiveness of pesticide targeted for developing countries, the group strongly recommended that assistance be given to developing countries:

for end-user education

to help local industry to supply easy-to-use formulations of low toxicity, and provide suitable protective clothing to workers in industry and in the field.

ii) Having discussed the lack of availability of pesticides in many developing countries, the group recommend that assistance should be given to those countries:

to concentrate on the manufacture of formulations that are safer and cost effective and on the production of carefully selected commodity active ingredients

to help in getting licensing agreements to manufacture new active ingredients (Patented products).

Recommendation 4

Having considered the fact that there will be a general increase in pesticide production/use to support the increasing population and also that substandard pesticides are being used in the region, the group strongly recommended assistance to:

local industry to improve their quality standards

government to implement quality control of agrochemicals.

Recommendation 5

Having discussed in detail problems faced by industry in developing countries to produce newer/safer pesticide formulations, and the commonly produced emulsifiable concentrates (EC), wettable powders (WP), and dust formulations which are safe, the group strongly recommended assistance to:

local industry to promote production of safe, reasonably priced, high quality formulations in developing countries.

Recommendation 6

i) Having discussed issues such as seed treatment and granular application and taking into consideration various advantages (including environmental) of relevant formulations, the group recommended assistance to:

local industry to make these safer during production and handling and including establishing centralized seed treatment facilities.

ii) Taking into account definite advantages of ULV application the group recommended that:

care be taken on drift problems

industry make available more formulation types and provide effective machinery

operators be educated and that local special teams be created for spray application

use of safer spray type formulations adaptable to existing conventional application techniques/equipment.

Recommendation 7

i) Having discussed the framework of integrated pest management (IPM), and having defined various agronomic/cultural practices, the group recommended that the following should be advocated in such a system:

use of pest/disease resistance crops

correct timing of pesticide application(s)

crop rotation, intercropping

water management

effective formulations for seed treatment

correct choice of safe and effective pesticides

use of appropriate application techniques.

ii) Having considered the inter-disciplinary nature of such a task and taking into consideration the necessity of close interaction between industry and government, the group strongly recommended subsidies or assistance to industries to produce and supply effective application equipment instead of subsidizing the import of pesticides and to provide training to extension workers/farmers/operators.

Recommendation 8

Having discussed biopesticides and natural products from plants and microbial sources and taking into consideration the perceived limitations, and having observed that this field offers scope to generate leads, the group recommended:

that more co-ordination is needed among different organizations, especially UNIDO/FAO, for modifications and commercialization of pesticides of natural origin.

Recommendation 9

i) Resistance of Fungicides

Having discussed the use of fungicides in developing countries and the recent exhaustive work on resistance management, the group strongly recommended:

use of mixtures

use of disease-resistance crop varieties

judicious use of fungicides.

ii) Resistance to Herbicides

Noting that herbicide resistance is limited in developing countries, but to be on the cautious side and prevent large-scale occurrence of resistance, the group recommended to:

avoid repetitive use of single herbicides and make herbicides with different modes of action available to farmers.

maintain a close watch on the performance of herbicides.

iii) Resistance to Insecticides

Having deep concern about large scale occurrence of resistance by insects in China and the region, the group stressed the importance of:

understanding the biology of the insect or other pests

developing integrated strategies appropriate to different geographical situations and agricultural systems

educating advisers/farmers on the use of early warning systems.

iv) Having recognized the need for Integrated Resistance Management (IRM) with a sound communication network exchanging information between industrialized and non-industrialized countries and information filtering through to producers and users, the group recommended close collaboration between UNIDO and FAO to assist developing countries in dissemination of information.

Recommendation 10

Having discussed the expertise available within organizations such as UNIDO, the group reommended:

close liaison be kept with other organizations such as the FAO and the WHO to implement recommendations, especially on IPM

training of workers both in industry and in the field

follow-up of projects after end of assistance

provision of stimulation to industry to modernize plants, thereby promoting not just the cheapest but clean and well understood technology

massive investment in upgrading established pesticide plants.

CONCLUSIONS

It was concluded that the International Seminar held in a developing country had given an opportunity to participants from industries and Government institutions to discuss at national and international level topics of great relevance to developing countries, especially those problems that could be solved by close co-operation between developed and developing countries.

The Seminar put great emphasis on formulation, environmental safety and management of resistance to pesticides. These were the areas in which the meeting clearly recognized the role of international organizations to assist developing countries for a sound and safe development of the pesticide industry.