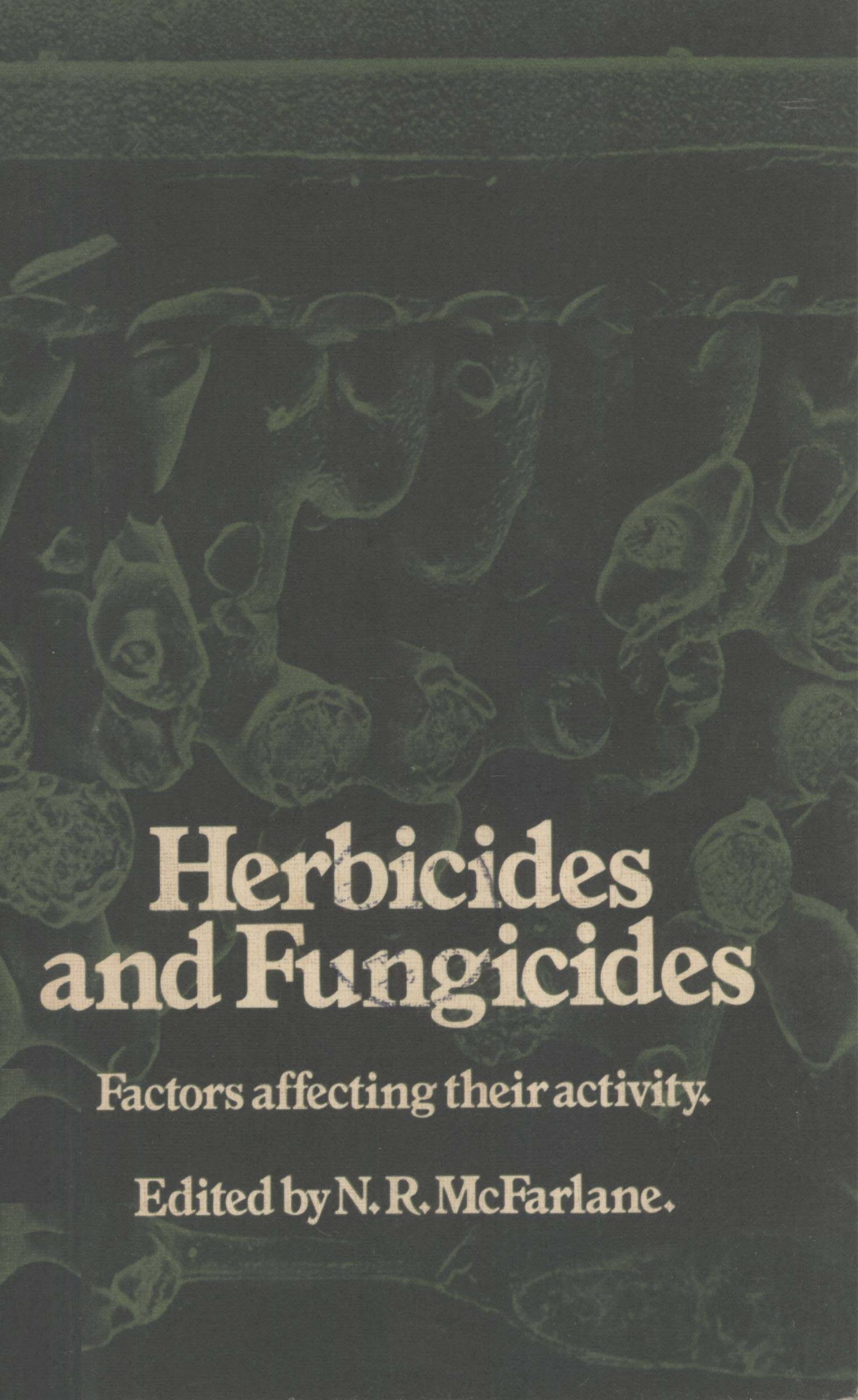

Herbicides and Fungicides

Factors affecting their activity.

Edited by N. R. McFarlane.

Special Publication No 29

Herbicides and Fungicides - Factors affecting their Activity

Bangor, Wales, 15–17 September, 1976

The Proceedings of a Symposium arranged jointly by the Fine Chemicals and Medicinals Group of The Industrial Division The Chemical Society and the Pesticides Group of The Society of Chemical Industry

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Preface

The planning and arrangement of a good scientific meeting can be quite involved and some may say that the arrangement of a joint meeting can be doubly difficult. It is a pleasure, therefore, to report that a small working party, from the Chemical Society and the Society of Chemical Industry, proved to be most effective in promoting this meeting, which was so well received by the delegates.

Herbicides and Fungicides have many general features in common and these are often associated with the interactions with plants. Recent years have seen an increasing demand for more knowledge concerning the interactions and reactions of pesticides, and a large proportion of this can be gathered under the general title of Biophysics. It is not surprising then that many of the papers presented are concerned with this subject. It was the intention of the working party to try to expose some of the features of herbicidal and fungicidal action that relate to organic molecules without becoming extensively involved in synthetic organic chemistry. This is not because the prominent position of synthetic chemistry in pesticides research is becoming less important but, rather, that increased understanding of biology and 'organized matter' has promoted other scientific disciplines to a strong supporting role for synthesis. The modern synthetic chemist needs to be aware of a wide range of factors, physical, chemical, biochemical, and environmental, if he is to make full use of his resources and talents to create new and valuable products. Thus this meeting was designed to bring together those involved in pesticide research and development to discuss the factors affecting the activity of herbicides and fungicides. It is hoped that a great understanding of these factors will assist in the more rational design of new, useful, biologically active materials which will be of benefit to all.

These, then, were some of the reasons for promoting this meeting and the areas upon which the working party wished to focus. The organizers gained considerable satisfaction from the response of delegates to the meeting itself and hope that this monograph is found equally acceptable by those who did not attend the meeting. It is arranged so that the early papers provide the historical and current perspective of the general areas, with the central group of papers giving details of current experimentation, while the final papers move to more theoretical aspects of the subject. This allows the reader to progress through the subject matter in a convenient logical manner.

The production of the monograph is the result of work commenced nearly two years earlier when the meeting was first discussed, and many people concerned with the arrangements warrant recognition for their contributions. Of particular importance in this regard are the members of the working party from the Chemical Society Fine Chemicals and Medicinals Group, Dr. S. Turner and Dr. E. W. Parnell, who, together with myself, representing the Pesticides Group of the Society of Chemical Industry, brought the meeting into being.

The sponsoring Groups provided continuous support and we are grateful to Dr. L. F. Wiggins, Chairman of the Fine Chemicals and Medicinals Group, for his encouragement and his opening address at the meeting. The Session Chair-

men also deserve our thanks for their expertise in handling the very active discussion periods. The papers evoked many questions and with such extensive delegate participation and interest in all aspects of the papers the sessions proved to be quite challenging for the Chairmen. Dr. D. Woodcock and Mr. J. M. Winchester were diplomatically firm in keeping the sessions moving while not detracting from the general participation of the delegates.

The Conference Reception and Dinner warrant mention as the major social events associated with the meeting, and Monsanto Ltd deserve our thanks for their financial support in this regard. The speaker at the Dinner, Mr. K. C. Bryant, President of the Industrial Division of the Chemical Society, expressed firm views regarding the great value of such associations between the two Societies at this joint meeting. Mr. Bryant's remarks were very well received by the delegates.

It would be remiss not to mention the considerable assistance received from the permanent staff of the Societies, in particular Mrs. J. Axworthy of the Society of Chemical Industry and Mr. R. Sharp of the Chemical Society Publications Department. The staff at University College, Bangor, provided friendly assistance with the organization and this, together with the modern facilities and pleasant situation, aided in the enjoyment of the meeting.

The papers as presented have been rearranged slightly for publication. The paper presented by K. Holly on Possible New Methods of Attack on Weeds, which was part of the original programme, is the only omission from the volume.

Finally, on behalf of speakers and delegates I hope that readers find the work reported here to be of interest and of value to their own research. The wider understanding of the factors affecting the biological activity of herbicides and fungicides provides complex challenges which, it is felt, will receive increasing attention in future years and this volume will, perhaps, be of value in assisting the progress and development of the work in this area.

N. R. McFarlane March 1977

Contents

Generally speaking, forecasters seem reasonably confident that in the next decade or so, the demand for pesticides will continue to expand and so maintain their important contribution to increasing global food production and protection of health. Also that this will be achieved principally by further intensification of food production in developed countries, and the latter will therefore continue to be the major consumers of pesticides.

It is also widely assumed that Industry will be able and willing to continue production of well established pesticides or equivalents, to replace those which have been phased out for regulatory or other reasons with alternatives, and continue to introduce novel products for damaging pests not yet satisfactorily controlled.

These forecasts and underlying assumptions are discussed in the context of economic and other constraints now affecting Industry, in particular returns on R & D investment, and increasing risk associated with market-instability and restricted potential of many new pesticides.

Various strategies have been proposed to resolve some of these problems and to meet the changing circumstances of pesticide R & D, production and use. Their relevance to the overall objective of securing additional food production and improved health protection is discussed. They include: provision of Pest Management Services by Industry, demand forecasting and purchase of buffer stocks of pesticides by State and international organisations, greater involvement of the latter in the development of pesticides having relatively small use potential, and R & D cost-sharing between members of Industry and State.

The outlook for these strategies is assessed in relation to pressing problems and uncertainties surrounding the future of pesticides. It is concluded that none adequately deals with the central problem and crucial need to establish widely agreed concepts and methods for the assessment of risk associated with the development and use of pesticides.

Although there is an extensive range of commercially available herbicides, there appear to be relatively few cellular sites at which an initial molecular involvement occurs. A large number interact with the process of photosynthesis either by preventing chloroplast electron transport or by diverting the reductive energy of the chloroplast to generate toxic products. Some herbicides uncouple mitochondrial electron flow from phosphorylation and thus prevent the normal cellular processes of conservation and supply. The auxin-type herbicides are applied to plants as an active herbicidal compound or alternatively as a compound which is metabolized by the plant to an active compound. The eventual morphological aberrations are most probably initiated by events at the level of cell membranes and/or in the transcription of genetic information. Other herbicides exert their action by the inhibition of biosynthetic pathways.

After an initial herbicide interaction, a series of events follow which eventually lead to cellular disorganisation and death. These events are discussed with particular reference to the effects of excess excitation energy, free radicals, and superoxide.

The mode of fungicidal action of some conventional surface fungicides is outlined, and the proposed mechanism of action of some important systemic fungicides discussed. The next three sections deal with the problem of the emergence of strains of fungi tolerant to sytemic fungicides, the mechanisms of resistance, and the reasons why the phenomenon of resistance is more widespread against systemic fungicides as compared with surface fungicides.

Some ideas of possible new methods of attack on fungi are given, such as, (i) the screening of chemicals for inhibition of chitin synthesis; (ii) the isolation and investigation of more naturally occurring antifungal compounds (phytoalexins); (iii) the development of chemicals that translocate downwards from the foliage to the roots for the control of root pathogens; and (iv) chemicals acting indirectly so as to increase the natural resistance of the host plant to pathogenic attack.

Biological methods include crop breeding to produce more resistant plants. Acquisition of more precise knowledge of the life cycle of the pathogen may enable it to be controlled by altering its environment. The discovery of more specific fungicides attacking only the target pathogen will enable more integrated chemical and biological control measures to be developed. This would reduce the amount of chemical fungicide needed to effect control and would reduce the dangers of environmental contamination.

The relatively recent introduction of commercially effective systemic fungicides has accelerated the search for products which possess biological activities differing from the traditional protectants.

Screening techniques had moved towards *in vivo* tests more closely approximating to the field situation even before the discovery of these systemic compounds. Their arrival, however, did focus greater attention on the need to ensure that lethal quantities of the toxicant, either as a 'plant' surface residue or as an accumulation within the plant, are present when the plant is challenged by the fungus particularly in the infection court of the pathogen.

Of the fungicides which have been most widely used three broad categories may be recognised, based on the hypothesis that success is as much a function of a favourable interaction with the host/pathogen as their inherent fungitoxicity.

These are (a) the true protectants typified by the inorganic materials, (b) the organic fungicides with partition factors which confer some degree of curative activity against a characteristic group of fungi, (c) systemic compounds with potential for extensive movement within the plants.

The morphological and physiological factors which control solute uptake and translocation in plants are considered from the point of view of herbicide and fungicide applications. Analytical microscopy techniques such as cathodeluminescence, *X*-ray diffraction, and fluorescence enable us to view the active compounds and their formulation additives *in situ* and measure their interaction, penetration, and responses to changes in the environment.

Penetration of the herbicide or fungicide across the cuticle into the cell walls leads to the possibility of translocation to other parts of the plant. Lack of translocation can be regarded as a positive attribute of the solute, resulting from its retention behind membranes or adsorption onto apoplast, symplast or vacuole components. Xylem systemic action requires only the dissolution of the active ingredient in the water of the transpiration stream but phloem transport apparently demands penetration across a membrane with highly selective permeability characteristics. The nature of the chemical properties conferring phloem mobility is discussed in relation to problems of identifying potential phloem systemic compounds.

The physico-chemical and biophysical factors governing cuticle penetration, short and long-distance translocation will be reviewed with reference to certain foliage-applied herbicides. The efficiency of cuticle penetration is governed by a variety of factors which can be categorised as ‘plant’, ‘herbicide’ or ‘environmental’ in nature.

The ‘plant’ factors include the surface of application (adaxial or abaxial), leaf age (nature and thickness of cuticle and amount of birefringent wax), sites of preferential entry (viz. cracks, perforations, stomata, glandular hairs, cuticle adjacent to veins, anticlinal walls, etc.). The ‘herbicide’ factors include the molecular structure and configuration, formulation, hydrophilic/lipophilic balance, nature and concentration of surfactant and other additives, pH, droplet size and distribution, etc. Important ‘environmental’ factors include temperature, humidity and light.

Penetration of the symplast and translocation in the phloem system may be directly correlated with absorption and is apparently also influenced by many of these ‘herbicide’ and ‘environmental’ factors. The critical ‘plant’ factors may include the type of plant (‘C3’ or ‘C4’), age of treated leaf (importing or exporting assimilates), relationship of source to sink, orthostichy, susceptibility of energy metabolism to the penetrating compound, etc.

The cuticular complex is the first part of the plant with which a herbicide makes contact. The constituents of the cuticular complex include hydrocarbons, aldehydes, ketones, long chain esters, alkyl acetates, free fatty acids, fatty alcohols, cutin and pectin. To study the penetration of 2,4-D through this complex, the standard analytical procedure using electron-capture gas liquid chromatography has been modified to give improved detection. With this improved technique, the progress of 2,4-D through the surface waxes of some British weeds has been monitored, providing some unexpected results.

Penetration of the cuticle of plant foliage can be a serious problem when using foliar applied chemicals and can often lead to an irregular response and generally reduced effectiveness by the applied chemical. Cuticular penetration is also dependent on the environment which infringes on the plant, before, during and after spraying. One approach to improving the effectiveness of these herbicides is to limit their use to suitable environments. This naturally restricts their use to certain geographical regions and probably also to specific times in the day.

A second and more constructive approach is to incorporate adjuvants into the spray solution in order to minimise the influence of environmental effects upon the cuticle barrier, thus leading to more efficient penetration of the herbicide. This should result in a more efficient response from less chemical.

The discussion will centre round the effect of humidity upon amitrole (3-amino-1,2,4-triazole) penetration by bean leaves under growth room conditions, the influence of Tween 20 and glycerol (used separately and in combination) when added to the spray fluid on this process and the interaction of these two adjuvants with humidity.

The results of the work reveal that penetration is the result of a complex of interacting factors at least some of which can be partially controlled by incorporating in the spray fluid one or more adjuvants at the required concentration.

Some of the practical implications of these findings are discussed.

The overall effect of a plant growth regulating compound when applied to a plant will depend upon a complex of physico-chemical, morphological and biochemical factors. Most growth regulating compounds are amphipathic and hence would be expected to be adsorbed at lipophilic/hydrophilic interfaces such as cell membranes. As the outer cell membranes of plant roots have an essential function in the accumulation of ions and molecules from the soil, plant growth compounds might be expected to have a significant effect on the overall metabolism by acting at these sites.

By measuring the electrical potential of the solution in contact with the xylem fluid of excised maize roots with respect to the bathing solution, it has been shown that the application of compounds such as 2,4-dichlorophenoxyacetic acid to the bathing solution has a pronounced effect on some properties of the outer membrane. This has been confirmed using micro-electrode techniques on root cortex cells.

Such compounds also affect the rate of volume flow from the xylem vessels and greatly increase the sensitivity of the root to changes in pH.

The evidence suggests that the growth compounds such as 2,4-dichlorophenoxyacetic acid can modify the properties of the outer membrane of the root epidermal cells in such a way as to greatly reduce the plant's ability to take up ionic nutrients.

The mode of action would appear to be partly physicochemical and partly biochemical in nature.

A range of inorganic glasses have been developed containing various inorganic ions as their major constituent. By adjustment of the glass composition it is possible to design the glass to release the biocidal constituent at any desired rate in a predetermined aqueous environment.

Despite the limitation imposed by the restriction to inorganic materials, the advantages consequent on the physical properties of the biocide and the fact that the slow-release feature is inherent in the material as a whole and not imposed by a coating or encapsulation makes these biocides attractive for some special applications.

p-Tetrachlorobenzoquinone (Chloranil) is a potent inhibitor of fungal spore germination but under field conditions it is too rapidly deactivated by oxidation and hydrolysis reactions concomitant with photodegradation to be of commercial interest. We have prepared a series of alkylated spirolactones which undergo slow hydrolysis in neutral aqueous solutions to give chloranil and a 2-hydroxy-acid. Although the spirolactones are ketals as well as lactones, determination of activation parameters by kinetic analysis clearly indicates that the mechanism of hydrolysis is not acid catalysed but proceeds by base catalysis using water as a nucleophile.

torted, and moreover the optimal log P changes markedly. If, however, one discards a fixed test-time and looks for maximal response, then a parabolic type relationship is not obtained; instead, biological activity approaches a maximum asymptotically. The time to maximal response is shown to vary markedly with log P, the relationship being approximately parabolic with a minimum.

These considerations have significant implications for those involved in the search for new biologically active compounds, for they indicate that test procedure and test organism may be critical for the correct prediction of activity.

The Future of Pesticides: Problems and Opportunities

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Introduction

Generally speaking, forecasters seem reasonably confident that in the next decade or so, the demand for pesticides will continue to expand and so maintain their important contribution to increasing global food production and protection of health. It is expected that this will be achieved principally by further intensification of food production in developed countries, and the latter will therefore continue to be the major users of pesticides.

It is also widely assumed that Industry will be able and willing to continue production of well-established pesticides or equivalents, to replace those which have been phased out for regulatory or other reasons with alternatives, and to continue to introduce novel products for damaging pests not yet satisfactorily controlled.

These forecasts and underlying assumptions are discussed in the context of economic and other constraints now affecting Industry, in particular the returns on R & D investment and the increasing risk associated with market-instability and restricted potential of many new pesticides.

Various strategies have been proposed to resolve some of these problems and to meet the changing circumstances of pesticide R & D, production, and use. The outlook for these strategies is assessed in relation to pressing problems and uncertainties surrounding the future of pesticides.

Pesticide Rationale

Modern pesticides emerged after the Second World War in an era of acute food shortage, stagnant production, and accelerating decline of agricultural manpower. The objective was urgent and straightforward: to expand food production as rapidly as possible at almost any price. In these circumstances pesticides were rapidly adopted, and for two decades they played a key role in the impressive post-war increase in agricultural productivity, attained principally through intensification of crop and animal husbandry. Significant modification of this early rationale is now evident (Table 1), although objectives are essentially similar. Greater emphasis is placed on the role of pesticides in increasing average economic yields, and less on maximizing production *per se*. The economic, ecological, and sociological impact of pesticides has assumed greater importance.

Pesticide Design

Modification of rationale is already reflected in pesticide design (Table 2). Features such as minimal persistance in and impact on the environment, and increased specificity of action are directly attributable to the new rationale; others are

Table 1 *Pesticides rationale*

	Phase 1	*Phase 2*
Objective	minimize loss, maximize gain simplify, expand, intensify production	prevent loss, optimize gain increase productivity
Emphasis/criteria	quantitative gain short-term economic benefit major crops and pests entrepreneurial cost/benefit to individual producer cost seldom limiting	efficiency, flexibility production system improvement total pest/crop environment regional pest management long-term risks/benefits to consumer cost limits usual
Problem	introduce novel practices/ products improvize application methods control obvious most damaging pests	disseminate established products improve application methods control hidden/incipient pests prevent new problems arising
Opportunity	introduce new agronomic tools	expand use available products adapt/develop systems integrate optimize pesticide use

Table 2 *Pesticide design*

	Phase 1	*Phase 2*
Spectrum activity/use	broad, multipurpose	narrow, specific
Persistence	short to long emphasis on soil/crop residues	zero to short emphasis on food chain
Toxicology	emphasis on acute aspects and exposure risks to user	emphasis on chronic effects and consumer risks
Mode of action	seldom influences development decision	often influences development decision
Environmental impact	wide tolerance	minimal impact mandatory

indirectly related. For example, the mode of action is now of greater significance because of the resistance problem, a major constraint in development of certain insecticides and fungicides.

R & D Profile

It would be surprising if the profile of pesticide R & D did not reflect the trends noted above. The profile now includes substantial public funding of research, *e.g.* that directed towards better strategic use of pesticides, and study of resistance.

In industry the need for multidisciplinary teams employing a less empirical approach may be expected to gain momentum and to alter the spread of R & D resources as forecast in Table 3.

R & D Performance

Forecasting the impact of present trends in the pesticide scene on future R & D performance is difficult since assumptions are involved which are largely subjec-

Table 3 *Pesticides R & D profile*

	Phase 1		*Phase 2*
Funding	predominantly commercial		commercial and public
Allocation effort	synthesis, screening	31%[a]	20%[b]
	field development	32%	25%
	toxicology, metabolism	13%	20%
	chemical development	18%	20%
	registration	6%	15%
Approach	largely empirical and strong chemical emphasis		multidisciplinary and semi-empirical
Emphasis	broad spectrum activity novel chemistry low-cost compounds		high potency, specificity novel mode of action 'clean' compounds

(*a*) Ernst Trade Assoc. Survey (1971). (*b*) Author's assumptions

tive and changeable. In the past, success tended to be judged by the number and novelty of R & D products; nowadays it is the number of products successfully registered. These criteria are not necessarily related, and although increasingly important, 'registeribility' does not exclusively measure R & D performance. The number of novel products submitted for registration will decline, for example, if less risk or better financial returns apply to expanded use of existing or similar materials than to 'new generation' pesticides. It may be significant therefore, that relatively few such products are emerging; this could indicate that exceptionally high development costs and limited market potentials apply to them. On balance it would seem that some decline in R & D performance is to be expected, as measured by the number of novel products likely to be successfully introduced (Table 4).

Table 4 *Pesticides R & D performance*

		Phase 1[a]	*Phase 2*[b]
Screening success		1 : 3000 to 1 : 7500	> 1 : 10 000
Pesticides introduced		600	200
Successful	major	160 (27%)	40 (20%)
	other	360 (60%)	140 (60%)
Unsuccessful		80 (13%)	40 (20%)
Market success ratio		0.87	0.80

(*a*) Based on Edson (1974). (*b*) Author's assumptions

Viability of Pesticides R & D Investment

Viability is related to the cost of R & D and to the sales potential of new products introduced. Expressed simplistically, R & D is viable when the ratio of sales to R & D investment is greater than unity.

Table 5 *Pesticides industry: viability of R & D investment*

	Phase 1			*Phase 2*		
	$ M/ann.	no./ann.	ratio	$ M/ann.	no./ann.	ratio
Sales potential (20th year)	2000			5000		
R & D investment (4% sales)	80			200		
Product introductions		30			10	
R & D investment/ product introductions	2.66			20		
Sales/product introductions (20th year)	3.33			25		
Annual sales/ann. investment (ROI)			1.25			1.25
Market success ratio (MSR)[a]			0.87			0.8
Viability index (ROI × MSR)			1.1			1.0

(*a*) See Table 4

The data in Table 5 represent an attempt to compare R & D viability allowing for market success, at the end of two phases during which sales and R & D investment increased $2\frac{1}{2}$-fold, rate of product introduction declined to one-third, and market success declined marginally from 87 to 80%. The data indicate a decline in viability (1.1 to 1.0) despite a six-fold increase in sales potential per product introduced and identical return on investment before allowing for market success.

Table 6 illustrates the effect of varying R & D investment level from 3 to 5% of constant sales and within the constraint of unit viability. As R & D investment increases, and return on investment declines, improvement in market success from 66 to 100% is required to restore unit viability.

Table 6 *Pesticide industry: viability of R & D investment*

R & D investment level (% sales)	3%		4%		5%	
	$ M/ann.	ratio	$ M/ann.	ratio	$ M/ann.	ratio
R & D investment	150		200		250	
Annual sales/annual investment (ROI)		1.66		1.25		1.0
Market success ratio (MSR)		0.66		0.8		1.0
Viability index (ROI × MSR)		1.0		1.0		1.0

Internal Factors

According to Edson,[1] the world pesticide market expanded about six-fold between 1955 and 1973 when sales reached £1500 million and industrial R & D investment reached £80–100 million per annum (5.3–6.6% of sales). In 1975 Roberts[2] forecast a 2.4- to 4.2-fold increase in the level of consumption of pesticides by the end of the 1980's. These estimates imply a decline in future growth of up to 60%. Cooke,[3] in a recent study of the pesticide industry, notes the close correlation between growth and inventiveness. He forecasts a decline in the number of member companies due to difficulties and costs involved in meeting increasingly stringent toxicological and environmental conditions being placed on the introduction of new products. Goring[4] suggests that product registration and development (accounting for two-thirds of R & D costs) are increasing at the expense of 'discovery research'. He attributes the decline in major new products to over-regulation and lack of standard methods for assessing environmental and other risks. Edson[1] and Roberts[2] also predict decline in the introduction or uptake of new products because of increasing R & D cost, less attractive markets, and the impact of safety and environmental factors.

External Factors

The steady expansion of pesticides through the 1950's and 1960's has been interrupted, and an imbalance of demand and supply has developed in the 1970's. Pesticides no longer enjoy their earlier apparent immunity to the stop/go conditions which have applied to much of industry for a considerably longer period. Pesticides are not only more sensitive to overall trends of the industrial economy, but also to the instability of global agriculture, which is in process of considerable structural and social change. All these factors suggest that pesticides will face unstable and more competitive market conditions for some time ahead.

Discussion

Despite the general long-term optimism of forecasters, there can be little doubt from present trends that, in the immediate future, pesticides face many problems, Increased risk and uncertainty loom large. The chief internal factor is probably the increased difficulty and cost of developing new products. Externally increasing market instability and declining growth rate are the main problems. The corresponding opportunities are to rationalize regulatory control, and to seek optimum use of pesticides to stabilize as well as increase agricultural productivity, taking account of new conditions: slower growth, fewer novel products, and static or even reduced levels of R & D investment.

Various other strategies have been proposed to relieve this situation, and some are being explored. They include: provision of pest management services by Industry, demand forecasting and purchase of buffer stocks of pesticides by state and international organizations, greater involvement of the latter in the development of pesticides having relatively small use potential, and R & D cost-sharing between members of Industry and state.

[1] E. Edson, *Phil. Trans. Roy. Soc.*, 1973, B267, 93.
[2] E. H. Roberts, *8th British Insecticide and Fungicide Conference*, 1975, 3, 891.
[3] J. Cooke, 'Agrochemicals – an Industry Review', Wood Mackenzie & Co., 1975.
[4] C. A. I. Goring, *8th British Insecticide and Fungicide Conference*, 1975, 3, 915.