Designing more efficient herbicides

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Summary

The primary role of the agriculture industries is to produce a reliable supply of food to feed the burgeoning world population, safely, and without adverse effects on the environment. Over the past half century and more, crop protection chemicals have played a major role in consistently achieving this objective. The degree of technical success has been quite remarkable and shows promise of continued improvements well into the next century. In spite of this success, the crop protection chemical industry is facing widespread hostility. The industry is perceived by many of our citizens to be unsafe, both to mankind and to the environment, and also unnecessary. Furthermore, there is presently intense competition in the market-place and price erosion in real terms means that most of the chemical majors are under pressure with regard to profitability. This situation is exacerbated by maturity in several market sectors with little real growth in prospect at least in the short term.

In spite of these negatives, the author believes that there is a bright future for crop protection chemicals and that these will form the keystone of crop protection methods for at least two further decades. It is essential that the industry does not neglect its science base because technical differentiation will become increasingly important. Furthermore, greater understanding of toxicological and ecological effects will assist in ensuring that even more benign and efficacious compounds emerge into the market-place. This paper will address the characteristics that will be required in the new products of the next century, and will illustrate some of the research methodology which will be required to invent them. Examples will be drawn largely from the area of herbicides.

Introduction

The world market for crop protection chemicals in 1989 was estimated at $US24 billion. Whereas this represents a 7.5% increase in 1988 US dollar terms, the real growth was negligible if currency moves and inflation are taken into consideration. In 1990 the world market was estimated at $US26.4 billion. Most observers agree that whereas the markets for crop protection chemicals have increased very significantly in the last decades, the 1990s promise to be a period of low real growth. In the developed world, the area which is already receiving sprays of crop protection chemicals often exceeds 90%, partly explaining the maturity now being experienced in the market-place. However, there are expectations of considerable growth in the developing economies of the Pacific rim, in Eastern Europe and indeed in some parts of Southern Europe. There are also selected opportunities in the lesser developed countries, but unfortunately food production and consumption are likely to continue to be constrained by poverty, with yield increases scarcely matching the rate of population growth (12).

The top fifteen agrochemical companies (1990 turnover) are listed in Table 1, together with sales data (2).

Over 90% of the total market is accounted for by three major sectors. The biggest sector is herbicides, which constitutes about 44% of the total. Insecticides (together with acaricides) follow next with 29% of the market, whereas fungicides account for 21% of this total. The remaining 6% is given largely to plant growth regulators and nematicides.

The areas of the major crop plantings worldwide are shown in Table 2 (for 1989/90). From this can be seen that monocotyledonous crops, i.e., coarse and small grains such as corn, wheat, barley and rice, are vastly predominant (3).

Given the limited opportunities consequent upon the factors listed above, there is intense competition between the major agrochemical companies. Price erosion of crop protection chemicals has been a constant feature in recent years and this is expected to continue well into the 1990s. Some observers believe that towards the end of the decade, growth will return due to the need to feed the world's rapidly increasing population. It is predicted that the world will need to accommodate about 11 billion people by 2050, roughly a doubling of the present day world population.

In spite of the harsh conditions presently facing the industry, it is not difficult to be optimistic about the future for innovative crop protection chemicals. Environmental pressures will ensure that many of the "golden oldies" available in today's market-place will disappear, frequently due to unrewardable costs of re-registration. There is an increasing requirement for even more ecologically benign and toxicologically safe chemicals to replace some present day treatments. Furthermore, the appearance of resistance to many crop protection treatments will demand a continuous supply of new molecules. In this context, novel modes of action will be highly prized in order to avoid resistance problems and also to allow participation in programs to extend the life of existing favourites to which resistance is being expressed. Until recently, commercial levels of resistance were commonplace in the insecticide and fungicide areas, but it is only in the last few years where serious cases have been reported in the herbicide area.

The above factors, taken together with the failure of robust competing technologies to emerge to date, underline the optimism about the future for crop protection chemicals in general and indeed for herbicides in particular (10). The latter are expected to outstrip the other sectors in the developing world due to labour shortages created by urbanization.

Requirements for new products

Novelty and innovation in research

As indicated above, there are still numerous new product opportunities for the industry, even though there are few control problems for which no practical, chemically-based control measures exist. Nevertheless, as we move into the future, there will be an increased need for chemicals which are more highly differentiated, both in terms of biological activity and environmental properties. Price erosion in existing products, taken together with the need for companies to produce adequate returns, will ensure that the highest priority is given to novelty and innovation in research programs, leading to products with high added value.

The characteristics which will be required for new products will include:

- highly active and/or effective in terms of treatment cost per hectare,
- ecologically benign,
- safe to the farmer, operator and the consuming public at large,
- flexible and convenient in use,
- compatible with mixture products and appropriate for use in integrated pest management programs,
- high margins of safety to the treated crops under a range of conditions.

Multidisciplinary teams and holistic programs

In the past, the discovery effort dedicated to herbicides has tended to be dominated by the skills of chemists and biologists. Consequent upon progress in the biochemical sciences and spectacular advances in molecular biology, the discovery effort of the 1990s looks quite different. The present day project team is highly multidisciplinary, involving from the earliest stages the skills of ancillary scientists. Projects are increasingly holistic, in the sense that there are no set patterns to research, but rather a combination of all productive science inputs used to attack the problem from many angles. A major objective of the team will be to establish in vitro and in vivo tests which indicate for all the essential characteristics of a premium product (e.g., biological activity, soil behaviour, ecology, toxicology). This objective will sometimes be at least partly achievable prior to the commencement of a major program in synthetic chemistry. Such research will require a truly interdisciplinary team effort involving for example the skills of the molecular biologist, biochemist, physiologist, ecologist and toxicologist from the outset. Thus, the choice and validation of targets both at the agronomic and molecular levels, will become increasingly important in the discovery process, and will consume a major proportion of the research effort.

Forecasting and Targeting

In his Bawden lecture at the 1988 British Crop Protection Conference, John Finney, R&D Director of ICI Agrochemicals, stated, "forecasting is rarely straightforward, but forecasting in agriculture (...) is a particularly precarious pastime" (11). Nevertheless, the company which is best at forecasting future trends in agriculture and its markets has enviable advantage. Major efforts are expended in prediction of political and macro-economic trends. Regulatory experts are urged to pronounce on likely future strictures. However, the most onerous task, but possibly the most important to the R&D-based industry, falls to the agronomist. They are asked to predict trends in husbandry, plantings, new crops, and crop protection usage. Furthermore, predictions of changes in the distribution of weed species in terms of these factors is also demanded (1,8). Indeed, definition of the word "efficient" in the title of this talk, rests heavily on the opinions of the agronomist.

Efficiency in Herbicide Usage

A dictionary definition of "efficient" is "functioning or producing effectively, and with least waste of effort". In the context of the design of more efficient herbicides, efficiency to the user can mean fewer applications, less cultivation, reduction in application costs/volumes and convenient availability. Each of these topics is considered below, together with an analysis as to whether the issue is a characteristic of the specific active ingredient toxophore or of the usage or type of product.

Efficiency to the user - fewer applications

Table 3 firstly indicates the aspect of fewer applications, relating to efficiency to the user. For example, with post-emergence treatments, greater flexibility in the weed growth-stage window relies upon the inherent characteristics of the active ingredient toxophore. This characteristic is best delineated by design of appropriate screening methodology, but given the state of current knowledge, it would be impossible to design de novo these characteristics within the chemical invention process. Longer residual activity is also related to the chemical properties of the active ingredient. This characteristic will again be efficiently unearthed by a screening process, and there are positive steps which can be taken in chemical invention to achieve optimal properties. In the pre-emergence context, products formulated as slow release granules will display longer residual activity. As a further example, pre-emergence herbicides will provide more robust treatments if rainfall dependence/leaching could be lessened. Again, this is a factor which relates to the chemistry of the active ingredient.

Efficiency to the user - other factors

The above analysis can be repeated for:

- less cultivation,
- reduction in application costs/volumes, as summarized in Table 3

The analysis can continue under other headings, listing further favourable properties and use factors:

Environmental

- Low soil persistence,
- Low leachability,
- No damage to beneficials,
- Low mammalian toxicology.

Formulation/packaging

- Low application rates,
- Amenable to solid rather than liquid formulations,
- Easy disposal,
- Safe/enclosed systems,
- Use of adjuvants to optimize activity.

Production of active ingredient

- Simple and cheap,
- Low number of synthetic steps,
- Low impact of the process in safety, health and environment terms,
- Flexible plant.

This analysis is then used to target chemical synthesis. The biological screen (and other indicator screens) are established to unearth the required factors and properties and this information in turn is used to drive the synthesis chemistry. It should be clear that the skill and background knowledge which is used to conduct such an analysis is a vital component of an efficient modern day discovery effort. The current costs to take an idea through R & D into the market-place (estimated about $US100 million) are too onerous to allow serendipity to play the major role in the discovery process.

It should be noted that this information will be useful at several distinct stages of research and development to continuously assess the viability of the project:

- Targeting of research,
- Evaluation of leads,
- Driving synthesis chemistry,
- Decisions on which compounds to develop,
- Product positioning and marketing.

The Discovery Process (5)

There are four basic sources of new chemical leads which act as a starting point for synthesis:

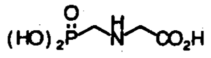
- Random selections of chemicals submitted to targeted biological screens.
- Derivative chemistry based on a competitor's proven biological activity.
- Clues taken from natural products which display biological activity.
- Rational design based upon biochemical principles.

In practice, all four philosophies are espoused by researchers in agrochemical companies. To date, the first two conceptual origins have been responsible for almost all modern products. There are some notable examples of natural product-derived crop protection chemicals (largely insecticides and fungicides) but as yet the rational design process has paid no dividend in terms of the introduction of commercially successful products. These conceptual origins are discussed below in more detail:

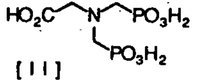
Randomly selected chemicals

As mentioned above, this method relies upon a targeted biological screen to generate leads. As such, the screen is carefully constructed to reflect commercial targets using the analytical process mentioned in the two previous sections. Chemicals obtained at random (either by synthesis, from collaborators or from other parts of the chemical industry) are subjected to the screening process and the positive hits which emerge are pursued. This approach is often referred to as 'blue sky' chemistry. It should be noted that whereas the generation of the first hint of activity is indeed random, or at best based upon chemical intuition, the process by which the lead is established and optimized to provide a compound with commercial levels of activity is very highly skilled. It will involve a co-operative application of expertise in many areas ranging from computer-aided molecular modelling at the inception stage through in vitro biochemical screens to whole cell and physiology studies.

An example of the random screening approach is provided by the discovery of glyphosate, [I] the greatest commercial success of the industry to date.



[I]



[II]

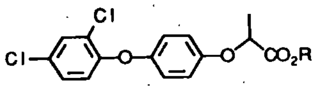
Research at Monsanto before 1970 led to the synthesis of over 100 hundred aminomethylphosphonic acids, aimed at non-agricultural screens (13). Subsequent biological evaluation of this group in agrochemical screens provided compounds showing activity as plant growth retardants. As a secondary interest, some herbicidal activity against perennial species was observed, although this activity was far too low for commercialization. Many more analogues were made in an attempt to optimize herbicidal activity but progress was very limited until the activity of glyphosate was unearthed. The properties of glyphosate as a herbicide for total vegetative control, coupled with almost zero residual effect in soil, has led to glyphosate becoming a most remarkable success world-wide. Interestingly glyphosine [II], a commercialized sugar cane ripener, was unearthed in this program prior to the discovery of glyphosate.

The mode of herbicidal action of glyphosate has been shown to be competitive inhibition of 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase. However, there was no component of rational design involved in this discovery. EPSP synthase is an important enzyme in the shikimate pathway, which leads to the biosynthesis of aromatic amino acids and numerous phenylpropanoid biosynthetic intermediates.

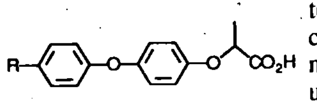
Analogue chemistry

The second method is to take a lead from a competitor's area of activity, exemplified in the patent literature. The objective then is to develop the lead into a novel and patent-free area, followed by structural optimization to provide the desired product (15). While this has proven to be the most reliable way to achieve biological activity to date, there exists the possibility of insufficient differentiation of products so derived - i.e., 'me - too' molecules. Furthermore, the derivative products will share the same mode of action as parents, with consequent disbenefits if resistance has been a problem in this herbicide type.

An example of the success of the analogue chemistry process is provided by the aryloxyphenoxypropionates. These are a series of herbicide grass killers with superb selectivity in many broad leaf crops. It is interesting to note that this series of chemicals had its origins in the pharmaceutical industry. Hoechst filed two patents to phenoxyalkane carboxylic acids in 1969 and 1971 as pharmaceutical preparations (hypolipodemic agents). In 1973, Hoechst filed patents claiming herbicidal activity for this type of compound. From this invention, Hoechst developed three related compounds as herbicides based upon acids given the trivial names diclofop [III], clofop [IV], and trifop [V]. The first two compounds are cereal-selective grass killers, whereas trifop is a wider spectrum grass killer for use in broad leaf crops. These compounds are invariably applied in the field as ester derivatives, but it is the corresponding acid which is the actual active compound. Of these three compounds, only diclofop methyl [VI] was eventually commercialized.

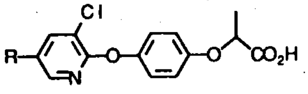


[III] R=H
[VI] R=Me

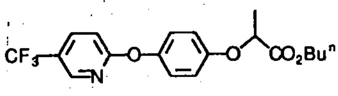


[IV] R=Cl
[V] R=CF$_3$

Ishihara (ISK) made an important further advance by developing chlorazifop [VII] which has similar herbicidal properties to trifop. Just over a year later, ISK, ICI and Dow filed patents on a similar series of para-trifluoromethyl compounds **within three weeks of each other**. The ISK/ICI compound was commercialized as fluazifop butyl [VIII] and Dow introduced haloxyfop methyl [IX]. More recently, Hoechst and Nissan have entered the commercial field as winners of several hotly contested patent races. Thus, the farming world enjoys the usage of several similar molecules, all with their special niches in the market-place. It should be borne in mind however, that there were many losers in these patent races, underlining the risk taken in expending too much effort in derivative rather than differentiated chemistries.



[VII] R=Cl
[IX] R=CF$_3$
(as methyl ester)



[VIII]

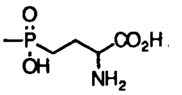
The mode of action of these molecules is via fatty acid biosynthesis inhibition, the enzyme acetylCoA-carboxylase being the specific target site. It is of great interest that the crop selectivity observed for this series is expressed at the enzyme level. Thus, haloxyfop has been shown to inhibit the maize enzyme but not that derived from peas. This explains the usage which these compounds enjoy as grass killers with extremely good margins of safety in broad-leafed crops.

Natural products

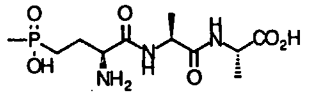
Nature presents us with an opportunity to observe an extensive arena of highly complex interactions involving chemical warfare between the myriad species that fight to establish their ecological niche. For example, the defensive substances used by insect species to avoid the deleterious attentions of predators may provide clues to novel insecticidal toxophores. Clues can thus be taken from chemicals which occur in nature but unfortunately, there are relatively few notable cases under this heading which have led to successful commercialization. Aside from the inherent chemical complexity which characterizes many natural products, the chemicals which occur in nature frequently have insufficient potency or have the wrong specificity to act as strong leads for synthesis.

In spite of all this, there have been some notable successes, perhaps pre-eminent amongst these being the pyrethroid class of insecticides, derived from a chrysanthemum species. In the fungicide area, many of the major companies are presently pursuing leads derived from the strobilurins and oudemansins, two families of natural products isolated in the 1960s and 70s from several genera of fungi. Although no compounds have yet reached the market-place, the level of interest in development in several companies remains high. Least success to date has been experienced in the herbicide field. An example is provided by the discovery of the herbicide phosphinothricin [X]. However, whereas phosphinothricin is a naturally occurring phosphonoamino acid, it is believed that its discovery as a herbicide emanated from a synthetic program. Interestingly, it was also the target of a rational design program aimed at providing herbicides by inhibition of the enzyme glutamine synthetase. Racemic phosphinothricin (glufosinate) has been introduced commercially by Hoechst as a herbicide for non-residual total vegetative control.

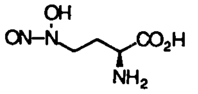
Closely related is the discovery by Meiji Seika of the tripeptide equivalent bilanafos [XI]. This discovery resulted from a random screening program utilizing fermentation broths. Bilanafos is derived from a *Streptomyces* species.



[X]



[XI]



[XII]

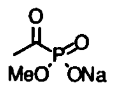
It has been reported that homoalanosine [XII], a functionally modified amino acid derivative, is presently being evaluated as a rice-selective paddy herbicide.

Biorational design (16)

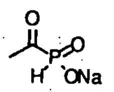
The most intellectually attractive concept is that of biorational design. This requires consideration of the target plant, fungus or insect as a biochemical machine. An enzyme (or receptor) is chosen for attack based upon criteria such as physiological importance and level of occurrence. It is vital that effective inhibition of this enzyme is fatal to the organism concerned. Inhibitors for the target enzyme are then rationally designed and synthesized. Large amounts of certain enzymes have been made readily available in recent times by the application of molecular biology techniques. It is now possible to produce sufficient enzyme to allow crystallization and subsequent X-ray studies. This can lead to construction of a molecular model (by computer-aided technology) to provide a template against which inhibitors are designed. Although this approach has enjoyed only limited success to date, it is clear that the area is advancing rapidly. However, rational design of inhibitors active in vitro is only a small part of the full story. Candidate inhibitors must also be successful in uptake, translocation and survival of metabolism within the plant (9).

As stated earlier, there is no example of successful rational design leading to commercialization to date, but there have been several near misses. One such example of that is provided by the case of pyruvate dehydrogenase (4). In this instance, activity was demonstrated at an impressive level in the field, but the development was terminated due to insufficient commercial potential. The design of inhibitors of pyruvate dehydrogenase was closely based upon existing knowledge of the mechanism of action. Although no X-ray data were available to permit construction of a detailed molecular model, sufficient of the mechanistic details were understood to allow design. This process led to a series of acylphosphinates which were prepared as mechanism-based inhibitors and some of these were both very powerful inhibitors and herbicidal. A substantial body of evidence obtained through biochemical testing supports strongly the view that susceptible plants died as a direct result of the enzyme inhibition. Two examples of such inhibitors are shown in [XIII] and [XIV].

It is interesting to note that the design of selectivity into herbicides through a knowledge of comparative metabolic fate in crops and weeds has been reviewed, and that the authors have concluded that the current state of knowledge has not provided significant success to date (6,7).



[XIII]



[XIV]

Herbicide resistance

There are two distinct features here - firstly, resistance of weeds to established herbicides, and secondly the genetic engineering into a crop plant of resistance towards a commercial herbicide. The former is a problem to the agrochemical industry, whereas the latter is a major opportunity for a seeds business.

Resistance to commercial herbicides

This topic will be covered elsewhere in this Symposium, but as noted earlier, commercially significant levels of resistance to herbicides is now a common factor in the market-place. From the perspective of designing more efficient herbicides, the key strategy is that of avoidance of known modes of action, and particularly those to which resistance has already been demonstrated. In particular, herbicides which act by inhibition of acetolactate synthase or acetyl CoA-carboxylase appear to have been particularly affected.

In the insecticide and fungicide areas, a long-standing objective has been to continuously supply novel modes of action and this imperative is now a feature of herbicide discovery research.

Biotechnology and herbicide resistance

Whereas it is difficult to see how biotechnology could provide completely new methods of weed control, the principles of genetically-engineered herbicide resistance are now well established. Most herbicides which are currently registered, and which have suitable weed control spectra, are almost certainly presently under study. There are, however, several uncertainties which may limit the impact of this technology.

From the perspective of an agrochemical company which derives its profit from sales of a broad-spectrum chemical herbicide, it might be necessary to spread the resistance gene as widely as possible through the very fragmented seeds market. However, this process can limit the competitive advantage, and hence the profit for any individual seed company. We can expect commercial testing of these concepts in the next decade.

Commercial considerations aside, resistance to herbicides which act at the enzyme acetolactate synthase has been easy to achieve through pollen mutation, somoclonal selection, and gene mutation. However, this ease is also reflected in the rapidity with which weed resistance has arisen in the field, and the increased use in combination with genetic resistance will increase the selection pressure further. With compounds such as glyphosate, where natural resistance has not been reported, resistance has proved more difficult to engineer, and despite much excellent scientific work, practical field resistance has been hard to achieve. Furthermore, the level of farmer acceptance is uncertain because farmer choice becomes more limited. Economic comparisons with selective herbicides need to be made through experience. The resistant crop varieties which are now nearing sales will begin to resolve these questions

The future (14)

In my introduction, I indicated my belief that chemicals will provide the mainstay of crop protection methodology for at least two more decades. This belief is based upon concerns over the robustness of alternative technologies to date, rather than upon an unwillingness to see change. Indeed, continuous improvement is required in the area of chemical crop protection. This paper has described many areas in which such improvements are demanded. I believe that we should support research into alternative technologies at a major level of funding. Such research is the responsibility of universities, public sector bodies and industry alike. One fruitful avenue for future research will be the integration of a novel technology (e.g., biological control agent) with a robust chemical crop protection methodology. The synergy which can be derived from such integration will rely very heavily upon advances in the science of our subject. Indeed, it is abundantly clear that good science is the essential ingredient required for progress in almost every aspect of our endeavour to provide the world with the food that it needs to feed its burgeoning population.

Acknowledgements

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Table 1 *Top 15 agrochemical companies (1990)*

COMPANY	RANK	SALES ($m)
Ciba-Geigy	1	>2500
ICI	2	2000-2300
Bayer	3	
Rhône-Poulenc	4	
DuPont	5	1500-2000
Monsanto	6	
Dow-Elanco	7	
Hoechst	8	1300-1500
BASF	9	
Schering	10	700-1300
Sandoz	11	
American Cyanamid	12	
Shell	13	
FMC	14	400-700
Sumitomo Chemical	15	

Table 2 *Major crop plantings World-wide 1989/90 (million hectares)*

CROP	1989	1990	% CHANGE
Wheat	225.5	231.1	+2.5
Coarse Grains	322.9	322.0	-0.3
Rice	146 .31	146.1	-0.1
Total Grains	694.7	699.2	+0.6
Cotton	32.0	33.5	+4.7
Soybeans	57.8	55.0	-4.8
TOTAL	784.5	787.7	+0.4

Table 3 *The design of more efficient herbicides*

			Research Focus	
Effeciency to the user	**Product Issue**	**A.I. Toxophore Issue**	**Target Definition/ Screen Cascade**	**Optimisation of Chemical Structure**
Fewer applications				
Wider weed growth-stage window	-	+	+	-
Longer residual activity	+	+	+	+
Less rainfall dependence/leaching	-	+	+	+
Faster absorption, more rainfast	+	+	+	+
Broader spectrum	-	+	+	-
Multiple modes of action to mitigate resistance	-	+	+	+
Better compatibility	+	-	+	-
Less Cultivation				
Post emergence/PES rather than PPI	+	-	+	-
No-till/min-till rather than conventional tillage	+	-	+	-
Reduction in application costs/volumes				
Accept lower levels of control/more risk	+	-	-	-
Post-emergence: better translocated, giving more effective kill at lower volumes	-	+	+	+
PES: solid granules banded or broadcast	+	-	-	-
Application by herbigation in irrigated cultures	+	-	-	-

(PES = Pre-emergence spray; PPI = Pre-plant incorporation)