Session 3A

High Throughput Screening as an Approach to New Product Discovery (1)

Chairman	Professor A H Cobb
Session Organiser	Dr J C Ormrod
Papers	3A-1 to 3A-2

CURRENT SCREENING PRACTICES IN THE PHARMACEUTICAL INDUSTRY

J S MAJOR
Lead Discovery Department, ZENECA Pharmaceuticals, Alderley Park, Cheshire, UK

ABSTRACT

In response to mounting competitive pressures, the current trend in the pharmaceutical industry is to shorten the time scale for all aspects of drug discovery. While advances in computation, structural chemistry and molecular modelling are facilitating rational design activities, empirical screening continues to play a crucial role in Lead Identification. Because the ability to test large numbers of compounds quickly and efficiently can provide a competitive advantage, high throughput screening (HTS) has become a key goal. To achieve the necessary productivity, effective integration of compound supply, assay operation and data management is essential. HTS is a very high technology enterprise that must take full advantage of the latest advances in bioscience, biotechnology, engineering and electronics. Notwithstanding the enormous success of pharmaceutical research, the industry is currently in the midst of growing regulatory and financial pressures and there is little doubt that this trend will continue. Innovation, however, will continue to be an important determinant of profitability. Technical advances in HTS and chemistry, the application of molecular biology and discoveries arising from genome analysis will be major driving forces. For pharmaceutical companies that can exploit these advances and successfully address the challenges, there are huge opportunities to satisfy unmet medical need and to continue the tradition of success and profitability that has been characteristic of the industry.

INTRODUCTION

The pharmaceutical industry has been enormously successful as witnessed by its record of profitability and the numerous life-saving drugs it has produced. In the traditional drug discovery process three phases, Target Identification, Lead Identification and Lead Optimisation can be identified. Target Identification involves defining the therapeutic effect to be achieved and the means by which it will be accomplished. The drug target, at the molecular level, may be a receptor, enzyme, ion channel or some other component of the cell. Screening systems using isolated cellular components, isolated cells and tissues and disease models in experimental animals have been the vehicles for drug discovery in the pharmaceutical industry for many years. This is in contrast to the typical agrochemical screening paradigm where it has been possible to screen against the actual target organisms or closely related "indicator" species.

In the quest for novel chemotherapeutic agents, most pharmaceutical companies use a combination of rational, or structure-based design, and empirical screening. The latter is a process by which "actives" are found by experimentation, i.e. by testing a wide range of

different compounds with no preconceptions about what type of structure might be active. Rational design, on the other hand, depends on a detailed knowledge of the structure of biological mediators and the forces controlling their interaction; compounds are designed specifically to interact with the target. Because our understanding of the necessary interactions may be imperfect, the technical feasibility of rational design can be low in the absence of a suitable lead. This is particularly true of targets involving peptide and protein interactions. In such cases, empirical screening can identify low molecular weight compounds that can be enhanced by the medicinal chemist. Either by rational design or empirical screening, therefore, the Lead Identification phase of pharmaceutical research aims to discover the initial lead structures that interact with the target of interest. Starting with these leads, the optimisation phase involves the synthesis of compounds with enhanced activity and with a range of properties tailored to the precise therapeutic requirements (the target compound profile). Typical screening cascades comprise elements to test for each of the essential properties required. While technical advances have facilitated increased screening efficiency over the years, the concept of the screening cascade has remained relatively unchanged. Primary screens at the top of the cascade are relatively simple; they provide a simple measure of potency and can accept relatively large numbers of compounds. Secondary and tertiary screens using increasingly sophisticated *in vitro* and *in vivo* models provide progressively more detailed information about potency and duration of action. As compounds pass through the cascade, those with inferior properties are rejected. Only compounds exhibiting the desired pharmacodynamic and pharmacokinetic properties defined in the target profile will progress all the way through the cascade. These are the candidates that will be considered for further development provided they have an acceptable general pharmacology and toxicology profile and patent property has been secured. Entry of compounds into formal Development represents the end of the Lead Optimisation phase of Research. While the processes may differ in detail, the objective of Lead Identification and Lead Optimisation in the pharmaceutical and agrochemical industries is entirely analogous.

CURRENT SCREENING PRACTICES

Screening strategy

While advances in computation, structural chemistry and molecular modelling are facilitating rational design activities in pharmaceutical discovery, empirical screening continues to play a crucial role during the initial lead identification phase and this, in turn, is dependent on the availability of large numbers of compounds to test. Many large, well-established pharmaceutical companies have compound collections comprising hundreds of thousands of unique chemical entities. Such collections are reservoirs of potential new leads. In addition, the modern trend is to increase the structural diversity through new synthesis, combinatorial chemistry, purchase of compounds from commercial sources and academia and by sharing collections across and between industries. In addition, microbial and plant extracts, together with other naturally occurring materials, provide additional diversity. Hundreds of thousands to millions of compounds are potentially available for evaluation.

While the numbers of compounds to be tested can be reduced by pre-selection on the basis of diversity analysis or some other criteria, there is a tendency to reduce the risk of missing unexpected activity by designing screening programmes that can test all of the available

compounds. High sample throughput, therefore, has become a key objective in modern empirical screening. To be competitive, the available compounds must be screened within a short time frame (weeks to a few months) and leads with the potential for optimisation identified. Screening systems and associated infrastructures are required that can sustain testing rates of many thousands of compounds per run. Effective integration of compound supply, assay operation and data management is essential. Standardisation and attention to work flow design can facilitate the necessary productivity and enable effective automation.

Throughput requirements

In the late '80s a typical goal would be to test 10,000 compounds per year against several targets. Testing 10,000 compounds per month against 10 to 20 targets is now commonplace and a throughput of 10,000 per week is a goal of many companies and this has been achieved by those at the leading edge. This need arises because given a typical collection of 250,000 compounds and a weekly throughput of 2,500, it will take at least two years to complete the lead identification phase of drug discovery and this is now considered uncompetitive. A throughput of at least 10,000 per week and preferably higher is required. Traditional approaches where solid samples are retrieved from a compound store and are processed by weighing and solubilization for individual screens are no longer appropriate. Parallel processing where sample solutions are replicated to feed many screens is used wherever possible. To achieve very high throughputs, however, the modern trend is to store multiple sets of solubilized samples in a suitable format (see below) and to feed screens from these stores. This, of course, raises questions about the stability of solubilized compounds on storage and there is an absolute requirement for sophisticated computer systems to manage the compound store, the delivery of samples to particular screens and for tracking progress.

Standardisation

While high throughputs can be achieved with tube-based assay systems in a fully automated "round the clock" environment as in the typical clinical chemistry laboratory, the impact of the 96-well microplate cannot be underestimated. Although other well densities such as 24, 48, 384, 864, etc., are available, and there will be continuing development, the 96-well plate with its uniform footprint is the acknowledged standards for microassays. The power of the 96-well plate is based on its ability to support parallel processing in 8, 12 or 96 channel formats. The ability to deliver liquids to all 96 wells and similarly to read signals in all wells simultaneously, be they colour, fluorescence, luminescence or radiochemical, offers huge advantages over processing individual samples sequentially. There can be little doubt that the 96-well plate and the associated instrumentation, have been crucial in enabling the high throughput screening operations that are now typical across the pharmaceutical industry. The present trend is to combine the efficiency of parallel processing in the 96-well format with advanced automation and robotics to achieve even greater efficiency and throughput.

Assay considerations

Using conventional *in vivo* and *in vitro* methodology, throughputs ranging from a few compounds to several hundreds per assay are typical. Isolated cells, whether mammalian or microbial, and biochemical methods, on the other hand, can provide a basis for testing many thousands of compounds per assay run. Such methods can satisfy most of the key

requirements for practical and efficient high throughput screening. Screens must be robust and reliable, cost-effective, simple and user-friendly and amenable to rapid implementation, standardisation, automation and if possible miniaturisation. Advances in biochemistry and molecular biology together with the application of modern detection methods and engineering have increased the range of drug targets that are amenable to HTS and most drug targets of current interest can now be addressed effectively.

Typical targets for chemotherapeutic agents include enzymes, receptors, functional proteins, ion channels and structural components. In the case of many enzymes it is possible to design assays that involve mixing the components, incubating to a suitable end-point and measuring a signal, e.g. a change in optical density or fluorescence. This type of "mix and measure" approach is ideal for high throughput screening. Many drug targets, however, have not been amenable to such simple assay designs and have required complex coupled reactions or some form of separation step. This has limited the throughput that can be achieved at reasonable cost and has been a significant obstacle to effective automation. Technical advances, however, are making hitherto "difficult" targets amenable to "mix and measure" approaches.

Some of the most successful drugs are those that act on cell surface receptors. One of the most widely used and successful screening strategies in this area is radioligand binding. Technical developments over the years have transformed the traditional filtration methodology from a relatively cumbersome low throughput technique to an efficient screening technology capable of very high throughput. Important advances have been the introduction of automated cell harvesters and multi-channel radiation counters, particularly those capable of counting samples directly on filter mats or in microtitre plates. Emerging second generation robotics will further facilitate screening using filtration methodology. Unfortunately, the inherent disadvantages of separation and multi-step methods are retained. These methods, however, are now being replaced by new, non-separation methods.

The development by Amersham International of the scintillation proximity assay (SPA) has been a significant advance (Bosworth & Towers, 1989). The principle depends on the limited path length of β-particles in aqueous media (e.g. 1.5 μm for tritium, 1.0 and 17.5 μm for the auger electrons of ^{125}I). If the β-particle collides with a suitable scintillant molecule, its energy will be converted to light that can be detected in a scintillation counter. If a scintillant molecule is not close enough to the disintegrating nucleus, no energy transfer will take place and the β-particle's energy will be dissipated in the medium. The disintegration will go undetected. By integrating a scintillant into microspheres, the principle can be applied to biochemical assays. Target molecules of interest, such as receptors, can be bound to the microspheres and these can then be suspended in aqueous buffer systems.

When a radioligand is introduced into an aqueous suspension of fluomicrospheres, most disintegrations will not be sufficiently close to the microspheres to allow energy transfer and only minimal signal will be generated. However, if the radioligand binds to an immobilised target molecule, it is brought into sufficiently close proximity for energy transfer to take place. Light is emitted as the assay signal. The quantity of light emitted is proportional to the quantity of radioligand bound while radioligand free in solution is not detected. There is no need for labour intensive separation processes as the technique discriminates "bound" radioligand from "free". Assay assembly is simply a "mix and measure" process that can be highly automated. Use of the 96-well format allows the signal to be detected using

microplate counters. Radioligand binding assays carried out using SPA are generally in good agreement with those using conventional filtration methods (Major, 1995). While scintillation proximity is ideally suited to ligand-receptor interaction assays, numerous other applications including protein:protein interactions (Pernelle *et al.*, 1993), immunoassay and various types of enzyme assay are possible.

Although scintillation proximity is one of the most important screening advances in recent years, there are many pressures to develop alternative technologies that don't require radiochemicals. Fluorescence assays have been a focus of much attention because, in theory, they are amongst the most sensitive and have the potential to compete with radiochemicals in the assay of low concentration interactions such as those involving typical receptors and their binding ligands. Also, fluorescence emission can be modulated by various types of physicochemical interactions including those that can arise when assay components are brought into close proximity or separated. Modulation of fluorescence can give rise to a usable assay signal under appropriate conditions. Fluorescence assays have been successful where the labelled reagents are present at relatively high concentration. However, because of natural fluorescence of many assay samples, conventional fluorescent labels have serious limitations in sensitivity. Rare earth chelates as fluorescent labels have advantages. They exhibit long fluorescence emission lifetimes allowing time-resolved measurement. This partially overcomes the problem of sample fluorescence which tends to be short-lived. Recently, a new range of rare earth chelates "the cryptates" have been developed that further address the limitations of existing chelates. Amplification of the cryptate fluorescence by non-radiative energy transfer to an acceptor together with time resolved signal detection provide an effective basis for homogeneous immunoassay in the presence of biological fluids including serum (Mathis, 1993). The technology can be applied to ligand:receptor and protein:protein interaction assays. In coming years we are likely to see fluorescence signalling becoming a serious challenge to the use of radiochemicals. This is attractive on cost, safety and environmental grounds. Traditional separation-based methods, therefore, are being replaced by non-separation technologies capable of very high throughputs. In addition to these biochemical methods, advances in molecular and cell biology are providing cell-based screening systems with reporter gene or grow / no grow outputs that can provide significant advantages. For example, using cell-based reporter systems, 10,000 compounds can tested easily within a normal 8 hour working day. Furthermore, the operational costs of these screens are significantly lower than, for example, a typical radioligand binding approach. This notwithstanding, while reporter screens offer tangible advantages over cell-free biochemical systems, there are disadvantages, e.g. specificity can be an issue because of the multiple potential intervention sites along the signal transduction pathway.

Automation

High speed fixed automation such as that found on production lines offers remarkable productivity but, in general, it is not appropriate for the type of operations typical of HTS for chemotherapeutic agents. Flexible automation, on the other hand, using programmable manipulative robots, has the versatility to match the needs of the screening laboratory. Using manipulative robots to execute each activity, however, is relatively slow compared to a human operator and the cost can be comparatively high. The use of automated workstations for specialised tasks such as liquid handling, plate washing, signal detection, etc. and where plates are moved, ideally in stacks, between the workstations can be efficient and versatile

and can support very high throughput. As plate numbers increase, however, manual handling becomes increasingly burdensome and error prone. The trend, therefore, is to use manipulative robots to move plates between automated workstations and to incorporate positive tracking to trap errors. Automated systems are now available that incorporate 2-metre and 3-metre tracked robots with precise and powerful articulated arms. Systems with user-friendly software are now able to process assay plates for virtually any type of assay with a significant increase in capacity over previous systems. While these large, complex and expensive robotic systems can be used to automate the complete sequence of operations comprising a typical assay, a higher level of productivity can often be achieved by careful attention to work flow, standardising as many of the operations as possible and introducing automation selectively where this can deliver the maximum benefit.

Data handling

Screening hundreds of thousands of compounds per year against multiple drug targets requires the ability to process millions of data points. Effective HTS, therefore, requires efficient data management systems for automatic data capture, on-line data reduction and analysis and transfer of results to central databases. The database must integrate biological and chemical data for each sample and provide the ability to compare screening results for many compounds and across many screens. Databases of this type provide the ability to investigate structure-activity relationships and selectivity using traditional "what-if" and "how many" types of query. As databases increase in size and complexity, however, conventional interrogation methods are being augmented by newer computing techniques referred to as knowledge mapping or database mining. These techniques can be based on neural networks or expert systems. The concept of data mining is that it should uncover useful, previously unknown information. These computing methods have been successful in determining insurance risks, predicting gas demand and detecting fraud. The ability to detect patterns in databases of biological and structural information may provide insights into hidden SAR and assist in the identification of meaningful activity in high throughput screening data.

Competitive pressures

Notwithstanding the enormous success of pharmaceutical research, and advances in empirical and rational design strategies provided by technical innovation, the industry is in the midst of growing regulatory and financial pressures. Profitability and survival hang in the balance. In the major territories that are the primary consumers of pharmaceutical innovation, concerns about the percentage of the nation's wealth consumed by the provision of healthcare and the steeply rising costs of such care are driving healthcare reforms. Although drugs account for a relatively low percentage of a typical developed nation's heathcare budget, pharmaceutical companies are, nonetheless, considered to be prime targets for cost control. Powerful managed care organisations and large government buyers are replacing independent physicians, hospitals and pharmacies as the primary customers for the products of pharmaceutical research. This is already driving a trend towards the use of generic and intra- and inter-class therapeutic substitution to limit product selection to as few as two or three choices for most therapeutic categories. Increasingly, the trend will be to prescribe the cheapest drug that will produce the desired therapeutic effect with only the most innovative products able to command a price premium. The primary effect of these price and volume pressures is to decrease the sales revenue and profitability of pharmaceutical companies.

This, together with the generally held view that the pharmaceutical industry is spending too much on research and development in the current cost-conscious climate, is driving the intense merger and acquisition activity being witnessed across the industry.

There seems little doubt that the risks associated with pharmaceutical research will continue to increase while the rewards will remain under intense pressure. Innovation, however, will continue to be an important driver of profitability. There will be a continuing need to shorten the time scales involved in lead identification, to increase the number and diversity of compounds available for test and to identify new drug targets to address unmet medical needs and to develop the necessary screening methods. Technical advances in high throughput screening and chemistry, the application of molecular biology and discoveries arising from genome analysis will be major driving forces in coming years.

FUTURE TRENDS

High throughput screening (at least 10,000 compounds per run) will become the industry norm while an additional order of magnitude may become feasible. Exploitation of "hits" from HTS is not optimal. Inadequate discrimination of true actives from false positives at the primary screening stage results in substantial additional work to identify meaningful "actives." This situation will become more acute as throughputs increase. As larger numbers of targets are subjected to high throughput screening, it will be possible to use cross-screen selectivity to a larger extent to assist in lead selection. Pattern recognition computing may be capable of identifying hidden structure-activity relationship (SAR) and trends. The use of increasingly sophisticated analysis via emerging computer techniques will be critical because the shear volume of data will overwhelm conventional techniques.

The mechanical logistics of handling and tracking many thousands of compounds in HTS will be facilitated by powerful computers running purpose-built software. Robotic and liquid handling systems designed to support enhanced HTS are currently being developed and deployed by a number of manufacturers. As these machines become established and further developed for miniaturised assays, fully automated very high throughput screening will become a cost-effective reality. The integration of these machines with sample tracking and data processing computer systems will provide true "walk-away" automation.

It is likely that there will be a steady move from radiochemical-based assay systems to those using fluorescence end-points. The further development of sophisticated fluorescence systems operating at longer wavelengths than the current norm and using time-resolved signal detection will facilitate the move away from radiochemicals for high throughput screening as has already happened in the clinical diagnostics area. Provided sufficient assay signal can be generated, costs will be reduced and handling improved by miniaturisation. It seems likely that within a five-year time frame the standard for HTS will have moved from 96-well plates to a higher density format with the same footprint.

Screening capacity, however, is only one aspect of a successful lead identification operation. The availability of a large, diverse collection of compounds is crucially important. While most pharmaceutical companies have extensive collections, they are usually relatively restricted in chemical and/or pharmacophore diversity. Although this can be overcome to an

extent by sharing compound collections across and between industries, the efficiency of HTS could outstrip compound availability. To provide the numbers of compounds necessary to support HTS and the essential increase in diversity, there will be a continuing interest in natural products as potential new leads. Many of the problems of natural product research will be solved by increasingly sophisticated analytical and purification methodology working in harmony with automated screening. Increasingly, however, combinatorial chemistry and automated multiple parallel synthesis will underpin not only lead identification through HTS but also lead optimisation. Structure-based design using computer modelling of the three-dimensional structure of therapeutic targets and the output from HTS together with efficient and rapid automated synthesis will provide fully complementary approaches that will shorten the time scales for discovery and optimisation. This will provide competitive advantage to those companies that can harness and integrate the necessary technologies.

Molecular biology will play a key role by providing engineered cell lines and recombinant proteins but perhaps more significantly by facilitating the identification of new drug targets as developments and refinements in bioinformatics enable the output of genome analysis to be fully exploited. HTS will become not only a mechanism for lead identification but also target identification. The world-wide human genome effort will provide numerous potential drug targets by identifying genes that play pivotal roles in physiology and possibly pathophysiology. A significant need will be to evolve novel assay methods to rapidly screen these potential targets. Cell-based screens, either in mammalian cells or micro-organisms, that can faithfully reconstruct the potential drug targets, will facilitate the ability of HTS processes to identify "quality" targets. The generic nature of these approaches will allow many screens to be run in parallel in order to seek specificity at an early stage.

There is no doubt that drug discovery and development will become increasingly competitive and there will be continuing horizontal and vertical integration as the industry responds to cost constraints and regulatory pressures. Drug discovery through high throughput screening and rational design will continue to be a very high technology enterprise and it will be essential to take full advantage of the latest advances in biotechnology, engineering and electronics. For pharmaceutical companies that can successfully address the challenges, there are huge opportunities to satisfy unmet medical need and to continue the tradition of success and profitability that has been characteristic of the industry in past years.

REFERENCES

Bosworth, N & Towers, P (1989) Scintillation proximity assay. *Nature* **341**, 167-168.

Major, J S (1995) Challenges of high throughput screening against cell surface receptors. *Journal of Receptor and Signal Transduction Research* **15 (1-4)**, 595-607.

Mathis, G (1993) Rare earth cryptates and homogeneous fluoroimmunoassays with human serum. *Clinical Chemistry* **39**, 1953-1959.

Pernelle, C; Clerc, F; Dureuil, C; Bracco, L; Tocque, B (1993) An efficient screening assay for the rapid and precise determination of affinities between leucine zipper domains. *Biochemistry* **32**, 11682-11687.

SCREENING PRACTICES IN THE AGROCHEMICAL INDUSTRY

J C ORMROD, T R HAWKES
ZENECA Agrochemicals, Jealott's Hill Research Station, Bracknell, Berks., RG42 6ET

ABSTRACT

Whole organism *in vivo* screens have been the backbone of new agrochemical discovery, but such screens are not obviously suited to some of the new technologies which are being deployed in pharmaceutical high throughput screening programmes. Agrochemical companies have to decide whether to stick with the traditional highly-focused, target-based approach, or to take the opportunity to develop a high throughput screening approach suited to emerging technologies, or perhaps to take both approaches. This paper takes a strategic look at the potential applications of new screening technologies to pesticide and, in particular, herbicide discovery.

INTRODUCTION

Screening philosophy in the agrochemical industry has been dominated by the capacity to test new compounds on target organisms, from the first lab or glasshouse test right through to the field crop situation. Desired biological characteristics can be recognised early on and leads quickly progressed to field testing alongside market standards. *In vitro* screens have taken something of a back seat to whole organism screens for new lead generation because of this, and because the success rate in translating *in vitro* activity to *in vivo* effect has been (or is perceived to be) unacceptably low in comparison. This contrasts with the pharmaceutical industry where translating activity from *in vitro* to *in vivo* is part of the process.

The divergence of approaches to screen design in the two industries has had a major impact on screening philosophy. In agrochemicals it has been possible to rely on discovering new products with a screening rate of low tens of thousands of compounds per annum on whole organisms. In pharmaceuticals, both structure-based design and empirical screening approaches have been adopted, but for the latter it has been necessary to drive the technology to cope with thousands of samples per week per assay in order to remain competitive in discovery (Major, 1995). So is low throughput *in vivo* more successful than high throughput *in vitro*? A direct comparison is probably not possible at this point, but what is clear is that the rate of discovery of new agrochemical toxophores continues to decline, increasing the pressure for new technologies to be used in discovery.

There are, of course, a number of options for attempting to increase the rate of discovery of agrochemicals, one of which is (ultra) high throughput screening (HTS). However, the automation technology required for HTS, developed for a 96- or 384-well microtitre assay format in clinical and pharmaceutical research laboratories, is not readily transferable to whole organism screening. Agrochemical companies will therefore have to decide whether to move to HTS using microtitre-based assays, or to stay with the traditional target-based screens, or to use a mixture of both. Compounding this is the advance of robotic chemical synthesis and

chemical library technology which will surely play an increasingly significant role in future discovery strategies.

In this paper we examine various options for HTS in agrochemical discovery and draw upon examples across the agrochemical sectors, but with the emphasis on the herbicide sector.

CURRENT SCREENING PRACTICES

In this section we will attempt to highlight the main driving factors behind screening strategies used in agrochemical discovery. For specific details of experimental design the reader is referred to more comprehensive reviews (e.g. Giles, 1989; Bartley and Youle, 1995).

In vivo screens

Screening at the whole organism level has been the backbone of new product discovery in the agrochemical industry. The ability to test new compounds directly on target organisms is very convenient, enabling fast turnaround of relatively high quality information. Moreover, in terms of empirical screening for new leads, it enables the biologist to identify product-type characteristics (e.g. fast knock-down insecticidal activity, systemic anti-fungal activity, or crop-selective pre-emergence herbicidal activity) directly. Clearly it would be foolish to ignore such an opportunity.

The most commercially-attractive opportunities usually require activity against a number of species, forcing screens to be correspondingly broad. Although a limited number of target, or proxy, species can be used in the early stages of a screen cascade, it is usually the practice to broaden the spectrum to include all key target species at later stages. There is usually a perceived minimum number of species which must be included in the first test of any screen cascade to eliminate false negatives. In this respect it is usually possible to use the lowest number in herbicide screening, where it is possible to detect virtually all phytotoxic activity with just a single grass and broad-leaved weed, provided they are wisely chosen and the chemical application rates are appropriate. However, because replication is not usually the norm, and possibly because there is a reluctance for risk-taking in case something is missed, most companies have a first herbicide test which comprises 4 - 12 species.

Screen cascades tend to be rigid in terms of the species used and chemical application rates. Once a lead area is discovered it is possible to introduce a more flexible array of tests (e.g. including physical chemical, soil and plant physiological assays) to complement the biological data. Hence, from *in vivo* screening a great deal of quality information can become available at a relatively early stage.

Exploiting this opportunity to screen directly on target organisms does, however, come at a cost. On a per-compound basis it is extremely resource-consuming when compared with, for example, high-throughput screening in pharmaceuticals. It also requires a large amount of chemical which means that any attempt to increase the number of compounds screened would have significant implications for biological and chemical resource, as well as requiring significant changes to screening practice.

In vitro screening using enzymes and receptors

Advances in the understanding of pesticide action at the molecular level have afforded the agrochemical industry with an increased opportunity to apply enzyme and receptor based-screening to discovery. Probably most agrochemical companies have, in the past, screened compounds *in vitro* to discover novel inhibitors of the better known targets for pesticides (e.g. for herbicide discovery, acetyl CoA carboxylase (ACCase) and acetolactate synthase (ALS)). The current trend is toward the discovery of compounds with more novel modes of action driven, in part, by the growing perception that repeated applications of pesticides with the same few mechanisms of action can quite quickly lead to the evolution of resistance amongst pest populations (e.g. weed resistance to herbicides which inhibit ALS, Saari *et al.* (1992), resistance to benzimidazole fungicides, Staub and Diriwaechter (1986) etc.). The patent literature on *in vitro* methods has also begun to reflect the trend towards new modes of action. Hawkes (1995a) described a method for detecting inhibitors of isoleucyl-tRNA synthetase, Schiedegger *et al.* (1991) claimed cDNA coding for histidinol dehydrogenase from plants, a method of purifying the enzyme and an assay to detect inhibitors. Similarly, Davis *et al.* (1993) claimed a method of screening for inhibitors of fungal dihydro orotate dehydrogenase.

Some of the practical issues raised by *in vitro* screening are best illustrated by example. Imidazole glycerol phosphate dehydratase (IGPD) is an enzyme involved in the biosynthesis of histidine. Triazole phosphonate herbicides are potent competitive inhibitors with Ki values in the nM range or less (Hawkes *et al.* 1993). The structure activity relationship around these is narrowly defined and closely related to the enzyme mechanism. Perhaps not surprisingly, screening 1500 compounds of diverse structures turned up only a single example of an apparent weak inhibitor with a novel structure. However it turned out that even this was only active because of contamination with Zn^{2+}! By contrast, screening versus glutamine synthetase yielded some 175 candidate novel leads (with I_{50} values less than ~ 50 μM) from 7300 compounds screened. A few interfered with the colorimetric assay; most were rejected as non-specific enzyme inhibitors with many having obvious potential to act as alkylating agents or to modify thiols. Of the 57 that remained, 10 had I_{50} values in the range 1-10 μM. A number were probably reactive (e.g. maleimides) and others were representatives of old areas (e.g. 4-hydroxypyridines) of no further interest. Many were herbicidal, but in no case was glutamine synthetase the primary site of action (based on the failure of glutamate and glutamine to reverse inhibition of the growth of plant cell culture using phosphinothricin as a control). The important points are perhaps 1) relatively few compounds were screened 2) *in vitro* screens required considerable follow-up work and 3) inhibitors were discovered but some three or more orders of magnitude less potent than the standard, phosphinothricin.

Overall, it is probably fair to state that the industry has done little more than experiment with *in vitro* screening. It has never been clear whether the technology should best be regarded as a means of rapidly turning around structure activity studies for current chemistry, a diagnostic for mode of action or a primary means of discovery.

Cell-based screens

Cell-based screens, have, until now, probably not played a major role in agrochemical research, other than those used in toxicological testing. Despite relatively wide-spread

publication on a number of systems, especially highlighting the convenience of plant cell cultures for screening, their use has apparently been confined to other aspects of invention, for example uptake and metabolism studies, mode of action work or cytotoxicity testing.

Although it is preferable to screen for fungicides *in situ* using pathogens on host plants, methods for testing against isolated cells are available. Fromtling (1987) described a system widely used in pharmaceutical discovery where fungal cells are inoculated onto the surface of agar which has been pre-incorporated with candidate drugs at several doses, and MIC data are obtained by comparison of growth with controls. However, because of the obligate nature of certain key pathogens (e.g. powdery mildews and rusts) such assays could only act as preliminary indicators.

The case for using plant cell cultures or unicellular green algae in herbicide pre-screening has been extensively reviewed elsewhere (Gressel, 1987; Felix *et al.*, 1988; Thiemann *et al.*, 1989; Nurit *et al.*, 1990; Grossmann *et al.*, 1992; Davidonis, 1993; Olofsdotter *et al.*, 1994). On the face of it, a plant cell-based assay for herbicide pre-screening is attractive because of the reduced resource required. However, on closer examination, there are a number of significant hurdles which would have to be overcome. Firstly, a photoautotrophic system would be required to detect modes of action which require light for herbicidal activity (Sato *et al.*, 1987). Such a system may not detect root-acting herbicides due to metabolism and/or tissue specificity. Certain graminicides are considerably less active against cells derived from dicot rather than monocot species. Increasing the application rates can broaden the range of herbicides detected but this will also increase the number of non-specific false positives. The inclusion of 2,4-D in the growth medium for cultured cells has been observed to change the sensitivity to hormone-type herbicides over time (e.g. Oswald *et al.*, 1976). Finally, there are a number of practical problems to be overcome, e.g. in obtaining exponential growth in small volumes of growing medium, in maintaining uniform cultures over long periods of time, and in the choice of method for assaying activity. Algal systems have also been evaluated, but again finding a "universal" system to detect all herbicides is difficult. Felix *et.al.* (1988) for example, detected 20 out of 24 standards using *Dunaliella bioculata*, but glyphosate, amitrole, 2,4-D and fosamine were either difficult to detect or could not be detected. Gressel (1987) concluded that a universal plant cell culture pre-screen is possible but not straightforward, and that "dedicated" assays are far easier to develop.

In conclusion, cell-based methods for screening have attracted much attention, and have found roles in certain areas, but a number of practical difficulties and the need to translate activity to the whole organism has prevented them from playing a primary role in discovery.

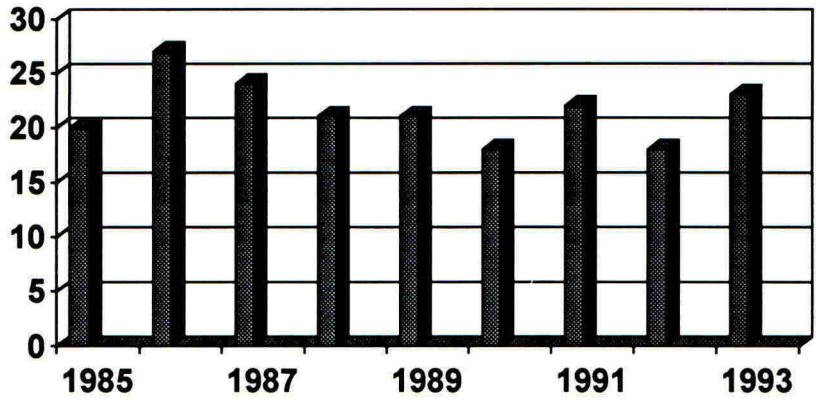
ARE CURRENT SCREENING PRACTICES SUSTAINABLE?

Rates of invention

There is a widely-held view that it is becoming more difficult to invent new agrochemicals. Statistics for the average number of compounds which need to be screened for each new agrochemical are quoted from time-to-time as one in x thousand, with x steadily increasing, thereby illustrating a slowing down in invention rate. However, such statistics need qualifying

since, over the past decade, the number of new agrochemicals introduced to the market has not declined:

Rate of new product introductions



Source: ZENECA

New herbicides introduced to the market over the past decade have been dominated by ALS and ACCase inhibitors. If these are removed from the analysis, then the invention rate looks considerably weaker. Relatively few *novel* toxaphores with product-like potential have been described in recent years.

Whether current invention rates using conventional agrochemical screening practices are acceptable and/or sustainable will, to a large extent, depend on the strategies and situations of individual companies. However, with an increasingly competitive market place the pressure to invent and introduce innovative, so-called blockbuster products will not subside.

The impact of robotic and chemical library synthesis

The use of robotics in synthetic chemistry is now widespread. Synthetic chemical library technologies are rapidly being developed and used increasingly in screening programmes. These technologies are applicable to both lead optimisation and lead generation, and are aimed primarily at increasing the number of compounds made in a given time. Although compounds can be produced in quantities sufficient to allow screening on whole organisms, some library technologies (e.g. using beads supports in library construction) produce large numbers of compounds but in insufficient amounts for anything other than *in vitro* screening.

OPTIONS FOR HIGH THROUGHPUT SCREENING

Screening on target organisms

In order to be able to screen at high throughput on whole organisms it will be necessary not only to design a test which can cope with the numbers of compounds, but also one which will be robust using much lower sample weights than have hitherto been used. With fixed resource this would require substantial simplification and miniaturisation, as well as some degree of automation. This is possibly most achievable for fungicide screening where whole organism screening at the micro level is already used in pharmaceutical research (but activity against obligate pathogens must somehow still be detected). Perhaps HTS *in vivo* screening is the ultimate goal, but it won't be achievable without considerable effort, a change away from current agrochemical practices, and some risk.

Enzyme/ receptor-based screening

The attractions of screening versus individual enzyme targets are 1) compatibility with library technologies (the possibility of screening high numbers of compounds in tiny amounts) 2) the facility to rapidly explore structure activity relationships and 3) the ability to recognise leads with 'intrinsic' activity (i.e. without being confounded by poor uptake or metabolic detoxification). A profusion of new methods to detect protein/ protein and protein/ ligand binding suitable for high throughput screening have been described including scintillation proximity assays (Holland *et al.* 1994), fluorescence depolarization (Checovich *et al.* 1995) and surface plasmon resonance (Brigham-Burke *et al.* 1992)

The main difficulty comes in deciding which screens to use. For herbicides, plant metabolism offers such a wealth of known and potential targets (e.g. inhibition of photosynthesis and the biosynthesis of most primary metabolites) that it is difficult to make the case for narrowing a screen to a single molecular target. Discovery of a *useful* lead would, presumably, be much rarer even than is observed currently versus whole plants which offer the entire array. Furthermore, the probability will vary according to the target. Some targets will be susceptible to potent inhibition by many and various structures of inhibitor, (i.e. be more 'selectable'). Possibly on account of having a quinone binding site (Schloss *et al.* 1988) as well as a combination of other unusual factors (Hawkes, 1993), ALS does seem to be one such example. ACCase, which offers unique potential for the discovery of graminicides, appears somewhat similar with a range of structural types being potent inhibitors (Gronwald, 1994). By contrast, the inhibitors which have been described of many other herbicide target enzymes have been less diverse and restricted to molecules which resemble catalytic intermediates. Examples include glyphosate as an inhibitor of as 5-enolpyruvyl shikimate-3-phosphate synthase, triazole phosphonates as inhibitors of IGPD, triketone inhibitors of hydroxyphenylpyruvate dioxygenase, phosphinothricin as an inhibitor of glutamine synthetase and inhibitors of the ketolacid isomeroreductase, isopropylmalate isomerase and isopropylmalate dehydrogenase steps in the biosynthesis of branched chain amino acids (Hawkes 1993). However, it would be prejudicial to assume either that these sites are more representative or, that they are really less selective than ACCase and ALS without first trying the experiment of screening them *in vitro*. Perhaps the best argument that ACCase and ALS are genuinely atypical is the fact that we already know of them as the targets of diverse chemistries (i.e. selectable targets might be expected to have already selected themselves). Is the best option therefore to screen ACCase and ALS *in vitro*? Ten years ago the answer may well have been yes

but, probably in direct relation to the promiscuity of these enzymes for inhibitors, resistance (based on selection of herbicide-insensitive forms of the enzymes) has arisen relatively quickly amongst herbicide-treated populations of weeds. For herbicide discovery, it may be that screening versus individual enzymes will only be worthwhile with the identification of some new and suitably selectable (or otherwise unique) target (i.e. a 'new' ALS or ACCase is needed). For fungicides and insecticides it might be argued (but is certainly debatable!) that the set of valid targets can be defined more narrowly and that, in these disciplines, it is more reasonable to propose establishing an array of targets for *in vitro* screening as a primary route to discovery.

One way of avoiding the specificity of using individual enzymes is to extend *in vitro* methodology to chains of coupled enzymes or even whole pathways. Laber and Amrhein (1989) described an assay for lysine biosynthesis starting from aspartate, and Hawkes (1995b) described the coupled transcription and translation of a reporter gene to detect inhibitors of RNA and/or protein biosynthesis with potential activity as antibiotics and/ or herbicides. Not all of these methods would be easy to translate to high throughput methodology and it is difficult, if not impossible, to achieve even sensitivity to inhibition at all steps in any long series of coupled assays. Nevertheless such whole system assays may become a method of choice in future.

However, the fundamental problem with all *in vitro* leads remains the question of how to convert them to potential products. Typically, better than nanomolar levels of intrinsic potency need to be combined with the litany of secondary properties (crop selectivity, low cost of manufacture, uptake, stability in plants, biodegradability in soil, mobility in phloem etc.) required to make a product. How often will it be possible to add such properties to an *in vitro* lead without losing the activity in the attempt? In practice, will *in vitro* leads always need to start out with at least *some* of the other properties needed and, this being the case, why pick on intrinsic activity as the preferred parameter to pre-screen for? Pharmaceuticals have a very different set of options for delivering molecules to their targets and also face quite a different set of obstacles in converting *in vitro* actives to products (with very high intrinsic potency and low cost of manufacture not figuring so prominently).

Using cultured cells as a pre-screen

Cells represent something of a half-way house between whole organisms and *in vitro* systems. A barrier to uptake and metabolism are restored although not necessarily as *in vivo*. Cultured cell pre-screens assessed for simple inhibition of growth appear to offer good potential for high throughput screening in agrochemicals. Certainly it should be possible to achieve the requirement for lower sample weights and the step-jump in throughput required. However, the quality of information gained from this type of test will arguably be lower than for both *in vivo* and *in vitro* enzyme/receptor assays, in that the activity will still need to translated to the whole organism and also the specificity of any activity seen will not be known at the pre-screen stage. Obtaining a "universal" pre-screen may come at the cost of, for example, a high number of false positives and a proportion of false negatives. Data from cell culture screens will therefore need to be used in conjunction with other information.

Specific cell-based assays

There are a multiplicity of ways in which whole cell and whole organism tests can be engineered to detect preferentially inhibitors of particular cell functions, metabolic processes or even individual enzymes. Some examples follow.

a) Tests for detecting rapid effects on cell function

A number of methods allow more rapid detection of effects on growth than simply awaiting the eventual effect on biomass. Screens to detect early indicators of cell dysfunction preferentially detect certain modes of action. For example, inhibitors of respiration and uncouplers act quickly. ATP levels fall very quickly in dying tissues and can be measured through bioluminescence. Similarly, living tissues and cells generate heat and microcalorimetry can also be used (Lawrence and Yuen, 1995). Inhibitors of cell proliferation have been detected using the reduction of a tetrazolium dye (MTT) to report changes in the reductive capacity of treated tissues although the specificity of this test as an indicator for mitochondrial electron transport has been questioned (Berridge and Tan 1993).

b) Cell-based assays to detect inhibitors of particular metabolic processes

Testing for the ability of small metabolites to specifically reverse the inhibitory effects of chemicals is well known as a technique to orient grow/ no grow tests toward the detection of inhibitors of particular metabolic pathways (e.g. Powell and Rees, 1989). Inhibitors of fungal cell-wall growth have been detected by inhibition of the restoration of cell walls to protoplasts (Selitrennikoff, 1983) or by osmotic protection with sorbitol (Frost *et al.* 1995). Kirsch (1994a) described a cell-based method for screening for inhibitors of ergosterol biosynthesis in yeast based on detecting the specific induction of lanosterol 14-C demethylase (reported via a gene fusion with β-galactosidase) in response to any general inhibition of sterol biosynthesis. The assay is 'smart' in the sense that inhibitors are positively indicated. Similarly, Kirsch (1994b) described an assay to detect inhibitors of fungal spindle pole body formation based on the fact that growth of a specific mutant, a diploid esp1-1 strain, was defective due to the overproduction of such bodies. Thus inhibitors were detected positively through the restoration of growth to this strain.

c) Cell-based assays to detect inhibitors of individual enzymes

Compared with screening the enzyme directly, it might seem retrograde to use whole cell assays to detect inhibitors of individual enzymes within central metabolism (the case being quite different from that for receptors which are expressed on the *outside* of cells and where, uniquely, cell-based assays afford the opportunity to assay effects on function). However, some molecular targets are very difficult to assay *in vitro*. Strains specifically engineered to overexpress these (e.g. *via* increased gene dosage) may be used as the basis for cell-based assays to detect inhibitors (Rine *et al.* 1983). Similarly, a plant cell culture line which massively overproduced sterols (Schaller *et al.* 1992) was specifically de-sensitised to herbicides which inhibit the 14-C demethylase step in sterol biosynthesis and could therefore be useful in an assay to detect further such inhibitors. Kirsch (1994c) compared the relative inhibition of growth of two specific strains of yeast, one 'supersensitive' and the other with reduced sensitivity, as a specific means of detecting inhibitors of cytochrome P450 reductase. Finegold (1990) described an elegant assay to detect inhibitors of ras farnesyltransferase based on their specific ability to restore growth to a strain of yeast disabled

through disruption of the alpha subunit of a heterotrimeric G protein. In its absence, the dimeric beta-gamma complex transmits a growth inhibitory signal. This lethality was specifically blocked through inhibition of farnesylation of the alpha subunit and, thus, inhibitors could be detected through restoration of growth.

For plant enzymes with microbial counterparts which fulfil the same function, it should be possible to specifically 'vegetalize', for example, strains of yeast by deleting the corresponding yeast gene and complementing the function by transformation with the plant version of the gene. This would generate a yeast line specifically sensitive to inhibitors of the plant enzyme which might be useful as the basis of a differential grow/ no grow type assay for compounds which inhibit the plant but not the fungal enzyme. However, this would only seem worthwhile for herbicide target enzymes which were hard to assay *in vitro* and where the inhibitor specificities of plant and microbial enzyme were significantly different

d) Fluorescent dyes as indicators of specific cell function

A range of dyes are able to penetrate cells and indicate specific changes in cell function. For example highly selective fluorochromes for Ca^{2+}, K^{+}, Na^{+}, H^{+} etc. allow the detection of the effects of chemicals on specific parameters such as intracellular pH, membrane potential, intracellular Ca^{2+} and respiratory activity. Fluorescent dyes may also be released as a result of reporter gene expression. These techniques may be powerfully combined with confocal microscopy (for information on intracellular localisation) and flow cytometry (to resolve specific cell subpopulations).

e) Cell-based assays for receptor function

Receptors on the cell surface present no barrier to applied chemical and can be thought of as *in vitro* although the overall complexity of cell-based assay systems means that interpretation of results can become complicated. The expression of specific receptor subclasses in specific cell lines (or, indeed in lines where they are naturally expressed) can be coupled to the use of indicator dyes (e.g. to detect concentrations of intracellular Ca^{2+}) or translationally fused reporter genes (e.g. β-galactosidase) to detect not only inhibitors which interfere directly with receptor function but, potentially, also at any site downstream in the signal pathway. Examples of different approaches include a G protein coupled receptor assay yielding expression of luciferase (Weyer *et al.* 1993) and the fusion of a cAMP response element to chloroamphenicol acetyltransferase to report the function of specific subtypes of human α2 adrenergic receptor in transiently transfected cells (Pepperl and Regan 1993). Messier *et al.* (1995) described an assay for receptor-mediated cell proliferation achieved through co-transfection of cells with receptor and a readily detected marker enzyme. Potenza *et al.* (1992) described an assay system for various receptors able to alter the pigmentation of frog melanophores. Jones *et al.* (1991) described an assay based on the ability of recombinant receptors to elicit the release of a detectable marker enzyme, hexosaminidase, from transfected leukaemia cells.

CONCLUSIONS

High throughput screening is one alternative approach to the traditional target-based, highly-focused screens historically used in agrochemical discovery programmes. HTS brings with it

a number of constraints which dictate that significant changes will be necessary to current practices if it is adopted. It also brings with it the opportunity to test a much higher number of compounds with only small amounts required, and is more compatible with emerging technologies, for example combinatorial chemistry. Agrochemical companies will need to decide whether to follow the HTS approach, or to stay with target-based screens, or to run with a combination of the two.

The principal constraints with HTS are that some degree of automation is essential, and that the existing technology has been developed around the microtitre-based assay format which is most suitable for *in vitro* assays. Cell-based assays may become a method of choice for herbicide pre-screens although it will require some ingenuity to invent 'smart' screen methods which detect inhibitors by the *restoration* of growth and it is not yet clear how to apply the technology of cell-based assays for receptors to herbicide discovery.

REFERENCES

Bartley, M.R. and Youle, D. (1995) The use of in vitro and in vivo bioassays to screen for novel agrochemicals: approaches to experimental design. *Pesticide Science*, in press.

Berridge, M.V. and Tan, A.S. (1993) Characterization of the cellular reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT): Subcellular localization, substrate dependence and involvement of mitochondrial electron transport in MTT reduction. *Archives of Biochemistry and Biophysics* **303**, 474-482

Brigham-Burke, M.; Edwards, J.R. and O'Shannessey, D.J. (1992) Detection of receptor-ligand interactions using surface plasmon resonance: model studies employing the HIV-1 gp120/CD4 interaction. *Analytical Biochemistry* **205**, 125-131

Checovich, W.J.; Bolger, R.E. and Burke, T. (1995) Fluorescence polarisation - a new tool for cell and molecular biology. *Nature* **375**, 254-256

Dardonis, G. (1993) Plant tissue culture and herbicide research. In: *Bioassays*, CRC Press, Boca Raton, pp. 173 - 183

Davis, G.E.; Gustafson, G.D.; Henry, M.J.; Smith, A.J. and Waldron, C. (1993) Method for screening fungicides utilizing dihydro orotate dehydrogenase (DHOD) inhibitor. *European patent application* EP 0 554 042 A1

Felix, H.R., Chollt, R., Harr, J. (1988) Use of the cell wall-less alga *Dunaliella bioculata* in herbicide screening tests. *Annals of Applied Biology* **113**, 55-60

Finegold, A.A.; Schafer, W.R.; Rine, J.; Whiteway, M. and Tamanoi, F. (1990) Common modifications of trimeric G proteins and ras protein: Involvement of polyisoprenylation. *Science* **249**, 165-169

Fromtling, R.A. (1987) In vitro methods in the evaluation of antifungal agents. In: *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents.* R.A. Fromtling (Ed) pp. 7 - 14

Frost, D.J.; Brandt, K.D.; Cugier, D. and Goldman, R. (1995) A whole-cell *Candida albicans* assay for the detection of inhibitors towards fungal cell wall synthesis and assembly. *The Journal of Antibiotics* **48**, 306-310

Giles, D.P. (1989) Principals in the design of screens in the process of agrochemical discovery. In: Comparing Glasshouse and Field Pesticide Performance. L.G. Copping *et al.* (Eds.) *Aspects of Applied Biology* **21**, pp. 39 - 50

Gressel, J. (1987) In vitro plant cultures for herbicide pre-screening. In: *Biotechnology in Agricultural Chemistry*, ACS Symposium series **334**. LeBaron HM et al. (Eds), pp.41-53

Gronwald, J.W. (1994) Herbicides inhibiting acetyl-CoA carboxylase. *Biochemical Society Transactions* **22**, 616-621

Grossmann, K., Berghaus, R., Retzlaff, G. (1992) Heterotrophic plant cell suspension cultures for monitoring biological activity in agrochemical research. Comparison with screens using algae, germinating seeds and whole plants. *Pesticide Science*, **35**, 283 - 289

Hawkes, T.R. (1993) Acetolactate synthase; The perfect herbicide target? *Proceedings of the British Crop Protection Conference-Weeds* **2**, pp 723-730

Hawkes, T.R.; Cox, J.M.; Barnes, N.J.; Beautement, K.; Edwards, L.S.; Kipps, M.R.; Langford, M.P.; Lewis, T.; Ridley, S.M.; and Thomas, P.G. (1993) Imidazole glycerol phosphate dehydratase: A herbicide target. *Proceedings of the Brighton Crop Protection Conference-Weeds* **2**, 739-744

Hawkes, T.R. (1995a) Assay procedure and application in identification of herbicides *International patent application* WO 95/09927

Hawkes, T.R. (1995b) In vitro assay to detect inhibitors of protein and/or mRNA biosynthesis. *International patent application* WO 95/09925

Holland, J.D.; Singh, P.; Brennand, J.C. and Garman, A.J. (1994) Nonseparation microplate receptor binding assay *Analytical Biochemistry* **222**, 516-518

Jones, S.V.P.; Heilman, C.J. and Brann, M.R. (1991) Functional responses of cloned muscarinic receptors expressed in CHO-K1 cells *Molecular Pharmacology* **40**, 242-247

Kirsch, D.R. (1994a) Cytochrome P-450 reductase screen for ergosterol biosynthesis inhibitors. *European Patent Application* 0 626 453 A1

Kirsch, D.R. (1994b) Spindle pole body screen for fungicides. *European Patent Application* 0 626 454 A1

Kirsch, D.R. (1994c) Enzyme induction screen for ergosterol biosynthesis inhibitors *European Patent Application* 0 627 491 A1

Laber, B. and Amrhein, N. (1989) *In vitro* reconstitution of the diaminopimelate pathway. In: *Prospects for amino acid biosynthesis inhibitors in crop protection and pharmaceutical chemistry British Crop Protection Council* Monograph No. **42**, 81-83

Lawrence, E.B. and Yuen, H.K.(1995) A microcalorimetric technique for rapid assessment of fungicide activity. *Plant disease* **79**, 605-608

Major, J.S. (1995) Current screening practices in the pharmaceutical industry. *Proceedings of the Brighton Crop Protection Conference - Weeds 1995.*

Messier, T.L.; Dorman, C.L.; Brauner-Osborne, H.; Eubanks, D. and Brann, M.R. (1995) High-throughput assays of cloned adrenergic, muscarinic, neurokinin and neutrophin receptors in living mammalian cells. *Pharmacology & Toxicology* **76**, 308-311

Nurit, F., Gomez de Melo, E., Ravanel, P., Tissut, M. (1990) The use of cultured *Acer* cells as a screening tool for mitotic inhibitors. I. Reference herbicides. *Plant Growth Regulation* **9**, 47 - 57

Olofsdotter, M., Olesen, A., Andersen, S.B., Streibig, J.C. (1994) A comparison of herbicide bioassays in cell cultures and whole plants. *Weed Research* **34**, 387 - 394

Oswald, T.H., Smith, A.E., Phillips, D.V. (1976) Herbicide tolerance developed in cell suspension cultures of perennial white clover. *Canadian Journal of Botany* 55, 1351 - 1358

Pepperl, D.J. and Regan, J.W. Selective coupling of α_2-adrenergic receptor subtypes to cyclic AMP-dependent reporter gene expression in transiently transfected JEG-3 cells. *Molecular Pharmacology* **44**, 802-809

Potenza, M.N.; Graminski, G.K. and Lerner, M.R. (1992) A method for evaluating the effects of ligands upon Gs protein-coupled receptors using recombinant melanophore-based bioassay. *Analytical Biochemistry* **206**, 315-322

Powell, K.A and Rees, S.B. (1989) Screening techniques for amino acid biosynthesis inhibitors. In: *Prospects for amino acid biosynthesis inhibitors in crop protection and pharmaceutical chemistry British Crop Protection Council* Monograph No. **42**, 31-39

Rine, J.; Hansen, W.; Hardeman, E. and Davis, R.W. (1983) Targeted selection of recombinant clones through gene dosage effects. *Proceedings of the National Academy of Sciences (USA)* **80**, 6750-6754

Saari, L.L.; Cotterman, J.C.; Smith, W.F. and Primiani, M.M. (1992) Sulfonylurea herbicide resistance in common chickweed, perennial ryegrass and Russian thistle. *Pesticide Biochemistry & Physiology*, **42**, 110-118

Sato, F., Takeda, S., Yamada, Y. (1987) A comparison of several herbicides on photoautotrophic, photomixotrophic and heterotrophic cultured tobacco cells and seedlings. *Plant Cell Reports* **6**, 401 - 404

Schaller, H.; Maillot-Vernier, P.; Belliard, G.; and Benveniste, P. (1992) Increased sterol biosynthesis in tobacco calli resistant to a triazole herbicide which inhibits demethylation of 14α–methyl sterols. *Planta* **187**, 315-321

Scheidegger, A.; Ward, E.R.; Ryals, J.A. and Nagai-Hayashi, A. (1991) Histidinol dehydrogenase protein, DNA and muteins and transgenic plants thereof. *European patent application* EP 0 478 502 A2

Schloss, J.V.; Ciskanik, L.M. and Van Dyk D.E. (1988) Origin of the herbicide binding site of acetolactate synthase. *Nature* **331**, 360-362

Selitrennikoff, C.P. (1983) Use of a temperature-sensitive, protoplast-forming Neurospora strain for the detection of antifungal antibiotics. *Antimicrobial Agents Chemotherapy* **23**, 757-765

Staub, T. and Diriwaechter, G. (1986) Status and handling of fungicide resistance in pathogens of grapevine *Proceedings of the British Crop Protection Conference-Pests and Diseases* **2**, pp 771-780

Thiemann, J., Nieswandt, A., Barz, W. (1989) A microtest system for the serial assay of phytotoxic compounds using photoautotrophic cell suspension cultures of Chenopodium rubrum. *Plant Cell Reports* **8**, 399 - 402

Session 3B

The Future of the Agrochemicals Industry

Chairman	Mr D A Walker
Session Organiser	Dr A H Buckenham
Papers	3B-1 to 3B-4

SUSTAINABLE AGRICULTURE IN THE 21st CENTURY: CHALLENGES, CONTRADICTIONS AND OPPORTUNITIES

J N PRETTY
International Institute for Environment and Development, 3 Endsleigh St, London WC1H ODD

ABSTRACT

The projected increases in world population are giving an urgency to debates on the future of agriculture. Emerging evidence is showing that a more sustainable agriculture could supply the food needed whilst protecting the environment. But this will need fundamental reforms in farming and its services. There are three stages in the transition to sustainable agriculture, involving first shifts in efficiency of resource use, then substitution of new technologies and practices, and finally redesign. The transition to redesign, however, implies new roles and responsibilities for public and private professionals and institutions. These will have to become more oriented towards provision of integrated services focusing on knowledge and management skills rather than on ready-made technologies.

COMPETING SCHOOLS OF THOUGHT ON FEEDING THE WORLD

Farmers and their private and public support services and institutions face some extraordinary challenges in the coming decades. Each year, the world's population grows by 100 million, pushing up towards 8 billion by 2020. Although we currently produce enough food in aggregate to feed everyone in the world, some 700 million people do not have access to sufficient food. About 1.1 billion people live in poverty, and 180 million children are underweight and suffer from malnutrition. Are we on course for an unprecedented Malthusian disaster, with agricultural production reaching and passing ecological limits, or will we find ways to ensure everyone has at least an adequate diet? There are very different views on how we should approach these challenges (for summaries, see McCalla, 1994; Hazell, 1995; Pretty, 1995a).

The *'industrialised world to the rescue'* lobby believes that many Third World countries will never be able to feed themselves, for all sorts of ecological, institutional and infra-structural reasons, and so the food gap will have to be filled by modernized agriculture in North America and Europe (Avery, 1995; Carruthers, 1993). Increased production in large, mechanised operations will allow small and 'inefficient' farmers to go out of business, so conserving natural resources in protected areas and wildernesses. The large producers will then be able to trade their food with those who need it, or have it distributed by famine relief.

A second group, what we might call the *'new modernists'*, argues that agricultural growth can occur, but will only come from high-external input farming, either on the existing high potential lands (where the 'Green Revolution' of the 1960s-1970s occurred) , or expanded to those areas that have been missed by the past 30 years of agricultural development (Borlaug, 1992; S-G2000, 1993; Paarlberg, 1994). It is argued that farmers use too few fertilizers and pesticides, which are said to be the only way to improve yields and so keep the pressure off natural habitats.

A third group, though, is making the case for the benefits of *'sustainable intensification'* on the grounds that growth is possible whilst at the same time protecting or even regenerating natural

resources (McCalla, 1994; Scoones, 1994; Hazell, 1995; Pretty, 1995a). Empirical evidence is indicating that low-input agriculture can be highly productive, provided farmers participate fully in all stages of technology development and extension. This evidence indicates that potential productivity is as much a function of human capacity and ingenuity as it is of biological and physical processes.

Clearly something different is needed. Should we be following a modernist approach emphasising external inputs (fertilizers, pesticides etc) alone, or can sustainable intensification offer realistic opportunities? The nature of this debate is currently extremely polarised. Some argue that low-external input agriculture is always low output, that fertilizers and pesticides are the only way to feed the world, that the risks from chemicals are minimal, and that chemical inputs protect world food security (Avery, 1995; DowElanco, 1994; Borlaug, 1992; JSWC, 1990; Knutson et al, 1990). Others take an equally extreme stance, arguing that all synthetic chemicals are dangerous to human health and the environment. This paper examines the opportunities and contradictions arising out of concerns for sustainability, and indicates how farmers' livelihoods can be protected, the environment conserved, and food production secured.

MODERNIZED AGRICULTURE FOR INTENSIFICATION

It is well established that modern agriculture has had a remarkable impact on world food production. Food production per capita has since the mid-1960s risen by 7% for the world as a whole. Between 70-90% of these increases in production have been due to increased yields, and the remainder to expanded area under agriculture (World Bank, 1993). During this time, farmers have intensified their use of external resources: nitrogen consumption has increased to 75 million tonnes; pesticide use in many individual countries has increased by 10-30% during the 1980s alone; and the area under irrigation grew from 100 to 170 million ha between 1960 and 1990. But these increases have been associated with a growth in adverse environmental and health impacts.

These environmental and health problems are a result of farms becoming more specialized with greater use of external inputs. These inputs, though, are never used entirely efficiently by the receiving crops or livestock, and some are lost to the environment. Some 30-80% of applied nitrogen and significant but smaller amounts of applied pesticides are lost to the environment to contaminate water, food and fodder and the atmosphere (Conway and Pretty, 1991). Water is often wasted or used inefficiently, leading to groundwater depletion, waterlogging and salinity problems.

Many environmental problems have increased in recent years (Conway and Pretty, 1991). These include contamination of water by pesticides, nitrates, soil and livestock wastes, causing harm to wildlife and disruption of ecosystems; contamination of food and fodder by residues of pesticides, nitrates and antibiotics; damage to farm and natural resources by pesticides, causing harm to farmers, the public and wildlife; contamination of the atmosphere by ammonia, nitrous oxide and methane, which play a role in ozone depletion, global warming, and atmospheric pollution; overuse of natural resources, causing depletion of groundwater and loss of wild foods and habitats, and of their capacity to absorb wastes, causing waterlogging and increased salinity; the tendency in agriculture to standardise and specialise by focusing on modern varieties, causing the loss of traditional varieties and breeds; and new health hazards for workers in the agrochemical and food-processing industries.

SUSTAINABLE AGRICULTURE FOR INTENSIFICATION

Over the past fifty years, agricultural policies throughout the world have successfully promoted external inputs as the means to increase food production. Pesticides have replaced biological, cultural

and mechanical methods for controlling pests, weeds and diseases. Inorganic fertilizers have substituted for nitrogen-fixing crops, livestock manures, and composts. Information for management decisions comes from input suppliers, researchers and extensionists rather than building on local knowledge and practices.

A more sustainable agriculture tries to do things differently. It pursues an incorporation of natural processes such as nutrient cycling, nitrogen fixation, and pest-predator relationships; a reduction in the use of external and non-renewable inputs that damage the environment or harm the health of farmers and consumers; a more equitable access to productive resources and opportunities; a greater productive use of local knowledge and practices; and an increase in self-reliance amongst farmers and rural people.

When these components come together, farming becomes integrated, with resources used more efficiently and effectively. Sustainable agriculture, therefore, strives for the integrated use of a wide range of pest, nutrient, soil and water management technologies. Sustainable agriculture aims for an increased diversity of enterprises within farms combined with increased linkages and flows between them. By-products or wastes from one component or enterprise become inputs to another. As natural processes increasingly substitute for external inputs, so the impact on the environment is reduced.

THE IMPACTS OF SUSTAINABLE AGRICULTURE

There is now emerging evidence that regenerative and resource-conserving technologies and practices can bring both environmental and economic benefits for farmers, communities and nations. The best evidence comes from countries of Africa, Asia and Latin America, where the concern is to increase food production in the areas where farming has been largely untouched by the modern packages of externally-supplied technologies. In these complex and resource-poor lands, whole farming communities adopting regenerative technologies have doubled or trebled crop yields, often only using few or no external inputs (Bunch, 1991, 1993; GTZ, 1992; UNDP, 1992; Krishna, 1993; Shah, 1994; SWCB, 1994; Balbarino and Alcober, 1994; Mausolff and Farber, 1995; Pretty, 1995a).

Although these are highly significant for food security, they are not the only sites for successful sustainable agriculture. In the high-potential and irrigated lands, farmers adopting regenerative technologies have been able to maintain yields whilst substantially reducing their use of inputs (Bagadion and Korten, 1991; Kenmore, 1991; van der Werf and de Jager, 1992; UNDP, 1992; Uphoff, 1992, Kamp et al, 1993; Pretty, 1995a).

In the very high input lands of the industrialised countries, farmers have been able to maintain profitability, even though per hectare yields fall by 10-20% in the short term, as input use has been cut dramatically, such as in Europe (Jordan et al, 1993; Pretty and Howes, 1993; Reus et al, 1994), and in the USA (NRC, 1989; Faeth, 1993; NAF, 1994). All of these successes have three elements in common. They have made use of resource-conserving technologies, such as integrated pest management, soil and water conservation, nutrient recycling, multiple cropping, waste recycling and so on. In all there has been action by groups and communities at local level; and there have been supportive and enabling external public and private institutions.

SUSTAINABILITY AS A CONTESTED TERM

Although it is relatively easy to describe goals for a more sustainable agriculture, it becomes much

more problematic when we attempt to define sustainability. Since the Brundtland Commission's[1] definition of sustainable development in 1987, a great deal of effort has gone into trying to define sustainability in absolute terms. There are now at least 80 more definitions, each different in subtle ways, each emphasising different values, priorities and goals.

But precise and absolute definitions of sustainability, and therefore of sustainable agriculture, are impossible. Sustainability itself is a complex and contested concept. To some it implies persistence and the capacity of something to continue for a long time. To others, it implies resilience, and the ability to bounce back after unexpected difficulties. In any discussions of sustainability, however, it is important to clarify what is being sustained, for how long, for whose benefit and at whose cost, over what area and measured by what criteria.

Contested views of sustainability become crucial during the three phase process of transition, as we may ask 'how much are farmers expected to change?' Some regard changes in efficiency as sufficient to indicate that a sustainable agriculture has been achieved (see Table 1). With the adoption of precision farming, targeting of inputs and use of decision-support systems, so losses to the environment are cut. But such increases in efficiency produce only some of the benefits possible with sustainable agriculture.

The next stage involves greater change, with the substitution or introduction of new practices or technologies, such as green manures, biopesticides, contour farming or resistant varieties or breeds. The final stage, implying fundamental changes in the use of human and physical resources, is redesign. Here positive resource linkages and processes within and between farming systems are emphasised, leading to substantially greater returns. As sustainable agriculture addresses all resources in an integrated fashion, it can become as much a philosophy as a management system.

REDESIGN AND TECHNOLOGY DEVELOPMENT

This three stage process has important implications for the process of technology development for sustainable agriculture. If the transition to redesign is to be made, then farmers will need to be at the centre of technology development. A recent analysis of sustainable agriculture initiatives in Guatemala and Honduras has made an important contribution to our understanding of sustainability. A learning group[2] of farmers and professionals returned to areas where projects had ended three, four and 15 years previously, and used participatory methods with local communities to investigate subsequent changes (Bunch and López, 1994). They found that those communities within the project areas were still better off economically and socially.

But, surprisingly, many of the technologies known to be 'successful' during the project (those that had increased crop yields without damaging the environment) had been completely replaced by new practices and, in all, some 80-90 innovations were documented. This has led Bunch and López (1994) to conclude that *"technologies are not sustainable: what needs to be made sustainable is the process of innovation itself"*. It is critical, therefore, that farmers are not prescribed a concretely defined set of technologies, practices or policies. This would only serve to restrict their future options. Although many resource-conserving technologies and practices have been widely proven on research stations to be both productive and environmentally-sensitive, the total number of farmers using them is still small.

---

[1] The United Nations' World Commission on Environment and Development (1983-1987)

[2] From the non-governmental group Asociación de Consejeros una Agricultura Sostenible, Ecológica y Humana, Tegucigalpa

Table 1. Stages in the transition towards more sustainable agriculture

Stages	Technologies and Practices Emphasised	Rationale and Issues
INCREASED EFFICIENCY	Precision farming, targeted inputs and patch spraying, using global positioning systems and satellite mapping Integrated crop management (ICM) Decision-support systems Low volume and low drift applications Scouting and pest monitoring Soil testing Deep placement, slow release and banding of fertilizers No-till conservation	Conventional systems altered to reduce wastes and environmental impacts Optimising of inputs Fits context of currently acceptable business activities and corporate strategies But existing rights and privileges not challenged and causes of problems not confronted
SUBSTITUTION	Biological pesticides Bacterial and viral pesticides Pheromones Resistant varieties and breeds Beetle banks, flowering strips, filter strips Animal manures and composts Releasing natural enemies Integrated pest management (IPM) Legumes, green manures, *Azolla* and cover crops Contour bunds and contour farming New livestock (eg pigs, cattle, goats, sheep, fish)	Finite and environmentally damaging technologies replaced by benign ones Substitution of internal for external resources where possible Matching of traditional and modern practices Increasing the diversity of farming systems
REDESIGN	Integration of crop, livestock and tree components System-wide integrated pest management (IPM) Catchment management Integrated soil and water conservation and harvesting Collective and cooperative action by communities Community credit groups Diverse rotation patterns, multiple cropping and crop mosaics New system components, such as fish in irrigation channels, raised beds and chinampas, silt traps and gully fields, agroforestry Permaculture and holistic resource management	Maximising positive resource linkages within farming systems New corporate philosophies and practice needed Sustainable agriculture seen as both philosophy and system of management Emphasis on developing self-reliant and self-regulating systems Agriculture seen as important component of vibrant rural economies Needs fundamental changes in use of human and physical resources

Sources: adapted from MacRae et al, 1993; Vorley and Keeney, 1995; Pretty, 1995a

Occasionally an environmentally-beneficial technology is developed that appears to require no knowledge of farmers' conditions. The Integrated Pest Management (IPM) programme to control cassava mealybug (CMB) (*Phenacoccus manihoti*) in west and central Africa is one example. CMB was first recorded in Africa in 1973, and an effective natural enemy, the wasp *Epidinocarsis lopezi*, was found in 1981. Since releases began, it has became established in 25 countries, providing good control of CMB. It is to some extent a 'perfect technology' for scientists, as it is released from the air without the knowledge of farmers. It is, however, not necessarily a perfect technology for farmers. The contrast with another IPM programme in Togo is significant when it comes to issues of sustainability (Box 1).

As conditions and knowledges change, so must farmers and communities be encouraged and allowed to change and adapt too. Sustainable agriculture is, therefore, not simply an imposed model or package. It must become a process for learning and perpetual novelty.

Box 1. Comparison of farmers' involvement in two IPM programmes

A: Cassava Mealybug (CMB) control with *E.lopezi*

The programme has involved close collaboration between the International Institute for Tropical Agriculture (IITA) and national agricultural research systems, involving training of local technicians to participate in releases. Now mass rearing of *E.lopezi* is done in Benin, from where they are transported by air for air release. According to IITA, an important component of success has been that farmers and extension agents have not had to be involved. Farmers do not, therefore, know anything about the releases. One survey of farmers in Ghana and Cote D'Ivoire found that they recognised CMB and how it was a devastating pest. All those where *E.lopezi* had been introduced at least 6 months before had observed a significant decline in CMB. But as none of them knew about the programme, they attributed the decline to recent heavy rains and other climatic factors.

B: Mango mealybug control in Togo

The CMB programme is in contrast to the successful introduction of the parasitoid *Gyranusoides tebyii* to Togo in 1987 to control the mango mealybug (*Rastrococcus invadens*). The parasitoid was found in India, and following testing, rearing and release, it rapidly spread over the whole of Togo. By 1989, no mango trees could be found on which mango mealybug was present without being parasitised. But success would be threatened without public interest, as any use of chemical control methods would kill the parasites. A great deal of publicity was given, using radio, TV and advisory leaflets. Considerable economic losses are now being prevented by the biological control system.

Source: Kiss and Meerman (1991)

IMPLICATIONS FOR PEST MANAGEMENT

A guiding principle of sustainable agriculture is that it must enshrine new ways of learning about the world. But learning should not be confused with teaching. Teaching implies the transfer of knowledge from someone who knows to someone who does not know. Teaching is the normal mode of educational curricula, and is also central to many organisational structures (Ison, 1990; Bawden, 1991; Pretty and Chambers, 1993). Public and private institutions reinforce the teaching paradigm by giving the impression that they are custodians of knowledge which can be dispensed or given to a recipient. Where these institutions do not include a focus on self-development and enhancing the ability to learn, then "*teaching threatens sustainable agriculture*" (Ison, 1990).

A move from a teaching to a learning style has profound implications for public and private agricultural development institutions (Pretty, 1995b; Scoones and Thompson, 1994). The focus is less on *what* we learn, and more on *how* we learn and *with whom*. This implies new roles for development professionals, leading to a whole new professionalism with new concepts, values, methods and behaviour.

The implications for IPM are significant, as it requires analytical skills and basic training in crop monitoring and ecological principles. Where farmers have been trained as experts, such as in Honduras (Bentley et al, 1993) and in the rice-IPM programmes of SE Asia (Kenmore, 1991; FAO, 1994), then there are substantial benefits. Ordinary farmers are capable of rapidly acquiring and applying the principles and approaches.

Programmes are now not teaching farmers new technologies and knowledge; rather they are concerned with developing farmers' own capacity to think for themselves and develop their own solutions. These are producing substantial reductions in insecticide use, whilst maintaining yields and increasing profits (Table 2). But where extension continues to use the conventional top-down approach, then few farmers adopt, let alone learn the principles. As Pat Matteson (1992) put it: *"few IPM programmes have made a lasting impact on farmer knowledge, attitudes or practice"*.

Table 2. Impact of IPM programmes involving farmer learning on pesticide use and crop yields

Country and crop	Changes in pesticide use (as % of conventional treatments)	Changes in yields (as % of conventional treatments)
UK	15-55%	85-105% [1]
Denmark	55%	100% [1]
Netherlands	10-15%	98-118% [2]
USA, northwest	30%	95-105% [2]
Togo, cotton	50%	90-108%
Burkina Faso, rice	50%	103%
Thailand, rice	50%	nd
Philippines, rice	62%	110%
Indonesia, rice	34-42%	105%
Nicaragua, maize	25%	93% [2]
Bangladesh, rice	0-25%	113-124%
India, groundnuts	0%	100%
China, rice	46-80%	110%
Vietnam, rice	57%	107%
India,rice	33%	108%
Sri Lanka, rice	26%	135%

[2] Net returns are higher than conventional (100%) for all these examples; nd = no data; UK data gathered from a wide range of farms and experimental schemes (eg LIFE, LEAF, Boxworth project, Talisman)
Sources: Pretty, 1995a adapted from various sources

TOWARDS 2020: FOUR MAJOR TRENDS

Over the next twenty five years, there are four important trends that will change the face of farming in both the industrialised and Third World countries.

1. Consumer and public perceptions of environmental problems arising from modern agriculture will continue to become polarised, regardless of the 'actual' status of risk and damage. These perceptions will directly influence regulators and politicians.

2. A substantial increase in uptake of sustainable agriculture technologies and practices will occur. This change will increasingly be supported in Europe and North America by payments and subsidies tied directly to environmental and social goods.

3. A shift in emphasis will occur in private and public agricultural organisations away from supplying ready-made technologies towards provision of services and knowledge. Such agriculture implies a cut in external input use with potential to damage the environment and substitution with knowledge- and management-intensive technologies.

4. An increase in food production in currently food-insecure regions of the world combined with a decrease in outputs in industrialised countries, with maintenance of or increase in farmers' profitability and status of the natural resources.

The coming 25 years represents a crucial phase in agricultural development. The greatest challenge in this period of transition will be in the fundamental redesign of services to support food producing systems that are explicitly beneficial to local economies and environments.

REFERENCES

Avery D. 1995. *Saving the Planet with Pesticides and Plastic.* The Hudson Institute, Indianapolis

Bagadion, B. U. & Korten, F. F. 1991. Developing irrigators' organisations; a learning process approach. In: Cernea, M. M. (ed). *Putting People First*. Oxford University Press, Oxford. 2nd Edition.

Balbarino E A and Alcober D L. 1994. Participatory watershed management in Leyte, Philippines: experience and impacts after three years. Paper for IIED/ActionAid Conference *New Horizons: The Social, Economic and Environmental Impacts of Participatory Watershed Development*. Bangalore, India: Nov 28 to Dec 2

Bawden, R. 1991. Systems thinking and practice in agriculture. *Journal of Dairy Science* **74**, 2362-2373.

Bentley J W, Rodríguez G and González A. 1993.Science and the people: Honduran campesinos and natural pest control inventions. In: Buckles D (ed). *Gorras y Sombreros: Caminos hacia la Colaboración entre Técnicos y Campesionos* Dept. of Crop Protection, El Zamarano, Honduras

Borlaug, N. 1992. Small-scale agriculture in Africa: the myths and realities. *Feeding the Future* (Newsletter of the Sasakawa Africa Association) **4**, 2.

Bunch, R. 1991. *Low Input Soil Restoration in Honduras: The Cantarranas Farmer-to-Farmer Extension Programme*. Sustainable Agriculture Programme Gatekeeper Series SA23. IIED, London.

Bunch R. 1993. EPAGRI's work in the State of Santa Catarina, Brazil: Major New Possibilities for Resource-Poor Farmers. COSECHA, Tegucigalpa, Honduras

Bunch R and López G. 1994. Soil recuperation in Central America: measuring impacts 4 to 40 years after intervention. Paper for *IIED/ActionAid New Horizons* conference, Bangalore, India. November 1994. IIED, London

Carruthers I. 1993. Going, going, gone! Tropical agriculture as we knew it. *Tropical Agriculture Association Newsletter*, **13** (3), 1-5

Conway G R and Pretty J N. 1991. *Unwelcome Harvest. Agriculture and Pollution*. Earthscan Publications Ltd, London.

DowElanco. 1994. *The Bottom Line.* DowElanco, Indianapolis

Faeth, P. (ed). 1993. *Agricultural Policy and Sustainability: Case Studies from India, Chile, the Philippines and the United States*. WRI, Washington DC

FAO. 1994. *Intercountry Programme for the Development and Application of Integrated Pest Control in Rice in South and South-East Asia, Phase I and II.* Project Findings and Recommendations. Terminal Report, Rome

GTZ. 1992. *The Spark Has Jumped the Gap*. Deutsche Gessellschaft für Techniscle Zusammenarbeit (GTZ), Eschborn, Germany

Hazell P B R. 1995. *Managing Agricultural Intensification.* IFPRI 2020 Brief 11. IFPRI, Washington DC

Ison R. 1990. *Teaching Threatens Sustainable Agriculture*. Gatekeeper Series SA21, IIED, London

Jordan V W L, Hutcheon J A and Glen D M. 1993. *Studies in Technology Transfer of Integrated Farming Systems. Considerations and Principles for Development.* Institute of Arable Crops Research, Bristol

JSWC. 1990. Sustainable agriculture: perspectives from industry. *Journal of Soil and Water Conservation*, Jan-Feb, 31-33

Kenmore P. 1991. *How Rice Farmers Clean up the Environment, Conserve Biodiversity, Raise More Food, Make Higher Profits. Indonesia's IPM - A Model for Asia.* FAO, Manila, Philippines

Kiss A and Meerman F. 1991. *Integrated Pest Management in African Agriculture.* World Bank Technical Paper 142. African Technical Dept. Series. World Bank, Washington DC.

Knutson R D, Taylor J B, Penson J B and Smith E G. 1990. *Economic Impacts of Reduced Chemical Use.* Texas A&M University

Krishna, A. 1993 *Watershed Development in Rajasthan: the New Approach.* Watershed Development, Government of Rajasthan, Jaipur

MacRae R J, Henning J and Hill S B. 1993. Strategies to overcome barriers to the development of sustainable agriculture in Canada: the role of agribusiness. *J. Agric. and Environmental Ethics*, 21-51

Matteson P C. 1992. 'Farmer First' for establishing IPM. *Bulletin of Entomological Research* **82**, 293-296

Mausolff C and Farber S. 1995. An economic analysis of ecological agricultural technologies among peasant farmers in Honduras. *Ecological Economics* **12**, 237-248

McCalla A. 1994. *Agriculture and Food Needs to 2025: Why We Should be Concerned.* Sir John Crawford Memorial Lecture, October 27. CGIAR Secretariat, The World Bank, Washington DC

N.A.F. 1994. *A Better Row to Hoe: The Economic, Environmental and Social Impact of Sustainable Agriculture.*

St Paul, Minnesota: Northwest Area Foundation

N.R.C. 1989. *Alternative Agriculture.* National Research Council. National Acad. Press, Washington DC

Paarlberg R L. 1994. Sustainable farming: a political geography. IFPRI 2020 Brief 4. Washington DC

Pretty J N. 1995a. *Regenerating Agriculture: Policies and Practice for Sustainability and Self-Reliance.* Earthscan Publications Ltd, London and National Academy Press, Washington DC

Pretty J N. 1995b.Participatory learning for sustainable agriculture. *World Development* **23**, No. 8, 1-17

Pretty J N and Howes R. 1993. *Sustainable Agriculture in Britain: Recent Achievements and New Policy Challenges.* IIED, London.

Pretty J N and Chambers R. 1993. *Towards a learning paradigm: new professionalism and institutions for sustainable agriculture. IDS Discussion Paper* DP **334**. IDS, Brighton

Reus J A W A, Weckseler H J and Pak G A. 1994. *Towards A Future EC Pesticide Policy.* Centre for Agriculture and Environment (CLM), Utrecht

Scoones I. 1994. *Uncertainty and Risk in Dryland Africa.* IT Publications Ltd, London

Scoones I and Thompson J. 1994. *Beyond Farmer First.* IT Publications Ltd, London

S-G2000. 1994. *Developing African Agriculture: New Initiatives for Institutional Cooperation.* Sasakawa Global 2000 Project. Sasakawa Africa Association, Tokyo

Shah P. 1994. Participatory watershed management in India: the experience of the AKRSP. In: Scoones I and Thompson J (eds). *Beyond Farmer First.* IT Publications Ltd, London

SWCB 1994. *The Impact of the Catchment Approach to Soil and Water Conservation: A Study of Six Catchments in Western, Rift Valley and Central Provinces, Kenya.* Ministry of Agriculture, Nairobi

UNDP. 1992. *The Benefits of Diversity. An Incentive Toward Sustainable Agriculture.* United Nations Development Program, New York

Uphoff N. 1992. *Learning from Gal Oya: Possibilities for Participatory Development and Post-Newtonian Science* Cornell University Press, Ithaca

van der Werf E and de Jager A.1992. *Ecological Agriculture in South India: An Agro-Economic Comparison and Study of Transition.* Landbouw-Economisch Institut, The Hague

Vorley W T and Keeney D R. 1995. Sustainable pest management and the learning organisation. Paper for IFPRI workshop Pest Management, Food Security and the Environment, Washington DC.

World Bank. 1993. *Agricultural Sector Review.* Agricultural and Natural Resources Department, Washington DC

THE MARKET FOR AGROCHEMICALS PRESENT AND FUTURE

A T WOODBURN
Allan Woodburn Associates Ltd., 18 Newmills Crescent, Balerno, Midlothian, UK. EH14 5SX.

ABSTRACT

As there have been considerable changes in the agrochemicals industry, especially over the past ten years, either brought about as a result of the increasingly competitive marketplace or the difficulties in terms of time and money in bringing new products to the market, so too will the future be characterised by change. New technologies, the continued global population growth, reduced crop areas, trade agreements and/or disputes, political meddling, environmental pressures, etc., are some of the problem areas which will affect the potential market for agrochemicals, positively or adversely, and which will confront the industry into the new millennium and beyond.

INTRODUCTION

To all intents and purposes, the modern agrochemicals or crop protection chemicals industry celebrates its 50th anniversary this year. Unfortunately, statistics relating to the performance of the industry in its first twentyfive years (1945-1970) are virtually non-existent. However, the growth was such over this initial period that the end-user market in 1970 was valued at approaching US$3 billion, equivalent to over US$11.5 billion in today's money terms (Woodburn, 1995).

Throughout the 1970s, the real growth, after stripping out the effects of inflation and currency rate shifts, averaged 6.3% per annum. However, the first signs that the agrochemicals industry was approaching maturity were becoming evident. Whereas the average real growth at the beginning of that decade was nearly 10% p.a., by the end of the 1970s it had dropped to only just over 4.5% p.a. This trend continued through the 1980s with the real growth in the end-user market falling to an average of only 2.2% p.a. over the decade. The first significant political tinkerings in agriculture, with the introduction of the Payment-in-Kind (PIK) scheme in the United States of America in 1983, resulted in the first-ever recorded decrease in the global agrochemicals market value.

It can be argued that further political interference, principally as a result of the introduction of the European Community's 1992 Common Agricultural Policy (CAP) reforms, has been the prime reason for the end-user market value actually decreasing, in real terms, in three of the past four years. Largely because the bulk of the effects of these reforms had passed through the system by 1994, allied to weather conditions which were conducive in many of the major herbicides markets to weed promotion, and insect infestation levels which were also above-normal in a number of significant areas, the agrochemicals end-user market value rose by over 5% last year, in real terms, the largest annual increase since the post-PIK 1984 season. However, this upturn was not sufficient to bring the 1990s to-date into an overall real growth situation. The market in 1994 was still 2.2% below the peak sales level achieved in 1990, as measured in 1994 dollars.

It would appear that 1995 will turn out to have been a pretty good year for agrochemicals demand, though probably not as good as 1994. Overall though, for the rest of the decade, the real average growth is predicted to be at a level below 2% p.a. Thereafter, the uncertainties surrounding a number of potentially impacting demand factors, e.g. the introductions of new technologies, the continued global population growth, the reducing crop agricultural area, the prospects of trade agreements and/or disputes, the aspirations of the populations in the developing countries, political machinations, etc., all conspire to make forecasting future agrochemicals growth rates extremely difficult.

THE CURRENT AGROCHEMICALS MARKET SITUATION

The end-user crop protection chemicals market in 1994 was valued at US$25,885 million. Herbicides accounted for the largest share, followed by insecticides and fungicides (Table 1) (Woodburn, 1995a).

Table 1. The agrochemicals market products split in 1994

Product Type	Value (US$m.)	%age
Herbicides	12105	46.8%
Insecticides	7580	29.3%
Fungicides	4750	18.3%
Others	1450	5.6%
Total	25885	100%

In terms of the regional importance for agrochemicals demand, North America has recently regained the top spot which it had lost to West Europe throughout most of the 1987-1991 period. In 1994, North America accounted for 30.7% of the global end-user market value, while the Far East region had also overtaken West Europe with 25.7% compared to West Europe's 24.9%. Thus, the impact from the implementation of the recent CAP reforms is self-evident. Latin America contributed nearly 9% to the global total in 1994 with the rest of the world being responsible for the remaining 10%. Significantly, over the last five years, the East European region's share of the total has fallen substantially as a result of the collapse of the Communist system, the lack of infrastructure and the individual countries' substantially diminished foreign exchange capabilities.

One of the most significant effects of the slowdown in the growth of the agrochemicals market over the past fifteen to twenty years has been the reduced profitability of the companies involved in all facets of the industry, i.e. from basic research screening through to marketing of the products directly to the end-customer. The industry's profit margins, as a percentage of agrochemical sales, have been analysed over the 1981-1990 period (Woodburn, 1991) and a significant decrease is evident (Table 2).

Table 2. The agrochemicals companies' profit margins 1981/1990

	1981	1985	1990
Industry average (as %age of sales)	11.4%	8.8%	8.1%

Over this timeframe, the two major reasons for the global reduction in agrochemicals companies' profit margins were the impact of a more competitive marketplace and the significant increase in the cost and time to discover, develop and register new active ingredients. Allied to the latter problem was also the reduction in time available to the companies to recoup the enormous investment in a new product, since, as the time from discovery of a new molecule to its commercial introduction increased, the period from launch to patent expiry decreased. Also, many companies in the industry devoted considerable resources to imitative R&D, often at the expense of innovative R&D, further compounding the pressures.

If anything, these problems have not decreased since 1990 as the global market has become even more competitive, partly due, as indicated, to political interferences in the agricultural scene, and partly due to the increased number of generic products being introduced, while the additional substantial costs of re-registering existing products in an increasing number of markets has added a further block to even sustaining current, low, profit margins.

One of the ways in which the industry has reacted to the situation over the past decade has been through internal reorganisations or streamlining of activities, while the other principal method has been to consolidate. Since 1985, the following major R&D companies have gone the way of FBC, which had been acquired by Schering in 1983 - Velsicol, Shell, Union Carbide, Stauffer, Chevron, Celamerck, Dr. Maag and Fermenta (Diamond Shamrock), as also have a number of concerns which had more minor agrochemicals interests, companies such as 3M, Mobil, PPG Industries and Duphar. Additionally, Dow and Eli Lilly have combined their agrochemicals interests in the 60:40 joint-venture, DowElanco, as also have Hoechst and Schering in AgrEvo.

As this paper is being written, there has been considerable recent speculation surrounding the future of the agrochemicals interests of American Cyanamid (now part of American Home Products), Zeneca (which has been demerged from ICI) and Sandoz (in the process of demerging). It would increasingly appear that a number of companies, which are already heavily involved in the considerably more profitable human pharmaceuticals industry, are seriously questioning whether, strategically, they should be heavily committed to two high-risk, R&D-driven, sectors.

In 1994, there were a total of eleven companies which each achieved crop protection chemicals sales in excess of US$1,000 million. To varying degrees, all of these companies marketed products from outside sources, either to plug a gap in their own product range or to gain expertise in a previously unentered crop segment. The leading company in the industry in 1994 was Ciba, whereas in 1980, the top sales performer had been Bayer (Table 3).

Table 3. Companies' shares of the global agrochemicals market

Company	Estimated market share position	
	1980	1994
Ciba	10.6%	11.3%
Zeneca	5.3%	8.3%
Du Pont	4.1%	8.2%
AgrEvo	6.1%	8.1%
Monsanto	7.2%	8.0%
Bayer	13.9%	7.7%
Cyanamid	2.6%	7.1%
DowElanco	7.9%	6.8%
Rhone-Poulenc	5.2%	6.7%
Basf	4.5%	4.9%
Sandoz	1.6%	4.1%

In each case, the 1980 market shares reflect the business each company was running at that time and takes no account of subsequent acquisitions or other corporate initiatives, except that for DowElanco and AgrEvo, the constituent companies' market shares have been combined.

A relatively small number of crops consume the majority of the agrochemicals used globally (Woodburn 1995b) (Table 4).

Table 4. Agrochemicals usage split by crop in 1994

Crop	%age share of agrochemicals usage
Rice	14.1%
Maize	10.9%
Cotton	9.9%
Wheat	9.6%
Soybeans	8.4%
Sugar beet	3.3%
Barley	3.2%
Oilseed rape	2.0%
Conglomerate fruit and vegetables	21.8%
Rest	16.8%

Considerably over half of the 1994 global use was destined for only five crops. As a result of this concentration of demand level on a relatively small number of important crop outlets, the R&D efforts of the major companies are increasingly being directed at discovering and developing new products for these outlets, leaving growers of minor crops with the prospect of generally not having access to the latest product developments.

THE AGROCHEMICALS MARKET IN THE FUTURE

The shape of the agrochemicals industry in the future will be largely linked to the changing environment for crop production, which itself will be affected by numerous factors (Wise, 1993).

Economists predict that global economic growth will continue and that the overall world demand for key agricultural produce, such as cereals, milk, meat and edible oils etc., will increase. As part of the slowly changing world patterns, there is a likelihood that crop prices will decline after an initial increase and that, especially, the countries of eastern Europe and the Far East will increasingly feature as exporters of foodstuffs of ever-rising quality. This has important ramifications for the likes of West European farmers with the inevitable conclusion that survival will only be accomplished by the most efficient.

Political decisions are also likely to continue to affect crop production. In the short-term, guaranteed crop prices will come under pressure in western Europe as the European Union moves towards greater use of income maintenance and set-aside programmes. The Uruguay round of GATT will be severely tested as a number of countries find it difficult to phase out non-tariff measures. In the United States of America, planned Farm Bills will most likely focus on exports, increasingly with regard to the fast growing trade in processed foods as opposed to bulk commodity crops.

Over a longer timespan, there will probably also be attempts to rationalise crop cultivation patterns around the world - cereals in one area, fruit and horticultural produce in those areas favoured by optimum levels of temperature, sunlight, rainfall etc. However, it is difficult to believe that this commonsense approach will ever be acceptable to farmers or to proponents of free trade.

Increasingly, consumers in the developed areas of the world are focusing on the quality aspects of food rather than on its availability or otherwise. Health and consumer organisations and more and more, the consumers themselves, are generally more concerned about the health and safety aspects of what they eat and drink, the perceived environmental impact of modern farming practices and the use of radical new technologies, than about reduced market prices. However, contradicting this somewhat, consumers do not yet appear to be ready to cough up the premium that "organically-farmed" produce inevitably requires to be paid.

Additionally, as we look toward the next millennium, the implications of global warming cannot be ignored. Alterations in the distribution of crop growing and hence the nature and instance of insect and disease problems in particular are highly probable. These cultivational changes will not be politically-led but an economic necessity, though there will undoubtedly be political inspired interferences in support of national farming lobbies.

There will therefore be changes, at the moment unquantifiable, in both the methods and the geography of crop cultivation, largely brought about by economic concerns, augmented by technological, environmental and climatic considerations, all encompassed in a blanket of political intrigue. The nett effect will be that farmers will increasingly have to become more efficient in their chosen area of operations. This will entail even greater professionalism amongst the farming community with decisions at all levels being taken on economic considerations. This, however, should not be allowed to develop too far to the detriment of the environment and the alienation of the non-farming community.

Assuming that the economists are right in their predictions that global economic growth will continue, the environmental lobbying forces will become increasingly more vocal again - significantly they find greatest support in times of economic well-being. One of the focal points will be the use of pesticides but increasingly we can expect heightened public sensitivity to issues such as biotechnology and gene therapy in food production.

There are a number of ways in which the industry can prepare itself to rebut some of the more excessive, scientifically-dubious charges from publicity-seeking, largely self-appointed, environmentalists. There has been, and will continue to be, an increasingly important place in crop cultivations for the use of diagnostic techniques to ascertain the level of a specific problem and whether remedial action requires to be undertaken. As experience in utilising such measures becomes more standard and acceptable by the farmers, there should be a gradual reduction in the use of all-over prophylactic treatments in favour of spot treatments of highly targeted specific products to combat the effects of the yield-threatening problem. Generally this will result in a significant overall reduction in the volume of active ingredients applied although the newer specialised products will have to claim premium prices in the marketplace to repay the continuing huge investment in Research and Development (R&D).

Similarly, the excellent work already being undertaken by industry groups (such as GIFAP's Insecticide and Fungicide Resistance Action Committees, IRAC and FRAC) into the problems of resistance has already contributed to greater understanding of the nature of the difficulties and has led to the institution of a number of programmes, both educational and practical. Further cooperation within the industry and throughout the agricultural community will result in greater benefits being accorded to all involved. However, farmers and distributors are not yet universally aware of the need for effective anti-resistance strategies. This will improve as the industry focuses on the communication and education aspects of the benefits to be gained.

There are also a number of other ways in which agrochemicals will be used more target-directed and at appropriate dosage rates to specific problem areas in the future. Many of these developments are already being addressed by the industry and their adoption will be fairly rapid, especially in the developed agricultural economies (Table 5).

Table 5. Aspects likely to be more widely developed/introduced

reductions in application rates of existing products
combinations of chemical and biological products
use of elicitors
integrated seed coatings
early-stage crop management (transplanted seedlings)
advanced formulation technologies
use of IT, aerial surveying and GPS (global positioning systems)

There are a number of other aspects which will impact the agrochemicals market in the future, not all of which are necessarily controllable, or capable of being influenced, by the crop protection chemicals companies. As agricultural decisions become more and more "bottom line driven", the contraction in the number of farmers and the companies supplying agricultural inputs will continue. A worry in this regard is where the next generation of farmers and the generation thereafter will come from. Already, in many parts of the world, crop cultivation is being undertaken by an aging population while the younger members of the community are being put off entering agriculture as a profession because of a number of factors, e.g. the high entry costs of land and buildings, the need for expensive, sophisticated machinery, the increasingly adverse public perception of farming, the long, anti-social work patterns and the seeming better-paid, pensions-guaranteed positions of many of their counterparts in service and manufacturing industries. Unless something is done to combat this problem, the future for agriculture, and the implementation of new technologies, will become increasingly difficult.

The sizes of the agricultural, agrochemical and food industries are contracting at every level as all participants in the chain from the R&D-led agrochemical companies through the distribution system to the farmers, and further on through the processors and the retail outlets to the consumers, have been placed under financial pressures. With the margins on agrochemicals being continually squeezed, there will have to be changes in the marketing of the products and these have already commenced in many parts of the world (Gillard, 1993).

Table 6. The changing environment for marketing agrochemicals

fewer distributors
specialist distributors for minor crops or specialised uses
direct farm sales or farm deliveries
cost savings on packaging/formulations, where safety permits
manufacture to order on low margin, highly-seasonal, agrochemicals

In the future, the sales of crop protection chemicals will become even more tightly controlled than is the case today to ensure that the users, consumers and the environment are not put at undue risk. As the number of farms decreases due to financial and other pressures, it will increasingly become possible to completely change the method whereby agrochemicals products are sold and recommended. Within the next twentyfive years, in at least the developed agricultural nations, agrochemicals will probably be available by prescription only.

Because of the high costs associated with the research, development and registration of new molecules, there will continue to be a need for cheaper, effective generic products. It is probably worth pointing out that many of the current key generic products are marketed by the major research-based companies, thus providing a measure of cash flow stability even though most of these products are relatively low margin. Also, the speciality or patent-protected products of today are the generic products of tomorrow. By and large, it will ultimately be the farmer who will decide, on economic and efficacy grounds, which products succeed in the markets of the next century, while the regulatory authorities will monitor the environmental and safety effects. The likely outcome is that there will be an increase in the use of formulated mixtures of generic and speciality products.

On the manufacturing front, there will be more and more pressure on western agrochemicals companies to shift production to Asian sites, both from the standpoints of supplying the growing Asian market and to compete with Asian-based companies.

Overriding all of these considerations for agriculture and agrochemicals demand levels in the future is the spectre, or promise, of agricultural biotechnology. This topic is widely covered in other parts of the conference, but suffice to say at this juncture that there is considerable scope for the new technologies to have both positive and negative impacts on the agrochemicals industry, as we know it today.

SUMMARY

Great changes have taken place in the nature of crop protection chemicals in recent years. In response to concerns for the environment, manufacturers have developed and introduced substances that are less persistent, are used at considerably lower dosage rates but which are equally if not more efficacious. The agrochemicals products of the future will be even safer for both the user and the environment, of necessity they will have to be cost-effective and they will also assist the grower in overcoming resistance problems which he may encounter. While there have also been significant improvements in the methods of applying agrochemicals in recent times, there are potentially further important advances which can be expected to be brought forward to ready acceptance.

The surviving companies will be those which will be able to adapt best to change, not only the changes which can, to a large extent, be controlled, such as the introductions of new technologies, the competition initiatives which innovative marketing companies will employ, the place in the future for generic products and the opportunities which are likely to be afforded by regulatory and/or legislative demands, but also to those factors which are uncontrollable, e.g. the variability of the weather, the swings in commodity crop demand levels and prices, the shifts in global trade patterns and overall, the changes which will undoubtedly take place in agriculture itself.

In the face of an increasingly competitive marketplace, only those companies which can supply agrochemicals products to the farmer at a price which enables profitable trading at all levels in the industry, will survive and, hopefully, continue to introduce new products and technologies.

REFERENCES

Gillard, G (1993) The task ahead for marketing agrochemicals. In *Second Annual European Crop Protection Conference* proceedings, IBC Technical Services Ltd., London, UK.

Wise, C J C (1993) The changing environment for crop production. In *Biotechnology in Agriculture* conference proceedings, IBC Technical Services Ltd., London, UK.

Woodburn, A T (1991) The profitability of the agrochemicals industry. In *Agrochemicals - Into the 1990s*, Allan Woodburn Associates Ltd., Edinburgh, UK, pp. 18-21.

Woodburn, A T (1995a) Global and regional market estimates. In *Agrochemicals - Executive Review*, 6th edition, Allan Woodburn Associates Ltd., Edinburgh, UK, pp. 12-13.

Woodburn, A T (1995b) 1994 products sales estimates. In *Agrochemicals - Executive Review*, 6th edition, Allan Woodburn Associates Ltd., Edinburgh, UK, p128.

THE REGULATORY CONTROL OF PLANT PROTECTION PRODUCTS : BEYOND THE MILLENNIUM

B THOMAS
AgrEvo UK Limited, Saffron Walden, Essex CB10 1XL

ABSTRACT

Possible future developments in the regulatory control of plant protection products are discussed with specific reference to harmonisation of requirements and procedures, political influences and the use of quantitative criteria for judging registrability. Particular emphasis is placed on current experiences with the European Registration Directive and its likely effect on the evaluation of data in the areas of ecotoxicology, environmental fate, toxicology and residues. Conclusions are drawn regarding the possible implications to the Crop Protection Industry and the challenges it faces in the future.

INTRODUCTION

Experience has shown that attempting to predict what the regulatory scene will be like in the future time is fraught with difficulty. This is particularly the case at present as the introduction of the European Registration Directive (Official Journal 1991) is still at an early stage and the full implications of its requirements have yet to be established.

Experience would also indicate that whereas some areas of regulatory data requirements have remained relatively stable over the past 10 years (eg toxicology) others have significantly increased (eg environmental fate and ecotoxicology). Given the overall political concern with environmental issues it seems likely that this trend will continue. Political changes can also influence overall agricultural policies with consequential effects on agricultural production and productivity and, by association, on the use of crop protection products.

All predictions of the future must be based on historical and current experience and the comments given below are no exception. They attempt to identify the general trends in the regulatory control of crop protection products and also to predict some quantitative criteria by which the registrability of products may be assessed. Despite their obvious limitations, these comments provide sufficient evidence to indicate that significant changes in the regulatory control of plant protection products can be expected in the foreseeable future with consequential implications for both Regulators and Industry alike.

GENERAL TRENDS

Harmonisation

Regionally harmonised registration systems (eg European Union, North America, South America) are being developed in various parts of the world as governments see their advantages in eliminating trade barriers and sharing the workload of the regulatory officials. Global harmonisation is considerably further away but current initiatives by OECD (Grandy, 1994) could show significant changes 10 years from now.

These harmonisation processes tend to follow a set pattern, namely harmonisation of:

i) Data requirements
ii) Test protocols
iii) Evaluation and risk assessment

One of the consequences one might expect therefore is a move towards more global agreement on what is acceptable in terms of registration and what is not. Whereas local environmental conditions will always have to play a major role in the final registration decision, a more general agreement on criteria for registration will be of benefit in assessing the territorial registrability and hence marketability of a new compound (and its products). The disadvantage of such a harmonisation process lies in the fact that historically such harmonisation tends to lead to a highest common factor approach. In other words the most stringent requirements and evaluation processes from each partner are combined to form the 'common standard'. Clearly this in turn leads to loss of regulatory flexibility between different countries or regions.

Political Influences

Some countries have clearly established policies on reducing the use of crop protection products. Most notably such policies have been implemented and their effects seen in Sweden, Denmark and the Netherlands. The European Union also has a declared policy of an overall reduction of 50% in pesticide usage but the implementation of such a policy has not really been taken up by most Member States. The entry of Sweden, Finland and Austria into the European Union may however lead to a more active implementation of this reduction of use policy throughout the Union. In this context it is likely that 'registrations' will be used as a vehicle by which such a policy could be implemented, ie the requirements and criteria to achieve registration will be more stringent.

Political influences are, of course, not confined to the European Union. They are a powerful influence on the regulatory scene in the USA and examples are given below in the discussion on Toxicology. Similarly they are factors to be taken into account in monitoring the regulatory developments currently underway in South America and in Central and Eastern Europe.

Alternatives Policy

As part of the reduction in use policies referred to above the concept of 'safer alternatives' has been partially implemented. Under this concept the registration of an old product may be withdrawn if it is judged that a new product which provides the same benefits is judged to be 'safer'. Similarly the registration of a new product may be refused when it is judged to be less safe than the equivalent product already on the market.

Although the implementation of this 'alternatives' policy has primarily been restricted to some countries such as Sweden, it is possible that its adoption may find more support over the next 10 years, particularly within the context of the Review Programme for existing active ingredients currently underway within the European Union. If this policy is more rigorously implemented its impact on the Crop Protection Industry is readily apparent as the 'defence' of 'old' molecules becomes increasingly important in circumstances under which 'new' molecules are both more difficult to discover and more difficult to register.

Qualitative or Quantitative Criteria for Judging Registrability

Various Regulatory Authorities have established criteria against which the registrability of a crop protection product can be judged. The specific nature of these criteria are discussed in more detail below but at this point it is worth considering the advantages and disadvantages of such a regulatory approach. The main advantage is that criteria provide a 'benchmark' against which the properties of a new research compound can be judged and its future registrability evaluated. This may not always be a simple process however as many compounds may comply with some of the criteria but exceed others. In such circumstances a judgement has to be made as to the regulatory significance of those criteria which have been exceeded and the extent to which some degree of mitigation can be argued. Thus for example exceeding the criteria might indicate the need for further, more extensive studies (eg field studies) from which risk assessments relating to actual use conditions can be undertaken, or to specific restrictions on use (eg application only at a specific distance from water).

By contrast the main disadvantage of registration criteria is the danger of such benchmark values being used in a very 'black and white' manner and with more administrative bias than scientific rationale. Denmark provides an example where such an extreme approach has been adopted.

A further disadvantage could arise where such quantitative criteria are applied in a very rigid sense during the review of existing active ingredients and products and to the exclusion of significant in-use experience both in terms of time and quantity.

Quantitative criteria form an integral part of the EU Registration Directive but it is too early to predict how these criteria will be used in practice. The current view is however that the criteria will be used more as a guide to the need for further testing (eg field studies) rather than as 'cut-off' values for registration. Whereas such an approach is to be welcomed in as much as it does not exclude eventual registration, it could nevertheless lead to greater demands for field studies with the obvious consequences in terms of development costs and development time.

Fast-track Registration

A regulatory concept associated with that of registration criteria is the so-called fast-track registration. Under this concept the possibility exists whereby products which are judged to be of 'low risk' are registered more rapidly than those which are considered to be of 'higher risk'. This concept, which is currently being explored within the context of the European Registration Directive, has obvious weaknesses, eg all products not classified as 'low risk' (ie safe) may automatically be considered 'high risk' (ie dangerous). As a full evaluation of the data package must be undertaken to decide whether or not the product can be considered as low risk, it is difficult to see how the registration time can be significantly reduced. This would seem to be the view taken by many Member States in the European Union but as the concept has obvious political, as opposed to scientific, appeal it may well be developed further at sometime in the future.

A similar process has been attempted in the USA where there is a reduction in both the registration fee and registration time for 'low risk' pesticides.

Both the European and USA approaches suffer from one major weakness. They are based on the assumption that such 'incentives' will encourage Companies to develop 'safer' products whilst ignoring the fact all Companies are in any event striving towards such an objective.

SPECIFIC ISSUES

The registration of a crop protection product ultimately depends on the evaluation of a complex and comprehensive dossier and a judgement that the use of the product does not lead to any unacceptable risks to consumers, users or the environment. Viewed on a global basis it is clear that in assessing these potential risks Regulatory Authorities in different countries place different emphasis on the various sections of the registration dossier. Thus in a very broad and possibly oversimplistic way the registration of a product may be possible in Europe but not in the USA

Against this background the following comments can be made relating to the broad sections of the registration dossier:

Ecotoxicology

This is an area where regulatory demands both in terms of data requirements and critical evaluation of those data have increased over recent years and it is very unlikely that this trend will diminish in the future. Under the Uniform Principles of the EU Registration Directive (Official Journal 1994) the following criteria have been set whereby registration would a priori be excluded unless a risk assessment based on field data indicates that registration is in fact possible. These criteria are given in Table 1:

Table 1 : Regulatory Criteria for Ecotoxicolgy

Parameter	Criteria	Value
Avian Toxicity	Long-term Toxicity/Exposure Ratio	< 5
	Acute Toxicity/Exposure Ratio	< 10
	Bioconcentration Factor	> 1
Fish Toxicity	Long-term Toxicity/Exposure Ratio	< 10
	Acute Toxicity/Exposure Ratio	<100
Daphnia Toxicity	Acute Toxicity/Exposure Ratio	<100
Algal Toxicity	Growth Inhibition/Exposure Ratio	< 10
Honey Bee Toxicity	Hazard Quotient (oral or contact)	> 50
Beneficial Insects Toxicity	Population Affected	>30%
Earthworm Toxicity	Long-term Hazard Ratio	< 5
	Acute Hazard Ratio	< 10
Microorganism Toxicity	Population Affected after 100 days	> 25%

Similar though slightly less demanding criteria are used by US EPA although in this case they play a more 'advisory' role than the European values. A less stringent classification system for aquatic toxicity also exists in Japan.

A key element to the use of these criteria is the prediction of exposure and, in particular, the so-called Predicted Environmental Concentration (PEC). Various models are available for estimating PEC's but this is one area which will certainly receive more attention in the future

with, hopefully an improvement in the accuracy of these estimations. Industry has, on several occasions, argued that some of these criteria are too stringent and their application will inevitably lead to an increase in (unnecessary) field testing. Such arguments have not found support amongst Member States although the possibility exists that from data gained over the next few years it may be possible to relax these criteria to a certain extent.

Environmental Fate

Similar criteria have been established for Environmental Fate parameters and these are given in Table 2.

Table 2 : Regulatory Criteria for Environmental Fate

Parameter	Criteria	Value
Soil behaviour (active ingredient and metabolites)	Persistence	DT50 >3 months and DT 90 >1 year
	Bound residues after 100 days	>70%
Presence in groundwater	Concentration (experimental or model calculation)	>0.1µg/l

Clearly the most important and most politically sensitive issue here relates to the limit of 0.1 µg/l (0.1 ppb) in ground water. The Uniform Principles allow for a 5 year conditional registration if this value is exceeded provided a comprehensive monitoring programme is undertaken to demonstrate unequivocally that the level is not exceeded under field conditions. This provision however is currently being challenged by the European Parliament which serves to emphasise the political 'sensitivity' of pesticides in water and the probability that the 0.1mg/l will remain as a 'standard' for the foreseeable future.

In effect the requirements of the Uniform Principles represent a compromise between the politically based limit of 0.1µg/l for the concentration of pesticides in drinking water and the scientifically valid approach of establishing parametric values or maximum allowable concentrations for individual pesticides in drinking water. It is extremely difficult to predict how this compromise will work in practice as there are clear divisions of opinion both within the European Commission and between individual Member States. It is of fundamental importance to the Crop Protection Industry that scientific reason prevails as a failure to do so could have a dramatic negative effect on the continued registration of some existing crop protection products and on the future registration of new products.

Although groundwater issues may also arise in the USA, the regulatory approach here is both more pragmatic and more scientific than that seen in Europe.

Toxicology

By contrast to the ecotoxicology and environmental fate areas, the relative positions of the USA and Europe are reversed when toxicological data are under consideration. Two well known

toxicological problems exist in the USA, firstly the need to ensure that in long term toxicology studies, the animals are exposed to the Maximum Tolerated Dose (MTD) which in reality may represent a dose which bears little or no relationship to potential human exposure but which may well lead to the occurrence of tumours in animals exposed to such high doses. This may subsequently lead to the classification of the compound as a carcinogen which in turn results in difficulties in the second major problem area, namely the 'Delaney Clause'. This imposes restrictions on the potential uses of the product because it specifically excludes the establishment of Maximum Residue Limits (MRLs/Tolerances) for processed foods for compounds classed as animal carcinogenics. Failure to establish an MRL results in a failure to achieve product registration.

These issues are by no means new and despite almost cyclical reviews by US Government and despite occasional and optimistic predictions of changes it seems likely that both the MTD and Delaney will remain problems for the foreseeable future.

Residues

Problems associated with residues in crops are in reality more ones of public perception than a real risk. Nevertheless residues data continue to play an important role in the registration dossier. The European Registration Directive offers a means by which EU MRLs can be established much more quickly than at present. This, and other factors such as residue levels in minor crops, particularly those grown in Southern Europe, will probably lead to a more critical consideration of calculated total dietary intakes on an European basis and their comparison with the ADI (Acceptable Daily Intake).

Recent developments within the context of the Codex Committee on Pesticide Residues are aimed at a more pragmatic approach to the estimation of the Theoretical Maximum Daily Intake of pesticides. This development bodes well for the future but experience has shown that changes in this area are not achieved quickly and in the short term future the assessment of consumer risk from pesticide residues is likely to remain as very conservative.

Nevertheless the overall trend in the requirements for residues data is one which is to be welcomed with the emphasis moving away from quantity and towards quality, and along with the recognition in Europe that appropriate residues data can be generated on a regional rather than a country-specific basis.

The registration procedure, delays in registration and mutual recognition

It is perhaps inevitable that as regulatory requirements have increased and the regulatory procedures become more demanding then the time taken to achieve registrations has also increased. The rate of this increasing delay will vary from country to country with the greatest increases being seen in those parts of the world where new procedures and requirements are being introduced, eg South America and Central and Eastern Europe.

The European Community is no exception and the concerns of the Crop Protection Industry regarding registration delays have been expressed on numerous occasions (eg Thomas, 1995). Initial experience of the EU Review programme would seem to confirm the significant resources required by Regulatory Authorities in the Member States to complete the evaluations of the 87 active ingredients currently under review. The potential workload involved in extending the Review Programme to the remaining active ingredients and to product re-registration at the Member State level can best be described as daunting.

Thus to repeat the Crop Protection Industry's considerable concern regarding the delays in achieving new registrations is, in the opinion of the author fully justified.

In the Industry's view it is therefore imperative that maximum use is made of the Mutual Recognition of registrations allowed for under Article 10 of the European Registration Directive. Guidelines on how Mutual Recognition will operate are currently being drafted for eventual adoption by Member States. Clearly these need to be as simple as possible to ensure maximum benefits to both Member States and the Industry. In addition Member States will need to adopt a positive attitude, underwritten by an element of trust, to the decision taken by their counterparts within the European Union.

CONCLUSIONS

Whereas the prediction of regulatory requirements and evaluative criteria for the future is difficult it is clear that achieving registration for new compounds and defending 'old' compounds will certainly not get any easier. Indeed it would seem that the introduction of specific criteria by which registrability can be assessed will make it even more of a challenge for Companies to find new compounds which are judged to be acceptable by Regulatory Authorities. As a minimum the criteria will lead to more demands for field testing for environmental effects with consequent impact on increased development costs and lengthier registration times.

The possibility of more global harmonisation offers potential benefits in terms of more effective registration procedures but experience, not least with the European Registration Directive, has shown that such an objective is likely to take a considerable period of time to achieve.

In the meantime the Crop Protection Industry is faced with a twofold challenge. Firstly to monitor and influence regulatory development so as to ensure that pragmatism and scientific principles are at the forefront of these developments. Secondly to ensure that the practical consequences of these developments are integrated within the Research and Development programmes so that new compounds stand the best chance of regulatory success.

REFERENCES

Official Journal of the European Communities No L230/1, 19 August 1991, p.1. Council Directive of 15 July 1991 concerning the placing of plant protection products on the market : 91/414/EEC

Official Journal of the European Communities No L227/31 1 September 1994. Council Directive 94/43/EC of 27 July 1994 establishing Annex VI to Directive 91/414/EEC concerning the placing of plant protection products on the market.

Grandy, N J (1994) The OECD Pesticides Programme - Achievements and Future Plans in *Registration of Agrochemicals in Europe*, IBC Technical Services, London.

Thomas B (1995) New Directions : Report from Europe in *Eighth International Congress of Pesticide Chemistry* N Ragsdale et al (Eds), Washington, American Chemical Society, pp 382-388.

THE AGROCHEMICALS INDUSTRY IN 25 YEARS - CHANCES AND CHALLENGES

KURT KÜSGEN
Bayer AG, Director Marketing Europe and International, Crop Protection Business Group, 51368 Leverkusen

ABSTRACT

The worlds' population growth will lead to a further intensification of the agricultural production in the most suited areas. Production has to increase by about 2% per year in order to assure quantity and quality of food for all people. To avoid destruction of forests and wild life refuges the major part of this increase has to be achieved by higher yields on existing farm land by using all available modern tools. The agrochemicals industry has to offer modern and efficient crop protection products all over the world. As land labour will become increasingly expensive, especially the demand for herbicides will increase. Modern products with low dosages, optimal environmental behaviour and low risk for applications will replace older products with undesirable properties and influence manufacturing requirements. Biotechnology will play a complementary role but not replace agrochemicals. Huge expenses for research and development in modern products will lead to intensive cooperations with partners within the industry. Responsible care for the whole life cycle of agrochemicals and the consequent application of the methods of integrated crop management worldwide are accepted principles of agrochemical industry for the next 25 years.

INTRODUCTION

Many international organisations and a number of learned scientists have submitted estimates and scenarios about the world as it may look in about 25 years time. I have no way of further improving these projections by scientific means but can just offer a few comments, based on common sense.

The shape of the agrochemical industry and the role it will have to play in 2010 or 2020 will depend on its ability to adjust to the growing food requirements of a rapidly increasing world population, and the acceptance of consumers that it can contribute to the well-being of mankind by ensuring healthy and plentiful nourishment and by safeguarding our natural environment. In my opinion this will mainly depend on the ability to continuously develop and bring to market new improved products, to demonstrate responsible care for its products and to gain broad acceptance as an indispensable tool in a sustainable agriculture.

WORLDS' POPULATION GROWTH - THE NEED TO INTENSIFY AGRICULTURAL PRODUCTION

It is generally agreed that world population will reach in 2020 a level of aproximately 8 billion people. Presently, population is increasing by about 100 million people per year. This means that in the next 25 years at least another 2 billion people will have to be fed, mainly in the areas outside the OECD and mainly concentrated in the urban centers of the world. But it will not be enough to just produce the additional calories in the form of cereals. At the same time there is a rapidly increasing demand for fresh fruits and vegetables as well as far animal protein in form of poultry, meat and fish as a number of developing countries, particularly in

South East and South Asia reach a higher stage of development which makes higher expenditure on food affordable to them. This means, however, that production of cereals for food and feed will have to increase even for the present world population because calories in the form of poultry require double the cereal equivalent and meat goes up to a factor of six. The oceans as a source of protein have already reached a situation of large scale overfishing and will not be able to contribute much more.

Overall, agricultural production will have to increase by about 2 percent per year in order to assure quantity and quality of food for all people. The major part of this increase will have to be brought about by higher yields on existing farm land. It is generally agreed that the further extension of farm land in tropical areas with poor soil structure or in semi-arid range land will mean the large scale destruction of forests and wild life refuges. Such a development would mean a real ecological disaster with the extinction of many species of wild life, tremendous soil erosion and unforseeable consequences for world climatic conditions. To me it's absolutely clear that the increase of yields on existing farm land will have to be the major contributing factor to feeding the growing world population.

LIBERALISATION OF TRADE AND LESS SUBSIDIES - CHALLENGE FOR AGRICULTURAL POLITICS

Though I would consider it most desirable to increase agricultural production in the areas where the additional demand will be located, I fear that this will be only possible in a limited way. Poor soil fertility, lack of water, missing know how of small scale farmers and shortage of capital will be limiting factors in a number of countries facing the fastest population growth. Therefore, we have to increase high intensity production in the present prime producing regions, which have a unique combination of soil fertility, sufficient rain fall or irrigation and experienced farmers with a high standard of technology. The careful use of all modern tools to increase production, like high yielding varieties, specific fertilisers, modern crop protection products and biotechnological tools, will be to my opinion a very valuable contribution to a really ecologically oriented, sustainable agriculture in a global perspective.

Looking ahead to 2020, I am sure that also agricultural politics will have to adjust to the changing requirements of the world. Particularly in Europe I would predict a gradual trend to more economically oriented agriculture with much less subsidies being paid to this sector. This is of course initiated by the GATT-agreements, but I think that mainly due to the rapidly increasing volume in trade for agricultural commodities, there will be an upward trend in prices, so that farmers in Europe will be competitive even without subsidies. By the way, for cereals at present market price levels this is already true for a number of key producing areas in Europe. On the other hand, I think that the present level of subsidies will be simply no longer affordable, particularly considering the fact that with the predicted opening of the European Union to the Middle Eastern European countries, huge additional agricultural production areas will come into the community. But I would like to stress again that the concentration on economically viable areas may release uncompetitive and at the same time environmental sensitive areas out of production and open them for e.g. reforestation or for ecological niche areas. The current trend to reduce set-aside in areas of high productivity, both in Europe and the United States, shows that there is already an urgent need for increased production. The former mountains of wheat, butter, milk powder and beef in the European Union have already largely disappeared and world food stocks are at dangerously low levels.

INDUSTRY TO FULFILL THE REQUIREMENTS OF A CHANGING AGRICULTURAL PRODUCTION

In the past, industry has certainly benefited from the highly subsidised agricultural systems in Europe, Japan and North America. I think that in future we have to refocus our attention

much more to the needs of the rapidly developing areas of the world. Food production in these areas will not only mean basic satisfaction of calorie requirements. The demand for fruits and vegetables in the ever-growing megacities of this world will increase rapidly. This has to happen for the sake of public health with adequate supply of essential vitamins and micro nutrients. We will see a huge surge in production of vegetables partly under cover of plastic or glass houses near the big cities with efficient drop irrigation systems. The agrochemical industry will increasingly be challenged by these new indications. Moreover, a number of countries have very good chances to specialise in certain crops and become large scale exporters of fruits, vegetables and flowers. Of course, they will have to maintain international standards for residues in their crops. This means that also in these countries environmental concerns will lead to restrictions on substandard and outdated products. For the research oriented agrochemical industry it is self understood that we have to offer modern and efficient products to the farmers all over the globe. I see particularly good chances for the increased use of herbicides because, despite high population increases, landlabour becomes scarce and increasingly expensive. Therefore we have to offer safe products which do not require much capital investment for applicators.

How can the industry cooperate successfully under these conditions in the year 2020? In the last decade, the industry has seen a considerable restructuring and concentration. I think that this trend will continue but possibly in a somewhat different manner. Though outright mergers and acquisition are certainly going to happen, there may be a number of other ways of cooperation, be it for single products or product groups. One main reason for this concentration process was and will be the huge expenses for research and development and the risks involved in the very long registration process. Therefore I think that the overall level of research costs will continue to gradually decline as a percentage of turnover. Funds will be redirected to basic research by abandoning the defense of outdated products. Automatization in first testing will on the one hand lead to savings, on the other hand improve the detection rate of effectiveness and other desired properties. The basic research oriented companies may have to refocus their research and development activities to different crops and regional areas. Population growth will occur mainly in the developing nations with mainly tropical or semi-arid conditions. Therefore, solutions for pest and disease control must be found which will be safe and efficient under shorter vegetation periods and very high pest pressure. Food needs will have to be satisfied by a greater variety of staple crops, better adjusted to local climatic conditions. This may require a modification of test methods.

INNOVATIVE RESEARCH, PREREQUISITE TO THE BENEFIT OF INDUSTRY AND AGRICULTURE

Research will concentrate on molecules with more and more specific action. This will lead to many small products with necessarily higher profit margins in order to cover the high development costs. Development in tiny niche markets, on the other hand, will no longer be affordable unless governments reach agreements to reduce testing for niche applications if the compounds have a complete data package for major crops.

Increasingly, research will use natural principles of activity as models for novel products. This will include the strengthening of natural defence mechanisms but also the chemical synthesis and modification of substances rather than the isolation of active ingredients from plants. I think that the companies that will be most successful will be those that succeed in bringing to the market products from new chemical classes with novel modes of action.

Today's products have already reached a very high level of activity. So in the future environmental properties, applicators' safety and anti-resistance strategies will be deciding factors for the success of new products. Hectare dosages will continue to decrease. Products in the 1 to 10 g per ha-range are foreseeable. This will reduce the volume load in the

environment. Combined with strict limits on leaching properties, this will lead to reduced drinking water residue problems even if the present non-scientific limits are maintained. A status as "safer pesticide" offers big advantages in bringing a product quickly and successfully to the market. While molecules will continue to become more and more complicated, I think that mainly due to the low dosages new products will be competitive with present solutions, if cost of application, storage, frequency of use etc. are taken into account. On the other hand, the maintenance of registration packages for the older products with less desirable properties will become ever costlier and less attractive. This will lead to shorter life cycles for products. The research oriented industry will strive for a faster replacement frequency. This will certainly not make life easier for generic producers.

The trend to more specific and low dosage products will lead to new manufacturing concepts. There will be a number of products in the 50 to 200 t p. a. range and products with thousands of tons capacity will be disappearing quickly. Capital investment in plants will be less important since such products will be produced in small multi-purpose plants. This means that economies of scale will be less important.

This trend will not only influence the manufacturing side, but also trade and distribution. I could imagine that the prime function of trade will no longer be the physical handling of volumes and collection of money but to really be a technically capable partner of farmers who can offer a complete package of best solutions for his needs. The research oriented agrochemical industry will need such partners besides its own technically qualified marketing organisation. The rapid introduction of new products despite all regulatory restraints will be of high economic importance. The clear target must be the replacement and consequent withdrawal of older products with undesirable properties.

BIOTECHNOLOGY - AN INCREASING CHANCE OF CROP PROTECTION

Biotechnology will play an increasing role in the defence against pest and diseases. For a long time, however, impact on chemical compounds will remain limited, though with varying intensity depending on region and crop. Public acceptance will be reached probably far sooner in America than in Europe. Up to 2020, we assume that about 10 to 15% of the present agrochemical uses may be replaced by the incorporation of resistance genes against pests and diseases. The breeding of seeds with higher yield potential will remain of prime importance for meeting future challenges. Inbred resistance may lead to initially reduced applications of agrochemicals, but the natural enemies will regroup their forces and find novel ways to attack the crops. Agrochemical producers offer a long time partnership for breeders to combine what they know best to the benefit of farmers and consumers.

The present trend to incorporate resistance genes against herbicides into various crops is a different matter. Here we see no replacement of agrochemicals but rather a shift in the products' use. For the farmer this offers a wider range of weed management tools. Novel herbicides with economically and technically competitive features will certainly remain strong competitors in such areas.

RESPONSIBLE CARE - THE SOCIO-POLITICAL COMMITTMENT OF RESEARCH BASED INDUSTRY

The responsible care for the whole life cycle of our products is already an accepted principle. Its importance will further increase, particularly for the world-wide safe use of our products under all climatic and social conditions. The safe use projects of GIFAP, national authorities and companies have already had a big impact on the safety awareness all around the world. In order to protect the health of people, I expect that by 2020 all the countries in the world will be able to implement and control proper registration processes which will eliminate those who sell substandard and fake products. As I mentioned already, developing countries

will derive considerable income from the export of agricultural products, so it's in their own interest that they use ecologically safe products to avoid problems with residues.

By 2020 application methods of our products will have considerably improved. Precision spraying with less volume and the recapturing of surplus spray liquid will lead to much reduced run off. Safer packs with adapters to the sprayers will avoid contamination of operators and will allow rapid switch of products. Satellite guided applicators are already under development, leading to more precisely targeted applications. Micro encapsulated products or formulations in water soluble packaging will further increase applicators' safety.

In this context I think that application by seed treatment will gain much increased importance in 2020. Application on the seed or in the seed box is the most targeted application and offers many ecological and economical advantages. But I think that there are opportunities to use it in many more crops in order to replace conventional spray application.

The use of returnable containers as well as the collection and recycling of packing material will form an integral part of responsible care.

So far I have given my opinion on a number of aspects and trends which will influence the position of the agrochemical industry up to 2020. Keeping the population development aside, the industry has the chance to influence these trends by refocussing and intensifying research and development. Public opinion on agrochemicals, however, remains a cause of major concern. We have to invest much more time and money in communicating our case. We can in the long run not do business against the consumers at large, but have to find a way of convincing them that they directly benefit from agrochemicals which ensure a healthy and affordable food supply and contribute to safeguard the natural environment. There is only a minority in the affluent countries who can afford to buy the so called bio food, but the realistic majority is aware that organic farming without applying biotechnological progress is not a solution for the problems described. I personally think that the consequent application of the principles of integrated crop management, as a guiding principle for the agrochemical industry not only in Europe, but world wide, offers a good long term chance to improve the level of our acceptance. We have to do good and talk about it. For the very large majority of the population in the developed countries, agriculture is a little known activity. So we have to invite people to come to our farms and show them that the use of agrochemicals is not a mischievous thing that farmers do for their own benefit, but that it is a necessity and to the benefit of all. In the developing areas of world, people tend to have still a much closer relationship to agriculture and know the threat of pests and diseases to public health. The industrialized countries should take note of their worries and their more sober and realistic attitude to agrochemicals.