SESSION 1

THE EIGHTEENTH BAWDEN LECTURE

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CROP PROTECTION--MEETING THE CHALLENGE

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THE CHALLENGE

Meeting the challenge in crop protection today is more demanding than at any other time in the history of the agrochemicals industry. On the one hand, there is a continuing need for pest[1] control technology to ensure a reliable, affordable and adequate food supply to feed the burgeoning world population. On the other hand, although pesticides are the most cost-effective pest control technology currently available, there is a ground swell of public resistance to their use.

This dilemma has brought society to a crossroads requiring decisions that could seriously affect the ability of farmers to meet worldwide food demands. I believe that the agrochemicals industry is in a position to solve this dilemma in a way that can meet the needs of global agriculture, the farmer, the consumer and the public.

The solution will require both short- and long-term strategies. In the short term, it is imperative that the agrochemicals industry work together to educate farmers, regulators, the food industry and the public about the positive steps being taken to ensure responsible pesticide use. Open dialogue and interaction with public and environmental groups are needed to better understand their issues and demonstrate a sincere interest in responding to legitimate concerns.

There is also an immediate need to encourage and support responsible use of all products through label instruction and training programs. Better information is needed on how to properly integrate pesticides into various cropping systems and how to minimize or avoid pest resistance. Every effort must be made to ensure that products are manufactured, transported, stored, handled, used and disposed of in the safest possible manner.

In addition, better management systems must be developed which allow the farmer to use the right pest control solution, at the right time and in the right place. We must learn to recognize the value of all pest control technologies -- chemical, genetic, cultural and biological -- in an integrated systems approach. Economic thresholds and improved pest diagnostic tests must be developed, and expert systems established for integrating the vast amounts of data needed to make intelligent decisions that result in the judicious use of pesticides. Equally important is the need to accelerate the development and implementation of improved formulations, packaging and application equipment to eliminate worker exposure, drift and waste.

Longer term, new approaches are needed for finding better, safer crop protection chemicals, novel microbial products and improved pest resistant crop varieties. Also, the promise of biotechnology must be realized to yield

1 Pests as used in this paper include weeds, insects and plant pathogens.

novel pest resistant crop varieties and microbial products to complement pesticides and allow for the development of more balanced pest management programs (Knutson & Anderson, 1989).

In considering each of these strategies, it is important to recognize that about 20 percent of all pesticides are sold in developing countries (World Health Organization, 1990). The requirements in these countries need special consideration since applicator training and protective equipment are often not readily available and the newer technology cannot be adopted or afforded on the same time frame as in the developed countries. Nevertheless, it would be a serious mistake to assume that the requirements for product safety or the desire to protect the environment and ensure a safe food supply are different. The agrochemical industry operates in a global community and any attempts to set different safety standards in one part of the world versus another will be short lived.

In this paper I will focus on three of the above strategies that have received only limited attention in previous Bawden lectures but which I believe are especially important for meeting the challenge in crop protection. First, I will discuss pesticide discovery research and the need for safer, more environmentally-sound crop protection chemicals. Second, I will address pest management and finally, delivery systems. By highlighting these last two areas, it is my intention to emphasize a new kind of leadership role the industry must play if it is to maximize the benefits of chemical crop protection technology. However, before discussing these strategies, it is important to recognize that pesticides are essential for meeting future worldwide food demands.

ASSESSING THE NEED

Benefits of Pesticides

Few would argue with the need for effective pest control technology. Since the beginning of time, man has faced feast or famine in his continuous battle with pests to produce food. The Irish potato famine of the mid-1800s and the devastating effects of the Southern Corn Leaf Blight on the U.S. corn crop in the early 1970s serve as important reminders of what can happen without effective measures for controlling crop pests.

The agrochemical industry was spawned by the need to more effectively control pests that limit worldwide food and fiber production. Because of the spectacular pest control achieved in the 1940s with such pioneering pesticides as DDT (dichloro diphenyl trichloroethane), BHC (benzene hexachloride) and 2,4-D (2,4-dichlorophenoxy acetic acid), agrochemicals were quickly adopted by farmers. The embryonic agrochemical industry responded vigorously to this demand with a more diverse arsenal of pest control chemicals. The convergence of chemical crop protection technology with other emerging new technologies such as hybrid seed production, synthetic fertilizers, irrigation and mechanization resulted in the birth of a powerful new agricultural production system unprecedented in the history of mankind. Remarkably, by the 1980s, this system had more than doubled agricultural productivity in many parts of the world (Urban & Dommen, 1989; National Research Council Board on Agriculture, 1989).

Pesticides have made a very significant contribution to agriculture and revolutionized farming practices by reducing labor requirements, conserving fossil fuels, increasing crop yields, lowering food costs and improving food quality (Borlaug, 1990; World Health Organization, 1990; National Research Council Board on Agriculture, 1989; Sweet et al., 1990; Smith, E.G. et al., 1990; LeBaron, 1990). The direct benefits to farmers range from 3 to 5 dollars for every dollar invested in the use of pesticides (Pimentel et al., 1991; LeBaron, 1990). Recent studies (Smith, E.G. et al., 1990; Urbanchuk, 1990) in the U.S. have also indicated that if crop protection chemicals were banned, yields of fruits, vegetables and grain crops would decline by 32 to 78 percent. With such striking benefits came an increased demand for the technology giving rise to today's $26 billion worldwide agrochemicals market.

Recognition of Risks

However, along with the benefits of agrochemicals came some drawbacks. Early pesticide research focused primarily on biological efficacy and little was known about the potential long-term adverse effects on the environment. As a result, the ability of some very persistent pesticides to accumulate in organisms and to move into surface and groundwater through run-off and leaching were not fully appreciated. Rachel Carson's book, Silent Spring, published in 1962, brought these issues sharply into focus. While these concerns have waxed and waned over the ensuing two decades, the 1980s saw a renewed intensity about the concerns over the use of pesticides.

The general fear of chemicals by the public, combined with the environmental movement that is sweeping many parts of the globe, has led to accusations by various antipesticide groups that pesticides are a major threat to public health and the environment. This has led to the recent banning of some pesticides such as atrazine, the promulgation of more stringent and costly regulations in most countries and plans in several countries, including Denmark, Sweden, and the Netherlands, to reduce pesticide use by 35 to 50 percent during this decade.

The last two Bawden lecturers (Graham-Bryce, 1989; Berry, 1990) have addressed some of the key issues in this debate, and while there are clearly some legitimate reasons for public concern, there are also many concerns that appear unfounded or misrepresented. Nevertheless, this is an issue where emotions, feelings and political agendas often far outweigh the facts, where scare tactics can turn relatively low-risk situations into seemingly major catastrophes, such as the 1989 Alar scare in the U.S. (Wall Street Journal, October 3, 1989). As a result, we now live in a society where chemical pest control technology is feared more than risks such as swimming and skiing shown to be considerably more hazardous (Upton, 1982).

Future Needs

By the year 2025, it is estimated that there will be an additional 3 billion people to feed, and by 2050, total world population is projected to increase to 11 billion -- more than twice today's population of 5.3 billion (Urban & Dommen, 1989). By the middle of the next century, we will have to produce more than twice as much food as is currently being produced (Borlaug, 1990).

Such a dramatic increase in population will put increasing pressure on land used for food production. Today, world cropland available per person is about a third of a hectare, down from nearly half a hectare in 1961 (Urban, 1989). Each available hectare must support more and more people as world population continues to increase at a rate of about 1.7 percent per year (90 million more people to feed and clothe each year), while the rate of expansion of world cropland is less than one-tenth this rate (0.15 percent per year or 50 to 60 million new hectares of cropland by 2010 (Urban, 1989)). Therefore, in less than 20 years, each person will have to be supported by only 0.2 hectares.

This means we must prepare for a more intensive agricultural production system where productivity-enhancing innovations will continue to be essential for meeting future worldwide food demands. As agriculture intensifies, so will man's battle with crop pests. Effective pest control technology will become even more important than it is today. Cultural, chemical, genetic and biological control methods will all contribute in this battle. However, on a worldwide scale there are no alternative new crop protection technologies on the immediate horizon which can reliably replace pesticides. Biotechnology offers the opportunity for breakthroughs in insect and disease resistant crop varieties and novel microbial products. However, based on the lack of demonstrated field performance, poor economics and the longer than expected development timelines for many of these potential new products, I believe the rate of replacement of synthetic pesticides by biologically-based products will be much slower than many have projected. As complementary tools in pest management strategies, the need for, and importance of these products is clear; but it is unlikely that they will account for more than a few percent of the worldwide crop protection market by the turn of the century (Giaquinta, 1990; Lisanky, 1989).

The conclusion that no alternative technologies currently exist that can reliably replace pesticides on a worldwide scale is consistent with the view reached by the National Research Council, the United Nations Food and Agriculture Organization and the World Health Organization (World Health Organization, 1990; National Research Council Board on Agriculture, 1989; Food and Agriculture Organization of the United Nations, 1987), as well as other noted scientists such as Nobel Laureate, Norman Borlaug (Borlaug, 1990). Reducing unnecessary pesticide use and potential ill-effects are common goals of these and many other organizations. However, most agriculturalists recognize that pesticides will continue to remain routine and essential inputs in most crops well into the 21st century.

Certainly pesticides can be used more judiciously, and their use can be eliminated where they are damaging to the environment or where they pose an unacceptable health risk. But to think we can do totally without them is to ignore facts that could have serious implications upon our ability to provide the world with an adequate food supply.

MEETING THE CHALLENGE

The need for pesticides brings with it a responsibility on the part of the agrochemicals industry to continually improve all aspects of chemical pest control technology. Clearly this cannot be done alone but will require cooperation and teamwork among industry, government and university scientists and administrators. As previously mentioned, pesticide discovery research, pest management and delivery systems are three areas that I believe must be critically addressed if society's concerns over food safety and the environment are to be alleviated.

Pesticide Discovery Research

I believe that just as the pesticides of the past have brought us to where we are today, only those of the future can take us where we want to go. Although there are many ways we can improve the safety and effectiveness of existing products, concerns such as persistence, leachability or adverse toxicology can only be overcome through product replacement. New product discovery research is one of the most important keys to meeting our challenge in crop protection.

Where We Want To Go: The goal of discovery research is best described as the relentless pursuit of the ideal pesticide. Regardless of the target market, such a molecule should have the following properties or features:

- Cost-effective, flexible, reliable and convenient to use.
- Safe to the crop, environment, user and consumer.
- Low use rate to minimize the amount introduced into the environment.
- Leaves no harmful residues.
- Persistence in the crop and soil tailored to desired effects.
- High specificity to target organisms.
- No off-target effects.
- Easily integrated with "best management practices".
- Does not lead to pest resistance.

Some would argue that finding a molecule that embodies all of these features is an unrealistic goal. While admittedly no such molecule currently exists, progress has been made. For example, in the area of weed control there are already examples of what the future can hold. Low use rate, broad-spectrum products, such as the sulfonylureas, now exist. Their manufacturing process frequently generates as little as 5 percent of the waste byproducts as compared to many conventional herbicides; farmers often need to apply only 1 percent as much herbicide to their fields; and these new products are safe to people and the environment and meet many of the other ideal product criteria listed above (Beyer et al., 1988, McMurray, 1991).

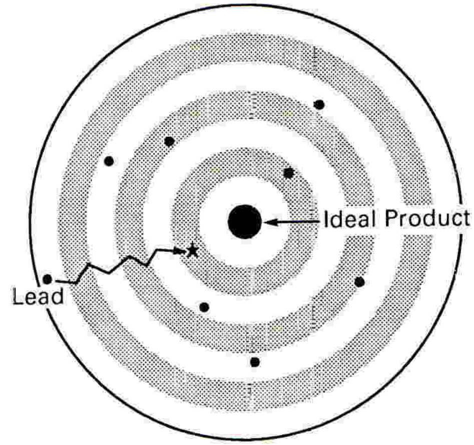
However, worldwide there is still plenty of room for improvement. The first task is to identify those areas where improvements are needed most, namely where safety and environmental risks are the greatest, and then to capitalize on the opportunities they represent for new discoveries. These assessments should include toxicity, environmental compatibility, worker safety, and potential to generate waste or leave harmful residues. Such evaluations can provide important clues for establishing research objectives and setting priorities.

A useful way to think about these evaluations is illustrated in Figure 1. The market need is represented as a target with the ideal product at the center or "bull's-eye". Existing products are then charted on the target at various distances from the center depending on their relative strengths and weaknesses.

Plotting exact product locations is difficult because many different types of data must be considered, as mentioned above, and value judgements must be made as to the long-term importance of specific product deficiencies. Also, the relative position of existing products changes over time as new products are introduced or as new concerns arise. For example, at one time atrazine was much closer to the "bull's-eye" as the ideal corn herbicide than it is today, but the detection of atrazine in groundwater changed this view. Likewise, the EBDC fungicides are less attractive today than they once were due to food safety concerns, and 2,4,5-T has been banned in many countries because of toxicity concerns.

Major advances in discovery research are rare whereas incremental improvements are more readily achievable. Therefore, while it is important to have the discovery process aimed at the "bull's-eye", it is critical to know how close to the "bull's-eye" a molecule must hit before it is worthy of commercialization. As illustrated by the crooked arrow in Figure 1, this understanding helps us establish a continuous improvement process where new leads can be systematically optimized until they become a truly significant advancement over existing products.

FIGURE 1. Market Opportunity



How We Get There: Having established the target, the next question is how to get there. Agrochemical research organizations struggle with this question every day. During the 1960s and 1970s, when the marketplace was less crowded and the bioefficacy expectations and regulatory hurdles were lower, the discovery process was less complicated than it is today. Chemists synthesized compounds and biologists developed screens and tested the newly synthesized product candidates for potential utility. Pest control spectrum, activity and crop safety were the primary measurements of success. If a molecule met these criteria, it was generally moved forward for development where there was a reasonable chance it would pass the less stringent regulatory requirements of that time.

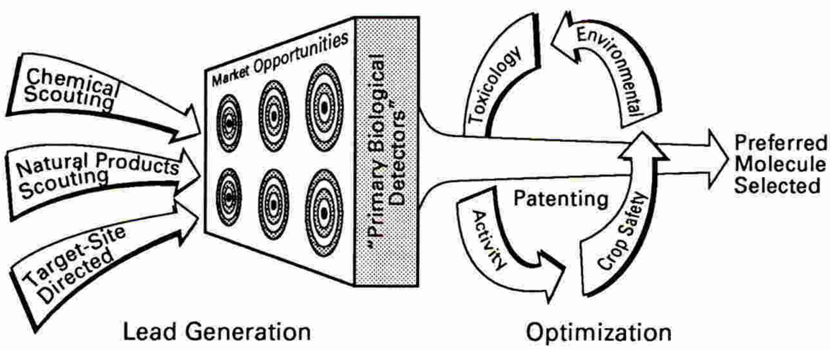
This all changed during the 1980s. Competition and regulations stiffened, environmental issues moved into the mainstream of public opinion, economics tightened as older products came off patent, and the growth of the worldwide pesticide market slowed down. These changes made the previous, but prolific, discovery process obsolete. It was clear that meeting the challenges of the 1990s and beyond would require a different approach.

Today, agrochemical discovery research is highly focused and approaching that of the pharmaceutical industry in complexity, sophistication and cost. The older, empirical approach is giving rise to an environmentally-sensitive, science-based approach that requires large multidisciplinary research teams. A broad mix of talent can be found in these teams with skills ranging from organic, analytical, physical and computational chemistry to molecular biology, biochemistry, toxicology, soil and crop science, and ecology.

However, such an approach is expensive. R&D budgets of 150 to 200 million dollars per year are not uncommon today, with one-third to one-half of this amount being spent on the discovery of new molecules. Facing such large financial investments, it is critical that we, who are responsible for these programs, become increasingly skilled and effective in finding new products that meet the more stringent safety and performance requirements of today.

As I view the discovery process, there are two key steps required for meeting this goal. As shown in Figure 2, the first is lead generation, which identifies promising new areas of chemistry and the second is optimization, which selects the molecule with the best possible combination of properties for subsequent new candidate development.

FIGURE 2. Discovery Process for Crop Protection Products



Lead Generation:

Lead generation is the most important activity carried out in discovery research since everything downstream depends on success at this step, including the long-term survival of the business. It is here that the prospecting occurs, where we, as scientists, search for that rich vein of chemistry that can be mined to yield the pest control molecules required for tomorrow's agriculture. It is here that intuition, creativity and serendipity abound.

Two things are required for successful lead generation: a source of novel chemistry and a biological detector system or set of screens to determine the potential market utility of new leads. The quality of the research, teamwork and decisions carried out at this interface, where chemistry and biology meet for the first time, determines the ultimate productivity of the entire process.

Enormous challenges are faced by the teams of chemists, modelers, biochemists and biologists involved in this step. For example, the chemistry is often complex with one or more chiral centers in the target molecule and up to a dozen steps required for its synthesis. Cost considerations make it imperative for these compounds to be highly active even at this early stage. Twenty years ago initial testing was frequently done at rates as high as 10 to 20 kg/ha. Today, compounds must show pest control activity at one-tenth this amount to be considered a viable lead. Moreover, during the past 50 years millions of compounds have been evaluated by the agrochemicals industry for pest control activity, thus making novel discoveries increasingly difficult.

Multiple approaches are used to generate potential leads. Although most agrochemical companies have large internal chemical discovery programs using these approaches, they also obtain leads through outside research collaborations and procurement agreements with universities, governmental and pharmaceutical laboratories.

> <u>Exploratory Chemical Scouting</u> involves synthesizing novel compounds and testing them for biological activity. This approach requires a thorough knowledge and understanding of the scientific and patent literature on biologically active molecules. This knowledge -- combined with personal experience, intuition and insight obtained from scientific training, meetings and colleagues -- provides the basis for quality scouting programs. Most major classes of agrochemicals have been discovered using this approach.

> <u>Natural Products Scouting</u> involves testing naturally occurring compounds from diverse sources such as bacteria, fungi and marine organisms -- sources that are often rich in potential leads. For example, the avermectin insecticides, the milbemycin and strobilurin fungicides and the herbicide glufosinate are compounds discovered from natural product scouting. Naturally occurring molecules are also used as templates for synthesizing novel structures such as the pyrethroids from pyrethrin and as model compounds for identifying pesticides with new modes-of-action.

> <u>Target Site Directed</u>, also called rational design, involves selecting a biological target such as an enzyme or receptor, and designing chemicals that inhibit or alter the target in such a way that the pest is controlled. Isolation of the target for <u>in vitro</u> testing, combined with a mechanistic understanding of its key biochemical and molecular features, is generally a prerequisite for success. While many agrochemical companies are actively pursuing rational design, it has met with only limited success to date.

An efficient lead generation process is virtually useless without a matching and sensitive set of biological screens or detectors. I have depicted such a system of detectors in Figure 2 as a target board labeled "Primary Biological Detectors". These targets or screens ideally reflect market opportunities 8 to 10 years from today, since it generally takes that long from lead generation to commercialization. Here, the goal is to simulate market needs in the laboratory, growth room or greenhouse so that leads can be detected. Figure 2 shows only six targets when in actuality most large agrochemical companies typically operate a dozen or more primary detectors or screens. Each target also includes an analysis of existing products as described in Figure 1 to pinpoint those areas where improvements in chemistry are most needed.

At this primary level of biological testing, the goal is simply to determine if the molecule synthesized or obtained from a natural source can control some important pest. Without this property, further work is not warranted. In principle, this process of lead generation is quite similar to other discovery processes whether it is for pharmaceuticals or new polymers. A detector system and a source of potential lead candidates are essential for success. Although somewhat empirical, the level of creativity needed to generate such leads demands the ingenuity of the best scientists. A "wiggle" of interesting pest control activity is all that is hoped for.

Experience shows that most attempts shoot wide and completely miss the target, accounting for the need to test many thousands of compounds. Moreover, when a "hit" is made, it is almost never close to the "bull's-eye"; thus, the need for the next step in the discovery process -- optimization. This was certainly the case for the discovery of the sulfonylurea herbicides. The original lead was of only modest interest since it had relatively weak plant growth regulant activity at 2 kg/ha. However, through optimization research the activity of this lead was increased several hundred fold, thereby reducing use rates from kg/ha to g/ha and setting a new standard for the industry.

Optimization:

The goal of optimization is to systematically modify the basic lead structure through analoging until the best possible combination of overall attributes is found. The ability to select the best compound from the vast sea of structural possibilities that often exists is generally dependent on the quality of the structure-activity relationships that can be developed around the molecule's attribute or property undergoing optimization. Other barriers to analoging include synthetic feasibility.

The complexities and challenges of determining such relationships are enormous because the structural features affecting each attribute are usually different. For example, the optimum structural features for improving pest control activity may be very different from those required for optimal degradation in the environment. Therefore, compromises must often be made so that the final molecule represents the best blend of cost-effective pest control along with a high degree of safety to people, wildlife, the environment and the crop. The decision making process in arriving at such compromises is an important aspect of ultimate success.

There are several critical areas for improvement in the optimization step. These include activity, crop safety, toxicology, environmental compatibility and economics.

Activity: An important first step is to optimize a molecule's activity. The goal is to achieve acceptable pest control while introducing the least amount of material into the environment. Also, as activity increases and use rates decline, there is less product to ship, store, carry and apply, as well as less waste for disposal. Early knowledge about the mode-of-action of a new area of chemistry can lead to the isolation of pesticide receptor molecules (e.g., enzymes) so that intrinsic activity can be optimized apart from the complicating effects of uptake, transport and degradation that occur when the entire pest organism is treated. Improvements in intrinsic activity of 100 to 1000 fold are not uncommon. Surfactants and other adjuvants are frequently added to the spray solution as additional aids for enhancing the molecule's activity through better uptake or penetration into the crop or target pest. An important need in this area is for better methods to quickly determine the mode-of-action of new leads. The tools of biotechnology offer promising new approaches for satisfying this need through the use of cell culture, recombinant DNA techniques and genetics.

Crop Safety: High biological activity without crop safety has little value in today's crop markets. Months and even years of research are spent finding the right structural features to confer crop safety. With the sulfonylurea herbicides over 15 years have been spent optimizing this chemistry for crop safety with success having been achieved first in wheat and barley, then in soybeans, rice and canola and most recently in corn and sugarbeets. Understanding the structural requirements for rapid inactivation of the pesticide lead by the crop is often the key to success. Progress is slow due to the limited knowledge that exists about these processes in crop plants. After exhausting all other avenues of modifying or tailoring the chemistry to meet the requirements for crop safety, alternative strategies are often sought. For herbicides, these include: genetically engineering the crop so that it is no longer injured by the herbicide or tank mixing the herbicide with a safener or antidote to protect the crop. Safeners have been important to the commercial success of several herbicides and a variety of herbicide resistant crops are in advanced stages of commercial development. These crops, which include soybeans, cotton and corn, were obtained using such techniques as tissue culture, mutational breeding and genetic engineering. A recent report (Duke et al., 1991) reviews the economics, regulation and potential impact of these and other resistant crops on weed management and the environment.

Toxicology: Toxicological tests are important to eliminate undesirable effects before the final molecule is selected for advancement to the new candidate development stage. Traditionally, such testing at this early stage has been limited because of the difficulty of obtaining useful, predictive information. This has severely limited the opportunities for improvement since once the final molecule has been selected for development, its intrinsic toxicological properties can no longer be changed. Until new areas of chemistry can be adequately optimized to eliminate adverse toxicological properties, many promising new candidates will continue to be lost during development when indepth, long-term toxicological studies are normally conducted. Thus, there is a clear need for the development of rapid, predictive and low-cost methods for optimizing the toxicological properties of lead areas of chemistry. Key areas include mutagenicity, carcinogenicity, teratogenicity and neurotoxicity.

Environmental Compatibility: Almost all agrochemicals or their metabolites end up in the soil. Therefore, it is essential that chemical and microbiological degradation, as well as mobility properties, be tailored to minimize any adverse effects. Understanding the underlying physical and chemical properties that lead to persistence and movement into groundwater, surface water and air is of paramount importance in designing better and safer molecules. Such an understanding has resulted in second generation sulfonylurea cereal herbicides like thifensulfuron-methyl and tribenuron methyl that have overcome the recropping concerns that have emerged in certain areas of the world with products like chlorsulfuron. While impressive advancements in detection technology and dissipation modeling have been made, additional improvements are badly needed. Fundamental information about degradative mechanisms deep in the soil profile and in groundwater are needed, as well as better predictive models. As in the area of toxicology, rapid low-cost tests are also needed to better assess potential adverse effects on non-target organisms including plants, microbes, fish, birds and other wildlife.

Economics: In order for a lead candidate to be commercialized, an economical manufacturing process must be discovered and developed. If this cannot be accomplished through process chemistry research, analoging can sometimes yield alternative structures that are cheaper to manufacture while retaining the other desirable attributes previously mentioned. Unfortunately, in some cases, an economically viable synthetic route may never be found; and, as a result, almost every agrochemical company has had to put promising new product candidates back on the shelf.

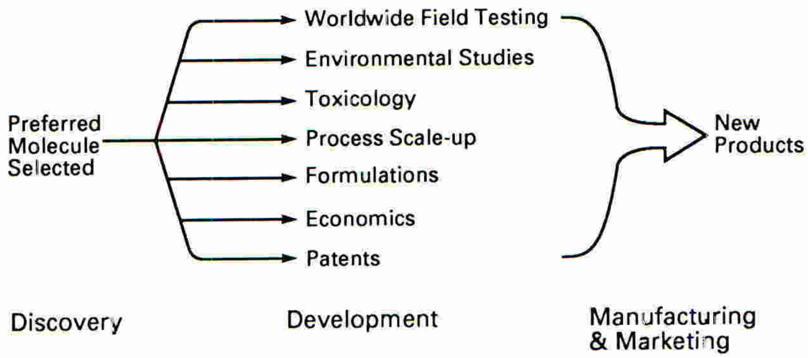
One of the great advances in optimization research over the past few years has been the widespread availability and use of sophisticated molecular modeling techniques. These techniques utilize software for determining the most stable configuration of new molecules, as well as having the capability of superimposing such structures on existing ones for three-dimensional comparisons. Extensive chemical and patent databases, consisting of hundreds of thousands of chemicals and related biological data, are available to help guide optimization research. Predictive models of translocation in plants, toxicological effects and environmental dissipation are becoming more commonplace; and other promising techniques are on the horizon such as neural networks and pharmacophore searches (Andrea & Kalayeh, 1991; Black-Schaefer et al., 1991).

Lead generation and optimization are very costly and can take many years. At Du Pont, after 15 years of optimizing the sulfonylurea herbicides, only 11 molecules have been commercialized from literally millions of possibilities. In many cases, leads never materialize for a given target market even after decades of research. Also, published chemistry in one company is sometimes exploited by other companies since patent coverage is limited in scope to the chemicals claimed. The urea herbicides, pyrethoid insecticides and triazole fungicides are examples where a basic breakthrough in chemistry made by one research group was exploited by several companies.

New Candidate Development:

The lead generation and optimization steps only select the preferred molecule for the long and costly next step -- development (Figure 3). Although a thorough discussion of development is beyond the scope of this paper, a few comments are necessary because of the importance of this crucial step.

FIGURE 3. Crop Protection Research & Development



Moving a new molecule into development is one of the most critical decisions made by agrochemical companies since it involves 40 to 60 million dollars and 6 to 9 years of development work. This is a decision filled with uncertainty because of the inability to accurately assess the marketplace this far out in time, as well as the outcome of the many lengthy tests yet to be conducted. These include long-term toxicological and environmental studies, process development, process scale-up for final manufacturing, formulation research and patents. In addition, many different biological tests must also be conducted, such as field performance trials under a wide variety of soil and environmental conditions, mixture studies with other products, resistance monitoring and recropping studies. Generally, it is necessary to do these long-term studies in parallel since even under the most aggressive time frames one-half of the patent protection period will have elapsed before sales can begin.

PEST MANAGEMENT AND DELIVERY SYSTEMS

I believe that the advantages of even the best pesticides will be lost if they are not handled and applied correctly; and their misuse, overuse or unnecessary use will come under increasing scrutiny because of economical, social and environmental demands. As discussed below, practical chemical pest management systems are needed that result in grower recommendations that are tailored, targeted and timed to optimize the chemical's overall benefits while minimizing potential risks. Also discussed is the critical need for new delivery systems for improving the accuracy and efficiency of pesticide applications while, at the same time, eliminating worker exposure, off-target drift, equipment contamination and container and rinsate waste.

Pest Management

As pointed out by Metcalf and Luckmann (Metcalf & Luckmann, 1982), the goal of pest management should not be to eradicate or exterminate but rather to prevent pest damage from exceeding the economic injury level or threshold by taking advantage of all pest control methods. These encompass the following:

(a) Cultural methods to reduce pest populations including the use of the most suitable pest resistant crop varieties, crop rotations, tillage practices, soil fertility regimes and planting dates;

(b) Chemical control methods such as the use of agrochemicals, attractants, repellants and growth regulators alone, or preferably in combinations to minimize the development of pest resistance;
(c) Biological approaches involving the protection or release of natural pest enemies, e.g., release of fungi to control weeds; and,
(d) Informational systems for predicting crop damage based on pest population dynamics, e.g. the use of monitoring techniques and expert systems.

Serious damage can be caused by pest outbreaks in most crops but especially cotton, rice, tree fruits and vegetables. This results in the need for emergency measures, particularly when managing insect populations and plant diseases, where sudden changes in the weather can trigger such outbreaks. Pesticides are universally recognized as the most effective, and in many cases the only, suitable and reliable method of intervention for managing such emergencies.

Fortunately, there is an increasing awareness and desire on the part of many farmers to adopt "best management practices" to enhance profitability while practicing good resource and environmental stewardship. However, the complexity of this task and the knowledge required for success have seriously hindered the widespread use of such practices. For example, rarely does a farmer know with certainty the economic threshold for a given pest and the responsiveness of the pest to different control methods under various cultural and climatic conditions.

Faced with such uncertainties, many farmers have become accustomed to using pesticides as their primary defense against potential pest damage. In many areas a farmer's management skills are often gauged by how "clean" or "pest-free" his field appears to his neighbors. While this level of control is generally recognized to be excessive, many farmers have been reluctant to change such practices because of the effectiveness, reliability, convenience, simplicity, flexibility and relatively low cost of many pesticides. This, in turn, continues to fuel antipesticide concerns over the unnecessary use of these chemicals.

Some countries are now proposing or mandating a reduction in the use of pesticides, creating a need for improved methods to monitor pest populations and to define the level of pest populations above which control is clearly justified on economic grounds. Without this information, many current practices will come under increasing scrutiny. In the area of weed control, more emphasis is needed on weed identification guides, weed population models and expert systems for designing prescription weed control programs that are tailored to the weed spectrum, stage of growth, density, local environment, fertility levels and cropping patterns, while providing environmentally sound, cost-effective weed control. There is a real need for the agrochemical industry to work with government and university agricultural specialists or directly with farmers to provide more quantitative information on herbicide application rates required to control specific weeds under a wide range of soil and climatic conditions. Also needed are sound recommendations on herbicide mixtures with different modes-of-action to minimize the potential for weeds to develop resistance.

Already, practical pest management systems exist (Metcalf & Luckmann, 1982; European Weed Research Society, 1990) that can be incorporated into established programs while more sophisticated, multifactor programs are being designed and validated. The development of such multifactor systems must be accelerated so farmers and agricultural specialists can make more intelligent decisions for maximizing profits while minimizing health and environmental risks. With proper funding, teamwork and the dedication and commitment of all agriculturists, today's goals in pest management can become the accepted practices of tomorrow's agriculture.

Delivery Systems

New delivery systems, or the better use of existing technology in the areas of formulations, packaging and application equipment, are crucial for accurate on-target application and for reducing or eliminating drift, worker exposure, equipment contamination and container and rinsate wastes. Today, the agrochemicals industry spends over a billion dollars a year on R&D to discover and commercialize improved products only to find that they are often being applied with outdated, ineffective spray equipment. Surveys continue to show that spray rig calibrations are often off by 10 to 30 percent, cleanout procedures are not faithfully followed, and spray booms are not always fitted with the correct nozzles or properly positioned over the crop canopy. As Graham-Bryce (Graham-Bryce, 1983) pointed out almost a decade ago, the opportunities for improved pesticides may actually be secondary to the real advances that could be made in formulation and application systems.

Moreover, it is estimated that 80 percent of worker exposure occurs during the mixing and loading operations (Dull,1989). This is of special concern in less developed countries where applicator training and protective equipment are often lacking (World Health Organization, 1990). Studies of dermal exposure to chemical pesticides demonstrate that by simply wearing resistant gloves operators involved in pesticide mixing and loading can reduce exposure by 90 percent (Baugher, 1989).

With the obvious need for better delivery systems, why then has progress been so slow? While there are many reasons, those noted most often (Evans, 1989) include the following:

(a) Profit margins on the manufacture and sale of application equipment do not justify the R&D expenditures needed for substantial advancements;
(b) Transfer of application technology is lacking between the farmers, chemical and equipment manufacturers, and researchers;
(c) There is little economic or regulatory incentive for farmers and commercial applicators to invest in state-of-the-art delivery systems;
(d) Recommendations on product labels, often due to liability concerns, do not encourage the grower to reduce rates for improved application efficiency; and,
(e) No economic or regulatory incentives exist for the chemical manufacturers to actively promote the reduction of pesticide use through better delivery systems.

I believe that failure to overcome these barriers will lead to more stringent regulations similar to those that forced the auto industry to reduce auto emission pollution. Mandatory sprayer inspections, applicator certification, restrictions on burning and disposal of pesticide containers in landfills, and the levying of fees to conduct research and disseminate information are already in force or under consideration in many parts of the world. As discussed below, I believe that significant improvements in pesticide application are needed most in the areas of worker safety, environmental impact, accuracy and efficiency.

Worker Safety:

Emphasis on worker training and certification must be increased. It is essential that those involved in applying pesticides understand the need for protective equipment, the correct procedures for preparing, applying, and cleaning up pesticides, and the environmental impact of misuse. For protective equipment to be used, it must be relatively inexpensive, light weight and provide a high degree of thermal comfort since many pesticide sprays are applied during the hot, humid summer months.

Improvements in formulation design offer considerable opportunity to reduce worker exposure. For example, dust free, water dispersible granules and tablets can eliminate splashing and dust emissions during loading; are free of potentially hazardous solvents; and, if a spill should occur, are much easier and safer to recover than liquid formulations. Tablets are an exciting new product form made possible by the introduction of highly active herbicides where only a few grams contained in a tablet can treat several hectares. Where dry flowable formulations are not feasible for technical or economical reasons, safer, aqueous-based liquid formulations are needed to reduce or eliminate solvents that may cause fire hazards, dermal irritation or other undesirable effects.

Container designs that facilitate the development and use of "closed systems" are also needed such as returnable containers with metering devices to load the chemical into the spray tank without the worker having to measure or pour the concentrated material. To overcome the drawbacks of early liquid closed systems, future systems will have to transfer the chemicals more rapidly, be more durable and much simpler to use. Similar closed systems are needed for dry formulations, but this requires the development of more accurate dry metering technology. An effective, proven technology for reducing worker exposure is to package pesticides in water soluble bags where the entire bag can be added to the spray tank. Broader application of this technology is warranted based on its potential for dramatically reducing worker exposure plus eliminating the need to rinse and dispose of contaminated containers.

Environmental Impact:

Reducing environmental hazards associated with pesticide application can be achieved through better waste management and improved on-target placement of the chemical. In the United States alone, manufacturers produce some 40,000 tons of pesticide containers each year (Grahl, 1990). The majority of these containers must be emptied, triple-rinsed and burned or taken to a landfill. While the trend toward using refillable and recyclable containers is helping to reduce this long-term environmental concern, additional measures are needed such as the development and use of biodegradable packaging materials. Recycling programs are underway in Europe and in the U.S. However, progress is slow, and in many countries such as the U.S., one percent or less of the plastic is currently being recycled. Experience indicates that, to achieve initial success, these efforts may have to be sponsored or subsidized. It is hoped that through the support and encouragement of the agrochemicals industry and the government a recycling industry will emerge to fulfill this need as recycling becomes more widespread, perhaps even mandated by governments.

Current practices of mixing the pesticide with water in the spray tank must be re-examined since large volumes of dilute aqueous waste are generated during sprayer tank cleanup. Chemical injection systems need to be implemented where, instead of mixing chemicals with water in the spray tank, chemicals and carrier are kept isolated until shortly before the mixture is discharged from the spray nozzles. This limits chemical exposure to only the injection device and the sprayer boom, while also greatly reducing the amount of rinsate generated during cleanup.

Direct, dry application of granular products can simplify cleanup procedures since an aqueous liquid dispersant is not needed. However, this application method currently works only for those materials, such as preemergence herbicides and soil insecticides, that do not have to be deposited directly on the foliage for effectiveness. Successful dry application systems are currently available for the pneumatic co-application of triazine herbicides with granular fertilizers and the aerial application of dry flowable formulations of bensulfuron methyl to rice paddies in the U.S.

Controlled-release technology can result in improved safety to the user, the crop and the environment. The soil mobility of some herbicides has caused concern because of their potential to move into groundwater. By incorporating the chemical into appropriate polymeric materials, the rate of leaching from the root zone can be retarded, allowing for more uptake by the weeds and less leaching in the case of heavy rains. This technology reportedly has reduced the potential for some herbicides such as alachlor to leach into ground water.

The environmental impact of spray drift is well known (Holst, 1989) and has led to restrictions in the use of aerial application in Europe and other areas of the world. However, aerial application is still important in many countries such as the U.S., where approximately a third of the total crop acres treated with chemical pesticides are applied by aircraft (Agricultural Research Institute, 1989). Surprisingly, there is only a limited amount of information on how different combinations of application equipment, formulations, adjuvants and climatic conditions affect spray drift. Recognition of this problem by industry has prompted the formation of a joint venture in the U.S., composed of 25 major agrochemical companies throughout the world for understanding in more quantitative terms the factors contributing to drift and ways to minimize it.

Much work is needed to improve the hydraulic nozzles that have been the mainstay of pesticide applications for the past 40 years. With each application, these nozzles produce a range of droplet sizes with the "fines" (less than 100 microns in size) being especially prone to drift off-target (Kuhlman, 1989). A better basic understanding of the fluid properties that govern atomization is needed to develop improved nozzles that produce droplets less prone to drift.

<u>Accuracy and Efficiency</u>:

The goal of application technology is to treat the target pest in the most cost-effective manner while minimizing the effects of the chemical on non-target organisms and the environment. Significant opportunities exist for improving the accuracy and efficiency of pesticide applications. This is especially true for herbicides that are generally applied to an entire field rather than only those selected areas where the weed density exceeds the economic threshold. Hopefully, this practice of applying uniform rates across entire fields regardless of weed density will change as more sophisticated delivery systems become available for the precise targeting of herbicide applications.

Accurate metering technology is available and in use for monitoring and maintaining a proper application rate of liquid sprays, but skips and overlaps are common because of the difficulty in tracking and maneuvering field application equipment. As the size and speed of this equipment have increased, so has the potential for such errors. Because skips are more obvious and can lead to weed problems, most operators tend to overlap, thereby doubling herbicide use in these areas. Onboard navigation systems are available for overcoming this problem but are not yet widely used. They have the added benefit of enabling applicators to treat crops at night when lower winds result in less chemical drift.

New technologies are under development that will allow herbicide rates to be varied depending on weed density, location and soil type. The use of video imaging, digital soil mapping and other remote sensing devices offers promise for improving herbicide application accuracy and efficiency. Information obtained using these devices can be programmed into onboard computers that control metering systems as a function of field characteristics and position. The Precision Farming System, under development by Trimble Navigation, is one such system that relates application rates to soil types in the field. Reported benefits include cost savings and reduced environmental impact. Other innovations include light sensing of emerging weeds, radar speed sensors to adjust application rates "on-the-go" and automatic self-leveling spray booms.

More research is needed on alternative methods for applying herbicides that improve accuracy by reducing chemical drift. The use of electrostatic, "air assist" and "air curtain" sprayers to facilitate the more direct delivery of herbicides to target weeds is continuing to receive attention (Bode, 1988). The "TWIN" system, recently introduced by the Danish company, Hardi, Inc., reportedly surrounds spray droplets with an air supply that guides the droplets to the target resulting in higher deposition on the target, reduced drift and improved penetration. Unfortunately, attempts to use electrostatic principles to direct the spray droplets to the foliage have had only limited success. For some herbicide treatments, such as that mentioned above for bensulfuron methyl to rice paddies, drift has essentially been eliminated through the dry application of granules.

LOOKING AHEAD

Clearly, meeting the challenge in chemical pest control in the 1990s and beyond will require foresight, planning and a commitment to safety and environmentalism unparalleled in the history of agriculture. Society's raised expectations concerning food safety and the environment will continue to change farming practices and the needs of farmers worldwide. Concerns expressed about water quality, soil erosion, pesticide residues in food and the depletion of water supplies and wildlife habitats have placed increasing demands on farmers and, in turn, on those who serve them.

As the needs of agriculture change, so must the agrochemicals industry. Once seen as a producer of bulk chemicals for the agricultural sector, the industry must now take a fresh new look at how it can better serve the changing needs of farmers. Progress to date has been nothing less than spectacular with the introduction of new ultra low dosage, low toxicity and more environmentally friendly products. Hundreds of millions of dollars continue to flow into these R&D programs each year and I am confident that even more impressive innovations in pesticide chemistry will be forthcoming.

My concern is that without equally impressive improvements in product stewardship, education, training, integrated pest management programs and delivery systems these gains in product chemistry will be lost. The discouraging situation that currently exists worldwide in the application of modern, sophisticated pesticides is one reason for my concern. It is time for industry to take a leadership role in bringing together the agrochemicals industry, application equipment manufacturers, regulatory authorities and research and extension personnel to develop an implementation plan for upgrading training, education and delivery systems worldwide. Failure to do so will seriously jeopardize the technical advances already made in pest control chemistry and place increasing constraints on the availability of this technology to farmers.

To ensure a bright future for pesticides, the agrochemicals industry must develop safer products, improve formulations and packaging, phase out less environmentally acceptable products, develop complementary pest control technologies, reduce manufacturing waste, develop training and education programs and support responsible legislation. While these initiatives are essential to future success, it is clear that no company alone can have sufficient impact to substantially improve pesticide use worldwide.

The industry must join hands with government, academia and international organizations to find ways to catalyze the development of integrated pest management systems, innovative delivery technology and services that facilitate the wise and judicious use of pesticides. Making a serious commitment of resources is a first step. It is estimated that well over one hundred times more money is spent today on developing new pesticides than on how they are applied. Finding ways to correct such imbalances is one of the many challenges we face as we look ahead to the 21st century.

Today we stand at a crossroads, faced with the dilemma of needing pesticides in a world where there is a ground swell of public resistance to using them. The direction we go will be determined by how well we respond to the challenges outlined above. Together we must meet these challenges since pesticides will be essential for meeting worldwide food demands well into the 21st century.

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