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Pesticide Resistance

STRATEGIES AND TACTICS FOR MANAGEMENT

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Chemical Strategies for Resistance Management

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The possible roles of chemical and biochemical research in alleviating the problems caused by pesticide resistance are explored. Pesticides play a central role in current and future crop protection strategies, and there is a need for the continued discovery of new compounds. Constraints, both real and perceived, have limited the discovery and development of new compounds by the agrochemical industry. Industry has responded to these constraints in a variety of ways. Several areas of research must be emphasized if chemical approaches are to have significant impact on the management of resistance. Administrative changes also might foster increased research activity in these areas or might increase the probability that novel approaches will be developed by the agrochemical industry or otherwise be made available for use in integrated pest-management programs.

INTRODUCTION

The Critical Role of Insecticides in Insect Control

The overuse and misuse of insecticides[1] have caused target pest resurgence, secondary pest outbreaks, and environmental contamination (Metcalf and McKelvey, 1976). Nevertheless, it is difficult to foresee how insect pests can be controlled effectively without chemical intervention. Highly produc-

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[1] We use the term insecticide in its broadest meaning as any foreign ingredient introduced to control insects.

tive agricultural practices and the high density of human population have been achieved at the expense of ecological balance. To maintain this imbalance in our favor, we must continue to use ecologically disruptive tools, including insecticides. Even novel pest-control strategies such as pest-resistant plant cultivars will not eliminate the need for chemical pest control. Given the choice of a more expensive and pest-infested food supply or pesticide use, we will continue to use pesticides (Boyce, 1976; Krieger, 1982; Ruttan, 1982; Mellor and Adams, 1984). Therefore, the chemicals available for insect control must lend themselves to rational and environmentally sound use.

Integration of Chemical and Nonchemical Control Tactics

During the past two decades the concept of the judicious use of pesticides has been formalized in integrated pest management (IPM). A key strategy of IPM is to use insecticides only when damage is likely to exceed clearly defined economic thresholds. Such procedures constitute the most fundamental approach to resistance management by minimizing the selection pressure leading to resistance. Reduced pesticide use not only decreases selection pressure on pest insects but preserves natural enemies and other nontarget species, reduces environmental contamination, reduces the exposure of farm workers and consumers to potentially toxic materials, and may reduce phytotoxicity. Thus, IPM increases agricultural profitability, improves public health, and reduces environmental contamination. Most IPM programs consider pesticides as nonrenewable resources and stress their judicious use. The limited availability of compounds that are compatible with IPM may restrict the broad application of this approach.

The Need for New Insecticides

Effective insect control requires not only the continued use of existing insecticides but also the continued availability of new insecticides. Existing compounds will probably continue to vanish from the market because of problems with human or environmental safety. Compounds that survive these challenges may still be lost, owing to the development of resistance. Other compounds, although technically still available, may become obsolete as a result of changing agricultural practices or may be replaced by compounds that offer a greater profit margin to the user.

Of these new agricultural practices, the one having the greatest impact on pesticide use patterns is likely to be low-till (or conservation-till) agriculture. Adoption of this practice will be encouraged by the lower costs resulting from reductions in energy consumption, erosion, and loss of tilth (Lepkowski, 1982; Hinkle, 1983). Since tillage is a major means of pest control, this practice will change pesticide use patterns and increase pesticide usage. Without suitable compounds, low-till agriculture will probably increase environmental and resistance problems.

The potential for loss of effective compounds to resistance has provided impetus for formulating resistance management strategies. The effective management of pesticide resistance, however, involves not only the judicious use of existing compounds but also the discovery and development of new chemical control agents. No management strategy can prolong the useful life of pesticides indefinitely. New chemical tools will be needed, particularly those that exploit new biochemical targets. Thus, rather than removing us from a "pesticide treadmill," IPM and resistance management will only slow the treadmill, thereby extending the usefulness of available chemicals.

Integrated pest management also requires new insecticides. That IPM programs use existing compounds is a credit to the skills of agricultural entomologists, because few if any of these compounds were developed for IPM. At best they are marginally compatible with IPM programs.

TRENDS IN INSECTICIDE DISCOVERY AND DEVELOPMENT

The Declining Rate of Insecticide Development

Although new and better insecticides are needed, there are fewer insecticides on the market, fewer compounds being developed, and fewer companies searching for novel compounds than a decade ago. A number of reasons for this decline have been proposed (Metcalf, 1980). The following four constraints are of particular concern.

Increased Cost of Discovery The cost of discovering new insecticides has increased dramatically. First, the cost of synthesis of new compounds for evaluation has increased because most of the simple molecules have been made and multistep, expensive syntheses are now required. Second, the discovery of highly potent groups of compounds, such as the pyrethroid insecticides and sulfonylurea herbicides, has raised the standards of comparison for new compounds. Levels of insecticidal activity that seemed highly competitive a decade ago are no longer competitive, particularly if the chemistry involved is complex. Third, the abandonment of complete dependence on random screening requires a commitment to the rational discovery and optimization of insecticidal activity. Such a commitment requires more sophisticated, and hence more expensive, biological assays.

Increased Costs of Registration The costs of registration can be reduced. Long-term toxicology testing accounts for most of the registration costs. Despite their imperfections these studies are essential to ensure that insecticide-related hazards are identified and minimized. The development of short-term assays may reduce registration costs, but the Environmental Protection Agency (EPA) generally requires new short-term assays while continuing to require the major long-term toxicology studies. In the absence of regulatory requirements, insecticide manufacturers would still conduct many of these studies to protect themselves against unanticipated adverse effects. Administrative delays and apparently capricious policy shifts also increase costs and stifle the development of new compounds.

Increased Costs of Production Increased chemical complexity increases production costs. Recently introduced compounds require expensive starting materials, multistep syntheses, isomer separations, and sometimes the preparative resolution of optical isomers. These costs are also indirectly increased by the costs of energy and petroleum-based feedstocks, transportation, and more stringent regulations regarding worker safety and chemical waste disposal. Although high production costs increase the level of profitability required of a product, they are not the most serious barrier to development. When a company has a promising product, careful market evaluations provide data needed to support decisions regarding capital investment. Continued improvements in production technology alone are unlikely to have a major impact on the rate at which new compounds are made available for use.

Increased Competition The market for agrochemicals is mature and diversified, and growth in most product areas is less than 5 percent per year (Storck, 1984). Most major insecticide markets are divided among several similar products. This competition increases the requirements for developing a successful compound.

Relative Importance of Problems Limiting Development of New Compounds

The four factors interact synergistically to make the development of insecticides unattractive despite the promise of one of the highest profit margins in the chemical industry. Agricultural chemical companies often emphasize the costs of production and registration as the major roadblocks to developing new compounds. Although high, these costs are not the only barriers to development. The cost and risk involved in the discovery process are significant and often unrecognized impediments. Discovery requires a large long-term investment that is separated by years or even decades from ultimate profit. Moreover, it can be addressed most readily by changes in policy.

Current Strategies and Approaches in the Agrochemical Industry

Industry has adopted several conservative strategies to minimize risk. The most drastic has been withdrawal from the agrochemical field. As some of these companies retire from the marketplace, society loses tremendous expertise in the development of pest control agents. This also reduces the diversity of chemicals that will become available, a diversity that is essential if IPM is to be a sophisticated management strategy rather than simply an exercise in timing insecticide applications.

A second strategy is for a company to emphasize its expertise in development or marketing while leaving the high risks involved in actual discovery to other firms (i.e., licensing compounds that have been discovered and patented by other companies). Thus, fewer organizations have the responsibility for new compound discovery. A related approach is to de-emphasize insecticide development and to emphasize development of materials such as herbicides that are perceived to be less risky or less expensive to register. For example, some of the explosive growth of industrial research in agricultural biotechnology has been at the expense of research on crop chemicals.

A third strategy involves increasing a product's market life. Petitions to register tank mixtures and combinations of existing pesticides are increasing. Use of mixtures or combinations may result in less environmental contamination—a new approach in resistance management—or may lead to the development of new classes of pesticides. The toxicological and environmental effects of such combinations, however, may include phenomena not predicted from studies on the individual components; therefore, these should be closely scrutinized.

A second example of this strategy is the patenting and development of derivatives of existing compounds. Many of these derivatives are "propesticides," which degrade to give an established compound as the active ingredient. Such derivatives may improve safety or environmental behavior.

The major advantage of these approaches is that industry can capitalize on its investment in a mature product without the high risks inherent in new chemistry. Maintaining a mature product on the market has little risk. The profits from an established agricultural chemical can support a great deal of maintenance, and the profits are immediate. When they become uneconomical, they can be dropped quickly without a great loss of invested capital. The extreme measures taken by some companies to maintain cyclodiene insecticides on the market exemplify this approach. Integrated pest management systems keyed to particular chemicals can also contribute to this approach if practitioners of these systems feel that the continued availability of a certain compound is critical.

Product maintenance can also indirectly benefit the development of new compounds. The future development of new compounds becomes more attractive because recovery of development costs can be expected over a longer period.

Companies actively seeking new insecticides have attempted to minimize risk by narrowing the scope of their development efforts. Most new insecticides are developed for one of only two markets: foliar application to cotton or soil application to corn. These two markets are perceived to be sufficiently large and stable so that a company can recover development costs and make a profit during the compound's patent life. Although these compounds may be registered for other uses, they are often forced into secondary uses for which they are not well-suited. This narrow targeting severely limits the diversity of insecticides available for use in pest management.

Companies also avoid risk by emphasizing "me too" chemistry. In this approach a competitor's product is used as a lead to identify related but patentable compounds. This action results in a series of active structures and produces large families of similar pesticides. It diverts resources from the development of novel compounds and may accelerate the development of resistance. Moreover, it does not promote industrial cooperation in resistance management. There is little incentive to preserve susceptibility in pest populations because it also preserves market opportunities for competitors. In contrast, companies that are sole exploiters of a chemical family have a great incentive to preserve their market through resistance management.

CHEMICAL AND BIOCHEMICAL SOLUTIONS TO PROBLEMS CAUSED BY RESISTANCE

Understanding Resistance to Existing Insecticides

Resistance management is based on the belief that rational and informed decisions on insecticide use can be made and that these decisions will prevent, delay, or reverse the development of resistance. To make such decisions, we must know why resistant populations are resistant and know (or estimate) the frequency of resistant genotypes. Resistance management may be very difficult without a comprehensive knowledge of the mechanisms by which insects become resistant.

To date, some resistance mechanisms have been identified: reduced rates of cuticular penetration; enhanced detoxication by elevated levels of monooxygenases, esterases, or glutathione-S-transferases; and intrinsic insensitivity of target sites. Knowing these mechanisms exist, however, is not enough on which to base resistance management decisions. Simple, rapid biochemical assays to detect the presence of these mechanisms in individual insects must be developed.

With such assays resistance mechanisms in field populations can be characterized and the relative abundance of resistant and susceptible individuals in a population can be determined. This information will benefit IPM systems and programs of resistance management. Sometimes the assays will be able to distinguish between heterozygous and homozygous individuals or determine the extent of gene amplification in resistant individuals.

Assays may be developed simply on the basis of a correlation between resistance and an observed phenotype, such as the presence of a particular isozyme. Advances in immunochemical technology are such that it may be possible to identify antigens present in a resistant population, but not a susceptible population. Although they are expedient, methods of detection based on fortuitous correlation rather than the measurement of actual resistance mechanisms may be misleading and must be used with great care even when based on hybridoma technology. Techniques such as internal imaging with monoclonal antibodies may help to explain resistance phenomena.

Research resources must focus on the developing biochemical diagnostic procedures. For enhanced detoxication the challenge is simply to develop microanalytical techniques to determine the level of activity of enzymes of interest in individual insects. Simple microassays can also be developed for one major type of intrinsic insensitivity, such as the altered cholinesterase involved in organophosphate and carbamate resistance. For some mechanisms of resistance, additional fundamental research is needed before diagnostic assays can be devised. An important example is nerve insensitivity resistance to DDT and pyrethroids. Although this type of resistance is well documented in a few species and is suspected in many others, there is no way at present to detect this resistance through diagnostic assays. Behavioral mechanisms may contribute significantly to some resistance. Ultimately, behavioral resistance must have a physiological basis, but it is likely to be even more difficult to find reliable markers for such resistance mechanisms (Lockwood et al., 1984). For these areas the development of diagnostic antigens may be expedient and may even help to discover the true resistance mechanism.

Diagnostic assays such as those outlined are extremely useful in identifying and characterizing resistance that results from a single mechanism. A potentially more serious problem involves the synergistic interaction of two or more mechanisms. To evaluate the underlying causes of polygenic resistance, we must conduct more studies of the distribution and fate of insecticides in both resistant and susceptible individuals. These pharmacokinetic studies have barely been exploited in insects, yet they are essential for us to understand how specific genetic changes act and interact to modify the availability and persistence of insecticides at their sites of action in living insects.

We also must study the metabolism and mechanism of action of insecticides in insect species important in agriculture, animal health, and medicine before resistance develops. Knowledge of sites of action and critical pathways of detoxication is essential when devising strategies to impede the development of resistance to a particular compound in a particular control system. The use of insect strains that are either resistant or susceptible to related insecticides or to other widely used insecticides can enhance the predictive value of these studies. Similarly, to identify potential resistance mechanisms, these studies must use insect species that exhibit natural tolerance.

Clearly, we need to expand the research base for rational strategies of resistance management. We must support and pursue research ranging from analytical biochemistry to insecticide neuropharmacology. These approaches are a necessary adjunct to more familiar experimental approaches if the rapid detection, characterization, and management of insecticide resistance is to become an integral part of pest management.

Discovering New Insecticides

Approaches to Finding and Optimizing Biological Activity The agrochemical industry is very skilled at optimizing the biological activity of a series of chemicals (Magee, 1983; Menn, 1983). Recent technological advances, many of which have been adopted by industrial research laboratories, are certain to refine and enhance this expertise. The use of linear free-energy parameters to establish quantitative structure/activity relationships has proved very effective in optimizing activity in some series. As computer time becomes less expensive, graphics capability more sophisticated, instruments easier to use, and software more powerful, these approaches will become even more useful.

Computer-assisted design in biochemistry, analogous to procedures already used in architecture, is becoming more accessible and affordable. These techniques use X-ray crystallographic data to generate three-dimensional images of complex macromolecules. The scientist can then view the structure of a target macromolecule in three dimensions as it interacts with a ligand, inhibitor, or substrate. These tools will be of tremendous benefit in optimizing chemical structures in a rational, cost-effective manner. The creative potential of these tools is of even greater importance, because they are a powerful resource for making logical transformations, not only from one substituent to another but also from a biologically active peptide to something as dissimilar as a synthetic hydrocarbon. In the field of spectroscopy, nuclear magnetic resonance (NMR) technology is evolving rapidly, not only to support structure elucidation but as a tool to probe the active sites of biological molecules and even physiological function in vivo.

The elucidation of enzyme-substrate interactions and enzyme reaction mechanisms has provided new paradigms for the discovery of new compounds. Several laboratories are applying transition-state theory, which describes the mechanisms of enzyme-catalyst reactions, to the design of exceptionally powerful enzyme inhibitors. A related approach involves the design of compounds that interact with enzymes as suicide substrates, which trick the enzyme into self-destructing in the process of catalysis. The proliferation of these sophisticated, targeted approaches depends on the continued growth of fundamental information about enzymes, receptors, and other regulatory macromolecules.

Recent advances in genetic engineering and biotechnology are facilitating basic research on many fronts. For example, the ability to isolate and sequence small quantities of peptides and proteins, to isolate their messages and genes, and to measure them with immunochemical and other tools will provide new leads for using classical chemistry. Moreover, these biological messages may be directly useful in developing microbial pesticides or for enhancing crop resistance to pests. Microbial pesticides may bridge the gap between classical chemical and classical biological control. The current industrial effort to develop avermectins, a group of fungal toxins with high insecticidal activity, illustrates that a very complex molecule can be made by a fermentation process that is competitive with classical industrial chemistry. This concept greatly expands the variety of structural types that might be used commercially for insect control and indicates that rigorous screening of plant and microbial natural products may meet with still further success. The *Bacillus thuringiensis* toxins represent another level of complexity, in which the marketed toxins are proteins (Kirschbaum, 1985). The potential for selectivity among these toxins is very exciting. The *B. thuringiensis* gene can also be expressed in both a crop plant and a plant commensal organism and may herald a new phase in research on plant resistance, in which the insecticide chemical or biochemical is produced by the plant itself or by an associated microorganism.

Advancing biotechnology also offers the prospect of new opportunities for exploiting insect viruses (Miller et al., 1983). These highly selective agents have shown considerable promise for insect control, but their wide use has been limited by difficulties in registration and, more seriously, problems in devising in vitro production systems. Continuing improvements in insect tissue culture may improve the economic feasibility of these materials. It may also be feasible to clone messages into viruses to block a critical physiological process in insects in vivo at very low levels of infection, while still allowing the virus to propagate in vitro.

Research in these areas may drastically alter our concepts of what an insecticide is. The move toward biorational design and genetically engineered biological insecticides or insect pathogens does not mean, however, that the resulting products will be free from the hazards we associate with classical insecticides. These novel materials will still require thorough investigation for their possible toxicological and environmental effects. For pathogens, suitable registration guidelines remain to be established, and answers to the public concern over the release of genetically engineered pathogenic organisms into the environment must be formulated. Resistance to these materials could develop if they are used in ways that lead to high selection pressure.

New Targets for Insecticide Development The four major classes of synthetic organic insecticides developed since 1945 are neurotoxins. Yet, most insecticides act at only two sites in the nervous system. Thus, genetic modifications that change the sensitivity of these sites of action (altered acetylcholinesterase for carbamates and phosphates, nerve insensitivity resistance for DDT and pyrethroids) produce cross-resistance that renders entire classes of compounds ineffective against resistant populations. These resistance mechanisms cannot be overcome by synergists. Resistance management strategies based on rotating compounds that differ in their sites of action have not been tested in the field and are limited by the lack of diversity of sites of action in our current armament of insecticides.

Ample opportunities exist for discovering insecticides that act at new sites in the nervous system. The discovery that both the chlorinated cyclodienes and the avermectins apparently act at the γ-aminobutyric acid (GABA) receptor (Mellin et al., 1983; Matsumura and Tanaka, 1984) highlights the potential significance of this target. Similarly, the discovery that chlordimeform acts at the insect octopamine receptor (Hollingworth and Murdock, 1980) has stimulated renewed interest in the formamidines as a class and in novel structures acting at this site. These compounds illustrate that successful control can be achieved without kill.

Beyond these, several novel sites remain to be exploited as advances in fundamental neurobiology define their properties. Several neurotransmitter systems are promising targets: the acetylcholine receptor in the insect central nervous system, the glutamate receptor at the insect neuromuscular junction, and receptors for peptide neurotransmitters and neurohormones are just now being discovered. Both the acetylcholine and glutamate receptors have previously been targets of insecticide development in industry without great success, but their significance as targets may increase as more information about the pharmacology of these sites accumulates. Other targets also exist beyond the level of transmitter receptors. The enzymes involved in metabolizing or maintaining homeostatic levels of transmitters are potential sites of action, as are the processing enzymes involved in the release of neuropeptides from precursor proteins and the peptidases that degrade bioactive peptides. The success of the drug Captopril, which inhibits the angiotensin-converting enzyme, illustrates the potential for biological activity in compounds that interfere with normal neuropeptide processing.

Targets also exist outside the nervous system (Mullin and Croft, in press), such as compounds that act on the insect endocrine system (e.g., juvenoids) and on the biochemical processes involved in insect cuticle formation (acyl ureas). The selective action of these insect growth regulators makes them highly suitable for IPM systems. They act only at specific times in insect development, however, and the interval between application and effect can be several days rather than a few hours, as with neurotoxic compounds. (Fast-acting herbicides once were the industry standard until highly effective slow-acting compounds became available.) Many developmentally active compounds exhibit a degree of selectivity that makes them more suitable than broad-spectrum neurotoxicants for use in IPM systems. Under current economic and regulatory constraints, however, they are less effective than neuroactive compounds.

Even a cursory knowledge of insect physiology shows numerous systems that may be exploited to control insects. For instance, the regulation of oxygen toxicity and water balance are critical in an insect, and therefore are susceptible to disruption. Phytophagous insects have unique systems for using phytosteroids that may provide biochemical leverage for the design of selective compounds. Exploitation of some of these systems may lead to the fast-acting toxins we have come to expect in agriculture.

Some of these targets may yield compounds very selective for pest insects versus beneficials (Mullin and Croft, in press). The term pest has no systematic basis, however, and the bionomics of pest versus beneficial insect interaction is unknown for many cropping systems. Although there are some limited generalizations regarding the comparative biochemistry and toxicology of pest versus beneficial insects, their general applicability is unknown (Metcalf, 1975; Granett, in press). It is not necessary to develop selectivity among insects by planned exploitation of a biochemical lesion. Once high biological activity is discovered, such selectivity can be developed by synthesizing compounds to exploit differences in xenobiotic metabolism or simply by testing a series of chemicals on pest and beneficial insects as part of the evaluation process. Just as industry invested in resistance management when it became financially advantageous, many companies will eventually include selectivity as a major criterion in the future selection of compounds.

Encouraging Fundamental Research

Although there are ample opportunities to discover novel insecticides, the critical problem lies in incentives to pursue these opportunities. Historically, the agrochemical industry has succeeded by optimizing biological activity in a series of compounds. Industry has not pursued sustained in-house research to discover new leads. One reason is the expense of long-term commitments of personnel and facilities to do basic research on insect biochemistry. Moreover, scientists attempting to pursue these efforts under the cloak of industrial secrecy are isolated from the free interchange of ideas and the honing influence of peer review in publication and the pursuit of funding. Consequently, basic research in an industrial setting runs the risk of losing contact with the leading edge of knowledge, particularly in some of the more progressively fast-paced fields of academic research (Webber, 1984).

This argument may imply that such research is most appropriately pursued In academic laboratories. Yet, we found very few academic scientists actively pursuing the definition of possible new sites for insecticide action, and the funds that were spent came largely from projects funded for other reasons. More scientists must be enticed into these areas by convincing them that a career based on such research is socially responsible and professionally profitable. There are a variety of mechanisms to accomplish this end, a few of which follow. Our suggestions raise questions regarding the role of the public sector in fundamental agricultural research. Ruttan (1982) argued that incentives are not adequate to encourage private research and that social return on public investment in agricultural research may exceed private profit. He concluded that "simultaneous achievement of safety, environmental, and productivity objectives in insect pest control will require that the public sector play a larger role in research and development."

National Institutes of Health and the National Science Foundation If gold stars were to be awarded to agencies for funding work leading to the discovery of new targets for insecticide development, the National Institutes of Health (NIH) and the National Science Foundation (NSF) would receive them. Most of this work is outside the mandates of these agencies, but they have provided a base level of funding presumably because the proposed science is good and because the agencies see some social value in the research product. Our observations on pesticides appear to apply to agriculture in general (Lepkowski, 1982). Some slight changes could be made in the mandates of certain institutes at NIH to facilitate the funding of such work "up front." For instance, a great deal of work is supported on the deleterious effects of pesticides on mammalian systems. One way to improve human health would be to encourage the development of insecticides that are less risky to humans and the environment. Ironically, the National Institute of Environmental Health Statistics (NIEHS) has recently designated such research as "peripheral" and "no longer relevant."

An agency like NSF, which funds the pure pursuit of knowledge, is of tremendous value to the scientific community. Its resources must not be diluted, because much of the work on fundamental chemistry and biochemistry that it funds is of great value in the elucidation of new targets for insecticides even when insects are not the subject of investigation. Yet, NSF should not eliminate from consideration good basic research simply because a pest insect is used as a model organism to evaluate a fundamental question in biology. Among the very best models for asking basic questions in biology are those related to resistance. The excitement demonstrated in this publication from population biologists is one illustration. The availability of strains of insects either susceptible or resistant to the toxin provides an unparalleled opportunity to determine the impact of altered biochemical processes on the functioning of intact organisms. The value of insects as models when investigating fundamental biological processes has been illustrated often.

U.S. Environmental Protection Agency Research funding by the U.S. Environmental Protection Agency (EPA) is generally restricted to areas that require additional information to support a regulatory decision. Nevertheless, EPA has funded some of the most exciting and innovative work on the development of new insecticides; it has also funded research that will improve environmental quality and encourage implementation of IPM programs. Certainly, research that leads to the discovery and development of insect control agents that promise fewer environmental and nontarget problems is a logical extension of the above programs.

U.S. Department of Agriculture Responsibility to support fundamental research as a basis for pesticide development is part of the U.S. Department of Agriculture's (USDA) mandate. Unfortunately, USDA has failed to fulfill this responsibility. This failure is due partly to the negative connotations that surround the idea of promoting pesticide research or pesticide use in any way and the obvious difficulties of selling the need for such work in the present political climate. To reverse this trend USDA must take a position of informed advocacy for these research needs rather than capitulating to prevailing public opinion.

The USDA is the only federal agency with an in-house research effort capable of addressing this problem. A recent review of USDA research recommended a renewed emphasis on basic research directed toward solving agricultural problems of national importance (Lepkowski, 1982). Research to define targets for novel insecticides fits within this recommendation. Although some excellent research has been done by USDA scientists, administrative neglect of these priorities and concomitant emphasis of other programs has left USDA laboratories with little in-house expertise in this area. A renewed USDA effort in target biochemistry would require not only a policy decision but also a commitment to hire new professional staff.

Fostering an environment of creativity and free scientific interchange within the USDA is essential. There is a constant tension within the USDA between the need for directed research and the negative impact of excessive direction on innovation. Several initiatives might improve the productivity and creativity of all research programs within USDA's broad mandate. Programs to encourage collaboration between some USDA laboratories and universities have been very successful and could be expanded. Additional funds could be designated, and individuals might be encouraged to take sabbatical leave at USDA laboratories. The development of an in-house career development program could greatly increase the level of innovative work as well as research esprit de corps. Researchers could be granted salary and support funding for five years, based on past performance or a competitive proposal.

The most immediate impact of USDA support of target biochemistry would be felt in universities. Academic laboratories already possess the expertise to pursue this research. The U.S. Department of Agriculture, through its Competitive Grants Program, can provide the opportunity. Unfortunately, the current guidelines for the program virtually exclude research in this area.

Simply broadening the objectives of the Competitive Grants Program would be of little help, as the program is too small to fund even the high-quality proposals submitted under current guidelines. Instead, we suggest an increase in funding specifically to support a new program area in target biochemistry. For example, supporting 50 research projects at a level of $60,000 per year ($40,000 in direct costs and $20,000 in indirect costs) would cost $3 million per year, a modest amount compared to the nearly $20 million increase recently designated to establish funding through the Competitive Grants Program for research in agricultural biotechnology.

Despite the need for this type of funding, the future of the entire Competitive Grants Program is regularly threatened in the budget process. The most recent example is the elimination of all funding for this program in the proposed executive budget for fiscal year 1986. If competitive funding is to have a large impact on research productivity, it must be a stable, integral, and significant part of the annual USDA budget.

Another approach would be to institute a strong, competitive postdoctoral program for in-house and extramural positions. This program, patterned after the highly successful NIH program, would encourage new Ph.D.s to prepare research proposals relating to fundamental problems in agriculture. It would encourage young scientists from a variety of disciplines to enter the field and, if properly administered, would further excellence in agricultural research. A second approach would be to establish a grant program to support new assistant professors in fundamental research related to agriculture. Such a program would encourage individuals in basic science departments to exploit the exciting models offered in agriculture. Once a young scientist has established a research direction related to agriculture, long-term funding might be obtained from other agencies. A similar approach might be taken with starter grants to encourage scientists to extend their research into new areas. Ideally these grants would be limited to two or three years and would be nonrenewable for a similar period. Such a system would encourage individuals to seek other support and prevent the funding from going only to a few established laboratories. These three programs would acquire for agriculture more basic research than agriculture actually supported. Such a course may be initially defensible, but ultimately, there is also the need to establish stable, long-term support for the fundamental science that will maintain our high level of agricultural productivity and profitability while still protecting the environment.

Universities Universities can increase research on target biochemistry. Experiment station directors and land-grant institutions can immediately encourage such work. Scientists lacking experiment station appointments could be encouraged to carry out collaborative projects in these areas.

The major commitment that a university must make is to hire faculty to work in the area of target biochemistry and physiology. It takes more than a two-week short course to convert an organic chemist into a creative leader of a biorational pesticide development program. The chemist must have either extensive cross training or colleagues who speak a similar language. Who will train these individuals? Many of the pioneers of post-World War II pesticide development have retired and have not been replaced. A teaching cadre in this area is critical if work along these lines is to continue.

Although agrochemical companies have the chemical expertise to exploit a biochemical system, they lack the in-house expertise in biology and biochemistry. Acquiring such expertise by extensively retraining existing personnel or hiring new staff is an expensive, long-term commitment. Collaborating with a university laboratory having the required expertise is a more logical solution.

Collaborative arrangements benefit both parties, but they are relatively rare in this country (Webber, 1984). Therefore, universities must develop reasonable guidelines to permit and encourage interaction with industry. Collaboration means far more than just accepting money. Acceptance carries with it the obligation to conduct research that will be meaningful to the sponsoring company. In return, industry must appreciate that university laboratories do not exist solely for subcontracting proprietary research. A great deal of basic research can be accomplished on a minimal budget in a university setting, but a major professor must protect the careers of students and postgraduates. Thus, industry must be willing to make a commitment to multiyear support and must have realistic expectations of productivity for research undertaken in the context of graduate and postdoctoral training. Areas of research must be explicitly defined so that university collaborators are not barred from publishing their results, and patent agreements must respect the rights of the university as well as the research sponsor.

Private and public investment in university-based agricultural research is sound (Ruttan, 1982). Such research is complementary to graduate education in agriculture. Public investment in a university setting will draw scientists from a variety of areas into agriculture. Since industry is in need of in-house scientists capable of developing new pest-control agents by both classical and molecular procedures, industrial support of university research provides not only the data needed but a pool of well-trained potential employees as well.

Chemical Industry The pesticide chemical industry invests roughly 10 percent of its gross profits in research, making it one of the most research-intensive industries (Ruttan, 1982). Companies must establish sufficient in-house expertise in insect biochemistry and physiology and must initiate basic research programs that are relevant to the company's objectives and complementary to university research efforts. The agrochemical industry tends to hire basic scientists and then assumes that basic research is simply the screening of experimental chemicals on an elegant in vitro preparation. Such work is important, but it should be a minor portion of the duties of an industrial scientist. The scientists must be free to explore new opportunities for chemical exploitation and to define the biorational models for directed chemical synthesis programs. Another problem is that industrial scientists doing basic research are often prevented from testing the validity of their ideas through publication in peer-reviewed journals. Companies can remedy this by establishing a tradition of peer review and publication of in-house basic research after an appropriate delay to allow its proprietary use.

State IPM and Commodity Groups Funding available to state IPM programs and commodity groups varies dramatically from state to state. The funding is characteristically applied to local problems, not to fundamental research on target biochemistry Developing selective materials is to their benefit. These groups should support legislative efforts to encourage fundamental research in agriculture even if the expected benefits extend beyond the individual state. When possible, these groups should fund long-term basic research directly, partly because they can have a more profound influence on growers to use selective materials.

ENCOURAGING REGISTRATION AND DEVELOPMENT

Industry will use any available information on target biochemistry to discover new compounds. Although broad-spectrum compounds will be developed, selective compounds are desperately needed for IPM programs, especially since regulatory law and economic constraints impede the development of diverse crop chemicals.

A variety of modifications of patent law and enforcement can encourage development. For instance, legislation to start the patent clock ticking when registration is granted has already been proposed. Patent life could be further extended for compounds considered to have exceptional value to IPM programs, especially if the compounds act by a unique mechanism. An extended patent life would give the company owning the compounds a major incentive to avoid resistance problems (Djerassi et al., 1974).

Although many regulatory costs cannot be reduced, costly delays in regulatory decisions can be eliminated. The EPA has often appeared to avoid making bad decisions by avoiding any decisions. An effort by EPA to process registration petitions as rapidly as possible would be of great benefit, particularly if extensions in patent life cannot be obtained.

Changes in the ways in which toxicological risks are evaluated would promote the development of novel, selective compounds. Current regulatory procedures may inadvertently encourage the registration of compounds that are acutely toxic to mammals over selective materials (Retnakaran, 1982; Ruttan, 1982). The evaluation of the toxicological risks of insecticides must be relevant to the expected routes and levels of exposure rather than requiring toxicological evaluation at maximum tolerated doses. To do this, we need well-trained, courageous regulators acting with legislative support. The public must understand that a blind effort to obtain zero-risk may only increase risk.

Further expanding the subsidized registration of pesticides for minor crop uses would give IPM practitioners a greater variety of compounds to work with. Eliminating some registration requirements for several closely related IPM-compatible compounds by the same company might encourage the development of highly selective compounds. Although registration cost will probably not decrease dramatically, some scientific improvements can be made. For instance, immunochemical technology can reduce the cost of residue analysis. Since efficacy and residue analyses are the major costs involved in minor crop registration, this technology could greatly expand the effectiveness of the IR-4 program with no increase in budget (Hammock and Mumma, 1980).

Another option is an orphan pesticide development program to encourage the development of compounds that cannot be developed economically by industry but are likely to be of great benefit. The recently established orphan drug program provides both a precedent for this approach and an administrative model for its operation.

CONCLUSION

Many resistance management tactics tend to focus on existing resistance problems and attempt to preserve the utility of compounds currently available. Although these efforts are valuable, we believe that the effective management of resistance to pesticides depends on the continued development of new compounds, as well as on the judicious use of existing materials. Therefore, the recent decline in the rate of development of new insecticides is a serious limitation to resistance management and the development of sophisticated pest-management strategies.

There is a great need to stimulate both basic research on the biochemistry and physiology of target species and development of selective insecticides.

We have identified many avenues of research in insect biochemistry that appear promising for the design of novel insecticides, and there are many more that we have not mentioned. Federal agencies and the agrochemical industry must recognize that research is critically needed.

The stimulation of the industrial development of new compounds is a more complex problem. Potent, broad-spectrum pesticides will continue to be developed, but economic and regulatory constraints work against the development of more selective compounds. The agrochemical industry exists to discover and sell products at a profit, not to develop ideal pesticides for pest management. They will not develop compounds that are perceived to be unprofitable or excessively risky. If, however, an increase in our knowledge of the biochemistry of target species and the impact of new technologies can decrease the cost of discovery, if the time and cost of regulatory compliance can be minimized without detriment to the public good, and if patent lives of compounds can be extended to compensate for marketing time lost in regulatory review, then the search for and development of novel insecticides will be perceived to be a sound, profitable business, and the tremendous potential that we see for the development of safe and selective pesticides by both chemical and molecular approaches will be realized.

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