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Role of Research and Regulation in 50 Years of Pest Management in Agriculture

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Pest management techniques have evolved over the past 50 years. Inorganic chemical pesticides were replaced by synthetic organic chemicals, and now biopesticides constitute a significant part of pest management technology. Requirements for the regulatory approval of pesticides changed dramatically in 1996 with the passage of the Food Quality Protection Act (FQPA). The FQPA directs the U.S. Environmental Protection Agency (EPA) to make more rigorous and conservative evaluation of risks and hazards and mandates a special emphasis on the safety of infants and children. The EPA provides incentives for the industry to register materials that are designated "reduced risk". The future for the registrant industry will include continued reduction in numbers of registrants through mergers and acquisitions. Conventional chemicals will remain as important pest management components, and the processes of combinatorial chemistry and high-throughput bioassays will allow the rapid synthesis and testing of large numbers of candidate compounds. Biopesticides will become more important tools in pest management, with microbial pesticides and transgenic crops being likely to play important crop protection roles. There will be a continuing need for research-based approaches to pest control.

THE PAST

Modern pest management techniques have made miraculous changes in agriculture. Prior to the advent of synthetic organic chemicals, growers of crops had to fight insects, diseases, and weeds with inadequate tools. Insects and other herbivores reduced crop yield by eating the crops, diseases attacked crops, and weeds competed with desirable crops and range forage. The growers lost a considerable proportion of crops to pests, during production, storage, and distribution. Animal food production also had to fight insect and disease pests.

Pest management techniques evolved dramatically in the 20th century, particularly in the past 50 years. Prior to the 1950s, crop protection tools included mechanical removal of weeds, a few synthetic organic chemicals, and rather toxic inorganic materials, including salts of lead, copper, and arsenic.

Prior to the 1940s, weeds were controlled by cultivation and the use of inorganic salts, sulfur, and oil. The introduction of the phenoxy herbicides, in particular 2,4-dichlorophenoxyacetic acid (2,4-D), in the 1940s started the use of synthetic organic herbicides for the management of weed pests. Research to discover new chemistries for weed control led to the development of new herbicide chemical classes such as the triazines, ureas, and others. Research also led to development of compounds with different modes of action and selectivity (*1*).

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Sulfur is the oldest effective fungicide and is still in use today. Sulfur and the copper-containing Bordeaux mixture were the major fungicides used in agriculture until the advent of synthetic organic compounds in the 1940s. Research efforts resulted in the development of the broad spectrum alkyldithiocarbamates, organotins, quinones, and phthalimides. Systemic materials, introduced in the 1960s, have more specificity in the organisms they control (*2*).

DDT was introduced for agricultural use after World War II, and by the 1950s the use of chlorinated insecticides was common. These materials were extremely effective, had a wide spectrum of action, and a long residual activity. Over the years, it became clear that these "new" organic materials also had adverse impacts on the environment, leading to reduced populations of birds and some aquatic organisms. One of the benefits, that of long residual life, was also a negative aspect. These insecticides had very long half-lives and became widely distributed in nature by accumulation through the food chain and by atmospheric distribution. Most of the organochlorine insecticides, like DDT, were banned from use by the U.S. Environmental Protection Agency (EPA) in the 1970s.

Organophosphates, originally discovered as nerve poisons, were recognized as reliable and effective insecticides in the 1940s. These chemicals were highly toxic, had a broad spectrum of activity against insect pests, and showed only moderate stability in soil, on crops, and in the environment. The latter was a positive characteristic from an environmental and human

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safety view, but it also resulted in the need to make several applications over a growing season, increasing the potential for exposure to humans and wildlife and the development of insect resistance. Another negative characteristic is their high acute toxicity, which resulted in hazards to loader/mixers, applicators, and field workers, a factor often judged to be unacceptable. Following implementation of the Food Quality Protection Act (FQPA), a number of the uses of organophosphates have been restricted or eliminated.

Carbamates also came into use in the 1950s and are still used today. These chemicals have relatively low mammalian toxicity and are selective in that they are toxic to target insect pests but not to most beneficial insects. They have low persistence in soil, plants, and the environment. The EPA is presently evaluating these compounds under the requirements of the FQPA.

To a certain extent, herbicides and fungicides followed a parallel development over the same 50 year period, namely, introduction of new, effective, synthetic organics beginning in the 1940s, banning or restricting the use of many in the 1970s to the present, and development of less risky alternatives that continue in widespread use.

Although difficult to quantify, the benefit of crop protection chemicals along with fertilizers, improved hybrid seeds, and mechanization very likely contributed heavily to an increase of farm productivity in the United States of approximately 250% from the 1940s to 1996 (*3*, *9*).

THE PRESENT

The FQPA has made a significant impact on safety standards for pesticides. A number of formerly registered uses of the organophosphates and carbamates have been curtailed or discontinued. Important provisions follow (*4*):

The FQPA amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). These amendments fundamentally changed the way the EPA regulates pesticides. The requirements included a new safety standard—reasonable certainty of no harm—that must be applied to all pesticides used on foods. The FQPA was also designed to resolve the Delaney paradox, to protect children from pesticides and address environmental endocrine disruption. To accomplish these goals, the law sets forth the following:

• The EPA must re-register pesticides every 15 years using the best available data.

• The law gave much attention to minor crops: these are crops grown on <300000 acres, or a minor use may be defined on an economic basis if the pesticide use is not supported by the company. A chemical may also be defined as minor use if it is the only alternative, or it is safer than other alternatives, or it is needed for Integrated Pest Management (IPM) and resistance management. The FQPA also provided incentives to develop and maintain minor uses and to implement a faster approval of reduced risk pesticides and those used on minor crops.

• The zero tolerance standard for certain pesticides in processed foods was eliminated (the old Delaney paradox), and the Act establishes new standards for setting tolerances in both fresh and processed foods. The Delaney clause, enacted in the 1950s, had a zero tolerance for pesticides that caused cancer in humans or laboratory animals ingesting any level of the pesticide.

• Tolerances (maximum residue value) must be "safe", that is, "provide a reasonable certainty that no harm will result from aggregate (dietary, water, and household) exposure". All existing tolerances must be reviewed by 2006, and the most toxic materials must be reviewed first.

• Risks, both aggregate and cumulative, from pesticides must be based on exposures to all chemicals that have a common mechanism of toxicity (e.g., all organophosphates, rather than on a chemical-by-chemical basis). In the past, exposure was based on pesticides in food only. Now all exposures must be considered: dietary, water, and household.

• Under previous regulations safety factors were used to address inconsistencies in toxicity due to intra- and interspecies variation. These safety factors ranged from 100- to 1000-fold. The FQPA allows use of an additional safety factor (up to 10×) to cover unique sensitivities of infants and children as proposed by the National Academy of Sciences report "Pesticides in the Diets of Infants and Children" (*5*). Thus, this additional factor can result in a 1000−10000-fold overall safety factor. To implement evaluation of the safety factor for infants and children, the EPA must pay special attention to residues in the foods that make up the diets of infants and children (e.g., apples, peaches, and pears).

• Endocrine disruption, caused by compounds that mimic or block the effect of hormones, such as estrogen, or act on the endocrine system resulting in developmental or reproductive problems must be considered when a pesticide is registered. The FQPA requires that industry develop appropriate test data to address potential endocrine disruption effects.

The FQPA applies these new standards for the registration of new pesticides as well as previously registered materials. As a result of a major concern for ensuring the safety of the food supply, maintenance of the environment, and the well-being of agricultural workers, a number of trends in pest management tactics have developed. These include development of materials with characteristics that make them safer to man and to the environment (reduced risk), biological pest control agents, and plant species that are less susceptible to diseases and insects. These approaches are considered to be far safer pest management tactics than the use of broad spectrum pesticides. The EPA's Reduced-Risk Initiative and Policy are designed to encourage the registration of safer pest management chemicals. The following describes that policy and the program to implement it:

"EPA's Reduced-Risk Initiative expedites the registration of *conventional* pesticides that the Agency believes pose less risk to human health and the environment than existing alternatives. The goal of the program is to quickly register commercially viable alternatives to riskier pesticides such as neurotoxins, carcinogens, reproductive and developmental toxicants and groundwater contaminants. The Initiative, begun in 1993, provides a major incentive for registrants to develop reduced-risk pesticides and ensures these pesticides are available to growers as soon as possible.

Definition: *Conventional* reduced-risk pesticides have one or more of the following advantages over existing products: low impact on human health, low toxicity to non-target organisms (birds, fish, and plants), low potential for groundwater contamination, lower use rates, low pest resistance potential, and compatibility with Integrated Pest Management. (*Biological* pesticides, which also have many of these desirable characteristics, are handled through a different expediting process.)

Incentives: The major incentive for a company to come in with a reduced-risk pesticide is registration time. Reduced-risk pesticides are registered in about one-third the time required to register a conventional non-reduced-risk pesticide (on average, 16 vs 38 months). This allows the chemical to be introduced into the market at the earliest possible time and displace riskier alternatives as soon as possible. It also allows the registrant several additional growing seasons under patent. In addition, although companies are not allowed to put a reduced-risk claim on their labels, EPA believes that companies use the reduced-risk status to marketing advantage." (*6*).

IR-4, the publicly supported project with the goal of providing pest management tools (conventional chemicals and biopesticides) for the growers of fruits, vegetables, and other minor crops, works primarily with reduced-risk chemicals. In fiscal year 2001, 80% of the field research efforts designed to collect data in support of new pest management uses were done using reduced-risk compounds.

Biopesticides are also a focus of safer pest management tactics. They also fall into the reduced-risk category, but, owing to other characteristics, they are treated differently by the EPA. The following describes what they are and how the EPA considers them.

"Biopesticides are certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals. For example, canola oil and baking soda have pesticidal applications and are considered biopesticides. At the end of 2001, there were approximately 195 registered biopesticide active ingredients and 750 products. Biopesticides fall into three major classes:

(1) Microbial pesticides consist of a microorganism (e.g., a bacterium, fungus, virus, or protozoan) as the active ingredient. Microbial pesticides can control many different kinds of pests, although each separate active ingredient is relatively specific for its target pest[s]. For example, there are fungi that control certain weeds, and other fungi that kill specific insects.

The most widely used microbial pesticides are subspecies and strains of *Bacillus thuringiensis*, or Bt. Each strain of this bacterium produces a different mix of proteins and specifically kills one or a few related species of insect larvae. While some Bt's control moth larvae found on plants, other Bt's are specific for larvae of flies and mosquitoes. The target insect species are determined by whether the particular Bt produces a protein that can bind to a larval gut receptor, thereby causing the insect larvae to starve.

(2) Plant-incorporated protectants (PIPs) are pesticidal substances that plants produce from genetic material that has been added to the plant. For example, scientists can take the gene for the Bt pesticidal protein and introduce the gene into the plant's own genetic material. Then the plant, instead of the Bt bacterium, manufactures the substance that destroys the pest. Both the protein and its genetic material are regulated by EPA; the plant itself is not regulated.

(3) Biochemical pesticides are naturally occurring substances that control pests by nontoxic mechanisms. Conventional pesticides, by contrast, are generally synthetic materials that directly kill or inactivate the pest. Biochemical pesticides include substances, such as insect sex pheromones, that interfere with mating, as well as various scented plant extracts that attract insect pests to traps. Because it is sometimes difficult to determine whether a substance meets the criteria for classification as a biochemical pesticide, EPA has established a special committee to make such decisions." (*7*).

Biopesticides have many potential advantages. They are often pest specific and thus harmless to nontarget organisms including humans. They are effective when used in small quantities and have a short residual activity, but they require much more knowledge for growers to use them with the same efficacy as with conventional pesticides.

THE FUTURE

Chemicals. The crop protection industry has been consolidating and will probably continue to do so. In 1990, there were more than 44 of multinational agrichemical manufacturers of conventional pesticidal chemicals; in 2000, there were 37 (*8*). There have been mergers and sales of businesses, which have resulted in fewer registrants. Between 1990 and 2000, Aventis came out of mergers/acquisitions of Hoechst/Schering/Noram (1994), Plant Genetic Systems (1996), Stefes (1997), Rhone-Poulenc (1999), and AgrEvo (1999). BASF, Bayer, Dow AgroSciences, DuPont, Monsanto, Sumitomo Chemical, and Syngenta are other examples of the single company that remains after numerous mergers both with other registrants and with seed companies (*9*). The most recent merger of Aventis Crop Sciences and Bayer to form Bayer Crop Sciences in May 2002 will create the world's largest crop protection company. The numbers of multinational companies in the pest management/seed business will continue to diminish.

Chemistry has achieved many pest management options, but the future for synthesizing and identifying new chemistries is clouded. The current testing requirements for EPA approvals are very stringent in terms of human and environmental safety. In addition, the issue of pest resistance further raises the bar. The target sites of the past are no longer viable, thus requiring new compounds with new modes of action. It is estimated that 40000−50000 (*10*) compounds must be screened to identify one viable new candidate chemical.

Through the process of combinatorial chemistry, large numbers of chemicals can now be synthesized. This process, often done in an automated system, yields large numbers of potential candidate compounds. These materials may then be screened using high-throughput bioassays. Hundreds of thousands of compounds per year pass through miniaturized test systems, which can be run quickly and efficiently to identify those materials with potential for continued development (*11*). Once a compound is identified that will control the pest and have only minimal impact on the environment and on nontarget organisms, then its development may begin. Doing all of the toxicological testing and assessing its environmental fate is a long and expensive process. It is estimated that 8−10 years will be required at a cost of $25−80 million (*12*).

One additional trend will be the increase in importance of off-patent pesticides (*13*). Many pesticides that have been in use for years are no longer protected by patents, nor are they the exclusive product of one registrant. Many of these off-patent or generic materials still have valuable uses, and large companies are aligning themselves with smaller companies that have specialized in the manufacture and sale of these off-patent materials (*14*). As the number of primary registrants has become smaller, there has developed a niche for companies that manufacture, formulate, and sell pesticides that are off-patent. This part of the industry will certainly grow as long as there are economic incentives for the production and sale of these older, but still effective and registerable, chemicals.

Development of safer, more precise application technology will become critical to sustain continued use of these chemicals. Development of predictive models of environmental fate pathways, based on physicochemical properties, microcosm/macrocosm studies, or other laboratory or field tests, will also be needed, both for older chemicals and for new ones (*15*). The important role of analytical chemistry in detecting residues for regulatory, risk assessment, and environmental programs will continue to be important. Particularly needed are rapid methods that can detect multiple analytes, often at the farm gate or in farm production channels, as a continuing safeguard against unwanted residues (*16*).

Biopesticides. The number of biopesticides will continue to increase. The human and environmental safety of the biopesticides and compatibility with integrated pest management systems will drive continued expansion of this industry. The industry has recognized the need to work together and has formed the Biopesticide Industry Alliance (BPIA), with a mission to improve the global market perception of biopesticides as effective products. BPIA plans to develop industry standards for product quality and efficacy (*17*).

Microbial Pesticides. Microbial pesticides have been used in agriculture for many years. They exhibit several advantages over synthetic chemicals that include safety for nontarget organisms, tendency to biodegrade, low cost to develop, and good compatibility with IPM programs (*18*–*20*). Drawbacks that might suggest further areas of research include limited product shelf life, unpredictable efficacy owing to environmental requirements of the biological, short effective life in the field, and requirement for a considerable knowledge base for effective use.

Bt-based microbial insecticides have been used successfully in many cropping and forestry systems for years, but the effective life of Bt in the field is only a few hours owing to various degradative influences. New approaches to extending product life are needed as illustrated by a plant-colonizing pseudomonad for delivery of Bt genes and a starch encapsulation process for Bt, designed to improve survival and efficacy (*21*).

A Bt enhancer, a natural substance produced in the Bt cell at low levels (*22*, *23*), was originally developed (*24*) as a fungicide (called zwittermicin A). When this compound is combined at higher levels with Bt, the Bt protein's ability to kill even the toughest Lepidopteran caterpillar is enhanced. These are examples of approaches to enhance the efficacy and stability of Bt. Future research will likely enhance these and find even more effective approaches to the stabilization of the Bts.

Baculoviruses and Entomopathic Fungi. Baculoviruses are insect viruses (e.g., nucleopolyhedrovirus and granulovirus) that infect and kill insects. Entomopathic fungi will also infect insects and cause their death. These agents exhibit many of the advantages and disadvantages of the other microbial pesticides.

Microbial and Natural Product Fungicides. Microbial fungicides (bacteria that compete with and attack fungi) make up a small portion of the fungicide market. Further commercial development will depend on the consistency of the products and the confidence of growers. Again, such products are valuable components in IPM programs and offer opportunities for effective use in the future (*25*).

Natural products, produced by microbes, plants, and other organisms, also offer significant potential. A number of products isolated from *Bacillus* species are known to control several important fungal diseases of corn, potatoes, beans, etc. (*26*). These materials have advantages that include a wide variety of active chemical ingredients, a good likelihood of finding new mechanisms of action, and low risks to man, the environment, and nontarget organisms (*27*).

Another use of microorganisms is the process of hypovirulence. Plants may be treated with nontoxic strains of an organism that if present in the form of a virulent strain would injure the plant. The benign strain protects the plant by infecting the virulent strain, rendering it nonvirulent (*28*). An analogous situation exists with atoxigenic *Aspergillus* spp., which compete well with indigenous *Aspergillus* yet produce no aflatoxins.

Transgenic Crops. For many years, crop selection for resistance to insects and disease has been one of the primary approaches to pest management in agriculture. The development of pest resistance has been the result of natural selection and breeding programs. More recently, however, crops with seed engineered to contain a gene for insect control or herbicide resistance have been great commercial successes (*29*). It seems likely that seed engineered for fungal and bacterial plant pathogen control will soon be on the market.

One problem that has existed is the lack of the ability to locate and insert genes that control nematodes or some other economically important pests. There are reports that progress is being made for insertion of genes to control of these other pests.

The incorporation of more that one gene has already occurred (gene "stacking"). An example would be a crop containing a gene for the Bt toxin and a gene for herbicide resistance or a crop containing several genes for conferring resistance to different resistant biotypes.

Genetic Engineering of Pests. Genetic engineering of pests offers long-term management options. An example of this approach is the eradication of the screw worm from areas of the United States (*30*) through release of sterile male insects into the population of nonsterile organisms. Successful mating of sterile males with the nonsterile females resulted in laying of eggs that did not develop properly. Multiple releases of sterile males resulted in the elimination of the screw worm.

The process of genetically engineering pests is highly complex scientifically and socially. Although there were reports of some success in the 1970s and 1980s, the research support was reduced in the late 1980s and 1990s. Development of techniques that would be useful in a large number of species would simplify the research problem which make such projects difficult (*31*).

Although substantial benefits could be realized through the use of genetically modified organisms—either crops or pests—there is an element of the population that opposes genetic modification. Thus, overcoming the scientific hurdles represents only a part of the difficulty.

Biopesticides are not without critics. Plant-incorporated protectants are the most controversial. When one makes crops resistant to a herbicide, so a grower can use that weed killer and not damage the crop, this can potentially result in over-use of that pesticide. Incorporating natural insect toxicants into plant material so that insect pests die when they consume that plant material could represent a health hazard for consumers of food from the plant. There is also concern about distributing genetic material to places where it does not occur naturally and potential development of herbicide-resistant weed populations.

However, this approach to pest management will likely grow in importance. The registrant community and the EPA, U.S. Department of Agriculture, and U.S. Food and Drug Administration have developed high standards to ensure safety to man, animals, and the environment.

CONCLUSIONS

There will also be a trend to move away from the use of the more toxic conventional pesticides. It would be surprising to see new organophosphate or carbamate pesticides come through the pipeline for registration. In addition, as the EPA adopts ways to implement cumulative risk assessments for all chemicals with a common mechanism of toxicity (*32*), it is likely that additional uses of these chemicals will be curtailed. The EPA recently published in the *Federal Register* (December 2001), for public comment, a preliminary approach to evaluating cumulative risk assessments for organophosphate pesticides. The EPA plans to publish a final rule in August 2002. Once a method for implementation of cumulative risk has been established for the organophosphates, it will be extended to the carbamates and probably all cholinesterase inhibitors. Biological control methods will continue to represent nonchemical alternatives for control of exotic and invasive pests, including weeds, insects, and diseases. They will continue to represent major challenges for pest control in agriculture and public health and require integrated approaches to detecting and controlling unwanted organisms.

Approaches to pest management have changed dramatically over the past 50 years and no doubt will continue to change. Pest management now requires more knowledgeable users for production of agricultural products in an economically successful fashion. A component of these more sophisticated approaches is the prescription use of pesticides for the control of specific pests in geographically defined areas. The United States produces an abundant, safe, and nutritious food supply. As the nature of pest pressures evolves, accompanied by societal concerns over pest control, and the economic realities of agriculture and pest management change over time, there will be continuing needs for new research-based approaches to pest control. Chemistry will play a major, if not dominant, role in these developments.

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