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Can synthetic pesticides be replaced with biologically-based alternatives?—an industry perspective

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Agricultural chemical companies have invested in the discovery and development of biological pesticides to complement synthetic pesticides for the control of insects, diseases, and weeds on agronomic and horticultural crops. For plant disease control, companies envisage biological fungicides entering markets where they have the best chance of performing and which are most receptive to using biological control methods. Fewer regulatory requirements can mean faster registration for a biological than a synthetic pesticide. However, industry's requirements for competitive performance, effective formulations, and economic production can mean significant investments in time and money for a biological pesticide, although total investment may be less than for a synthetic pesticide. One biocontrol project in which industry has invested is baculoviruses for insect control. Insect baculoviruses, genetically modified to kill insects faster than wild-type viruses, are attractive biocontrol agents because their selectivity to insect pests and safety to beneficial insects and mammals enable them to compete with synthetic insecticides. Industry is looking for similar biocontrol opportunities in disease control. Biocontrol agents for seedling disease, root rot, and postharvest disease control have been registered by the EPA and are trying to compete with synthetic fungicides for market share. To date, effective biocontrol agents have not been identified for the control of serious foliar diseases, such as grape downy mildew, potato late blight, wheat powdery mildew, and apple scab. Farmers must rely on synthetic fungicides and agronomic methods to control these diseases for the foreseeable future.

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Introduction

It might be surprising to learn that agricultural chemical companies are interested in biologically-based pest control technology and, in fact, are spending millions of dollars in developing biological pesticides. Is this not a conflict of corporate interests? Why would chemical companies be interested in biological control?

Indeed, the initial reaction by agrichemical company management to this radically different technology may have been similar to a story told by Vladimir Haensel, Professor of Chemical Engineering at the University of Massachusetts. This story, called 'Lucky Alva', originally written in 1967, was reprinted in a 1995 issue of *Research Technology Management* [1].

The story is about a young researcher named Thomas Alva Edison who works in a kerosene lamp company. Mr Edison has requested $3000 for the next 2 years to support research on a new project. The scene is a meeting of upper management reviewing Edison's research proposal. The President reminds those present that theirs is a leading company in the kerosene lamp business and that all research proposals will be appraised in terms of their potential value to the company's growth and profit objectives.

The Vice President of Research explains that Edison's early experiments have been crude but there have been moments when the carbonized thread does glow inside the glass bulb so that you can almost read by the light. He recommends funding further research at $2000 for the next 2 years.

The Vice President of Finance takes a dim view of the proposal because it would result in a product in competition with the company's major product. Besides, the new product would require a battery which was rather bulky and wires strung to all of the electric lamps, and the whole idea sounded preposterous. But not to discourage invention, he recommended a sum of $1500 for Mr Edison.

Next, the Vice President of Corporate Planning reminded the group of recent acquisitions of a wick-knitting company and an oil-treating company, both of which should provide substantial potential profit for many years to come. Also, they were negotiating with a small glass company about a new type of globe to fit their lamps. The Vice President questioned what would happen to these acquisitions if Mr Edison's program were to be successful.

The President concluded the review by thanking his staff for their excellent comments and announced that Mr Edison would receive a token stipend of $750. The President said: 'This will show our continued interest and encourage him to take this on as a type of supplemental program to his other more important work.'

As surprising as it might seem, agricultural chemical companies have seriously engaged in developing diverse non-chemical technologies and have resources that fit very well into biologically-based pest control.

For example, companies such as Cyanamid, Ciba, DuPont, Monsanto, Sandoz, and Zeneca have research programs to develop genetically engineered agronomic and horticultural crops with resistance to insects, diseases, and chemical herbicides. Ciba, Sandoz, and Zeneca own seed companies which provide them with in-house capabilities to develop and market their unique crop cultivars.

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Agricultural chemical companies know the market needs for new insect, disease, and weed-control products. They know how to develop products for these markets. And, many of the development and regulatory requirements that apply to synthetic pesticides also apply to biological pesticides.

Agricultural chemical companies evaluate natural products as sources of new pest control chemistries, including plant extracts and microbial fermentations. Knowledge of fermentation technology will be beneficial for the mass production of a biological pesticide.

Finally, many companies have diversified commercial interests or, like Cyanamid, are divisions of larger companies which market products in diverse global markets. New business ventures are commonplace as long as they meet the requirements of the company, which we will review shortly.

I will confine my remarks to the agricultural chemical industry. Certainly, other industries are developing and marketing biological disease control agents. However, I am most familiar with the agrichemical industry. Besides, the contrast between the two technologies in this industry makes for a more interesting story.

Incentives for industry to develop biological pesticides

There are incentives for an agricultural chemical company to develop biological pest control agents. One incentive is that the regulatory requirements in the US are less for a biological than a chemical pesticide. For example, documents addressing more than 120 safety and other issues must be submitted to the EPA to support the registration application of a chemical pesticide. Current EPA requirements for a biocontrol fungicide are for maybe a dozen studies. This difference translates into huge cost and time savings in favor of the biological. Whereas the registration costs of a chemical pesticide might be $10–12 million and take 5–8 years, registration costs for a biological pesticide might be one-tenth that figure, and the time period may be only 1–2 years. The high cost, long-term safety studies, such as on carcinogenicity, plant and animal residues, and ecological fate and effects, are not required for biological control agents.

A second incentive is rapid market entry. As with any product, rapid market entry is advantageous because a company can start recovering its investment sooner. Fewer regulatory requirements for biologicals translates into less time spent on running required studies and a market entry far sooner than with a chemical pesticide.

However, the time savings may not be realized on the other aspects of product development. For example, preparing a formulation that maintains viability of the biological agent, developing an economical production process, and optimizing field performance are important considerations for biological pesticides. The time required on each activity depends on the complexity of the agent. If difficult, there may be no cost or time savings over a chemical fungicide. However, the entire development process should be faster and cheaper for a biological pesticide.

Another incentive for an agricultural chemical company to develop a biological control agent is that it might open new markets that were previously unavailable to the company. Companies are always looking for new opportunities in the same or related markets. If a biological pesticide fits a market segment in which none of the company's existing chemical pesticides are marketed, then the biological can be a desirable product addition.

A good example is the postharvest fruit disease control market. Existing fungicides for postharvest disease control on citrus, pome fruits, and stone fruits have been reduced in number in recent years because of fungal resistance development and regulatory restrictions. The registration of synthetic fungicides for this use is difficult because chemical residues necessitate expensive analytical studies, and the market is not all that large to justify the costs. On the other hand, an effective biocontrol agent that does not leave a toxic residue would be easier and less expensive to register, and the concept of biological fruit protection might be more acceptable to the consumer.

A residue-free pesticide would be easier for a company to register than a pesticide that leaves a chemical residue on the harvested commodity. The presence of a chemical residue necessitates studies to determine the nature and amount of residue on raw agricultural commodities and processed foods. If the crops are used for animal feed, then animal residue studies must be conducted in the species affected. These studies are very expensive and time consuming. If a biological pesticide is effective for disease control in field, fruit, vegetable, and oil crops which enter human food and animal feed markets, not having to conduct chemical residue studies makes the biological pesticide more attractive because the work and development costs will be less.

Clearly, chemical companies are sensitive to public opinion, and public opinion today favors the concept of biological pest control. I do not know how much it would help a company's image in the mind's eye of the public, but it certainly should not hurt any for a chemical company to market biological products.

The major research dollars supporting biological pest control investigations in the US come from government funding. These dollars support USDA and university researchers who screen for wild-type agents to control insects, diseases, and weeds currently controlled with synthetic pesticides or in niche markets too small for chemical companies to profitably exploit. Private companies, including agricultural chemical companies, monitor public research to identify technologies worth licensing. Since investigative costs can be high, time-consuming, and without guarantees of success, and since public money favors biological research over chemical pest control research, it is an equitable arrangement for public money to support discovery research and for private money to support the development and marketing costs of effective biocontrol agents. Both the public sector and private industry benefit from this type of collaboration. However, industry has certain requirements of a biological pest control project that must be met before it will license the technology. These requirements will be discussed next.

What industry is looking for in a biological pesticide

Agricultural chemical companies could not survive and be profitable if the products they sold did not work. No farmer is going to buy a fungicide, at least more than once, that does not prevent a disease when used according to label directions. Good, predictable performance is essential to any new product that industry is going to market. And this applies to biological fungicides also.

One of the major shortcomings of biological disease control technology has been the lack of consistent disease control. Performance under controlled test conditions described in scientific publications has not translated to field performance, especially under the variety of temperature and moisture conditions of commercial agriculture. Biofungicides are subject to performance variability that is usually not a limitation for synthetic fungicides.

Therefore, the most important requirement of a biological control agent is that it must provide consistent disease control under conditions of commercial usage.

The second requirement is that the level of disease control provided by the biological pesticide must be acceptable to the farmer. Generally, this means that the biological agent must perform as well as a synthetic fungicide used for the same purpose. Otherwise, the farmer will have to have another compelling reason to use a biological agent that offers poorer disease control. Granted, the biological agent might require special handling for it to perform optimally. However, it must have the potential to equal the disease control offered by competitive measures, or the farmer will have little incentive to use it.

An exception to the high performance requirement might be where pathogen strains resistant to a synthetic fungicide predominate in a pathogen population, rendering the synthetic fungicide ineffective. The biocontrol agent, being unaffected by the resistant strains, controls the disease that was otherwise uncontrollable. In that case, any reasonable level of control provided by the biological would be acceptable to the farmer.

Another requirement is that the biological product must be profitable to the company. Private industry exists to make a profit. Although different product lines are profitable to varying degrees, all must be in the black or they will not survive the next profit-loss audit. Industry, unlike non-profit earning organizations, does not market ‘good will’ products for very long. An agricultural chemical company might introduce a biological fungicide knowing that it will not be a money-maker at the start. Unprofitable introductory years are planned for chemical fungicides also. But eventually, a new biocontrol project must have the potential to be profitable or else it will never be developed.

The market segment for a biological pesticide should be in a commodity area familiar to the agricultural chemical company. Companies are most successful when they focus on and become expert in specific markets, rather than trying to sell in all agricultural markets. Companies like to build product portfolios in specific markets to synergize sales and minimize costs. The opportunity for success, especially profitability, must be positive to convince a company to venture into a new market because of the additional costs and risks. An unknown market, added to the higher risk associated with a biological pesticide, could be enough to discourage a company from developing the new technology.

Generally, biological pesticides require special handling to perform at their best. Live agents must be protected in storage to maintain viability. Although they may be applied in a similar way to conventional fungicides, biofungicides may require additional applications, particularly during weather unfavorable to the agents. Special field scouting may be required to time applications to specific times in the disease cycle. Generally, more labor is required for biological pesticides, and to a farmer labor is money. Will the farmer adopt additional practices and accept higher costs to use a biofungicide? A company must effectively publicize the merits of this new product to convince the farmer to change practices. And after the sale, the company must work with the farmer to ensure that the biological pesticide is used properly and to resolve any problems that arise.

A prediction of success can be made by doing a technical feasibility study on the biocontrol agent during the development phase. Investigations are made into production, formulation, packaging, application, and toxicology of the agent. Areas of weakness are pursued to determine the extent of the problem and how they can be resolved. The results of these investigations are examined to decide whether to proceed with the project to market or to defer further development.

Critics might argue that because the technology is in its infancy new biocontrol pesticides should not be held to the same standards as synthetic pesticides. But that is an argument that will embrace failure. In the past, premature releases of biofungicides have resulted in poor disease control during commercial usage, and they produced reduced expectations for future biofungicides. It would be wiser to do the necessary development work first, defer technically weak projects, and only market those biological pesticides that have a good chance of performing in the hands of the end user.

Baculovirus program at Cyanamid

A research project that is currently under development at Cyanamid can serve as an example of the type of biological control technology that industry has supported and why it is of interest to Cyanamid. The project is not on the control of a plant disease. Rather, it is on insect control, and the biocontrol agent is a genetically engineered baculovirus.

A baculovirus is a virus that attacks and kills insects. It is specific to certain kinds of insects and will not harm mammals. Wild baculovirus is slow acting and does not kill insects for many days after infection. During that interval infected insects continue to feed and can cause significant damage to an agronomic crop.

Scientists at Cyanamid have taken a wild-type strain of *Autographa californica* (ACAL), a baculovirus that attacks lepidopteran pests of cotton and vegetables, and genetically modified it to kill the insects faster. They have done this by identifying a gene called AaIT that encodes for an insect-specific toxic protein from the venom of the North African scorpion, reconstructing it in the lab, and inserting it in the ACAL genome. After infection, the altered ACAL baculovirus produces the toxin inside the insect, paralyzing it and stopping feeding 60% faster than the wild-type virus.

This has not been trivial research, nor has it been totally Cyanamid's invention. Cyanamid acquired key technologies and patents from universities and government labs that were required to develop the modified baculovirus. Many years of research and university collaborations have brought the project to the current stage of field testing the best engineered strains. EPA approval was received in 1995 to conduct limited field studies. This approval was continued into 1996 where 24 field trials were conducted in 12 states for the control of cabbage looper and tobacco budworm on vegetables, cotton, and tobacco.

Cyanamid committed to the baculovirus project because management believed that a unique, competitive insecticide would result from the research. It was predicted that the biological insecticide would control economically important insects with no effect on beneficial species, could be safely applied to vegetables up to harvest, demonstrated no adverse ecological effects, and presented no toxicological hazards to mammals. And, the control of additional insect pests could be achieved through the usage of baculoviruses specific to the other species.

Conclusion

To answer the question 'Can synthetic pesticides be replaced with biologically-based alternatives?', a positive response would be that they can successfully integrate with, compete with, and even replace synthetic pesticides in certain applications. Biological pesticides currently marketed or under industrial development have the potential to produce commercially acceptable insect and disease control when used properly. One example we at Cyanamid believe will be successful is a genetically engineered baculovirus for insect control.

An example for plant disease control is Gustafson's Kodiak™, a bacterial seed treatment for control of seedling diseases of cotton, beans, and other crops. Kodiak is reported to be effective against *Rhizoctonia* and *Fusarium* pathogens, but it delivers optimum performance when mixed with synthetic fungicides for broad spectrum, residual disease control.

Another example is Ecogen's Aspire™, a yeast for postharvest disease control in citrus and pome fruit. When applied to disease-free fruit, Aspire is reported to protect fruit surface wounds from invasion by pathogenic fungi as well as synthetic fungicides. In fact, the biocontrol agent should give better disease control where fungal strains resistant to chemical fungicides are present in citrus packinghouses.

A potentially effective way of introducing farmers to the use of biological fungicides, particularly those that are not 100% effective, is to incorporate their application into integrated pest management (IPM) programs. Assuming compatibility with synthetic pesticides, the biocontrol agent could be applied early in the season when disease pressure is low, or alternatively with applications of synthetic fungicides throughout the crop season. The benefits would be to support the performance of biocontrol agents that are only moderately effective, reduce the risk of resistance development to the chemical pesticides, and conserve chemical usage.

Can biological pesticides replace all synthetic pesticides? The answer is no, not with current biocontrol technology. Relatively few effective biocontrol agents have been discovered for plant diseases, and generally they are effective only under specific environmental conditions. Obtaining consistent, commercially acceptable disease control in diverse environments and cropping locations is still a goal of most biocontrol research projects.

Biofungicides evaluated to date have failed to provide commercially acceptable control of the serious foliar diseases of most agronomic and horticultural crops. Control of diseases such as grape downy mildew, potato late blight, wheat powdery mildew, and apple scab is a difficult task even for chemical fungicides. The task is formidable for biological fungicides because these living agents are not available for action until weather conditions, particularly wet periods, favor their growth. Unfortunately, these same conditions are favorable to the pathogens, and many plant pathogens infect and reproduce very rapidly. As a result, biofungicides are at a disadvantage to synthetic fungicides for the control of many important plant diseases. This situation is unlikely to change in the near future.

In conclusion, the research challenge for tomorrow is to improve the field performance of biological pest control agents, particularly biofungicides, so that they can find commercial usage. Industry is much more likely to invest in and develop a biofungicide that provides consistent disease control than one that has large market potential but variable performance.

Reference

1 Haensel V. 1995. Lucky Alva. Res Tech Manag 38: 28–30.