PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Commercial Application of Biological Control: Status and Prospects [and Discussion]

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Commercial application of biological control: status and prospects

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The global market value of control agents used in crop protection and public health is approaching $16000 million annually, but less than 1% of this market is penetrated by biological control agents (BCAs). This paper examines the suitability of different types of BCA to research and commercialization, bearing in mind the sharply targeted approach employed by much of the industry. Advantages and disadvantages are discussed along with examples of failures and successes with BCAs. Commercialized products described range from specific chemical control agents which have no adverse effects on beneficial organisms to true BCAs such as pheromones, mass-produced bacteria, and predatory mites.

From a commercial viewpoint, greatest potential resides with the utilization of bacteria and fungi, particularly for insect control, but registerability (particularly for genetically engineered agents) patentability, reliability and cost-effectiveness must be achieved. Industry believes that biotechnology will increase the usefulness of BCAs and is therefore encouraging cooperation with academic researchers and performing in-house research to advance the technology. Even so, BCAs will not replace chemicals in the foreseeable future, but will complement them and allow the development of improved integrated control measures.

1. Introduction

The agrochemical industry has defined and quantified targets for pest, disease and weed control, and sets itself the goal of obtaining safer and more effective agents for use in the market place. Historically, the use of agrochemicals has been the most common approach, but the agrochemical industry is an effects business and the compounds used, for example in insect control, cover many modes of action from rapid kill to disruption of growth and the use of chemosterilants. For instance, plants can be protected from nematode attack without killing nematodes, whereas insect sex pheromones are employed to disrupt mating which reduces or eliminates the production of damaging progeny.

The stance of the agrochemical industry on using bacteria, viruses, fungi, nematodes and insects, and even plants for pest, disease and weed control has changed over the past decade. Technology has advanced and many examples of acceptable control can be cited. This paper concentrates on the benefits and drawbacks of biological control agents, bearing in mind factors such as reliability, patentability and registerability, and indeed cost-efficacy compared with conventional control techniques. It sets out to examine the common and erroneous thesis that all chemicals are bad and all biological control agents are good. Industry's views on the development of the different types of biological control agent are presented within this context, along with prospects for successful commercialization. Generally I shall try to encapsulate the stances of both large and small companies, but obviously the content reflects my personal views, although many, if not most, of the views expressed will be shared by my colleagues in my own company and in other agrochemical companies.

2. Definition of biological control

Biological control, by definition, can cover a broad spectrum of approaches ranging from the use of obligate parasites and pathogens, to facultative parasites and pathogens, to competitors, to toxin-producing pathogens, to toxins produced by pathogens, and finally non-toxic behaviour-modifying chemicals. This spectrum is outlined in figure 1, with some examples.

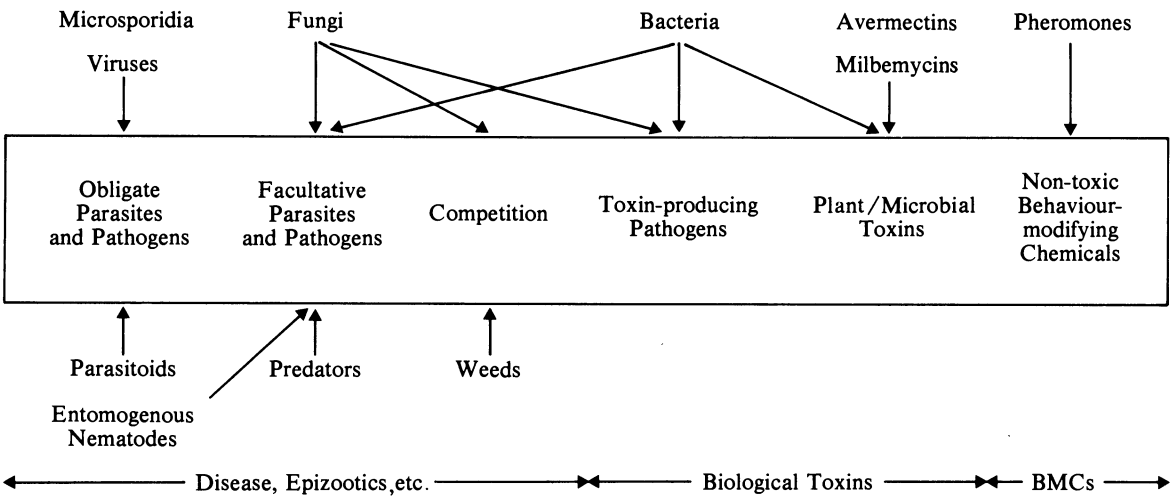


Figure 1. The spectrum of biological control agents.
(In this figure BMCs stands for behaviour-modifying chemicals.)

The group of biological control agents encompassed by this definition, which includes parasites, parasitoids, predators, pathogens and pheromones, will be referred to as BCAs (biological control agents) through the paper.

In addition to examining this range of BCAs, the use of selective agrochemicals, that is highly specific compounds such as insect growth regulators, will also be described.

Examples of the use of BCAs for reducing or controlling problem weeds and diseases will be cited, but the paper will concentrate primarily on pest examples, and particularly on entomological ones, as this is the area in which most commercial interest has been shown to date.

3. Pest, pathogen and weed markets

To examine the present and future impact of BCAs on the global pesticide, fungicide and herbicide markets, it is necessary to give a breakdown of the major commercial opportunities in the world.

An analysis of the global market for insecticides, fungicides and herbicides in 1985 (figure 2) shows that 44% of world sales are accounted for by herbicides, 31% by insecticides (including acaricides) and 18% by fungicides (Wood Mackenzie 1986). In total, sales in 1985 were estimated at \$15900 million.

These figures represent a 4.6% increase over 1984 (Wood Mackenzie 1986). However, the increase to the year 2000 is expected to be 2–3% per year throughout the period.

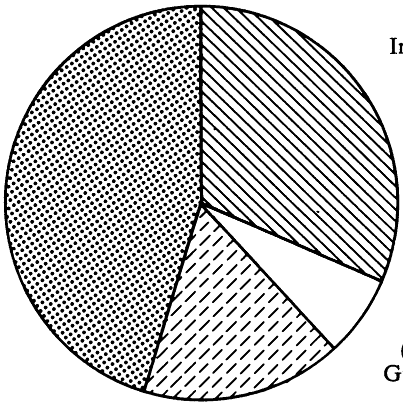


FIGURE 2. Global pesticide, fungicide and herbicide sales (end-user value given in millions of U.S. dollars at 1985 value).

TABLE 1. GLOBAL SALES OF PESTICIDES, FUNGICIDES AND HERBICIDES ON THE WORLD'S MAJOR CROPS (END-USER VALUE GIVEN IN MILLIONS OF U.S. DOLLARS AT 1985 VALUE)

herbicides	millions of U.S. dollars	percentage of sector
maize	1575	22
soya	1475	21
wheat	920	13
rice	650	9
fruit and vegetables†	610	9
sugar beet	350	5
cotton	340	5
		total 84
insecticides		
cotton	1335	27
fruit and vegetables†	1260	25
rice	825	17
maize	470	9
soya	155	3
sugar beet	145	3
wheat	95	2
		total 86
fungicides		
fruit and vegetables†	1290	46
rice	430	15
wheat	380	14
soya	55	2
maize	40	1
sugar beet	40	1
cotton	40	1
		total 80

† Includes vines.

It is estimated that insects, fungal diseases and weeds reduce yields in the agriculturally developed countries by around 25%, whereas in less developed countries losses run at 40%. In rice, losses are a staggering 50%. An examination of global sales by crop shows that the world market is dominated by five major crops: herbicides and insecticides in maize (corn), herbicides in soyabeans, insecticides in cotton, herbicides and fungicides in wheat, and compounds for pest, disease and weed control in rice (table 1). Fruit and vegetables as a group also account for significant sales, but this is split between many different crops.

The number of major global pest, disease and weed problems is limited, and a selection of these major targets is utilized by the agrochemical industry in searching for novel toxophores (some examples are shown in table 2). The expense in terms of research and development of new chemical agents, can only be justified in the specific outlets in the key market sectors listed.

Table 2. Some key pest, disease and weed targets of the world

target	species	common name
insects	*Heliothis* spp.	cotton bollworm, etc.
	Spodoptera spp.	cotton leafworm, etc.
	Diabrotica spp.	corn rootworms
	Myzus persicae	peach potato aphid
	Nilaparvata lugens	brown planthopper
	Nephotettix spp.	green leaf hoppers
diseases	*Pyricularia oryzae*	rice blast
	Erysiphe graminis	wheat powdery mildew
	Botrytis cinerea	grey mould
	Plasmopara viticola	vine downy mildew
	Venturia inaequalis	apple scab
weeds	*Avena fatua*	wild oats
	Sorghum halepense	Johnsongrass
	Agropyron repens	couch grass/quack grass
	Cyperus spp.	sedge
	Ipomoea spp.	morning glory, etc.
	Galium spp.	cleavers
	Xanthium spp.	cocklebur

4. Utility of BCAs

Niches for commercial exploitation

BCAs may ultimately be exploited in virtually any market provided that they are as good as (or better than) existing control agents in terms of cost, efficacy and reliability, or have a significant toxicological or environmental advantage. At present, however, there are only four specific market niches that can be commercially exploited.

1. Outlets where conventional chemical agents give insufficient levels of control, such as in certain diseases caused by soil-borne pathogens, or where there is insecticide resistance.

2. Outlets where conventional chemical agents are too expensive, for example the potential control of the bracken-fern (*Pteridium aquilinum*) with lepidopterous natural enemies (Heads & Lawton 1986).

3. Outlets where governments restrict the application of conventional chemical agents, as practised in Canadian forestry.

4. Outlets where the environment is contained and controlled, for instance in glasshouses where the fungus *Verticillium lecanii* is used to control aphids and whitefly.

Commercial and non-commercial successes and failures of BCAs

Successes

1. Use of the moth *Cactoblastis cactorum* to control prickly pear, *Opuntia* spp., in Australia.
2. Introduction of the predatory *Vedalia* ladybeetle, *Rodolia cardinalis*, for controlling cottony cushion scales on citrus in California in 1888–1889.
3. Introduction of the ectoparasite *Aphytis holoxanthus*, for controlling Florida red scale on citrus in Israel in 1956–1957.
4. Use of the parasitic chalcid wasp *Encarsia formosa*, for controlling whitefly under glass or plastic.
5. Use of the predatory mite *Phytoseiulus persimilis*, for controlling mites under glass or plastic.
6. Use of the bacterial pathogen *Bacillus thuringiensis*, for controlling lepidopterous and dipterous pests.
7. Use of the fungal mycoherbicide *Colletotrichum gloeosporioides*, for controlling Northern jointvetch.
8. Use of *Peniophora gigantea* to control *Heterobasidion annosum*, in forestry.

Failures

1. Extensive work to control Bermuda cedar scales failed despite the introduction of over fifty species of natural enemies, mainly coccinellid predators to cedar forests in Bermuda between 1946 and 1951.
2. Introduction of cane toads in sugar in Australia failed to control cane beetles and the toads became pests.
3. Release of sterile fruit flies in California was unsuccessful when non-sterile flies were released by mistake.
4. Commercialization of the nematode *Romanomermis culicivorax* for use against mosquito larvae failed due to difficulties in handling, storage and shipping, environmental limitations, host specificity, expense and user acceptance.
5. *Heliothis* spp. nuclear polyhedrosis virus (NPV) although technically successful, failed commercially because of poor forecasting of market needs and trends.

Overall, only 34% of predators and parasites released for insect control become established, and of these only 16% give satisfactory control. This means that only 5% of all deliberate releases actually achieved their aim.

Further examination of such examples yields technical and commercial insights of value in appraising the potential of BCAs and the level of commitment of industry to different types of BCA (see §5).

Penetration of the global market

Sales of BCAs and selective chemicals account for 1% of the world market of crop protection products, but the majority of sales are in the insecticide sector where they account for 2.5% of sales. This is attributed to sales of selective chemicals and *Bacillus thuringiensis*, with little contribution from other BCAs (table 3), although sales figures for predators and parasites may be underestimated.

Some analysts predict that BCAs will have a 50% market share by the year 2000, but industry in general believes this is highly unlikely despite political pressure such as that seen in Canadian forestry, and the potential for genetic manipulation.

Table 3. Penetration of the global insecticide market by biological control agents (end-user value given in millions of U.S. dollars at 1985 value)

1. sales of selective chemicals/pheromones		
selective chemicals		90
pheromones		2
	total	92
2. sales of predators/parasites and pathogens		
Bacillus thuringiensis (products for forestry, agriculture and public health)		30
viral insecticides		*ca.* 1
predators/parasites/other pathogens		*ca.* 3?
	total	34

5. Industry view of BCAs

General objectives

Many of the objectives implicit in developing BCAs are being achieved with chemicals by the agrochemical industry. These include reduced application rates, better application techniques, improved selectivity, and reduced toxicological and environmental hazards. However, as an effects business, the industry considers the value of BCAs very seriously, even though selective BCAs, by their very nature, are likely to command a small fraction of the global market. This has historically led industry to develop broad spectrum compounds, for sound commercial reasons (Braunholtz & Tietz 1980). The use of BCAs requires re-education of farmers, growers and pest-control operatives, especially if the apparent speed of effect is slow, because the user is generally looking for control as good as, or better than, that obtained with the product he now uses at the same, or a lower, price.

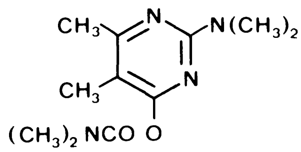
None the less, many large multinationals are now pursuing BCAs as control agents, where markets of sufficient size exist. The research programmes include genetic manipulation of pathogens, expression of genes from pathogens in plants, and plant or microbial toxins as starting points for developing other control agents. Generally, large companies are interested in selling selective agents if they complement their existing portfolio of products or if a series of small outlets can be identified which add up to make a robust business case. However, it is usually the small companies that provide supplies of predators, parasites and some naturally occurring pathogens, as they are usually specialized and have a limited product range, whereas large companies will run a large number of projects simultaneously, which must compete for the same resource.

In recent years, the agrochemical industry has tried to incorporate its products into integrated programmes. This has been prompted by practical and commercial reality, by a more responsible attitude within industry, and by the availability of certain control agents. In the sections following, selective chemicals and different types of BCA are discussed, with entomological examples.

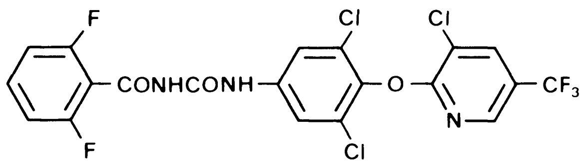
Selective chemicals

Industry supports the use of selective chemicals such as insect growth regulators, antifeedants and repellents, provided they form an attractive financial proposition. The structures of three such specific insecticides are shown in figure 3: pirimicarb (I.C.I.) is a specific aphicide, chlorfluazuron (Ishihara Sangyo Kaisha) is an insect growth regulator for lepidopterous, coleopterous and dipterous pests, and buprofezin (Nihon Nohyaku) is an insect growth regulator for homopterous pests.

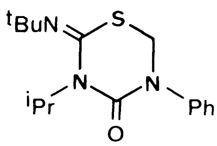
Pirimicarb



Chlorfluazuron



Buprofezin



Pink bollworm sex pheromone

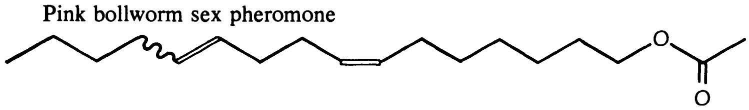


FIGURE 3. Examples of selective chemicals and a pheromone which are commercially available for use in pest control.

Pirimicarb is a fast-acting, selective carbamate aphicide which is active through contact, fumigant, translaminar and root-systemic routes, but at the rates necessary for good aphid control has no significant activity against other insects, including the beneficial pollinating and predatory insects, such as bees, ladybirds and lacewings. In addition, the compound is non-phytotoxic and causes no accumulation problems in the environment. The compound was discovered and developed by industry and is probably the best selective aphicide available. However, it does not dominate the market as it is one of a number of aphicides that are available, and most are broader-spectrum compounds and some are cheaper.

Similarly, many insect growth regulators have not enjoyed the success that might be derived from fairly specific control agents, probably because of the drawback of limited sales potential. Major changes in farmer perception are needed before compounds such as chlorfluazuron and buprofezin become a dominant force, even though they preserve essential beneficial organisms, are active on resistant strains, and can be used selectively as a management tool.

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Pheromones

Insect pheromones have been commercialized by a few companies and can be used in four ways: for monitoring purposes, for mass trapping, as mating disruptants, and in mixtures with conventional insecticides. Exploitation of pheromones for monitoring purposes is pursued by some small specialist companies, whereas some multinationals have developed controlled release formulations to allow sex pheromones to be used as mating disruptants, or with conventional insecticides in mixtures that function by attracting and then killing specific pests.

The present leading commercial formulations are plastic laminate flakes and hollow fibres which require specialized application equipment, twist–tie straws which are hand-applied, and microcapsules which are applied with conventional apparatus.

The commercial attractiveness of developing pheromone formulations is small and it is therefore of value to analyse industry's approach. Both the flakes and the fibres were researched and developed by companies having a limited interest in agriculture, who licensed multinational companies for global sales. In contrast, the leading microcapsule formulation was developed through collaboration between a large agrochemical company (I.C.I.) and a Government funded research group (Tropical Development and Research Institute).

The best example of technically successful pheromone use is the control of the pink bollworm, *Pectinophora gossypiella*, with its sex pheromone (figure 3). Large-scale trials have demonstrated that insect control and cotton yield obtained with pheromone is as good as that obtained with the same number of sprays of insecticide. Thus the pink bollworm can be successfully controlled by pheromones acting on the adults, whereas secondary pests are controlled by the naturally occurring predators and parasites which are not affected by the pheromone treatments.

Predators and parasites

The utilization of mass-released entomophagous insects and mites has been reviewed recently by van Lenteren (1986). At present, few natural enemies are mass produced and applied for pest control, and marketing is restricted to small specialist companies such as Koppert BV in The Netherlands. The large agrochemical companies do not find the market, as presently perceived, to be of sufficient size to warrant production bearing in mind overheads and internal competition for development resource. None the less, such agents can be cost-effectively employed in a repeated fashion, for instance, on glasshouse crops. Some examples of predators and parasites presently used are shown in table 4.

Similarly, 'one-off' attempts to eradicate specific pests with predators and parasites are not the domain of industry, as others are much better suited to exploiting this niche.

The use of predators and parasites will not supplant chemical means in the foreseeable future, but can be a valuable approach in integrated pest management, and some researchers are already working on the development of pesticide resistance in natural enemies. However, it is worth noting that as with agrochemicals, pests are capable of developing resistance to entomophagous control agents, by developing thicker cuticles, encapsulating parasite eggs, or changing behaviour, for instance by developing cryptic habits.

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Table 4. Examples of biological control agents which are commercially available for use in pest control: predators/parasites and pathogens

predators	*Phytoseiulus persimilis*
	Amblyseius mckenziei
	A. cucumeris
parasites:	*Encarsia formosa*
	Opius pallipes
	Trichogramma evanescens
pathogens:	
viruses	*Neodiprion sertifer* NPV
	Autographa californica NPV
bacteria	*Bacillus thuringiensis* var. *kurstaki*
	B. thuringiensis var. *israelensis*
fungi	*Hirsutella thompsonii*
	Verticillium lecanii
microsporidia	*Nosema locustae*

Pathogens

The utilization of pathogens, such as viruses, bacteria and fungi has been reviewed recently (Payne, this symposium), and fits closely with the skills and channels of trade of the agrochemical industry, particularly as such agents have considerable potential for use as pesticides. However, genetic engineering will be necessary before many potential applications are developed. Many species of virus, bacteria, fungi and microsporidia have been identified as biological control agents, but few have been commercialized, and only some of these can be regarded as successful. Some examples of pathogens which are commercially available are shown in table 4.

The agents with greatest usage at the present time are bacteria and fungi, then viruses. Generally, the user expects the agrochemical industry to provide new products which are as cost-effective as chemicals now used. However, there are a number of limitations that must be overcome. These include breadth of spectrum, speed of action, field persistence, shelf-life and cost of production. Some small companies and a few large ones are producing and selling pathogens, especially *Bacillus thuringiensis* for insect pest control. This approach is sound in the short term so long as targets, such as forestry, are selected in which the characteristics of existing BCAs are advantageous or, at least, not deleterious. However, in the medium-term, BCAs will have to be improved considerably if they are to penetrate the market in a big way, probably through rigorous strain selection, and in the long-term by introducing, for example, genes from *Bacillus thuringiensis* into plants to confer resistance to attack by insect pests.

Conclusions on industry's stance opposite BCAs

The level of interest shown by the agrochemical industry to the different types of BCA available is summarized in table 5, and it is evident that, at present, only bacteria stimulate as much interest as selective chemicals.

Industry, however, is committed to integrating BCAs into control programmes. A range of selective compounds is available which can be used in an integrated manner (see, for example, Collins *et al.* (1984)) and pheromones have been incorporated into spray programmes quite successfully (Critchley *et al.* 1984). Selective agents that spare beneficial organisms which can

TABLE 5. TYPES OF BIOLOGICAL CONTROL AGENT AND LEVEL OF INTEREST FROM INDUSTRY

biological control agent	interest from industry
selective chemicals	* * * *
pheromones:	
monitoring	*
mass trapping	*
mating disruption	* * *
use in mixtures	* * *
predators/parasites	*
pathogens, etc.	
microsporidia	*
viruses	*
bacteria	* * * *
fungi	* *
nematodes	*
insects	*

Key to interest from industry: *, Least interest; ****, greatest interest.

exert further control are used early in the season. Later in the season, broad-spectrum compounds are used when pest pressure increases and natural control fails. As additional BCAs become available commercially, further strategies can be formulated.

6. COMMERCIALIZATION OF BCAS

Characteristics essential for commercialization

Commercialization of BCAs involves selling such products in a competitive market with the expectation of recovering research and development costs and making a reasonable margin of profit. A number of factors are critical to achieving success, and four of these are described below.

Reliability

Once produced, a BCA has to be formulated and packed to maintain biological activity during storage and distribution, and to retain effectiveness when applied or released on to a target or substrate. Selective chemicals and pheromones, usually perform reliably provided that recommendations for use are adhered to, but pathogens, predators and parasites, on the other hand, are not always reliable.

Efficacy can be strongly affected by environmental conditions such as moisture, temperature, sunlight and pH. Timing of application can be critical, and persistence of effect may be disappointing.

Failings in terms of reliability of pathogens will be overcome through improvements, for instance in formulation and application. These include improving the stability of the product by using better stabilizers and gelling agents, obtaining better adhesion and spread on targets or substrates or both, and by improving persistence by incorporating ultraviolet stabilizers and the like. The sensitivity of microbial BCAs to ultraviolet light and humidity could be overcome by selecting targets where these environmental factors can be minimized or avoided, such as soil and rice paddy; by the production of more resistant mutants through strain selection; or by genetic engineering of the toxin coding genes either into the plant genome or into, for example, a bacterial epiphyte.

Patentability

Protection of a discovery by industry usually involves the filing of patents or keeping secret the nature of the discovery. Novel selective chemicals newly identified can be patented *per se* whereas industrial property for known published pheromones can be obtained through patenting new controlled release systems for delivering pheromones. Little protection can be obtained in producing predators and parasites, and reliance on intellectual property protection for naturally occurring pathogens is problematical. Production methods and formulations can be patented, but there is nothing to prevent competitors from developing other products based on the same agent.

There are, however, significant opportunities for patenting in this area when improved BCAs are obtained through the modern techniques of genetic manipulation, which can also provide improvements in biological effect. This approach can also be policed by the owner who has proprietary rights.

Registerability

The registration requirements for a so called 'biorational' pesticide, such as a pheromone or a naturally occurring pathogen, are less stringent than for a selective chemical, and hence can be obtained more quickly and at less cost. This process is being questioned, however, especially where non-indigenous organisms, pathogenic organisms or genetically engineered organisms are concerned. Commercially available BCAs have proved to be uncompetitive with the natural macro- and micro-fauna under field conditions and are thus often unreliable, but pose a limited environmental threat. The risk is that by producing reliable BCAs, undesirable pathogenicity may become a real problem, as has been demonstrated by myxomatosis and certain plant diseases. This may, however, be overcome by building into the BCA, sensitivity to factors such as ultraviolet light, oxygen, or high or low temperature. The stance of registration authorities is still developing, as is evidenced by responses to industrial requests to field test engineered organisms. None the less, in the U.S.A. the Environmental Protection Agency has stated its intention not to restrict progress in this area of biotechnology by over-regulation, otherwise BCAs will only be developed in the largest markets.

The importance of speed of registration cannot be over-emphasized. A company with proprietary property can only guarantee profitable sales for the life of the patent and if registration procedures are protracted then the sales life of the product may be reduced. If registration requirements were more harmonized between countries, the introduction of BCAs may become more likely as markets would be accessible at lower cost, and hence industry would be more likely to proceed with their development.

Cost-effectiveness

In a limited number of outlets, BCAs may be sold at a premium, but in the majority of markets globally, users will expect at least the same effect at the same price as can be obtained with conventional chemicals.

Bacillus thuringiensis is sold successfully in Canadian forestry at nearly twice the price of an acceptable chemical, fenitrothion. However, this is probably going to be the exception rather than the rule, in the future.

If production costs for microbial BCAs can be reduced by improving fermentation systems, reducing media costs, increasing yield, modifying culture systems, or even by inserting genes coding for toxins into 'easy to grow' organisms such as *Pseudomonas* spp., and efficacy can be improved, such agents should be able to compete effectively with conventional chemicals.

Collaboration between the public and private sectors

Most of the presently commercialized BCAs were known to be of limited potential, but were seen to be of value in overcoming significant local problems and were exploited through collaborative research between the public and private sectors.

Interaction continues to increase at all levels between government institutes, independent institutes and universities on the one hand, and biotechnology companies and agrochemical producers on the other. Successes include microencapsulated pheromones and *Verticillium lecanii*. This positive approach to understanding and exploiting 'the basic science' is laudable, but to market the product successfully, involvement of large multinational companies will be imperative.

BCAs as sources of novel control agents

Some toxins produced by pathogens have been isolated and identified, and examples include the β-exotoxin and δ-endotoxin from *Bacillus thuringiensis* and the avermectins from *Streptomyces avermitilis*.

Chemicals identified from pathogens showing promise as biological control agents can be exploited in three possible ways.

1. As commercially viable products in their own right.
2. As starting structures for the chemical synthesis of analogues.
3. As building blocks for further chemical/microbial modification.

Some success has already been achieved with these approaches in developing insecticides, acaricides, and nematicides, and some experts (Poole & Chrystal 1985) believe that this will be the only successful approach for exploiting microbial phytotoxins as herbicides.

BCAs: options for pest control

An examination of the BCA options available for insect, disease and weed control is an enormous task, but it is valuable to focus on a few such options. The best examples are the microbial BCAs and microbial toxins that have potential for controlling insect pests. Fungi have the widest spectrum of activity and have potential for controlling foliar chewing and sucking pests, soil pests, and insects of public health importance. Bacteria and viruses have the greatest potential for controlling foliar Lepidoptera, whereas bacteria show most promise for use in public health.

The microsporidia and avermectins, on the other hand, appear to have the least potential as insecticides, but it should be noted that avermectins, for example, also possess acaricidal and nematicidal properties.

If the characteristics of the three microbial BCAs – viruses, bacteria and fungi – which show greatest potential as insecticides are examined, then technical shortcomings which need to be reduced or overcome to ensure successful commercialization can be listed (table 6). The major failings of viruses are those of spectrum of activity and difficulty of production on a large scale.

Research is progressing in the mapping and identification of genes in some baculoviruses, and genes of particular interest are those that control specificity, host range and virulence.

Table 6. Technical shortcomings of viruses, bacteria and fungi for commercialization as biological control agents

characteristic	viruses for soil application	viruses for foliar application	bacteria for soil application	bacteria for foliar application	fungi for soil application	fungi for foliar application
lack of contact activity	* * *	*	* * *	*	—	—
speed of action	*	* * *	*	* *	*	* * *
ultraviolet sensitivity	—	* * *	—	* * ?	—	*
moisture tolerance	—	—	—	*	*	* * *
mobility	* *	*	* *	*	—	—
spectrum	* * *	* * *	* *	* *	*	*
ease of production	* * *	* * *	—	—	* *	* *
formulation stability	*	*	*	*	* * *	* * *

Key to symbols used: *, minor shortcomings; ***, major shortcomings.

Virus production at present involves *in vivo* methods, as insect larvae are efficient producers of baculoviruses, and it is possible that one easily cultured insect host could be employed to produce several different viruses. None the less, industry would probably favour *in vitro* production if this proved cost attractive, but opinions on the feasibility of developing such a process at present are diverse. Other shortcomings include sensitivity to ultraviolet light and speed of action when used as foliar applications, and lack of contact activity against the pest species in soil use. Problems with ultraviolet light can be overcome through formulation optimization, but the other problems remain to be tackled.

The technical shortcomings of bacteria are perceived as less acute than for viruses but much work must still be done to improve the spectrum of activity, to make the control agent more mobile and faster acting, to improve dispersion in the soil, and to enhance effectiveness under ultraviolet light. Some improvements here are already promised as genetic manipulation can be used to broaden the spectrum of activity and optimize the speed of action, while formulation research will yield a more persistent agent under field conditions.

The third group of pathogens with greatest potential for commercialization is the fungi. Ease of production is a problem, but the major technical problems are associated with formulation stability, moisture tolerance and speed of action when used on foliage. These shortcomings will have to be overcome before fungi can be exploited to any extent outside 'protected environments'. Again, genetic manipulation and formulation technology should allow fungi to be exploited as BCAs on a reasonable scale.

7. Conclusions and prospects for the future

Braunholtz & Tietz (1980) were 'uncertain that the present agrochemical industry would in the short to medium term become involved in any major way in the provision and practice of biological control measures'. However, they did believe that industry could aid progress though the development of new formulations, new target oriented chemicals and new application methods. Seven years later, science and technology have made great strides forward, and industry is interested in, and committed to, developing selected BCAs and selective chemicals.

BCAs for insect control are commercially available, but agents for controlling weeds and diseases are generally less developed. However, mycoherbicides, insects and competitive plants hold promise for weed control, and antagonists have potential for controlling disease. Of the agents at present available, predators and parasites provided by government agencies and a few small specialized companies, will continue to be used to decrease damage caused by pests, whereas selective chemicals and pheromones produced by the agrochemical industry will increase in importance if compatible with integrated practices (see papers by van Emden and Pickett, this symposium).

The most radical changes occurring in industry are in response to the perceived potential value of exploiting pathogens. The options available range from selling naturally occurring pathogens, which could even be produced by cottage-type industries in less developed countries, to the low technology approach of undirected mutagenesis, to the high technology options of genetically manipulating pathogens to improve the efficiency of production or widen the spectrum of activity, and getting genes from BCAs expressed in plants. The choice of option to pursue will be critical for a company which will have to weigh up the risks of factors such as increased research and development costs, uncertain registerability, unproven markets, and the impact of plant biotechnology. In fact, some small companies which market microbial pest control agents have already gone out of business.

Industry, and the large multinationals in particular, will be instrumental in commercializing BCAs for pest, disease and weed control, as the foundation is laid for the introduction of very exciting control techniques in the 1990s and the next century. However, even though the future looks bright for BCAs, the agrochemical industry does not expect them to replace chemicals, but to complement them and allow the development of better integrated control programmes.

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Discussion

J. M. Franz (*Gundolfstrasse* 14, 6100 *Darmstadt*, *F.R.G.*). During the past forty years I have heard many forecasts as to the future application of biological control issued by representatives of the pesticide industry. They were all wrong, and I am afraid that the present outlook is not correct either. Some examples may suffice to indicate the fundamental differences: first the difficulty of using the U.S. dollar as a basis for evaluation, considering its instability. Secondly, the dependence of public acceptance of BCAs for quite different (partly political) reasons. Thirdly, the increasing tendency to make the producer responsible for environmental problems (including resistance of pests to pesticides) caused by his products. The future will show who is right.

A. R. Jutsum. I would like to comment on the three specific points raised by Professor Franz. First, the U.S. dollar is the accepted currency for making comparisons in the agrochemical business, and the figures presented were given in dollars at 1985 values throughout. Secondly, I agree that there will be increased use of BCAs in some countries in response to political pressures, but this may be followed by counter pressure when people start to consider genetically engineered BCAs as hazardous. Thirdly, industry does take a responsibility for the environmental acceptability of its products, hence GIFAP's (International Group of National Associations of Manufacturers of Agrochemical Products) support for the International Code of Conduct on the Distribution and Use of Pesticides developed by the FAO (Food and Agriculture Organization of the United Nations, Rome). It is also worth emphasizing that the belief that 'pesticides are harmful to the environment' is a meaningless generalization and just not true.

J. W. Deacon (*Department of Microbiology*, *Edinburgh University*, *U.K.*). I suggest that the agrochemical industry will wish to exploit biocontrol in conjunction with any newly developed, basipetally translocated fungicides. If these have similar properties to those of currently available systemic fungicides then they are likely to have single-site modes of action, and resistance to them could develop quite rapidly. Effective biocontrol agents could be integrated with their usage to prevent or delay the build-up of resistance in target pathogens.

A. R. Jutsum. Preventative resistance management is a major target for the Fungicide Resistance Action Committee (FRAC), and is being tackled quite effectively with fungicide mixtures. Integration of chemical fungicides with BCAs will help preserve product life, but will only be acceptable, in the absence of legislation, if the BCA works at cost-effective rates and hence gains grower support.

C. C. Payne (*Glasshouse Crops Research Institute*, *Littlehampton*, *U.K.*). Would Dr Jutsum please comment on the rate at which new, active chemical ingredients are likely to be developed by the agrochemical industry? My understanding is that their rate of development is likely to be slowed and that the economics may shift in favour of diversification and greater exploitation of biological control agents.

A. R. Jutsum. Chemical invention rates are declining across the agrochemical industry, but this may be counterbalanced by biotechnology directed at improved inventiveness. Thus we may get a renaissance period. Development is another matter, and obviously rests on the outcome of cost and benefit analysis. As the agrochemical market matures, it becomes more difficult to justify development, particularly as registration costs increase. This makes effective BCAs relatively attractive but will require changes in acceptance at grower level before significant market penetration is achieved. On the subject of diversification, I agree in principle with Dr Payne if he is referring to niche specialization (for example for control of rice water weevil in a mature Japanese market) but if specialized means small yet expensive to register, then industry will not be able to afford to exploit such niches.

T. Lewis (*Rothamsted Experimental Station, Harpenden, U.K.*). How could the prospects for biological control change, and how would the agrochemical companies respond, if, for environmental reasons, governments decided to tax pesticides?

A. R. Jutsum. I am appalled by the concept of introducing an environmental tax which seems impossible to implement fairly: it would be preferable to register only environmentally acceptable pesticides and get away from the 'pesticides are nasty' syndrome. However, if a tax were levied, the agrochemical industry would either stop developing new products for particular markets if returns became unattractive, or develop broader spectrum products to add value to the development case, which may be less attractive to the advocates of integrated pest management but not to the growers.

It would be much better to encourage industry by providing incentives to develop selective chemicals and BCAs which are compatible with integrated pest management. In this way, environmental acceptability can be attained whilst retaining a viable agricultural economy.

R. R. M. Paterson (*C.A.B. International Mycological Institute, Kew, U.K.*). Would a purified pesticidal metabolite from a microbe be defined as a BCA or a conventional chemical?

A. R. Jutsum. I believe that purified pesticidal metabolites from microbes will be classified as chemicals. Both avermectin, a secondary metabolite from *Streptomyces avermitilis*, and thuringiensin, the purified β-exotoxin from *Bacillus thuringiensis* (*Bt*) have not achieved bio-rational registration. However, *Bt* endotoxin would, I suspect, be classified as a BCA in terms of bio-rational registration. Yet, *Bt* is in effect the crystal toxin enclosed in a bacterium which can even be dead.

Thus, microbial metabolites should be generally regarded as chemicals, but *Bt* remains effectively an anomaly.

J. K. Waage (*C.A.B. International Institute of Biological Control, Ascot, U.K.*). In the context of industrial development, what is the future of small biological control industries? Are they transient or stable? If stable, what makes them able (or willing) to develop BCAs which major industry is currently not doing?

A. R. Jutsum. Within the biological control industry, companies such as Koppert BV who work primarily with predators and parasites are relatively stable, but specialist microbial pesticide companies are inherently unstable, particularly when they have relied upon venture capital and have been unable to provide monetary returns in a short time period. Those biotechnology groups working in the area currently under venture capital or industrial sponsorship or both will probably get taken over by industry if they are good, or cease trading if they are not. As far as your final point is concerned, the successful small biological control industries concentrate on specialized, limited markets which are financially unattractive to companies with large overheads, and this allows them to operate in a different competitive environment.

H. F. van Emden (*Departments of Horticulture, and Pure & Applied Zoology, University of Reading, U.K.*). Could Dr Jutsum forecast future trends in the tonnage of pesticide chemicals used on those crop areas currently receiving some pesticide?

A. R. Jutsum. Wood Mackenzie's (1986) view is that there will be slow, sustained growth of the agrochemical business world-wide at a rate of 2.5% per year. However, as more efficacious chemicals are developed (but usually at a higher price per unit of active ingredient), the actual tonnage of chemicals used will decrease as rates of active ingredient applied are reduced. Use of BCAs will increase, but will not significantly erode the conventional business before the year 2000.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES