Session 8D

Efficacy of Biological Control, Using Living Organisms and Natural Products

Market Potential

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Biological control agents: requirements and potential in the market

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Introduction

Registered, commercially available examples of Biological Control Agents 'BCA's' show that safe and environmentally sound solutions of plant protection problems have been developed – usually by SME's – in the last decade and are used increasingly.

The IVB (Association of Producers of Biocontrol Agents of German speaking countries, see: www.ivb-ev.org) intends to promote in every respect the development, production, registration and marketing of BCA's, which are acceptable for organic farming. IVB currently consists of 14 companies as members, with 3 associated members.

Product examples

BCA's are usually based on the following groups of naturally occurring principles, substances or organisms:

Macrobials frequently called beneficials

More than 40 different beneficials (including, insects, mites,) are currently used in greenhouses for production of ornamentals and vegetables (Albert *et al*. (2007)). A special case is the group of entomopathogenic nematodes (Schmutterer & Huber (2005)), which have been developed more recently.

Micro-organisms

Viruses: especially two granulosis viruses against *Cydia pomonella* and *Adoxophyes orana* are used in large scale in orchards, although about 600 viruses have been described (Kühne *et al*. (2006)). Nuclear polyhedrosis viruses have been registered against different lepidopteran larvae in different European countries (Schmutterer & Huber (2005)).
Bacteria: most important are the different insect pathogenic strains of *Bacillus thuringiensis* (Schmutterer & Huber (2005)), but also different bacterial preparations for the control or reduction of plant diseases (Kühne *et al*. (2006)).
Fungi: a large variety of different fungal preparations is used for the control of insect pests (Schmutterer & Huber (2005)), plant diseases or as plant strengtheners (Kühne *et al.* (2006)).

Pheromones

Pheromones, (especially strait chain lepidopteran pheromones): used for monitoring, mass trapping or mating disruption in integrated and organic farming.

Plant extracts

Especially extracts containing Pyrethrine and Azadirachtin are marketed; in cases preparations on the basis of rape (canola) oil and garlic are used. A large number of products offered as plant strengtheners has been reviewed by the Federal Biological Institute of Germany (see: http://pflanzenstaerkungsmittel.bba.de/).

Minerals
Different minerals are used for control of diseases or as plant strengtheners; a new development in this area are products for the control of slugs.

Requirements and obstacles
One bottle-neck for the availability of BCA's is the unjustifiably high expense connected with the registration procedure, which frequently is very inappropriate for BCA's since it is historically based on the judgement of synthetic pesticides, with totally different properties, risks, mode of action etc. In this connection IVB highly appreciates the results obtained in the frame-work of the Rebeca project (http://www.rebeca-net.de/). It is self-understood that at least the same high demands are applicable with respect to the safety of workers, consumers, bystanders and the environment to BCA's as to synthetic pesticides.

A critical refurbishment of the experiences obtained in the course of the EU-re-evaluation of list 4 plant protection products may help to obtain more adequate registration procedures for BCA's.

Usually the expense in research and development of one new BCA is of the order of a few million € in a period of about 10 years. In cases where registration fees can not be reduced or waived these fees amount to a few million € for registration in all EU-countries as well. Thus these unacceptably high official fees are frequently a major obstacle for market introduction of a new BCA in EU-countries – and abroad.

Market potential
Discussions among plant protection specialists indicate that a major problem of synthetic pesticides is the development of resistance of the target organisms. BCA's are generally not very prone to the development of resistance; thus they can be used as a component in resistance management programs in integrated farming.

During the last year reports have increased on unacceptably high amounts of residues of synthetic pesticides especially in different, conventionally produced fruits and vegetables marketed in Europe. In integrated farming one solution of this problem may be the implementation of BCA's for example in spray programs.

Conclusions
The above examples show that BCA's can be developed and marketed successfully if registration requirements can be solved in a scientific and reasonable way and examples will be discussed in more detail in the presentation. It is as well a question to politics whether the future development of BCA's will be supported in order to increase the availability of biologically grown fruits and vegetables or at least reduce environmental impacts or excessive residues on agricultural produce.

References
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Current worldwide markets for biopesticides and success factors for the business

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This paper presents the results of a recent worldwide survey of markets for biopesticides. The survey was carried out by region, by country and by product type, e.g. bacterial, fungal, viral and other microbial products. Current commercial activities in biopesticides were also surveyed, including large and small companies as well as 'spin-outs' from government research institutes and universities.

The survey was the seventh carried out since 1987. During that time, the market for microbial biopesticides, which does not include pheromones or insects, has grown from <\$60m then to ~\$280m today. In total however, biopesticides still represent < 1% of the total global pesticide market after more than 40 years since first appearing on the market.

Microbial biopesticides are still widely regarded as expensive, difficult to use and, perhaps most critically, of poor or highly variable efficacy. However, in the developing world, locally produced microbial products can compete cost effectively with chemical pesticides and can confer social and economic benefits.

At present, products based on *Bacillus thuringiensis* (*Bt*), used to control lepidoptera and diptera in crop and amenity situations, dominate the market; taking a 60% share. This proportion is, however, significantly down on estimates made in the 1990s, which routinely and consistently, estimated the market share taken by *Bt* products as 80-90%. A further reason for the fall in the proportion of the market taken by *Bt* products is the substantial growth in the share taken by other micro-organisms.

Products based on other bacterial biopesticides are beginning to develop significant markets, e.g. products based on *Bacillus subtilis* are widely available and growing in market size, most notably in the US. Recent developments in Europe with a seed-treatment based on *Pseudomonas chlororaphis* and a rat-poison based on a species of *Salmonella* is now in use globally. Sales of the mosquito larvicide *Bacillus sphaericus* and the fungal antagonist *Pseudomonas fluorescens* are increasing.

The use of viruses, once very tiny and often non-commercial has grown particularly for control of *Anticarsia gemmatalis* in a market of ~\$3m *per annum*. In addition, products for the control of codling moth, *Spodoptera* spp and *Helicoverpa* spp are widely available.

The global use of fungal products is increasing significantly. There has been considerable growth in the developing world in the concept of local-production for local use with areas particularly active in this including Central and Latin America, e.g. Cuba, Brazil and Colombia, and some parts of south-east Asia, e.g. India, China and Indonesia. The main organisms in use are the insecticides *Beauveria bassiana*, *Metarhizium anisopliae* and the fungal antagonist *Trichoderma* spp.

The North American market represents the largest segment, but not the majority of worldwide biopesticide sales, especially as the market for *Bt*-based products against Lepidoptera has declined due to GM plants and to competition from new chemical products. Some predict that there is potential for this regional market to reach ~$260m by 2015 with the fastest growing sectors in mosquito control and fungicidal products based on *Bacillus subtilis*.

The Latin America biopesticides market has seen substantial growth since the early 1990s with significant local, small-scale production for local use, especially for viral- and fungal-based products. Cuba is the largest biopesticide market in the region, followed by Colombia and Brazil. In Africa and the Middle East however, market growth has been slower.

The change in commercial interest has been striking however, with most of the major crop protection companies abandoning their work on biopesticides, while simultaneously the survey identified 100 companies active in North America, 167 companies in Europe, 86 in Asia and Oceania and 160 companies in Latin America, Africa and the Middle East.

Perhaps this growth is due to some positive trends such as the rapidly expanding market for organic food of all sorts and the effective use of ICM and IPM systems in many crops. The more conservative business model being followed by smaller companies has helped them survive and achieve more gradual success; expectations of world-beating products, rapid growth and huge profits for investors have been scaled back. In addition, the demand that biologicals be like chemicals has been revised and alternative paradigms have become more acceptable.

In the past 20 years more than ~200 companies have gone into and out of biopesticides. Common mistakes are for companies to believe that biopesticides are easy to find and quick and cheap to make; to overestimate their own capabilities, believing that they, unlike their numerous predecessors, will avoid the pitfalls and pick the winners; to under-budget in time and resources and try to succeed 'on the cheap'; to think they are smarter and quicker than other companies; to enter the business thinking they can bring 'real' expertise to the marketing of biopesticides; or to think some extraordinary new technology will give them the easy winning edge.

Factors common to those remaining in the business are control of production capacity and capabilities, clear market understanding, a genuine corporate commitment to the effort, enough money for critical mass and needed time, highly focused efforts and good management – which is much easier to say than to do.

Market data obtained in this survey are presented along with a review of some of the success factors for companies and products in this market. The perspective is that of a business consultancy with many years experience gained with the companies, products and technology in this field.

Regulatory innovation and the biopesticide industry

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Biopesticides are crop protection products based on micro-organisms, semiochemicals and plant extracts, some of which have been commercially available for well over 20 years. However, despite their superior human and environmental safety profiles they still represent less than 1% of the global crop protection market. In Europe their commercialisation has long been impaired by a regulatory system designed for the assessment of chemical pesticides, and a lack of innovative will amongst intrinsically risk-averse regulatory authorities. Furthermore, industry pressure to simplify the registration of biopesticides has not always taken adequate account of either regulatory concerns or the constraints of procedural feasibility.

The European biocontrol industry is arranged into a number of trade associations of varying size and organisational sophistication, predominantly under the aegis of the International Biocontrol Manufacturers Association (IBMA). The UK branch of the IBMA was set up in early 2003 to represent the interests of the majority of producers, and to provide a single, coherent voice to the regulatory authorities.

Within a relatively short space of time the UK IBMA had brought its agenda to the attention of both government and media, and had started to engage the Pesticides Safety Directorate (PSD) in constructive dialogue. The outcome was the launch, in 2004, of the PSD's Pilot Scheme for biopesticides, a major initiative that offered free pre-submission meetings with applicants, a more pragmatic approach to risk assessment, and a significant reduction in fees. The scheme quickly doubled the number of active ingredients available to UK growers, before being formally adopted as the permanent Biopesticides Scheme.

Recognising that the industry had become so inured to regulatory problems that many companies were reluctant to come forward, the PSD agreed to host a biannual IBMA/PSD Liaison Group to discuss issues of mutual concern, and recently ran a very successful one-day seminar on the biopesticide regulatory process, aimed primarily at producer companies.

The UK experience is in stark contrast to the situation elsewhere in Europe, where the biopesticide industry has failed to engage effectively with the regulatory authorities. In some cases, Member States are actually withdrawing what little support they had previously offered this section of the industry.

Recent research at the University of Warwick discusses hypotheses of market and regulatory failure as explanations for the relative paucity of commercial products in Europe, but also points to poorly developed policy networks and a lack of political sophistication within the industry. This latter conclusion is particularly pertinent to current industry activities such as the REBECA Project – an EU funded initiative aimed at simplifying and harmonising the regulation of biological control agents. Bringing together regulators and industry representatives from across Europe, the project provided a unique opportunity to develop mutual understanding, and to use the UK experience to show how 91/414/EEC can be interpreted with the flexibility necessary to develop a more pragmatic framework for the regulation of biopesticides.

Unfortunately, poor preparation on the part of the wider European industry meant that the meeting achieved considerably less than it could have done.

There are many reasons for the industry's failure to engage with the regulatory authorities: unrealistic expectations, unclear goals, a lack of focus, and a lack of empathy with regulators' concerns and responsibilities. What is just as clear is that this failure will have consequences for the commercialisation of products throughout Europe. The European regulatory process, which requires that recommendations made by individual Member States are considered by the others, means that progress in the UK is of little consequence in isolation.

What is at stake is not whether there will or will not be regulation of biopesticides, but what form that regulation will take. It has been demonstrated that a system of regulation can be implemented which is of benefit to applicants and regulators alike, and there are no *prima facie* reasons why similar schemes could not be implemented in other Member States. However, if significant regulatory change is to be effected, it is imperative that the biopesticide industry in Europe comes to a consensus on the issues of fundamental importance, and engages with the regulatory authorities on a more pragmatic footing.

Induced resistance as a sustainable approach to plant disease control

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It is now well established that treatment of plants with a variety of agents can lead to the induction of resistance to subsequent pathogen attack, both locally and systemically. This induced resistance can be split broadly into systemic acquired resistance (SAR) and induced systemic resistance (ISR). SAR is characterised by a restriction of pathogen growth and a suppression of disease symptom development compared to non-induced plants infected with the same pathogen. The onset of SAR is associated with an accumulation of salicylic acid (SA) at sites of infection and systemically, and with the coordinated activation of a specific set of genes encoding PR proteins. Treatment of plants with SA or one of its functional analogues e.g. acibenzolar-S-methyl (ASM), induces SAR and activates the same set of PR genes. ISR develops as a result of colonisation of plant roots by plant growth promoting rhizobacteria (PGPR) and has been shown to function independently of SA and activation of PR genes, requiring instead jasmonic acid (JA) and ethylene (ET).

How effective is induced resistance?
Because induced resistance offers the prospect of broad spectrum disease control using the plant's own resistance mechanisms, there has been great interest in the development of agents which can mimic natural inducers of resistance. These include elicitor molecules released during the early stages of the plant-pathogen interaction, the signalling pathways used to trigger defences locally and systemically and the use of PGPR. Examples of the former include ASM, which is considered to be a functional analogue of SA and has been shown to elicit SAR in a wide range of plant-pathogen interactions. However, although ASM provided control against a range of important pathogens on a number of crops, reductions in infection intensity usually ranged between 4-70%.

In field trials on a range of crops, PGPR provided control of plant disease ranging from 6-89%, with the majority of studies showing reductions in disease severity of less than 80 %. Nevertheless, some PGPR strains proved to be remarkably effective under field conditions, providing consistently high levels of disease control.

Why is the efficacy of induced resistance so variable?
From the above, it is clear that the efficacy of induced resistance in the field is variable, with levels of disease control ranging from 4% to greater than 90%. This variability in efficacy is a serious impediment to the practical use of induced resistance and demands some explanation of the underlying mechanisms. Induced resistance is a complex plant response to pathogen attack and as such, will be modified by many factors including genotype and environment.

Perhaps surprisingly, little is known about the influence of genotype on induced resistance. Work using the synthetic chemical 2,6-dichloroisonicotinic acid (INA) showed that greatest protection against powdery mildew on cucumber was obtained in partially resistant cultivars. Cultivar-dependent differences in the expression of induced resistance have also been reported in other systems e.g. soybean and wheat. It has been suggested that induced resistance is associated with costs to the plant, for example, a diversion of resources away from plant growth towards defence. If so, it seems reasonable to suggest that any constraints on the availability of such resources should affect the expression of induced resistance. Indeed, the magnitude of costs associated with induced resistance was found to be dependent on environmental conditions, including nitrogen, water stress and inter-plant competition.

Induced resistance: a look to the future

Induced resistance has the potential to revolutionise disease control in crops. And yet, after decades of research, induced resistance still sits outside mainstream crop protection. Why? The answer lies in much of what has been presented above. It is inconsistent, providing high levels of disease control in some situations, but not others and it rarely provides levels of control that can be achieved with modern fungicides. Are we asking too much of induced resistance? Farmers and growers have come to expect very high levels of disease control provided by fungicides. But agriculture is changing, as are public expectations of, and attitudes to, agriculture. There is increasing concern for the environment and as a result a desire to reduce pesticide use. There is also the ever-present problem of fungicide resistance. There are also many crop-pathogen interactions for which there are no effective control measures. Viewed from this perspective, induced resistance could be useful. So what needs to be done in order to move induced resistance from the sidelines and into mainstream crop protection?

There is a real need for information on and understanding of the effects of genotype and environment on the expression of induced resistance and its efficacy in the field. Although it is possible that induced resistance could be used on its own to control certain diseases, for which no other effective control exists, it is more likely that induced resistance will be incorporated into crop protection programmes. However, this will require information on how best to fit it into existing programmes for particular crops and diseases. There is much work demonstrating the effectiveness of combining fungicides and agents that elicit induced resistance, either alternating their use in the same programme or applying them together. Combined use of induced resistance and fungicides should extend the effectiveness and lifespan of fungicides. However, this will require a much better understanding of the effect of induced resistance on pathogen population biology.

Although a great deal is known about the mechanisms underlying resistance induced by prior inoculation with necrotizing pathogens and use of plant activators like ASM, much less is known (in some cases nothing is known) about the mechanisms underlying resistance induced by other agents. This is an important area for future work, which will be greatly aided by developments in gene array technologies. By understanding the pathways activated and resistance mechanisms triggered by different agents, it should be possible to use cocktails of elicitors to provide effective and reliable protection.

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