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The development, regulation and use of biopesticides for Integrated Pest Management

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Over the past 50 years, crop protection has relied heavily on synthetic chemical pesticides but their availability is now declining as a result of new legislation and the evolution of resistance in pest populations. Therefore, alternative pest management tactics are needed. Biopesticides are pest management agents based on living microorganisms or natural products. They have proven potential for pest management and they are being used across the world. However, they are regulated by systems designed originally for chemical pesticides that have created market entry barriers by imposing burdensome costs on the biopesticide industry. There are also significant technical barriers to making biopesticides more effective. In the European Union, a greater emphasis on Integrated Pest Management (IPM) as part of agricultural policy may lead to innovations in the way that biopesticides are regulated. There are also new opportunities for developing biopesticides in IPM by combining ecological science with post-genomics technologies. The new biopesticide products that will result from this research will bring with them new regulatory and economic challenges that must be addressed through joint working between social and natural scientists, policy makers and industry.

Keywords: biopesticide, Integrated Pest Management, adoption, regulation

INTRODUCTION

In this paper we discuss the challenges and opportunities for Integrated Pest Management (IPM) in the developed economies, with emphasis on the European Union. We focus on a set of crop protection tools known as biopesticides. We are concerned in particular with understanding the factors that hinder or facilitate the commercialisation and use of new biopesticide products.

Over the next 20 years, crop production will have to increase significantly to meet the needs of a rising human population. This has to be done without damaging the other public goods – environment and social - that farming brings. There will be no 'silver bullet' solution to the impending food production challenge. Rather, a series of innovations must be developed to meet the different needs of farmers according to their local circumstances (see for example [1]).

One way to increase food availability is to improve the management of pests. There are estimated to be around 67,000 different crop pest species - including plant pathogens, weeds, invertebrates and some vertebrate species - and together they cause about a 40% reduction in the world's crop yield [2]. Crop losses caused by pests undermine food security alongside other constraints such as inclement weather, poor soils, and farmers' limited access to technical knowledge [3].

Since the 1960s, pest management in the industrialised countries has been based around the intensive use of synthetic chemical pesticides. Alongside advances in plant varieties, mechanisation, irrigation and crop nutrition, they have helped increase crop yields by nearly 70% in Europe and 100% in the USA [4]. However the use of synthetic pesticides is becoming significantly more difficult due to a number of interacting factors:

- The injudicious use of broad-spectrum pesticides can damage human health and the environment [5, 6]. Some of the 'older' chemical compounds have caused serious health problems in agricultural workers and others because of inadequate controls during manufacture, handling and application.
- Excessive and injudicious prophylactic use of pesticides can result in management failure through pest resurgence, secondary pest problems or the development of heritable resistance [7]. Worldwide, over 500 species of arthropod pests have resistance to one or more insecticides [8], while there are close to 200 species of herbicide resistant weeds [9].
- Pesticide products based on 'old' chemistry are being withdrawn because of new health and safety legislation [10, 11]. However, the rate at which new, safer chemicals are being

made available is very low. This is caused by a fall in the discovery rate of new active molecules and the increasing costs of registration [12].

- Further pressures on pesticide use arise from concerns expressed by consumers and pressure groups about the safety of pesticide residues in food. These concerns are voiced despite the fact that pesticides are among the most heavily regulated of all chemicals.

INTEGRATED PEST MANAGEMENT

There is an urgent requirement for alternative tactics to help make crop protection more sustainable. Many experts promote Integrated Pest Management as the best way forward and the European Union has placed it centrally within its 2009 Sustainable Use Directive on pesticides [13]. IPM is a systems approach that combines different crop protection practices with careful monitoring of pests and their natural enemies [14, 15]. The idea behind IPM is that combining different practices together overcomes the shortcomings of individual practices. The aim is not to eradicate pest populations but rather to manage them below levels that cause economic damage. The main IPM tactics include:

- Synthetic chemical pesticides that have high levels of selectivity and are classed by regulators as low risk compounds, such as synthetic insect growth regulators.
- Crop cultivars bred with total or partial pest resistance.
- Cultivation practices, such as crop rotation, intercropping or undersowing.
- Physical methods, such as mechanical weeders.
- Natural products, such as semiochemicals or biocidal plant extracts.
- Biological control with natural enemies, including: predatory insects and mites, parasitoids, parasites and microbial pathogens used against invertebrate pests; microbial antagonists of plant pathogens; and microbial pathogens of weeds.
- Decision support tools to inform farmers when it is economically beneficial to apply pesticides and other controls. These include the calculation of economic action thresholds, phenological models that forecast the timing of pest activity, and basic pest scouting. These tools can be used to move pesticide use away from routine calendar spraying to a supervised or targeted programme.

IPM can be done to different levels of sophistication. Prokopy [16] outlines four levels: the basic Level One combines different tactics against one pest on one crop; whereas the highest Level Four embraces all pests and crops on the farm within an overall Integrated Crop Management system that involves members of the broad policy network (extension services, industry, retailers, regulators) and takes account of the social, cultural and ecological context of farming.

An analysis of 62 IPM research and development projects in 26 countries, covering over 5 million farm households, showed that IPM leads to substantial reductions in pesticide applications [4]. Over 60% of the projects resulted in both a reduction in pesticide use (average reduction 75%) and an increase in yields (average increase 40%). Approximately 20% of projects resulted in lowered pesticide use (average 60% reduction) with a slight loss in yield (average 5% reduction) [4]. Some 15 percent of projects showed an increase of yield (average 45% increase) with increased pesticide use (average 20% increase); these were mainly conservation farming projects that incorporated zero tillage and therefore made greater use of herbicides for weed control. The published evidence on the use of IPM by farmers outside of R&D projects is somewhat thin. For outdoor crops, IPM is based around targeted pesticide use, choice of cultivar and crop rotations. From a survey of 571 arable and mixed farms in the UK, Bailey *et al*. [17] recorded reasonable levels of adoption of good pesticide practice, including use of seed treatments (c. 70% adoption) and rotating pesticide classes (c. 55% adoption), as well as good agronomic practice such as crop rotation (75% adoption). However adoption of more "biologically-based" IPM tactics was low, such as insect pheromones for pest monitoring (20%) and introducing arthropod predators for biological control (7%).

In contrast, biological control plays a central role in the production of many greenhouse crops. Pesticide resistance evolved in some key greenhouse pests as long ago as the 1960s, prompting the development of alternative methods of management. The pressure to reduce insecticide usage was reinforced by the adoption of bumblebees within greenhouses for pollination. Some highly effective IPM programmes are now in place, based around the biocontrol of insect and mite pests using combinations of predators, parasitoids, parasitic nematodes and entomopathogens. Short persistence pesticides are used on an at-need basis if they are compatible with biological control. Pest management strategies are also determined through a close interaction between growers, consultants, biocontrol companies and retailers. In Europe, IPM based around biological control is used on over 90% of greenhouse tomato, cucumber and sweet pepper production in the Netherlands [18] and is standard practice for greenhouse crops in the UK. In Almeria, Spain, the area under biocontrol-based IPM has increased from just 250 ha in 2005 to around 7,000 ha in 2008, while the proportion of the Dutch chrysanthemum crop grown under IPM increased from just 1% in 2002 to 80% in 2007 (R. GreatRex, Syngenta Bioline, pers. comm.). This use of biological control requires considerable grower knowledge but it has clear benefits in terms of reliable pest control, lack of phytotoxicity, a short harvest interval and better crop quality.

BIOPESTICIDES

Biopesticides are a particular group of crop protection tools used in IPM. There is no formally agreed definition of a biopesticide. We define a biopesticide as a mass-produced agent manufactured from a living microorganism or a natural product and sold for the control of plant pests (this definition encompasses most entities classed as biopesticides within the OECD countries, see for example [19]). Examples of some biopesticides are given in Table 1. Biopesticides fall into three different types according to the active substance: (i) microorganisms; (ii) biochemicals and (iii) semiochemicals. The US Environmental Protection Agency also classes some transgenes as biopesticides (see “future directions in biopesticide development” later in this paper).

Microbial biopesticides. Bacteria, fungi, oomycetes, viruses and protozoa are all being used for the biological control of pestiferous insects, plant pathogens and weeds. The most widely used microbial biopesticide is the insect pathogenic bacterium *Bacillus thuringiensis* (Bt) which produces a protein crystal (the Bt δ-endotoxin) during bacterial spore formation that is capable of causing lysis of gut cells when consumed by susceptible insects [20]. The δ-endotoxin is host specific and can cause host death within 48 hours [21, 22]. It does not harm vertebrates and is safe to people, beneficial organisms and the environment [23]. Microbial Bt biopesticides consist of bacterial spores and δ-endotoxin crystals mass-produced in fermentation tanks and formulated as a sprayable product. Bt sprays are a growing tactic for pest management on fruit and vegetable crops where their high level of selectivity and safety are considered desirable, and where resistance to synthetic chemical insecticides is a problem [24]. Bt sprays have also been used on broad acre crops such as maize, soybean and cotton, but in recent years these have been superseded by Bt transgenic crop varieties.

Other microbial insecticides include products based on entomopathogenic baculoviruses and fungi. In the USA and Europe, the *Cydia pomonella* granulovirus (CpGV) is used as an inundative biopesticide against codling moth on apples. In Washington State, the USA’s biggest apple producer, it is used on 13% of the apple crop [25]. In Brazil, the nucleopolyhedrovirus of the soybean caterpillar *Anticarsia gemmatalis* was used on up to 4 million ha (approximately 35%) of the soybean crop in the mid 1990s [26]. At least 170 different biopesticide products based on entomopathogenic fungi have been developed for use against at least five insect and acarine orders in glasshouse crops, fruit and field vegetables as well as broad acre crops, with about half of all products coming from Central and South America [27]. The majority of products are based on the ascomycetes *Beauveria bassiana* or *Metarhizium anisopliae*. The largest single country of use is Brazil, where commercial biopesticides based on *M. anisopliae* are used against spittlebugs on around 750,000 ha of sugarcane and 250,000 ha of grassland annually [28]. The fungus has also been developed for the control of locust and grasshopper pests in Africa and Australia [29] and is recommended by the FAO for locust management [30].

Microbial biopesticides used against plant pathogens include *Trichoderma harzianum*, which is an antagonist of *Rhizoctonia, Pythium, Fusarium* and other soil borne pathogens [31]. *Coniothyrium minitans* is a mycoparasite applied against *Sclerotinia sclerotiorum*, an important disease of many agricultural and horticultural crops [32]. The K84 strain of *Agrobacterium radiobacter* is used to control crown gall (*Agrobacterium tumefaciens*), while specific strains of *Bacillus subtilis*, *Pseudomonas fluorescens* and *Pseudomonas aureofaciens* are being used against a range of plant pathogens including damping off and soft rots [33 - 36]. Microbial antagonists, including yeasts, filamentous fungi and bacteria, are also used as control agents of post harvest diseases, mainly against *Botrytis* and *Penicillium* in fruits and vegetables [37].

Plant pathogens are being used as microbial herbicides. No products are currently available in Europe. Two products, 'Collego' (*Colletotrichum gloeosporioides*) and 'DeVine' *(Phytophthora palmivora*) have been used in the USA [38]. Collego is a bioherbicide of northern jointvetch in soybeans and rice that was sold from 1982 – 2003 [39]. DeVine is used in Florida citrus groves against the alien invasive weed stranglervine. It provides 95% to 100% control for about a year after application [39,40].

Biochemicals. Plants produce a wide variety of secondary metabolites that deter herbivores from feeding on them. Some of these can be used as biopesticides. They include, for example, pyrethrins, which are fast-acting insecticidal compounds produced by *Chrysanthemum cinerariaefolium* [41]. They have low mammalian toxicity but degrade rapidly after application. This short persistence prompted the development of synthetic pyrethrins (pyrethroids). The most widely used botanical compound is neem oil, an insecticidal chemical extracted from seeds of *Azadirachta indica* [42].

Two highly active pesticides are available based on secondary metabolites synthesized by soil actinomycetes. They fall within our definition of a biopesticide but they have been evaluated by regulatory authorities as if they were synthetic chemical pesticides.

Spinosad is a mixture of two macrolide compounds from *Saccharopolyspora spinosa* [43]. It has a very low mammalian toxicity and residues degrade rapidly in the field. Farmers and growers used it widely following its introduction in 1997 but resistance has already developed in some important pests such as western flower thrips [44]. Abamectin is a macrocyclic lactone compound produced by *Streptomyces avermitilis* [45]. It is active against a range of pest species but resistance has developed to it also, for example in tetranychid mites [46].

Semiochemicals. A semiochemical is a chemical signal produced by one organism that causes a behavioural change in an individual of the same or a different species. The most widely used semiochemicals for crop protection are insect sex pheromones, some of which can now be synthesized and are used for monitoring or pest control by mass trapping [47], lure-and-kill systems [48] and mating disruption. Worldwide, mating disruption is used on over 660,000 ha and has been particularly useful in orchard crops [49].

Biopesticides have a range of attractive properties that make them good components of IPM. Most are selective, produce little or no toxic residue, and development costs are significantly lower than those of conventional synthetic chemical pesticides [8]. Microbial biopesticides can reproduce on or in close vicinity to the target pest, giving an element of self-perpetuating control. Biopesticides can be applied with farmers' existing spray equipment and many are suitable for local scale production. The disadvantages of biopesticides include a slower rate of kill compared to conventional chemical pesticides, shorter persistence in the environment, and susceptibility to unfavourable environmental conditions. Because most biopesticides are not as efficacious as conventional chemical pesticides, they are not suited for use as stand-alone treatments. However their selectivity and safety mean that they can contribute meaningfully to incremental improvements in pest control [50]. A good example is the entomopathogenic fungus *Beauveria bassiana*, which is being used in combination with invertebrate predators against twospotted spider mites on greenhouse crops [51]. Spider mites are routinely managed using regular releases of predators, but there are often periods in the season when control breaks down. In the past, growers relied on conventional pesticides as a supplementary treatment but this has become ineffective because of pesticide resistance and it can have knock-on effects on other insect natural enemies. *Beauveria bassiana* is effective against spider mites, has a short harvest interval, and is compatible with the use of predators [51]. So it works well as an IPM component and is now the recommended supplementary treatment for spider mite on greenhouse crops across Europe.

BIOPESTICIDE COMMERCIALISATION

Worldwide there are about 1,400 biopesticide products being sold [52]. At present there are 68 biopesticide active substances registered in the EU and 202 in the USA. The EU biopesticides consist of 34 microbials, 11 biochemicals, and 23 semiochemicals [53], while the USA portfolio comprises 102 microbials, 52 biochemicals and 48 semiochemicals [54]. To put this into context, these biopesticide products represent just 2.5% of the total pesticide market [55]. Marrone [52] has estimated the biopesticides sector currently to have a five-year compound annual growth rate of 16% (compared to 3% for synthetic pesticides) that is expected to produce a global market of $10 billion by 2017. However the market may need to increase substantially more than this if biopesticides are to play a full role in reducing our overreliance on synthetic chemical pesticides.

Companies will only develop biopesticide products if there is profit in doing so. Similarly the decision for a farmer whether or not to adopt a novel technology can be thought of in economic terms as a cost-benefit comparison of the profits to be made from using the novel versus the incumbent technology. A number of features of the agricultural economy make it difficult for companies to invest in developing new biopesticide products and, at the same time, make it hard for farmers to decide about adopting the new technology:

- **Lack of profit from niche market products**. Many biopesticides have high levels of selectivity. For example, bioinsecticides based on baculoviruses, such as the CpGV mentioned previously, typically are selective for just one or a few species of insect. This is of great benefit in terms of not harming other natural enemies and wildlife, but it means that biopesticides are niche market products with low profit potential. To quote Gelernter [56] ‘The features that made most Biological Control Products so attractive from the standpoint of environmental and human safety also acted to limit the number of markets in which they were effective’.
- **Fixed costs**. Because conventional chemical pesticides are used so widely, the fixed costs associated with them are spread over many users and hence represent a small part of the total cost of pest control. The knowledge needed by farmers to get effective control with pesticides is lower than with tactics such as biocontrol [57, 58]. Potential adopters of biopesticides face large fixed costs of adoption that will only decrease once the technology is used more widely, thereby disadvantaging early adopters.

- **Farmers’ risk aversion**. For fruit and vegetable crops, cosmetic appearance is as important as yield when it comes to making a profit. The risks of producing an unmarketable crop are high, forcing growers to be risk averse with respect to new, untested crop protection technologies. Because conventional pesticides have been the mainstay of crop protection for over 50 years, there is a wealth of experience that gives farmers and growers confidence in their effectiveness. Farmers have achieved scale economies in pesticide use as a result of ‘learning by doing’ – the concept that one becomes more productive at a task the more it is repeated. In comparison, the more limited evidence base and practical experience with biologically-based IPM technologies creates uncertainty for farmers [59 - 61]. Farmers’ risk averse preferences can result in sub-optimal patterns of adoption of new technologies [62]. Risk aversion is made worse if farmers’ expectations of new technologies are more focused on the potential downsides rather than the benefits [63].
- **IPM portfolio economies**. Different IPM tactics work together as a ‘technology bundle’ or portfolio. If a farmer wants to switch from using a single chemical pesticide for pest control to IPM then (s)he will have to decide which combination of tactics to use. The number of potential portfolios to choose from increases rapidly as more tactics are included [64]: with three tactics there are a total of seven different portfolios, with four tactics there are 11 different portfolios and so forth. Choosing the best portfolio in such cases is extremely challenging. The only realistic option is to develop a portfolio incrementally. Where a portfolio is already in place, then a farmer has to consider the benefits of adopting a new IPM tactic in the light of the current portfolio. Farmers want to use the minimum number of different tactics for the maximum benefit. Should the new tactic be added to the existing portfolio, or should it be used to replace an incumbent tactic? In some instances it is possible to replace a conventional synthetic chemical pesticide with a biopesticide without disturbing the existing IPM system (as in the case of using *B. bassiana* for control of spidermites in greenhouse IPM). In such a case the new biopesticide technology can be adopted quickly and easily. However, IPM tactics may be synergistic, such that one tactic in the portfolio results in an improved performance in others [65, 66]. This is beneficial for IPM, but the interdependency of different tactics in this way can make it difficult to substitute with new technologies as they become available.

These factors mean that using conventional synthetic chemical pesticides applied on a calendar basis can be difficult to replace in favour of an IPM portfolio of alternative tactics including biopesticides. Chemical pest control may then become locked into the system until such a time that it fails, for example if pesticide resistance becomes widespread, as in the greenhouse crops industry. Pesticide 'lock in' also means that the adoption of new technologies will be biased towards tactics that closely resemble the incumbent pesticide technology. In the case of biopesticides, the products that have been most successful so far, such as microbial Bt, are very similar to chemical pesticides. This 'chemical model' of biopesticide development has encouraged companies to turn their attention away from the beneficial, biologically-based characteristics of biopesticides (such as the ability of microbial agents to reproduce within host populations) and instead focus on trying to use biopesticides as chemical pesticide 'clones', resulting in unrealistic expectations of chemical-like efficacy [67].

It is important to stress that chemical pesticides are and will remain a vital part of crop protection. When used appropriately they can give excellent control with minimal adverse effects. The use of chemical pesticides should therefore be promoted within an IPM framework so that they are used sparingly to minimise the evolution of resistance in target pest populations. However, IPM will only work if farmers have access to a range of crop protection tactics together with the knowledge on how to integrate them.

REGULATORY BARRIERS TO BIOPESTICIDE COMMERCIALISATION

Biopesticides encompass a very wide range of living and non-living entities that vary markedly in their basic properties, such as composition, mode of action, fate and behaviour in the environment and so forth. They are grouped together by governments for the purposes of regulating their authorisation and use. These regulations are in place: firstly, to protect human and environmental safety; and secondly to characterize products and thereby ensure that manufacturers supply biopesticides of consistent and reliable quality. The European Union also requires that the efficacy of a biopesticide product is quantified and proven in order to support label claims. Only authorized biopesticide products can be used legally for crop protection.

The guidance of the OECD is that biopesticides should only be authorised if they pose minimal or zero risk. For example, the OECD guidance for microbial biopesticides is that: '*the microorganism and its metabolites pose no concerns of pathogenicity or toxicity to mammals and other non-target organisms which will likely be exposed to the microbial* *product; the microorganism does not produce a known genotoxin; all additives in the microbial manufacturing product and in end-use formulations are of low toxicity and suggest little potential for human health or environmental hazard'* [68]. The biopesticide registration data portfolio required by the regulator is normally a modified form of the one in place for conventional chemical pesticides and is used by the regulator to make a risk assessment. It includes information about mode of action, toxicological and eco-toxicological evaluations, host range testing and so forth. This information is expensive for companies to produce and it can deter them from commercialising biopesticides which are usually niche market products. Therefore, the challenge for the regulator is to have an appropriate system in place for biopesticides that ensures their safety and consistency but which does not inhibit commercialisation. Until very recently, it is true to say that government regulators – with the probable exception of the USA - were unfamiliar with biologically-based pest management and were therefore slow to appreciate the need to make the regulatory process appropriate for biopesticides rather than treat them in the same way as synthetic chemical pesticides.

The decision whether or not to authorize a biopesticide product is made on the basis of expert opinion residing within the regulatory authority. When the regulators lack expertise with biopesticides, they tend to delay making a decision and may request the applicant provides them with more data. There is also a risk that the regulator – using the chemical pesticide registration model - requests information that is not appropriate. Some regulatory authorities, the UK for example, have acknowledged that basing the regulatory system for biopesticides on a chemical pesticides model has been a barrier to biopesticide commercialisation [69]. A key question is whether the regulator, having recognised a problem, is able to do something about it. Social science theory indicates that government regulators and other bureaucratic organisations are vulnerable to "goal displacement", during which they turn their focus away from achieving outcomes and instead concentrate more on internal processes [70]. This can lead to systemic problems and stand in the way of introducing innovations into the regulatory system. This is not to say that regulatory innovation is not possible, and where there is sound evidence that a particular group of biopesticides presents minimal risk the regulators have modified the data requirements. For example, the OECD regard semiochemicals used for arthropod control as presenting minimal hazard, with straight chain lepidopteran pheromones which form the majority of semiochemical-based biopesticides being thought sufficiently safe as to justify 'substantial reductions in health and environmental data requirements' [71]. Other innovations are also being developed, which we discuss in the following sections:

New EU legislation could promote biopesticide use. The EU passed a package of legislative measures in 2009 based around IPM, including the Framework Directive on the Sustainable Use of Pesticides (EU DG Environment). IPM principles do not become mandatory until 2014, but member states have been encouraged to use rural development programmes (funded under the Common Agricultural Policy) to provide financial incentives to farmers to start implementing IPM before this date. In the Commission's view, further research is still needed to develop successful crop-specific strategies for the deployment of IPM and this should include multidisciplinary research. The Commission also regards it as 'crucial that Member States support the development of certified IPM advisory services organised by cropping systems to bridge the gap between research and end-users and help farmers for the adaptation of IPM principles to local situations.' [72]. Although such services can be provided privately and their quality guaranteed by a system of certification, it may be that countries that have retained state extension services, such as Denmark, have an inherent advantage in providing IPM advice in a cost effective way.

Alongside the Sustainable Pest Management Directive, the EU also introduced a regulation which substantially amended the plant protection legislation embodied in Directive 91/414 [73]. This directive provided for a two-tier system of regulation involving the Community and member state levels. However, it quickly became evident that mutual recognition between different member states was not working, hence undermining the functioning of the EU internal market and deterring the development of biopesticides and other innovative products. One of the solutions advanced was to divide Europe into climatically similar zones ("eco zones") where registration in one member state would facilitate registration in others in the same zone. This proposal proved controversial during the passage of the legislation. It was eventually achieved with northern, central and southern zones and an EU-wide one for greenhouses.

The new legislation gives a specific status to non-chemical and natural alternatives to conventional chemical pesticides and requires them to be given priority wherever possible. Biopesticides should generally qualify as low-risk active substances under the legislation. Low-risk substances are granted initial approval for 15 years rather than the standard 10. A reduced dossier can be submitted for low risk substances but this has to include a demonstration of sufficient efficacy. One requirement for low risk substances, that is still to be elaborated, is that their half-life in the soil should be less than 60 days and this may cause problems for some microbial biopesticides, such as rhizosphere-competent antagonists of soil-borne plant pathogens.

The new European legislation does not give the biopesticides industry all that it may have hoped for, but it does give biopesticides legislative recognition and opens up the potential for faster authorisation processes and effective mutual recognition. This will require sustained work by those interested in the wider use of biopesticides. Many of the details of how mutual recognition in eco zones will operate in practice remain to be resolved, for example how member states will interact with one another during the process. The achievement of real gains is very sensitive to the detailed implementation of the new procedures. What is clear is that the considerable variations in the levels of resource available to regulatory authorities in different member states will be a constraint on effective delivery.

EU member state regulation. In the EU, having a system of mutual recognition of plant protection products means that it is possible for one member state to engage in regulatory innovation and gain a first mover advantage over other member states. In relation to biopesticides, it is arguable that Britain has taken such a position.

Concern about the lack of availability of biopesticides in the UK led to the introduction in June 2003 of a pilot project to facilitate their registration. Its aim was to increase the availability of biopesticides by improving knowledge and raising awareness of the requirements of the UK government regulator (at the time, the government regulator was the Pesticides Safety Directorate (PSD) but it has subsequently become the Chemicals Regulation Directorate (CRD)). In April 2006 the pilot project was turned into a fully-fledged Biopesticides Scheme. Prior to the introduction of the scheme, just four products had been approved between 1985 and 1997. Following the introduction of the pilot project, seven products were guided to approval. In April 2007 five products were at various stages of evaluation and several other companies were discussing possible applications with PSD. Two products were approved in 2009 and several were at various stages of the registration process.

In order to better operate the scheme the regulator provides specialist training on biopesticides to members of its Pesticide Approvals Group and has assigned a Biopesticides Champion. PSD thought it desirable to involve as many people in their Pesticide Approvals Group in this work as possible, rather than having a unit that only dealt with biopesticides and which would probably have insufficient work. Trained staff members are able to participate in pre-submission meetings with applicant biopesticide companies. Particularly if they are held early in the process, they can help applicants to plan the acquisition of the data they need for registration and also avoid the compilation of any material which would be superfluous. A number of such meetings were observed on a non-participant basis as part of our research. The meetings enabled the identification of gaps in the application dossier and mutually helpful discussions of how these could be filled, for example, by using data published in the scientific literature. The UK Scheme charges reduced fees for biopesticides: £22,500 for microbial biopesticides, £13,000 for pheromones and £7,500 for taking either through European Food Safety Authority (EFSA) procedures. Before the introduction of the pilot project, there was a standard fee of £40,000 for everything termed a biopesticide. In comparison, the cost of core dossier evaluation, provisional approval and EFSA review for a synthetic chemical pesticide would be between £120,000 and £180,000 from March 2007. CRD intends to continue to operate the Biopesticides Scheme with reduced fees.

The scheme has had to face a number of challenges. It has involved CRD reaching out to non-traditional 'customers' who may be suspicious of the regulatory authority because they have no experience of working with them. As a biopesticides consultant commented in interview in our research, 'Pre-submission is a key element because registration is still an unknown, a lot of fear, people want me to hold their hands, introduce them to PSD.' From a CRD perspective, the biopesticides scheme was seen as a pathfinder in Europe and it could make it the preferred regulation authority for such products providing it is able to maintain the process of regulatory innovation.

FUTURE DIRECTIONS

Governments are likely to continue imposing strict safety criteria on conventional chemical pesticides, and this will result in fewer products on the market. This will create a real opportunity for biopesticide companies to help fill the gap, although there will also be major challenges for biopesticide companies, most of which are SMEs with limited resources for R&D, product registration and promotion. Perhaps the biggest advances in biopesticide development will come through exploiting knowledge of the genomes of pests and their natural enemies. Researchers are already using molecular-based technologies to reconstruct the evolution of microbial natural enemies and pull apart the molecular basis for their pathogenicity [74 - 76]; to understand how weeds compete with crop plants and develop resistance to herbicides [77]; and to identify and characterise the receptor proteins used by insects to detect semiochemicals [78]. This information will give us new insights into the ecological interactions of pests and biopesticides and lead to new possibilities for improving biopesticide efficacy, for example through strain improvement of microbial natural enemies

[79]. As the genomes of more pests become sequenced, the use of techniques such as RNA interference for pest management is also likely to be put into commercial practice [80].

We stated earlier that biopesticide development has largely been done according to a chemical pesticides model that has the unintended consequence of downplaying the beneficial biological properties of biopesticides such as persistence and reproduction [67] or plant growth promotion. The pesticides model still has much to offer, for example in improving the formulation, packaging and application of biopesticides. However, it needs to be modified in order to investigate biopesticides from more of a biological / ecological perspective. For example, biologists are only just starting to realise the true intricacies of the ecological interactions that occur between microbial natural enemies, pests, plants and other components of agroecosystems [81]. Take entomopathogenic fungi for instance. We now know that species such as *Beauveria bassiana* and *Metarhizium anisopliae,* traditionally thought of solely as insect pathogens, can also function as plant endophytes, plant disease antagonists, rhizosphere colonizers, and plant growth promoters [82]. This creates new and exciting opportunities for exploiting them in IPM, for example by inoculating plants with endophytic strains of entomopathogenic fungi to prevent infestation by insect herbivores. There are opportunities also to exploit the volatile alarm signals emitted by crop plants so that they recruit microbial natural enemies as bodyguards against pest attack [83 - 85] and to use novel chemicals to impair the immune system of crop pests to make them more susceptible to microbial biopesticides [86, 87].

The biopesticide products that will result from new scientific advances may stimulate the adoption of different policies in different countries. We have seen this already with GM crops. In the USA, Canada, China, India and Brazil, farmers have been quick to adopt transgenic broad acre crops expressing Bt δ-endotoxin genes. For example, in the USA, 63% of the area of maize planted, and 73% of the area of cotton, now consists of GM varieties expressing Bt δ-endotoxin genes [88]. The US Environmental Protection Agency includes transgenes in its categorisation of biopesticides. In Europe, by contrast, there has been widespread resistance among consumers to GM crops and the EU excludes them from the biopesticide regulatory process. Another complex issue surrounds the regulation of biopesticides that have multiple modes of action. For example, species of the fungus *Trichoderma*, which are used as biopesticides against soil borne plant pathogenic fungi, are able to parasitize plant pathogenic fungi in the soil; they also produce antibiotics and fungal cell wall degrading enzymes, they compete with soil borne pathogens for carbon, nitrogen and other factors, and they can also promote plant growth by the production of auxin-like compounds [89, 90]. Some *Trichoderma* products have been sold on the basis of their plant growth promoting properties, rather than as plant protection products, and so have escaped scrutiny from regulators in terms of their safety and efficacy.

In general, the adoption of IPM tactics is correlated with farmer education and experience and the crop environment (with IPM being adopted more on horticultural crops [91]). We have mentioned previously that biocontrol-based IPM has been adopted widely by the greenhouse crops industry but is not used much by growers of broad acre crops. Greenhouses represent intensively managed, controlled environments that are highly suitable for IPM. Biocontrol adoption was undoubtedly helped by the fact that greenhouse crop production is labour intensive and technically complex, and thus growers already had a high level of knowledge and were used to technological innovation. How IPM and alternative technologies such as biopesticides can be taken out to broad acre crops and the wider rural environment - where human capital is spread thinly and where the ecological environment is far more complex and less stable than in a greenhouse - is an interesting question, and one where public policy is likely to play an important role.

One proposed solution is to develop a "total system" approach to pest management in which the farm environment is made resistant to the build up of crop pests, and therapeutic treatments are used as a second line of defence [92]. The total systems approach is based: firstly, on managing the agro-ecosystem to promote pest regulating services from naturally occurring biological control agents, for example by providing refugia and alternative food sources for natural enemies within the crop and in field margins; and secondly, on making greater use of crop varieties bred with tissue-specific and damage-induced defences against pests [92]. Biopesticides would have an important role as back-up treatments in this system, although some biopesticides could also be used as preventative treatments, e.g. fungal endophytes (see above). A big advantage of this approach would be in preventing biopesticides being viewed as just another set of 'silver bullet' solutions for pest control, and thereby avoid repeating the mistakes of the chemical pesticides era. To make IPM work in the total system concept, institutional arrangements would be required that: provide a market for natural pest regulation as an ecosystem service; promote biopesticides and other environmentally benign technologies in agriculture; value human and natural capital in rural areas; and synthesize knowledge on natural science, economics, and the social dimension of agriculture and the rural environment (see for example [93]). Such a holistic system for pest management would require far better integration of the existing policy network [94]. This may seem like an ambitious proposition but it is becoming increasingly necessary.

One area that certainly warrants greater consideration for the future is the attitude of the public and the food retailers to biopesticides and other alternative pest management tools. There is concern among the public about pesticide residues in food but there is little public debate about the use of alternative agents in IPM. In our research, we have found that the major food retailers have done little to engage in discussions about making biological alternatives to synthetic chemical pesticides available to farmers and growers. This is unfortunate given the importance of retailer-led governance in the agricultural economy. It is farmers and growers who are particularly affected by problems of pesticide resistance and the withdrawal of conventional plant protection products, and yet they are 'policy takers' rather than 'policy makers' and have to operate within the constraints of a stringent regulatory framework while at the same time coping with the market power of the supermarkets. Unfortunately, the public/mass media debate about the future of agriculture has become increasingly polarized into a conflict between supporters of 'conventional' versus 'organic' farming rather than considering what practices should be adopted from all farming systems to make crop protection more sustainable. It is our contention that biopesticides are not given due attention in debates on sustainability. In this regard it is worth concluding with Pretty's (2008) comment that sustainable agriculture 'does not mean ruling out any technologies or practices on ideological grounds. If a technology works to improve productivity for farmers and does not cause undue harm to the environment, then it is likely to have some sustainability benefits' [4].

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Short title for page headings: biopesticides for Integrated Pest Management

Table 1: Examples of some commercially-available biopesticides.

Category	**Type**	**Active ingredient**	**Product name**	**Targets**	**Crop**
Microorganism					
Bacteria	Insecticide	*Bacillus thuringiensis* var *kurstaki*	Dipel DF	Caterpillars	Vegetables, soft fruit, ornamentals & amenity vegetation
	Fungicide	*Bacillus subtilis* QST713	Serenade ASO	*Botrytis* spp.	Vegetables, soft fruit, herbs & ornamentals
	Nematicide	*Pasteuria usgae*	*Pasteuria usgae BL1*	Sting nematode	Turf
Fungi	Insecticide	*Beauveria bassiana*	Naturalis - L	Whitefly	Protected edible & ornamental plant production
	Fungicide	*Coniothyrium minitans*	Contans WG	*Sclerotinia* spp.	Outdoor edible and non-edible crops & protected crops
	Herbicide	*Chondrostereum purpureum*	Chontrol	cut stumps of hardwood trees & shrubs	Forestry
	Nematicide	*Paecilomyces lilacinus*	MeloCon WG	Plant parasitic nematodes in soil	Vegetables, soft fruit, citrus, ornamentals, tobacco & turf
Viruses	Insecticide	*Cydia pomonella* GV	Cyd-X	Codling moth	Apples & pears
	Anti-viral	Zucchini Yellow Mosaic Virus, weak strain	Curbit	Zucchini Yellow Mosaic Virus	Transplanted zucchini & cantaloupes, watermelons, squash
Oomycetes	Herbicide	*Phytophthora palmivora*	DeVine	*Morenia orderata*	Citrus crops
Biochemical	Insecticide	Azadirachtin	Azatin XL	Aphids, scale, thrips, whitefly, leafhoppers, weevils	Vegetables, fruits, herbs, & ornamental crops
	Fungicide	*Reynoutria sachalinensis* extract	Regalia	Powdery mildew, downy mildew, *Botrytis*, late blight, citrus canker	Protected ornamental & edible crops
	Herbicide	Citronella oil	Barrier H	Ragwort	Grassland
	Nematicide	*Quillaja saponaria*	Nema-Q	Plant parasitic nematodes	Vineyards, orchards, field crops, ornamentals & turf
	Attractant	Citronellol	Biomite	Tetranychid mites	Apples, cucurbits, grapes, hops, nuts, pears, stone fruit, nursery & ornamental crops
Semiochemical	Attractant	(E,E)-8,10-dodecadien-1-ol	Exosex CM	Codling moth	Apples & pears