Ralf-Udo Ehlers
Editor

Regulation of Biological Control Agents

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Preface

Regulation is implemented by governments when human activities may cause damage to the society or the environment in order to avoid, prevent or minimise impacts. Regulation should concentrate on safety aspects and try to minimise negative consequences for trade and the economy. Biological control agents (BCAs) are generally regarded as sustainable and environmentally safe tools to manage pest insects, nematodes, weeds and diseases in agriculture, forestry and horticulture. However, no human activity is without potential risks, so regulation of BCAs is necessary to avoid potential hazards.

Plant protection products based on micro-organisms, semiochemicals and botanicals are subject to registration in all OECD countries (Organisation for Economic Co-operation and Development). Their potential for use in plant protection and substitution of hazardous chemical substances is, however, not well exploited. One reason is the stringent regulation policy that basically follows rules implemented for registration of synthetic chemical pesticides. This situation motivated the EU Commission to call for proposals for appropriate and balanced regulatory systems for BCAs. As a result, the EU-supported REBECA (Regulation of Biological Control Agents) Policy Support Action (www.rebeca-net.de) was started and gathered experts from academia, regulation authorities and industry with the objective of elaborating proposals that can accelerate the regulation process for BCAs and make it more cost-effective without compromising the level of safety for human health and the environment. Based on assessments of the potential risks of BCAs, including invertebrate agents, proposals for improvement of existing registration requirements and administration of regulation were developed.

This book summarises the results of the REBECA Action. It is also a comprehensive guide for the registration practice and requirements to apply for authorisation of biological control agents. In the first part of the book, an overview on existing regulation requirements and the general practice in OECD countries is summarised and policy aspects are reviewed and discussed. In the second part of the book, information on benefits and risks of the different biological control agents are reviewed by experienced scientists who have been working for decades in the field of biological control. This part can also be used by authorities to get an overview on the real risks related to the use of these agents. In the last part, the results of discussion among

participants of the REBECA Action on how regulation of BCAs can be improved in the future is summarised by the members of the REBECA consortium.

This book will be of great help for those dealing with regulation of biological control agents in registration authorities and industry. It is also important for those who develop new products based on BCAs, as they should always have in focus the registration requirements during development of biocontrol products. Last, but not least, this book can function as the basis for future activities and discussions on how to improve existing regulation requirements. The REBECA Action was a successful platform for exchange of experience in regulation and development of possible amendments. I hope, policy-makers, scientists, member of regulatory authorities and the private sector will continue their co-operations started within the REBECA Action in order to make plant protection safer, life easier for farmers and provide healthier food produce for consumers.

The preface of this book is also a good opportunity to express my thanks to all who have contributed to the REBECA Action and to producing this book. The first acknowledgement goes to the unknown EU officials who took the initiative for the call (Sixth Framework Program of the EU. Call identifier: FP6-2004-SSP-4). Without their initiative we would today probably have to deal with more data requirements instead of fewer. Thanks are also due to the EU Commission for the financial support.

My particular thanks go to Olaf Strauch for his professional management during the Action's lifetime and to Miriam Döring and Heike Kuhlmann for their support in organisation of meetings and in administration. Thanks also to Dr. Ingmar Schmidt and Susanne Neufeldt at the Christian-Albrechts-University Kiel for keeping a scientist in line with EU administrative rules. My warmest regards go to my colleagues of the REBECA consortium, who were the backbones for success: Rüdiger Hauschild contributed his in-depth professional know-how in registration of BCAs; Anita Fjelsted managed to attract regulatory personnel and initiate fruitful networking among all stakeholders; Wyn Grant, the grey eminence, with an excellent feeling for what would be acceptable for EU and MS policy; Jeff Bale, who linked with the IOBC executives; Uli Kuhlmann, with his scientific excellence in risk assessment and links to friends of biological control all around the world; Bernard Speiser and Lucius Tamm with excellent contacts to organic agriculture and professional skills in Swiss-EU-network management; Heikki Hokkanen and Ingeborg Hokkanen-Menzler provided their expertise in socio-economics; and Hermann Strasser, who contributed the results of the previous EU projects on safety aspects (BIPESCO and RAFBCA). These were, of course, not their only qualities and I am particularly thankful to all of them for their support that made the REBECA Project a success. My gratitude also to the other authors of this book and their contributions to REBECA, in particular to Claude Alabouvette, for contributing his long-term experience in regulatory aspects and is never ending support to biological control. Thanks also to Roland Perry for proofreading and to Suzana Bernhart and Elisabete Machado (Springer) for their support.

I also want to thank all participants from biocontrol companies, universities and research organisations, regulatory authorities and consultancy companies, who

came to join the workshops and discussions during the REBECA Action. We would not have been able to provide so much information within such a short time without their input. I also thank colleagues from overseas, in particular Bill Schneider and Trevor Jackson. My sincere thanks also to Ulf Heilig for provision of his expertise as a consultant and his support to our activities to inform the biocontrol industry about REBECA.

I hope this book will stimulate co-operation and activities for further improvement of regulatory policy. Finally, for those who work in biological control and have for the first time been confronted with regulation of these wonderful biocontrol techniques, please do not get frustrated; there is light at the end of the tunnel.

Kiel, Germany Ralf-Udo Ehlers
August 2010

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Part I
General Aspects of Regulation

Chapter 1
Regulation of Biological Control Agents and the EU Policy Support Action REBECA

Ralf-Udo Ehlers

Abstract Biological control uses living organisms like bacteria, fungi, nematodes, insects or mites (including viruses) for the control of weeds or pests and diseases of crop plants. Information on the use of these biocontrol agents and associated risks are summarized. An overview on the regulation of biological control agents and an introduction into the objectives and the organisation of the Policy Support Action REBECA is provided. The history of regulation of chemical compounds is compared with the development of regulation of biocontrol. Often the precautionary principle is consulted to justify anticipatory restrictions in regulation. A comment of the European Commission on the use of the principle is analysed and the consequences for regulation of biological control agents are discussed. The different stakeholders (academia, industry, farmers and producers, consumers and the retail sector, environmentalists organised in non-government organisations, regulatory authorities and policy makers) and their interests in regulation are described.

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1.1 Biological Control and Regulation of Biological Control Agents

Biological control uses living organisms like bacteria, fungi, nematodes, insects or mites (including viruses) for the control of weeds or pests and diseases of crop plants. Chemical compounds of natural origin, like plant extracts and semiochemicals (molecules functioning in bio-communication), are also assigned to the group of biological control agents (BCAs).

In the European Union, the registration requirements for active ingredients of all plant protection products were laid down in the EU Directive 91/414/EEC (EU 1991). This directive was amended by Directive 2001/36/EC (EU 2001) and 2005/25/EC (EU 2005) to adapt to the special requirements for plant protection products based on micro-organisms (MBCAs). On October 21, 2009, Dir. 91/414 was replaced by EC Regulation No. 1107/2009 (EU 2009a). Registration requirements and a comparison of registration practice in different OECD (Organsiation for Economic Co-operation and Development) countries are provided in Chapter 2 (Hauschild et al., 2011).

In organic farming specific rules have been developed to define which substances are allowed for use and which are exempted. BCAs used in organic farming are not excluded from registration by the European Commissions authority DG SANCO (Directorate General for Health and Consumer Affairs) and subsequent national authorisation. Minimum requirements for organic production are laid down in EC Regulation No. 889/2008. Annex II provides a list of plant protection products referred to in Article 5(1) of the Regulation (EU 2008). In addition to the EU and national authorisation, different international and national organisations (e.g., Bioland, Demeter) review BCAs for their possible potential and applicability for organic farming within their specific system. The rules have been summarized by Speiser and Tamm (2011) in Chapter 4.

Nematodes, mites and insects belong to the group of invertebrate biological control agents (IBCAs) or macro-organisms. Nematodes used in biological control of insects belong to the genera *Steinernema* or *Heterorhabditis*. *Phasmarhabditis hermaphrodita* is used for control of slugs (Grewal et al., 2005). An overview on mites with control potential is provided by Gerson et al. (2003). The majority of parasitic insects used in biological control are in the order Hymenoptera (e.g., Wajnberg and Hassan 1994; Malais and Ravensberg 2003; Helyer et al., 2003). A comprehensive review on methods to assess the risk of introducing exotic IBCA for use in area-wide, classical biological control or commercial biocontrol was edited by Bigler et al. (2006). These marco-organisms are not subjected to registration of plant protection products of the European Commission, which were laid down in

the EU Directive 91/414/EEC. However, some member states (MS), like Austria, require some fundamental data for registration of IBCAs.

Risks related to the use of IBCAs are mainly due to import and release of exotic species. These aspects are summarized in Chapter 11 (de Clercq and Bale 2011). For the use of exotics in biocontrol there is no specific legislation in any jurisdiction within Europe so far. In those European countries, where regulation of IBCA is in place, it is either in the hands of authorities or institutes dealing with plant health or nature conservation and exceptionally dealt with by pesticide registration authorities. Hunt et al. (2011) reviewed the practice of IBCA regulation in OECD countries in Chapter 3 and Bale (2011) summarized proposals of the REBECA consortium on how to organize regulation of IBCAs (Chapter 16). An overview on IBCAs widely used commercially or in classical biological control in Europe and neighbouring Mediterranean countries is provided by the European and Mediterranean Plant Protection Organisation (EPPO 2010).

Viruses, bacteria and fungi need to be registered. Table 1.1 provides a list of all strains of microbial biological control agents (including viruses) that are currently authorized by the European Commissions Directorate General for Health and Consumer Affairs (SANCO). Table 1.2 lists all strains, for which the registration is currently reviewed.

Baculo- and nucleopolyhedrosis viruses are used in biological control of insects, almost exclusively against lepidopteran pests (Shuler et al., 1994; Hunter-Fujita 1998). Because of their safety for mammals (no transmission of mammalian pathogens) insect-baculovirus expression systems have received wide acceptance in pharmacology and medical research for production of recombinant proteins (Murhammer 2007). Safety aspects of baculoviruses were summarized in the document ENV/JM/MONO(2002)1 (OECD 2002). Chapter 12 presents the proposal to the EU authority SANCO for regulation of these viruses (Hauschild 2011).

Recently, mild strains of plant pathogenic viruses, which cause mild foliar mottle but no fruit symptoms, are inoculated to healthy plants to protect the crop against more virulent virus strains; however, these viruses have not yet received a registration as plant protection organism (Desbiez and Lecoq 2003).

One of the most successful biological control agents is the entomopathogenic bacterium *Bacillus thuringiensis* (Bt) (Charles et al., 2000). Comprehensive data material is available on the safety of Bts as insecticides (Glare and O'Callaghan 2000) and the World Health Oranisation (WHO) ranks Bt as the safest existing insecticide (International Labour Organisation and United Nations Environment Programme 1999).

Bacteria are also used to control plant diseases. Of major importance are members of the Enterobacteria, *Pseudomonas* and *Bacillus* spp. (Siddiqui 2006). Much research progress was made on the understanding of the mode of action of rhizobacteria for disease control and growth and plant health promotion (Bakker et al., 2008, Boland and Kuykendall 1998). Possible risks related with the use of bacteria in biological control are summarized in Chapter 7 (Alabouvette and Cordier 2011) and Chapter 8 (Berg et al., 2011).

Table 1.1 Microbial control agents (including viruses) listed on Annex 1 of the Directive 91/414/EEC until July 2010

Microbial control agent	Strain	Product name	Company	Use
Ampelomyces quisqualis	AQ10	AQ10	Intrachem, I	Powdery Mildew
Bacillus subtilis	QST 713	Serenade	Agraquest, USA	Fungal Control
Bacillus thuringiensis subsp. *aizawai*	ABTS-1857	Xentari	Valent Bioscience, USA	Lepidoptera
	GC-91	–	Mitsui Agriscience, J	Lepidoptera
Bacillus thuringiensis subsp. israelensis	AM65-52	Gnatrol	Valent Bioscience, USA	Fungus Gnats
Bacillus thuringiensis subsp. kurstaki	ABTS 351	Dipel	Valent Bioscience, USA	Lepidoptera
	PB 54	Belthirul	Probelte, E	Lepidoptera
	SA 11 and SA12	–	Mitsui Agriscience, J	Lepidoptera
	EG 2348	Leptinoc, Rapax	Intrachem, I	Lepidoptera
Bacillus thuringiensis subsp. tenebrionis	NB 176	Novodor	Valent Bioscience, USA	*Leptinotarsa decemlineata*
Beauveria bassiana	ATCC 74040	Naturalis	Intrachem,I	White Flies
	GHA	Botanigard	Laverlam, CO	Homoptera, Thrips
Coniothyrium minitans	–	Contans	Prophyta, DE	*Sclerotinia sclerotiorum*
Cydia pomonella NPV	Mexican	Madex	Andermatt, CH	Apple Codling Moth
	Mexican	Granupom	Probis, DE	Apple Codling Moth
	Mexican	Carpovirusine	Arysta, F	Apple Codling Moth
Gliocladium catenulatum	J1446	Prestop	Verdera, FIN	Fungal Control
Lecanicillium muscarium	Ve6	Mycotal	Koppert, NL	Homopteran Insects
Metarhizium anisopliae	BIPESCO 5F/52	Granmet	Agrifuture, I	Insect Pathogen
Paecilomyces fumosoroseus	Apopka strain 97	Preferal	Biobest, BE	Homopteran Insects
Paecilomyces lilacinus	251	Bioact	Prophyta, DE	Plant Nematodes
Phlebiopsis gigantea	several	Rotstop	Verdera, FIN	*Heterobasidium annosum*
Pseudomonas chlororaphis	MA342	Ceral, Cedomon	Bioagri, SE	Seed Treatment Fungi
Pythium oligandrum	M1	Polyversum	Biopreparaty, CZ	Fungal Control
Spodoptera exigua NPV	–	Spodex	Certis, USA	*Spodoptera exigua*
Streptomyces sp.	K61	Mycostop	Verdera	Fungal Control
Trichoderma aspellerum	ICC 012	Remedier, Tenet	Isagro, I	Fungal Control
	T11	Tusal	Newbiotechnic, E	Fungal Control
	TV1	Xedarvir	Xeda, F	Fungal Control
Trichoderma atroviride	IMI 206040	Binap T	Binap Bio-innovation, S	Fungal Control
	T 11 (T25)	Tusal	Newbiotechnic, E	Fungal Control
Trichoderma gamsii	ICC080	Remedier, Tenet	Isagro, I	Fungal Control
Trichoderma harzianum	T22	Trianum	Koppert, NL	Fungal Control
	ITEM908	Micover	Agrifutur, I	Fungal Control
Trichoderma polysporum	IMI206031	Binap T	Binap Bioinovation, SE	Fungal Control
Verticillium dahliae alboatrum	WCS850	Dutch Trig	BTL Bomendienst, NL	Dutch Elm Disease

Table 1.2 Microbial control agents, including granulose- (GV) or nucleopolyhedro-viruses (NPV). Listing on Annex 1 of the Directive 91/414/EEC pending until July 2010

Microbial control agent	Strain	Use
Adoxophyes orana GV	BV-0001	*Adoxophyes orana*
Aureobasidium pullulans	DSM 14940 + 14941	*Erwinia amylovora*
Candida oleophila	O	Post harvest fungal control
Helicoverpa armigera NPV	–	*Helicoverpa armigera*
Paecilomyces fumosoroseus	Fe9901	Insect control
Pseudomonas sp.	DSMZ 13134	Seed treatment fungi
Pseudozyma flocculosa	PF-A22 UL	Powdery Mildew
Spodoptera littoralis NPV	–	*Spodoptera littoralis*
Trichoderma atroviride	I-1237	Fungal control
Zucchini Yellow Mosaik Virus	weak strain	Zuchini Yellow Mosaic

Likewise, fungi are used to control insects and plant diseases. Fungi for insect and nematode control are in the genera *Metarhizium*, *Beauveria*, *Paecilomyces* and *Lecanicillium* (Butt et al., 2001). The major groups of fungi used in disease suppression are in the genera *Trichoderma* and *Gliocladium* (Verma et al., 2007; Kubicek and Harman 1998; Harman and Kubicek 1998), but non-virulent isolates of plant-pathogenic fungi, like *Fusarium* spp., are also used (Lemanceau and Alabouvette 1991). Of general concern during the regulation process of fungal BCAs are toxic fungal metabolites. These risks are reviewed by Strasser et al. (2011) in Chapter 9. Proposals for improvement of the regulation requirements for MBCA are summarized in Chapter 13 (Strauch et al., 2011).

Among the so called botanicals, some are highly toxic and thus are excluded from use as plant protection products (e.g., nicotine). Others, like neem or pyrethrum, are less toxic for non-target organisms and have long been used safely in integrated pest management (Regnault-Roger et al., 2005). Throughout evolution, organisms have developed semiochemicals that are involved in intra-and inter-specific communication and several molecules are currently used for monitoring insect pest populations or applied in mating disruption (sex pheromones) and others can be used as repellents (allomones) or attractants (kairomones) (Howse et al. 1998). The sex pheromones are long chain fatty acids, which are not subjected to registration when used in monitoring flight of adult insects or estimating their population density with, e.g., sticky traps; when used for area-wide control of mating (mating disruption), they need an authorisation. Safety of pheromones and other semiochemicals used for arthropod pest control has also been reviewed by the OECD (2003). Risks of botanicals and semiochemicals were reviewed by Regnault-Roger (2011) in Chapter 10 and recommendations on how to improve registration for botanicals is presented in Chapter 14 (Tamm et al., 2011) and for semiochemicals in Chapter 15 (Speiser et al., 2011).

Agricultural ecosystems benefit from the resident communities of antagonistic macro- and micro-organisms responsible for naturally occurring biological control of pest and disease species. The environmental and economic significance of

biological control by far exceeds chemical control when taking into account the economic benefit of the naturally occurring antagonistic spectrum present at any agro-ecosystem. These antagonists prevent outbreaks of most of the known pest and disease populations, thus avoiding major crop damage. Only a minority of pest and disease populations need to be reduced by control measures, the majority do not exceed the economic threshold level due to the antagonistic potential of BCAs. Knowledge-based ecosystem management (Pickett and Buggs 1998) can help to preserve or even promote the positive impacts of BCAs. Under these circumstances biological control is never regulated by any authority. Whatever is endemic at a certain place is considered to be part of the natural environment.

When used by man in plant protection, BCAs are introduced or applied as an inoculative release, an augmentative or an inundative application. The application can be limited to a glasshouse or field or can be area-wide, which is typical for classical biological control. In classical biological control, natural enemies are released against introduced exotic pests, diseases or weeds. They have been imported from the place of origin of the pest. Biological control makes use of these natural resources for plant protection. BCAs are taken from natural environments. They are not synthetic. Mankind and other organisms share a long-lasting evolution with these antagonistic beneficial organisms, of which some are also used in biological control. This does not imply that biological control agents are without risks.

Regulation comes into play only when biological control agents or botanicals and semiochemicals are artificially augmented in the environment. Whether used in commercial biological control or classical biological control makes no difference.

When it comes to inundative or inoculative use of BCAs, their economic significance is small, with an overall annual turnover of 3% of the total plant protection revenues (IBMA 2008), but is growing rapidly with annual increases of between 5 and 20% (Frost and Sullivan 2001). Commercialisation of BCAs is mainly in the hands of small-and-medium-sized enterprises (SMEs).

The potential of biological control for use in agriculture, horticulture and forestry is immense. Nowadays, fewer and fewer chemical compounds make it to the market. By contrast, the exploitation of the huge biodiversity with potential for biological control has only just begun and provides an impressive reservoir for plant protection with potential to substitute many hazardous chemical control products.

1.2 Regulation of Biological Control Agents in Europe – the REBECA Policy Support Action

Plant protection products (PPPs) can be harmful to humans and the environment. For this reason their risks need to be evaluated and active ingredients must be authorised prior to commercial use and authorities need to develop risk management strategies to minimize possible negative effects. Authorisation for use is only given if unacceptable negative effects to humans and the environment can be excluded. Registration of PPPs based on BCAs follows rules originally developed for the risk assessment of synthetic chemical compounds. Although the data requirements for

micro-organisms have been adapted twice to facilitate the registration process, the requirements still are one of the major hurdles for BCAs to reach the market. The stringent regulation policy for BCAs, based mainly on registration rules for synthetic chemical pesticides, has hampered the development and use of biological control in Europe.

The current situation for registration of BCAs is as follows:

- Considering the market potential, costs are too high (between 0.5 and 2.5 million €)
- The market size often cannot support costs, consequently few products are available
- BCA registration takes too long, sometimes exceeding 9 years for Annex 1 inclusion
- A major obstacle is the subsequent member state authorisation (additional 2 years)
- Countries vary in interpretation of guidelines
- Mutual recognition is not well implemented
- Guidelines/requirements are not set up for BCAs
- With a lack of knowledge and experience, regulation adopts the precautionary principle
- Efficacy trials are more difficult and costly for BCAs
- Regulation authorities and SMEs often have limited knowledge on BCA registration
- Registration is a blackbox that cannot attract venture capital and investment
- Registration is a major barrier of entry for SMEs

Much investment went into research and development of BCAs in the public and private sector. Despite these activities, progress in exploitation of BCAs in agriculture has been limited. This motivated the EU Commissionś General Directorate for Research to publish the following call for proposals: "Despite considerable research efforts on BCAs the number of such products on the market in Europe is currently still extremely low. BCA cannot be treated like synthetic chemicals and need different approaches for registration purposes". After 15 years of disappointing results with registration of biocontrol agents following Dir. 91/414, the need for a review of regulation procedures for BCAs was realized.

The result of an application to this call was the EU Policy Support Action REBECA (Regulation of biological control agents in Europe), which gathered all stakeholders in biocontrol in Europe to build a network for exchange of information and a platform for discussions on how to improve regulation of BCAs in Europe. The Action was supported by valuable contributions from experts from overseas.

The Action first wanted to review possible risks of biocontrol agents. In parallel, experts compared regulation in the EU with rules in other OEDC countries. The results were then presented in a first joint conference. The next activity was to work on the development of proposals for alternative or improved regulation rules. The proposals were then presented during the final conference held in Brussels. The

progress was reviewed by an Action Steering Group, which gathered members of science, policy, regulation and non-governmental organisations. The flow chart of the REBECA Action is presented in Fig. 1.1.

The work was divided into the following work packages (WP), which were managed by different REBECA participants.

- WP 1: *Management and co-ordination* was in the hands of Olaf Strauch, Miriam Döring and Ralf-Udo Ehlers (Christian-Albrechts-University, Kiel, Germany)
- WP 2: *Comparison of current legislation practice* was divided into two tasks, the review on IBCAs managed by Ulrich Kuhlmann (Commonwealth Agriculture Bureau International, Delemont, Switzerland) and all other agents organised by Rüdiger Hauschildt (GAB Consulting GmbH, Lamstedt, Germany) and by Bernard Speiser and Lucius Tamm (FIBL, Research Institute for Organic Agriculture, Frick, Switzerland)
- WP 3: *Risk assessment of microbial biocontrol agents* organised by Hermann Strasser (University Innsbruck, Austria)
- WP 4: *Risk assessment of botanicals and semiochemicals* organised by Lucius Tamm (FIBL, Switzerland)
- WP 5 RA: *Risk assessment of macrobials* organised by Jeffrey Bale (University of Birmingham, UK)
- WP 6: *Risk trade-off and cost-benefit analysis of regulation* organised by Heikki Hokkanen (University of Helsinki, Finland)
- WP 7: *Measures to accelerate regulation* organised by Anita Fjelsted (Danish Environmental Protection Agency, Copenhagen, Denmark)

The objectives of the Actions were to elaborate proposals that could help to

– develop less bureaucratic and more efficient regulation procedures
– develop more balanced regulation according to potential hazards
– maintain the same level of safety for human health and the environment
– accelerate market access
– lower registration costs
– define “low risk products”, which might be exempted from registration
– propose alternative regulation systems

The results of the Action and much additional information on regulation requirements and biocontrol safety information were disseminated on the webpage http://www.rebeca-net.de, which also made available the reports and deliverables.

1.3 History of Biocontrol Registration

In Europe, PPP regulation was introduced in the 1960s. On the initiative of the chemical industry, governments gave authorisation exclusively for those pesticides, for which evidence for their efficacy was provided. Environmental aspects were

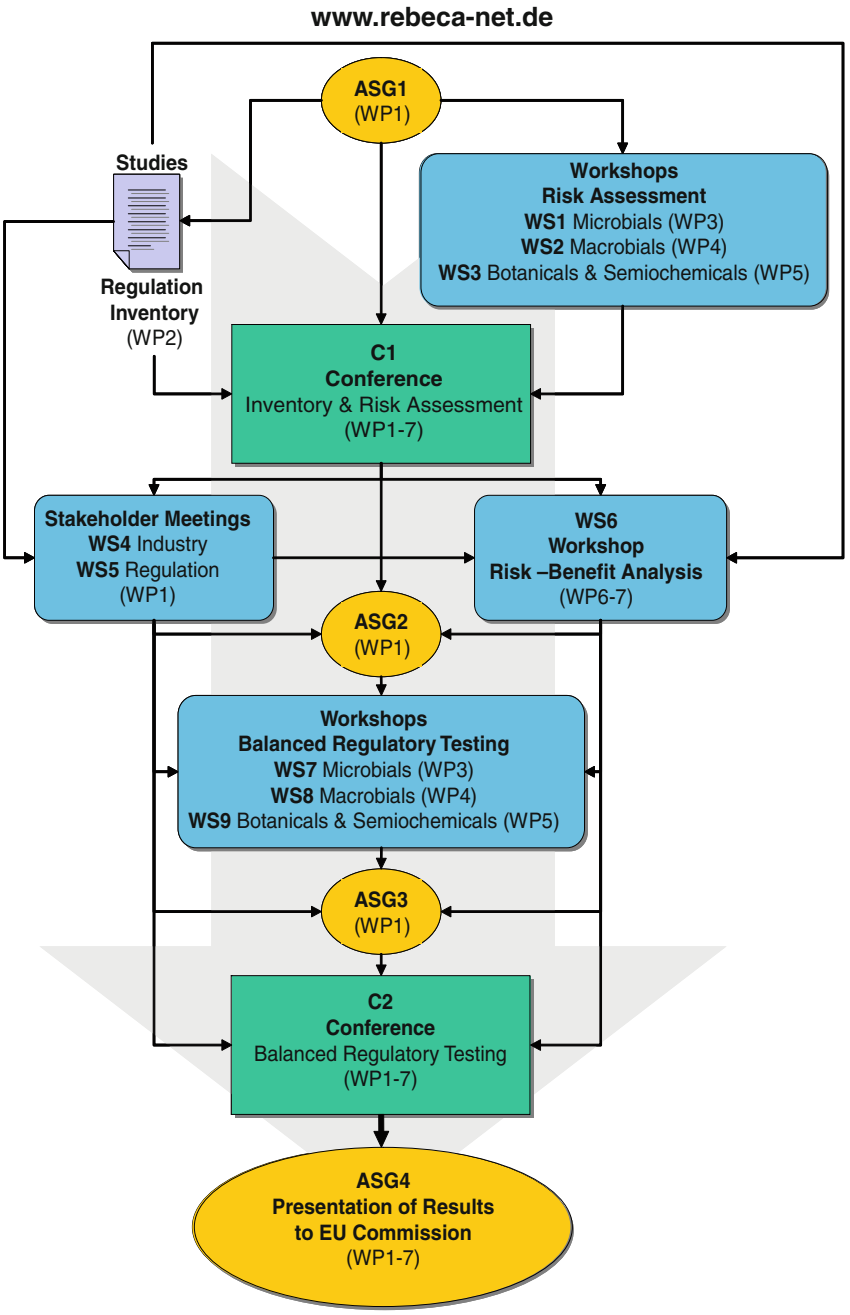

Fig. 1.1 Flow chart presenting the organisation of the REBECA EU Policy Support Action. AGS: Action Steering Group; WP: Work Package; WS: Workshop

only considered and included in the registration process in response to concerns about accumulation of the organochlorine insecticide DDT in the food chain. Since then PPPs posing unacceptable risks have been banned and/or substituted, and the chemical industry adapted to the increasingly strict standards by monitoring safety aspects at an early stage of product development. The history of regulation has been a process of replacement of one chemical group by another, which often exhibited another set of problems. This process was accompanied by the development of more and more stringent rules taking into account scientific reports of damage caused by synthetic compounds and anticipated risks of new compounds. Governments responded to reports of damage with the development of new rules to ensure that similar impacts will not occur with new compounds.

Since the introduction of regulation in Europe, registration requirements and guidance documents had always been developed in consultation with multinational agrochemical companies. Other than regulation of synthetic compounds, regulations for biological plant protection products have not evolved within such a process:

- Regulation of biological PPPs was not a gradual evolution involving industry
- Regulation was not based on scientific reports of damages, as there are hardly any reports on damage of BCAs
- There is no evolution of regulatory rules for BCAs; the rules for synthetic compound were imposed on biocontrol without consulting the biocontrol industry
- Adapted and more balanced approaches existing in some member states were even rolled back with the introduction of Dir. 91/414 as a consequence of better harmonisation.

For example, in Germany, before implementation of Dir. 91/414, the requirements for PPP based on insect viruses were much reduced after the first file (*Cydia pomonella* GV) had been processed. With the implementation of Dir. 91/414, applicants had to provide a complete data set again.

Although not a good example for handling even minor risks, for many years Italy had no regulation for microbial BCAs in place. Companies only needed to use the scientific name of the agents on their products. *Bacillus thuringiensis, Trichoderma harzianum* and many other micro-organisms had been marketed without evaluation of safety data until 2006. No damage was recorded.

With the introduction of the EU regulation old active ingredients had to undergo the process of re-registration. According to EU policy objectives, this process is targeted at the substitution of more risky PPPs. With increasing knowledge and scientific evidence about damage and potential risks of old synthetic compounds, a re-registration is a logic consequence. However, for biological control agents, which have been safely used for decades without any reports of damage and for which more and more knowledge has been gathered proving their safety, such a re-registration seems unnecessary. The re-registration requirement was the consequence of handling biologicals like synthetic PPPs and was not based on scientific information on damage and risks. Many biological control agents, for which re-registration has not been applied, are now out of the market. It does not mean that they are risky. The

market is too small to justify the registration costs. Farmers have lost safe natural products due to policy decisions, which aim to limit negative effects of synthetic compounds; as the same rules are implemented also for the safe alternatives, the effect is counter-productive.

Compared with the chemical industry, the participation of the biocontrol industry in defining regulatory rules was minor. One reason certainly was the rudimentary representation and ineffective group organisation of the comparatively young biocontrol enterprises. Another was the limited knowledge and experience available in these companies and also on the side of regulation authorities. Only a few years ago, the OECD asked for industry participation when discussing guidance documents for micro-organisms and invertebrates, but it was only with the start of the REBECA Action that an intensive dialogue between all stakeholders in regulation of biological control agents was introduced. The Action was very well attended and resulted in a better dissemination of knowledge and experience among all stakeholders. The policy aspects of regulation are reviewed by Grant (2011) in Chapter 5.

With the limited economic importance of biocontrol during the time of implementation of Dir. 91/414, one can understand why little emphasis was given to specify regulation for BCAs. However, this situation has now changed. Problems with chemical control compounds increase and growers in Europe are starting to realise the potential of BCAs. The biocontrol industry is flourishing with up to 20% increase in annual sales. Growers start to realize that BCAs have the potential to close control gaps and substitute some of the environmentally risky synthetic PPPs. In order to protect consumers more effectively from residues of synthetic PPPs, avoid hazards for users of synthetic PPPs and preserve agro-ecosystems, a rapid market access for biological products would be desirable. A better adapted regulation procedure would help to reduce restrictions and ease the market access for environmentally sound biocontrol PPPs.

In view of the history of regulation of BCAs, the REBECA consortium proposes to

- continue the dialogue between all stakeholders
- critically review the existing regulatory practice
- develop new and innovative strategies for BCA regulation
- consider more adapted regulatory measures according to the real risks of BCAs

1.4 The Precautionary Principle in Risk Assessment

The precautionary principle is the basis of European risk management and is thus also applied to biological control agents. It is often mentioned that BCAs might possibly pose risks similar to synthetic PPPs or pose unknown risks that have not yet been identified. These “unknown unknowns” are often a justification for the execution of the precautionary principle on BCAs and why rules similar to those developed for chemical compounds are applied.

The decision making in regulation is based on data from investigations and applying experimental models for assessment of potential risks. Data are used to predict

hazards and quantify the probability of occurrence and the development of risk management strategies. However, the system could not always prevent hazards to the environment. Atrazines, for instance, were detected in the ground water and their use had to be banned. Only recently, tolyfluanid-containing fungicides were banned because the compound is metabolised in the soil to dimethylsulfamid (DMS), which is displaced into the ground water.

These failures of the regulatory system to prevent hazards to the environment, have resulted in it becoming customary to demand the application of the precautionary principle for regulation of PPPs, including those of biological origin. This new approach is forming the basis of the European regulatory systems and is reflected also in the Rio Declaration (1992): "in order to protect the environment, the precautionary approach shall be widely applied by states. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation". The REBECA consortium could not identify major threats with severe consequences for humans and the environment related with the use of currently registered BCAs or invertebrate BCAs.

Within the EU Commission, the interpretation of the precautionary principle treats the principle less like a dogma but more as the beginning of a serious analysis of how to approach risks within the authorities dealing with risk assessment and management. The Commission published a communication on the precautionary principle (European Commission 2000) outlining the EU Commission's approach to use the principle and establishing guidelines for application. The Commission clearly states "that recourse to the precautionary principle presupposes that potentially dangerous effects... have been identified and that scientific evaluation does not allow the risk to be determined with sufficient certainty." Is this an argument to demand the application of the precautionary principle for the regulation of BCAs? Risks related with the use of BCAs have been described and in many cases their dimension has been scientifically assessed. The RAFBCA project (QLK1-CT-2001-01391) worked on fungal antagonists and the ERBIC project (FAIR5-CT97-3489) on invertebrate BCAs. Both projects identified potential risks and also concluded on their dimension and probability of occurrence. Together with the results gathered and summarized by the REBECA Action (www.rebeca-net.de: Safety information) or the biopesticide fact sheets provided by the Environmental Protection Agency in the USA (http://www.epa.gov/pesticides/biopesticides/#factsheet) much information is available to conclude that regulation of BCAs can be based on scientific evidence and that we do not need to apply the precautionary principle. Thus, we do not have so many "unknown unknowns" but rather a set of known risks with limited dimension.

The Commissionś communication further outlines the general principles of risk management measures (COM (2000)1):

- proportionality
- non-discrimination
- consistency,
- examination of the benefits and costs of action or lack of action
- examination of scientific developments

Measures should be proportional to the desired level of protection and should not be discriminatory in their application. A comparable situation should not be treated differently and different situations should not be treated in the same way. Taking this principle literally, we must analyse whether the reduced risks related to biological PPPs now paves the way for the separation of the risk assessment practice of biological and synthetic products.

The Commission demands that "measures should be consistent with the measures already adopted in similar circumstances or using similar approaches." Biological PPPs often only share their use in plant protection with synthetic compounds. Many other comparable agricultural practices are not regulated like BCAs. The use of organic fertilizers (containing a much higher amount of micro-organisms than used in biological control) is not regulated. Nitrogen-fixing *Rhizobium* bacteria are applied to seeds and are not regulated. In many countries the plant-growth promoting products are subject to lower level regulation. Even in the food industry alternative approaches are successfully used. The "qualified presumption of safety" (QPS) concept provides a generic assessment system for micro-organisms deliberately introduced into the food chain (see also Chapter 17). This system allows for experience to be introduced into the assessment and should be further elaborated for the assessment of plant protection products.

In addition, the Commission states that "measures.... shall be re-examined and if necessary modified depending on the results of the scientific research and the follow up of their impact." As much more scientific information is now available this seems to be a good opportunity to review the legislation of BCAs and develop more balanced, better adapted and more cost-effective regulation procedures for BCAs.

The REBECA Action was a starting point to produce a network of all stakeholders involved in regulation of BCAs. Within the time frame of the Action, the activities concentrated on providing proposals for a short term improvement of conditions. Further activities in the analysis of the risks and the development of innovative regulation strategies must now follow to provide the appropriate conditions for a faster development of biological control measures in European agriculture. The rules defined by the Commission need to be applied also to BCAs.

Reviewing the Commissionś communication of the precautionary principles the REBECA consortium proposes to

- treat BCAs in a non- discriminative way
- consider their lower risk compared with synthetic compounds
- take into consideration experience and available data from comparative use
- re-examine measures based on new scientific results on the safety of BCAs

1.5 Stakeholders

The REBECA Action tried to get as many competent stakeholders as possible to participate in the Action. In the area of regulation of BCAs, stakeholders are in academia and industry, and farmers and producers are affected; stakeholders

also include consumers and the retail sector, environmentalists organised in non-government organisations (NGOs), regulatory authorities and policy makers.

1.5.1 Academia

Scientists, who are working in development of BCA in public entities, are interested in successful implementation of their R&D results. Most of the BCAs currently in the market originate from the activity of public research organisations, institutes of higher education or governmental research organisations. Much research into the safety of BCAs is also undertaken by these research organisations, a motivation for the academic sector for more research activities into scientific assessment of risks and risk analysis. Often these activities result in more rather than less registration requirements.

1.5.2 Industry

An important stakeholder is the biological control industry. The structure of biocontrol industry is diverse. The large (transnational) chemical companies have no major interest in BCAs for several reasons. Most products have a short shelf life and thus do not fit well into the distribution logistics of the chemical companies. BCAs are often more expensive than the synthetic compounds in their portfolio. Marketing strategies for BCAs are more difficult to develop and biocontrol products would be competing with their own synthetic products. On the other hand, this industry has huge R&D and registration departments, which involve tremendous costs and the usually smaller markets of BCAs cannot show a financial return on the investment. The chemical companies prefer to go for "blockbusters" rather than for niche products, like BCAs. However, since the concerns regarding pesticide residues increase and are constantly highlighted in the media, chemical companies are currently developing interest in the biocontrol sector. For example, Bayer Cropscience (Monheim, Germany) is testing *Bacillus firmus* for nematode control and BASF (Limburgerhof, Germany) and AgraQuest Inc (Davis, CA, USA) have entered into a license, supply and distribution agreement for Serenade®, a bio-fungicide based on *Bacillus subtilis*. Syngenta Bioline Ltd (Little Clacton, Essex, UK) are producers of natural beneficial insects, mites and bumblebees for integrated pest management in horticulture.

In the past the economic significance of biological control was negligible but since the biocontrol industry has become the major supplier for PPP in the glasshouse sector and has now expanded applications into out-door crops, the biocontrol industry has become a small, but important, competitor. As a consequence this might also motivate competitive interests rather than support of activities to ease registration requirements for BCAs.

Most biocontrol companies are small and medium-sized enterprises (SMEs). Several biocontrol companies are spin-offs of public research organisations. These

start-up companies usually lack capital for larger investment into registration. Investment capital is difficult to obtain from the financial markets as business plans appear unattractive, due to the unpredictable duration of the registration process. Authorisation also of biocontrol products can last for more than 10 years and can involve costs exceeding 2 million €. Consequently, companies were either successful when they were marketing IBCA (insects, mites and nematodes), which are usually exempted from registration (e.g., Koppert, in The Netherlands or Biobest, Belgium) or when they were able to attract venture capital to support the registration (e.g. Agraquest). Some of these companies now have smaller product portfolios. Others were able to start joint ventures with, or were acquired by, larger companies in the food and agriculture sector who supplied the necessary financial resources for product registration (e.g. Bioagri AB in Sweden).

The biocontrol industry is organized within the International Biocontrol Manufacturers´Association (IBMA) (http://www.ibma.ch) and the BioPesticide Industry Alliance (BPIA) (http://www.biopesticideindustryalliance.org). Within the REBECA Action the IBMA was often represented by Ulf Heilig, a private consultant in registration support, who contributed a lot to the discussions and elaboration of proposals.

The interests of industry in the Action were quite diverse. On the one hand, larger companies, who run experienced registration departments and had registered products in the market, were more reluctant about reduction of the registration requirements. They had gone through the mill, why should other have an easier run? Other companies, who were new in the business and had not yet registered their results of R&D or had products in registration, were more open to support the Action. In the area of IBCA regulation the larger companies were the driving forces to define Europe-wide regulation rules and smaller companies did not participate in the work, due to lack of expertise and personnel.

Working with biocontrol industry one must always have in mind that registration is a possibility to protect markets and exploit competitive advantages. In the biological control sector innovation is not easily protected. Living organisms cannot be patented and the same is also the case for protection of results of genetic improvement by selective breeding. The biocontrol industry is trying to keep intellectual property in-house. Under these circumstances an authorisation for a biological control agent is of larger value than for a well protected chemical compound.

1.5.3 Farmers and Producers

Users of BCAs are found in the conventional and organic agricultural and horticultural sector. Forestry is increasingly moving away from plant protection, but in some countries produces considerable demands for BCAs, particularly for *B. thuringiensis* based products. As an increasing number of synthetic chemical compounds have not been defended (re-registered) by the chemical industry or have been withdrawn due to environmental concerns, the agricultural sector is lacking alternative PPPs. Of the previously existing active ingredients of PPPs listed in Annex 1 of Dir.

91/414, 67% were not defended, 7% were rejected and 26% approved within the re-registration process (Richardson 2009). Biological control would be able to fill part of this gap; however, the sparse financial input into registration resulted in limited product availability. As a consequence, the majority of the farmers and producers have not considered these products as realistic alternatives. The image of the early biocontrol industry was bad. In the past, the products were considered to be of low quality, too expensive and lower in control efficacy than chemical compounds. With this image of biocontrol products, producers did not lobby for biological alternatives to be supported by governments. The chemical paradigm (knock-down effect, cheap, easy-to-use, preventive treatment) is difficult to change and biological control products had major problems in persuading the conventional sector to use their products.

This has changed, not radically, but in small steps, since the conventional sector has experienced successful replacement of synthetic compounds by BCAs (e.g., in the greenhouse sector in Mediterranean countries, the use of CpGV against codling moth in apple orchards, *B. thuringiensis* products against lepidopterans with resistance to synthetic insecticides). The lobby of farmers still is more in favour for chemical compounds, however, the door has been opened and in the future producers might advocate more for political support of biological alternatives.

1.5.4 Consumers and Retail Sector

The debate about pesticide residues in food produce was one of the driving forces for the development of biological control. For a long time non-government organisations (NGOs), like Greenpeace, made public residues in vegetables and fruit and offered residue-free shopping lists on their webpage, without any major impact on the use of synthetic compounds. It was only when the NGOs began to search for residues in produce sampled from the shelves of different retailers that the campaign began to have an impact on the purchasing policy of the retailers. Suppliers are today put on contracts, in which they have to guarantee that pesticide residues in their produce would not exceed retailers specifications, which are below what governments allowed and which is limited to only two or three substances. Although the retail sector, in the beginning, had just implemented these rules without discussing alternative control strategies with the suppliers, this policy made many producers switch to alternative and residue-free control strategies in the horticulture sector. The further development of new products to supplement the PPP portfolio suddenly is of increasing interest and cooperation between the biocontrol and retail sector should in the future be intensified to enhance the confidence in the quality and potential of biological control strategies. Thus, the policy of the retail sector has become the major driving force for implementation of biological control. Whether the retail sector will support the activities to reduce registration requirements is doubtful as they are advocates for the safety of the consumers and have little expertise in judging risks of BCAs or comparing these risks with risks resulting from the use of chemical PPPs.

1.5.5 Environmentalists Organised in NGOs

PAN (Pesticide Action Network) and Greenpeace are two NGOs active in the assessment of risks related with the use of chemical PPPs. Their activities related to pesticide residues in food have resulted in an increasing implementation of biological control in the past decade. However, so far they have not participated in the discussion on risks and regulation of BCAs. Asked to participate in the activities of the REBECA Action, they confessed that they lack expertise as their focus is on chemical control substances. Criticism is more powerful when better alternatives can be offered. Consequently, the biological control sector should increase their efforts to integrate and cooperate with NGOs.

1.5.6 Regulatory Authorities

Regulation in Europe is a two-phased process. The active ingredient is authorised by the EU Commission DG SANCO and the formulated product is still a matter of national authorisation. However, one Rapporteur Member State (RMS), which is usually selected by the applicant, is in charge of putting together the data requirements and producing the Draft Assessment Report (DAR) for submission to SANCO. Northern Europe countries share a well developed infrastructure for pesticide registration; several Southern European member states have caught up, but new and smaller member states still lack the resources and expertise. The EU-wide harmonisation of registration rules was a necessary political step to exclude competitive advantages in the agricultural sector and improve on the safety for the consumers. As a result of the "mad-cow-disease", the EU created another European organisation, the European Food Safety Authority (EFSA), which is now advising the Commission in questions of pesticide safety. This organisation is building expertise and hopefully will, in the future, also provide excellence in reviewing risks of BCAs.

The re-registration of the PPPs was a tremendous workload for the authorities. Now the work is done and at the same time fewer chemical products are being developed and only a few make it to the market. As companies can select the RMS, authorities in Europe will face competition for submissions and might run into shortage to keep their departments busy and maintain the expertise. Some countries have already implemented guidance programmes to support authorisation of BCAs (GOENOG in NL and Biopesticide Scheme in the UK). The aim is to bring more biological products to the market, facilitate the initial contact between companies and authorities and help industry through the approval process (see Chapters 5 and 17). As it will reduce costs for the evaluation, it is a useful strategy to attract companies to those member state authorities that provide this support.

Regulators administrate the rules set by policy makers. They are dealing with the dossiers and transfer regulation into practice. The progress of the REBECA Action depended greatly on the contribution of regulatory personnel. Their expertise was very valuable as they were open to provide information and actively participated.

In the beginning of the Action, we anticipated much more input and innovative proposals for change from the biocontrol industry and less from regulation authorities. During one workshop a participant regulator mentioned that the job of a regulator was to regulate and not have visions about future solutions to ease the registration of BCAs. For several reasons the contribution from industry was less compared with the regulators, who contributed to the discussions and provided input for improvements.

1.5.7 Policy-Makers

Policy-makers did not participate in REBECA, possibly because the REBECA consortium was not able to attract their attention or because their awareness of biological control was/is remote, which is probably due to the rudimental level of representation of the biocontrol industry at the EU and MS administrations and its limited resources to support lobbying. In the past, the biocontrol industry had no lobby and thus was not noticed. This becomes apparent when analysing the decisions of European policy-makers on the reduction of the use of pesticides (EU 2009b). The European Parliament decided on a "Thematic Strategy on the Sustainable Use of Pesticides", stating that low pesticide-input farming needs to be promoted, priority should be given to non-chemical methods and meaningful support to organic farming. MS should be required to set up National Action Plans for reducing pesticide use and the development of plant protection products with a low risk profile should be encouraged. It is obvious that neither Parliament Members nor politicians on the MS level considered that the use of biological control agents would result in a significant reduction of chemical pesticides, otherwise they would have recommended the use of BCAs in their documents. In this aspect, policy is not meeting its own objective, which is to reduce pesticide use. Their support for biological control, with few exceptions, has always been of minor impact and was limited to support of research projects.

Another problem is that policy-makers are usually not aware that decisions taken to restrict the use of chemical pesticides have, at the same time, negative effects on biological control. As BCAs are covered within the same legislation as synthetic compounds, restrictions on the use of synthetic compounds automatically apply also for BCAs. These trade-off effects are often neglected by policy-makers.

Within the REBECA Action representatives of almost all stakeholders contributed to the success of the activities. Besides the provision of reviews on existing regulatory practice and the proposals made to improve the regulation of biological control agents, which are all summarized in this book, a significant success of the REBECA Action was the organisation of a platform for exchange of information and opinions for all stakeholders This initiated a Europe-wide discussion on regulation of BCAs, which will also lead, hopefully one day in the near future, to a further improvement of regulation for biological control agents and thereby accelerate the provision of environmentally friendly plant protection products for the agricultural sector.