Project no. SSPE-CT-2005-022709

REBECA

Regulation of Biological Control Agents

Specific Support Action

Sustainable management of Europe's natural resources

Final Activity Report

Period covered: from **01 January 2006**	to **31 December 2007**	Date of preparation: 28 March 2006
Start date of project:	01 January 2006	Duration: 2 Years
Project coordinator name: **Prof. Dr. Ralf-Udo Ehlers**		
Project coordinator organisation name: **Christian-Albrechts-University of Kiel**		

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Objectives

As set out in the CAP package 2003, developing agricultural techniques that are both ecologically sound and economically viable, will require new and powerful tools and assessment methods for the management of pests and diseases in European agriculture, horticulture and forestry. Biological control agents (BCA) are part of these tools. Despite considerable research on biological and natural control agents (beneficial insect, mites and nematodes, microbial plant protection products, plant derived substances and semiochemicals), the number of such products on the market in Europe is currently low.

Worldwide biological control agents are increasingly occupying their place in Integrated Crop Protection Programmes. They are sustainable and environmentally safe tools to manage invertebrate pests (e.g. insects, nematodes), weeds (e.g. *Convolvulus*) and diseases (e.g. *Botrytis, Sclerotinia*) in agriculture, forestry and horticulture. However, registration procedures have been established for micro-organisms, semiochemicals and botanicals, which prevent their immediate market introduction. In contrast, macrobials (insects, mites and nematodes) are exempted from registration in most European countries. European SMEs, through the sale of macrobial BCAs, increased their turnover from almost zero to > 100 million € within the last two decades.

Due to their nature and specificity of action, as well as dependence on environmental factors, these agents and substances cannot be treated in the same was as synthetic chemicals and therefore they need a different approach for risk assessment and management. Currently, microbials, botanicals and semiochemicals are regulated under the directive 91/414, which was originally developed for chemical pesticides. The directive 91/414 was amended in order to add the specific requirements of micro-organisms (see directive 2001/36/EC and 2005/25/EC). Macrobials are regulated in some MS following rules developed by MS authorities. Registration of all other biocontrol agents largely follows the systems developed for synthetic pesticides, which has been not well adapted for biological substances and products. Costly risk assessment studies and long term evaluation of dossiers inhibit the market development of these products.

Several European governments have developed strategies to reduce the inputs of chemical pesticides and concomitantly support the use of sustainable, biological control strategies. For instance the UK and NL have encouraged the registration of BCAs by reducing registration fees. During the ongoing negotiations among member states and the Commission on a new regulation of plant protection products Sweden has proposed strategies and amendments of the legislation to allow “products of low concern” to remain on the market, whereas many of these products are withdrawn from the market during the fourth round of the EU review of active ingredients. The urgent need for harmonisation and reduction of requirements have resulted in the development of more balanced directives[1] and guidelines[2]. Scientific publications have summarized the latest knowledge on risk assessment strategies (e.g.,

[1] Directive 2001/36/EC amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market.
[2] OECD Guidance for Registration Requirements for Microbial Pesticides, 2003

Hokkanen & Hajek, 2003)[3]. However, this has not yet resulted in easier access to EU markets.

The aim of this Action was to accelerate the market introduction of environmentally safe BCAs. These products are urgently needed by growers who are currently trapped between the diminishing number of chemical pesticides and lack of safe alternatives. Proposals for a balanced regulatory environment will lead to better access to BCAs for growers and farmers and therefore to further reductions in the use of chemical pesticides.

A major objective of the project was to accelerate the registration process of BCAs, to reduce costs and at the same time maintain the level of safety to producers and users of these compounds and to consumers of agricultural products. The aim of the project was to review the current legislation requirements for BCAs at EU and member state level and compare the regulatory process with those applied in other countries such as the United States, Canada and Australia, where BCAs have easier access to the market.

During the project proposals were developed on how the regulation of BCAs can be balanced in the EU according to their potential hazards. REBECA reviewed the risks related to the use of BCAs and proposed new and more appropriate risk assessment strategies. Risks to human health and the environment related to the use of BCAs are a central part of the whole Action. Because BCAs are a heterogeneous group of agents specific analysis of related risks according to their nature is necessary. Risks related with the use of semiochemicals, for instance, differ from those related with the use of microbials. The risk assessment thus needs to consider specific characters of the different groups of BCAs. REBECA contributed to the definition of low risk products, which might be exempted from registration and developed proposals for alternative regulation systems.

Potential risks were evaluated and a cost-benefit analysis of regulation was performed. Costs, necessary to perform the investigations to estimate potential risks were estimated. In a comparative analysis we tried to weigh the benefits and risks of regulation and compared these among different groups of plant protection products.

REBECA brought together stakeholders from industry, science, regulatory authorities, policy and environment to spread knowledge and experience in regulation and safety of BCAs and to identify those fields that need further research to assist regulation. A major objective of this Action is to form a network within Europe bringing together the expertise and critical mass necessary to improve regulation procedures for BCAs and to disseminate relevant information among companies developing BCAs and regulatory authorities on the EU and national level and other interested stakeholders. The Action has provided a list of potential experts, who can assist the EC and member states in the evaluation of risks and regulation of BCAs and identify future research tools to support the development of balanced regulatory strategies.

[3] Hokkanen & Hajek, 2003: Environmental Impacts of Microbial Insecticides – Need and Methods for Risk Assessment. Kluwer Academic Publishers.

The REBECA Action was divided into 7 work packages led by 9 contractors:

1. *Project management and dissemination of results*
   Ralf-Udo Ehlers, Olaf Strauch, University of Kiel, Germany
2. *Inventory of current legislation and guidance documents*
   Rüdiger Hausschild, GAB Consulting GmbH, Lamstedt, Germany
   Ulrich Kuhlmann, CABI Bioscience, Delémont, Switzerland
   Antoon Loomans, Department of Entomology, Plant Protection Service, Wageningen, The Netherlands
3. *Risk assessment Microbials*
   Hermann, Strasser, University of Innsbruck, Austria
4. *Risk assessment Botanicals & Semiochemicals*
   Lucius Tamm, Bernhard Speiser, FiBL, Frick, Switzerland
5. *Risks assessment Macrobials*
   Jeffrey Bale, University of Birmingham, United Kingdom
6. *Risk-benefit analysis of regulation*
   Heikki Hokkanen, Ingeborg Menzler-Hokkanen, University of Helsinki, Finland
7. *Measures to accelerate regulation processes*
   Anita Fjelsted, Danish Environmental Protection Agency, Copenhagen, Denmark

The results could serve as a basis for reviewing current legislation and guidance for BCAs. REBECA has established an internet page (www.rebeca-net.de) which gives an introduction to the Action, announces meetings, presents the results, and gives links to governmental and non-governmental organisations, related projects and legislative and guidance documents for BCA registration.

List of REBECA deliverables

All deliverables are published on the REBECA internet page (http://www.rebeca-net.de/).

No	Title	Workpackage
D4	Minutes of ASG meetings 1-4	1
D5	Minutes of discussions on workshops and conferences	1
D6	Web page for external communication making available all relevant information	1
D7	Web page for internal communication enabling orientation on activities	1
D8	Inventory documenting the current regulatory practice and data requirements on microbials, botanicals, semiochemicals and macrobials	2
D9	Interim report on relevant risks and tools to determine risks of microbial BCAs	3
D10	Proposals for improved regulatory procedures for microbial BCAs	3
D11	List defining knowledge gaps for microbial BCAs	3
D12	List for “low risk” candidates of microbials	3
D14	Summary of risks and tools to determine risks for botanicals and semiochemicals	4
D15	Compilation of objectives for WS8 on balanced regulatory testing for botanicals and semiochemicals	4
D16	Improved regulatory procedures for botanicals and semiochemicals and list of knowledge gaps	4
D17	SWOT analysis on improved regulatory road map based on case studies for botanicals and semiochemicals	4
D18	Positive list for “low risk” candidates semiochemicals and botanticals	4
D19	Draft guideline for hierarchical regulatory system for macrobial BCAs	5
D20	Description of research methodologies to underpin proposed regulatory system for macrobial BCAs	5
D21	Agreement on criteria for inclusion of species of macrobial BCAs on a 'Positive List'	5
D22	Evaluation of options for implementing a pan-European regulatory system for macrobial BCAs	5
D23	Proposal for regulatory system and testing guidelines for macrobial BCAs based on retrospective case studies	5
D24	Cost analysis, trade-off analysis, benefit analysis completed	6
D25	WS6 synthesis completed	6
D26	Comparative analysis comparing benefits/risks among different groups of plant protection products completed	6
D27	Proposals on how to accelerate regulation and reduction of fees	7
D28	Specification of “low risk products”	7
D29	Proposal for alternative regulation strategies	7
D30	Strategy for immediate implementation of results	7

General topics

Comparative studies on the current regulation practice

The REBECA project carried out comparative studies on the current regulatory practice in the EU, USA, Canada, Australia and New Zealand (see deliverable 8). One study was carried out regarding the regulation of micro-organisms, plant extracts and semiochemicals (Rüdiger Hauschild, GAB, Germany; Bernhard Speiser, FiBL Switzerland). Such BCAs are regulated in the EU under the same Directive (91/414) which regulates the placing of plant protection products on the market. The aim of this study was to identify EU specific hurdles for the registration of BCAs, reducing the availability of low risk biological plant protection products compared to countries outside the EU.

Further comparative studies were carried out for the regulation of beneficial insects, mites and nematodes (inside EU: Antoon Loomans, Plant Protection Service, The Netherlands; outside EU: Emma Hunt, Ulrich Kuhlmann, CABI Bioscience, Switzerland). At the present time, there is no uniform regulation of these beneficial organisms across member states. The use of beneficials is regulated at the level of individual member states, based on different national legislation and authorized by different institutions. Countries such as Australia, New Zealand, Canada and the USA have more coordinated systems for regulating the import and release of exotic invertebrate biological control agents (IBCAs). The aim of these studies was to develop recommendations based on features of the regulatory processes that work well in the investigated countries and that could be adopted to generate a workable Europe-wide regulatory system.

Evaluation and registration of plant protection products based on micro-organisms, plant extracts and pheromones in the EU, USA, Canada and Australia

Legislation - authorisation

The registration process in the EU has a different structure from all other systems. Registration is divided in two parts (1. Annex I inclusion of active substance; 2. authorisation of plant protection product), while such a division does not exist in the other parts of the world investigated during this Action. Annex I inclusion of the active substance is evaluated at EU level. The dossier containing all information on the active substance and on at least one representative product is submitted to a member state, the designated Rapporteur Member State (RMS). Authorities of the RMS carries out a risk assessment and distribute the Draft Assessment Report (DAR) to the applicant and the other member states. Further evaluation is done by the member states and the European Food Safety Authority (EFSA). Following this evaluation, the member states, and the European Commission decide on inclusion or non-inclusion of the active ingredient into Annex I of Directive 91/414. Plant protection products are regulated at the national level of member states. By contrast, the registration is processed mainly by one authority in the USA, Canada and Australia, as opposed to many authorities involved in Europe. In the USA however, a state may have more stringent requirements for registering pesticides for use in that

state or may also register an additional use of a federally registered pesticide product or a new end-use product to meet special local needs.

The process has a guaranteed maximum duration in the USA, Canada and Australia (missing information «stops the clock», or even resets it, and after arrival of the information starts it again). In the EU, timelines are also defined for the first step of the evaluation process (check of completeness, preparation of the DAR), but may be extended, if additional information is required. In the later steps of the evaluation strict timelines are not applied in the EU. Experience with registration in the EU shows that the time effectively needed for registration is much longer than in the USA. However, in the present EU negotiations on a new regulation of plant protection products more strict timelines are suggested, in particular for national authorisation of low risk products.

Data requirements

The formal data requirements are similar in the EU, Canada, Australia, and the USA. The individual micro-organisms and plant extracts used in plant protection products are very heterogeneous and data requirements have to cover all cases. Therefore, data are formally required even if the required information is not applicable to a particular active substance or micro-organism, a particular product or its intended uses. However, formal data requirements in all regulatory systems do not necessarily mean that this information has to be provided by a study, but may also be derived from published literature or unpublished, existing data. In the USA, Canada and Australia, certain data requirements may be met with a 'waiver'. The applicant has to apply for a waiver, by providing a scientific argument (mostly derived from published literature and own data of the applicant). If the waiver is granted, no study has to be provided. This 'waiver system' does not formally exist in the EU. A scientific argument in the dossier summary – without a formal waiver – serves the same purpose. However, it seems that waivers are accepted more easily in the USA, Canada and Australia than reasoned cases are accepted in the EU. Furthermore, the scientific justification might be evaluated differently in different EU member states, which may lead to additional data requirements during the evaluation process.

Summaries as provided in the OECD format dossiers are required in the EU and recently also in Canada. These summaries are considered to be very useful to scientific evaluators for the preparation of assessment reports and DARs, especially from a time-saving perspective. However, the summaries make up a significant proportion of the applicants' efforts for dossier preparation.

In the USA (and to a lesser extent also in Canada and Australia) the use pattern of the product and the nature of the micro-organism or substance greatly influence the data requirements. In the EU, only one set of data requirements exists, and studies are waived case-by-case. The flexibility of the data requirements in the EU creates uncertainty regarding the data requirements for specific cases, whereas the data requirements are more clearly defined in the USA.

A common interpretation of data requirements has not yet evolved in the EU (e.g.: what is a 'relevant metabolite'?). In this situation, many applicants choose to submit minimum data packages, in order to save costs for studies which might not

necessarily be required. This may lead to demands for further studies later on the registration process, thus considerably lengthening the process.

Regulation of invertebrate biological control agents in Europe

Within the framework of the REBECA action the current legislation, regulation and guidance practice in the European Union and in separate European countries was reviewed. Various EC-directives have been adopted that control the introduction of specific, assigned groups of exotic species, such as those that may pose a threat to economically important plants (crops) (Commission Directive 2000/29/EC). Almost all European countries have signed the Convention on Biological Diversity (CBD) and adapted the CBD principles for species of conservation concern (Article 22(b) in the Council Directive 92/43/EEC on the Conservation of Natural Habitats and of the Wild Fauna and Flora (Habitat Directive). Already in the European predecessor to CBD and the subsequent EC Habitat Directive, Article 11(2)(b) of the Convention on the Conservation of European Wildlife and Natural Habitats ("the Bern Convention", 1979), all contracting parties are held to "…strictly control the introduction of non-native species". The EU however, has no intention to regulate the import and release of IBCAs on a central level by legislative measures. DG-SANCO will not regulate macrobials, because they are not plant protection products and have no impact of health or consumers. Many European countries have legislation in place, but only a few have implemented an active regulatory process. In countries with an operational regulatory system this is based either on nature protection, plant protection, and/or pesticide acts. Eight countries (Austria, Czech Republic, Denmark, Hungary, Norway, Sweden, Switzerland, U.K.) have developed a regulatory and administrative procedures to some degree, six countries are still working on the design and implementation of a regulation system (Finland, Germany, Ireland, Netherlands, Slovenia, Spain) and another six, likely more, countries have no regulation implemented yet and would not have a regulatory system in place in the foreseeable future (Belgium, France, Greece, Italy, Poland, Portugal).

Data requirements vary largely between countries and depend largely on the type of regulation underpinning the legislation. In the case of approval as plant protection or plant protection products, most requirements stress human and plant health, but forms do not emphasize specific environmental criteria and characteristics. In those countries where nature conservation legislation has to be taken into account (Norway, Netherlands, UK, Switzerland), specific environmental criteria, such as information on the establishment in the wild, on host specificity and non-target effects have to be met. Usually, less data requirements are required for native species than exotic ones. Sometimes native species only need registration (Spain). Evaluation of native species usually follows a "short track" risk assessment, whereas exotic species are assessed more thoroughly.

There is a need for harmonization on a European level and several international organizations have developed guidelines and standards on the implementation of regulation of IBCAs and guidance documents on data requirements for environmental risk assessment. Since 1996, when EPPO [European and Mediterranean Plant Protection Organization] established its Panel on "Safe use of biological control", it has developed several standards on first import of exotic biological control agents for research under contained conditions, import and release

of exotic biological control agents, as well as a list of IBCAs widely used in the EPPO region. Although these standards are not legally binding, they are useful instruments for a National Authority (c.q. National Plant Protection Organisations) to structure the facilitation, implementation and need for information requirements for risk assessment of IBCAs. Guidelines mentioned above aim to facilitate procedures for a proper risk assessment, but they do not yet provide working instructions for the risk-assessment itself.

Regulation of invertebrate biological control agents in Australia, New Zealand, Canada and the USA

Europe lags far behind Australia, New Zealand, Canada and the USA in terms of implementing regulatory procedures for the import and release of invertebrate biological control agents (IBCAs). There are several recommendations that can be given for a European IBCA regulatory system based on the systems in place in Australia, New Zealand, Canada and the USA. These countries have been implementing some form of IBCA regulation for at least 40 years. Their regulatory systems have also been evolving in complexity over the years and thus the components that help make them efficient and workable systems, as well as those that do not, are by now quite apparent.

None of the four countries analyzed apply restrictions to the use of native IBCAs, except in New Zealand when the IBCA is a protected native species. As its first step, Europe should follow this lead and apply regulations only to exotic IBCAs, which can be described as ‘not native to a particular country, ecosystem or ecoarea (applies to organisms intentionally or accidentally introduced as a result of human activities). Australia, New Zealand, Canada and the USA all have legislation in place covering the import and release of IBCAs and this has so far proved to be an effective method of regulating the use of IBCAs across each country.

In terms of the dossier review process, this broadly operates in much the same way in Australia, Canada and the USA in that the dossiers are distributed to scientific experts within the country for independent review. In New Zealand, scientific experts are also often consulted or co-opted onto the review panel. Reviewers are a combination of university and government-affiliated scientists representing a broad range of expertise. The main difference between countries is that Canada and the USA both have a committee for the sole purpose of conducting these reviews. Although there is no specific review committee in Australia, the opinions of the 21 scientific co-operators also play a significant role in the outcome of the IBCA release application. In New Zealand, the opinion of scientific experts consulted or co-opted onto the review panel is also central to the decision-making process. The science-based independent review process has worked efficiently for the countries in which it operates. It is quite feasible that a similar system could be successfully implemented in Europe, with the creation of a panel of scientific experts reviewing dossiers.

It is clear from the analysis of the regulatory systems in Australia, Canada and the USA that having legislation and administrative bodies to oversee the introduction and release of IBCAs does not necessarily mean that the application process is expensive for the biological control practitioner. Administrative costs in Australia, Canada and the USA are covered by public money via the national governmental

bodies and the review process in these countries operates on a voluntary basis, so that scientists are not paid for the reviews they conduct. This leaves the applicant with minimal fees to pay upon dossier submission. In order to avoid biological researchers and industries in Europe being faced with additional administrative fees, it is recommended that a similar system be adopted for Europe.

Establishing a legislative and administration system in Europe does not automatically imply that the IBCA release application review process would require protracted periods of time. In New Zealand, there is a legal requirement for ERMA New Zealand to provide a decision within 100 working days of receiving a dossier and in Canada, an applicant may expect to receive a response within 6 months of submitting a dossier. With a simplified and efficient administrative process, Europe could certainly aim to attain equally reasonable and workable time scales.

Cost-benefit and trade-off analysis of BCA regulation

REBECA carried out a cost-benefit analysis of regulation. The objective of this study was to analyse how the level of regulation impacts the development and market access of BCAs, and to analyse whether the level of regulation has had an effect on the documented or suspected environmental or health hazards caused by BCAs. Furthermore, a tradeoff analysis examined the drawbacks of regulation in terms of consequences for plant protection, farmers, consumers and food safety.

The first part of this study concerned a detailed survey among all the companies involved in BCA development, registration and marketing in Europe. Several of the major companies were visited, and others were surveyd via a questionnaire sent to 52 other companies active in the BCA area. The survey focussed on the time and cost of registration of BCAs, and the impacts of regulations on the R&D activities and the overall company strategies.

Company survey feedback was obtained from a total of 21 companies: ABITEP, Agraquest, Agrisense, Andermatt, Becker Underwood, Bioagri, Biobest, Biocare, CBC Europe, Denka, e-nema, Exosect, Futureco, Intrachem Bio, Isagro, Koppert, Prophyta, Sautter & Stepper GmbH, Trifolio, Valent, and Verdera.

Information on the impact of regulatory costs and/or time on new R&D indicates that most companies still plan to bring new BCAs into market, while several others do not plan to invest into new R&D for BCAs. Products not requiring registration, of products (ai's) which already have been registered, have priority in the R&D of these companies. Several companies indicated that they would bring more BCAs into the European market if conditions for registration were more favourable; many replied that they prefer to focus on other geographical regions where the climate for this business is more favourable (North America, Asia ect.). Three companies indicated that they had shelved BCAs mainly due to registration costs/time. These companies had spent on average 200,000 € in R&D on these products by the time of deciding to discontinue their commercial development. Furthermore, several companies do not plan to initiate new R&D on BCAs under the current situation, but their plans depend on "positive results from REBECA".

The balance of costs and benefits was found to vary substantially across stakeholder groups. Thus, those who bear the private costs of development and application seem to have the most unfavourable balance of costs and benefits, while consumers of the final product and opinion formers have the most favourable balance. This emphasises the importance of considering the balance of private and public goods.

A trade-off analysis examines the drawbacks and benefits of current regulation of biological plant protection products in the EU in terms of its consequences for plant protection, farmers, consumers and food safety. REBECA WP6 organized a workshop on the topic. E. g. a costly and lengthy registration of BCAs can restrict severely their market entry in the EU, and would lead to trade-off effects in areas such as farming activities, human health, environment, and commercial biocontrol activities. Trade-off were indicated in the following fields:

- development of SMEs
- availability of specific acting small market products
- alternatives to chemicals
- residues on food
- external costs of plant protection products regarding human health and the environment

The conclusion from this study is that the replacement of chemical pesticide treatments by biological controls would bring immense socio-economic benefits to the society: the benefits from controlling the pests would still accrue, but the negative externalities would disappear. The current regulatory system for BCAs in the EU has severe trade-off effects. These contribute in several key areas to the EU not meeting their stated policy objectives:

– Pesticide reduction programmes
– Increasing proportion of organic production
– Safer food with less pesticide residues
– Safer and more diverse environment
– More jobs
– More SMEs

General proposals for improvements of the current regulation practice

Introduction

One task in the REBECA Action was to develop general proposals for improvement of the current regulation practise. This was done by first sending out a questionnaire to all participants of the first REBECA conference. Participants were asked to give a list of main obstacles and proposals to solve them. The received proposals were further discussed during several REBECA workshops, and the proposals were circulated to different stakeholders in order to get their comments and their opinion on advantages and disadvantages of the proposals. Based on this discussion the final list of proposals regarding the more general aspects of the regulation e.g.

communication, guidance documents, fees and strict and short timelines were developed.

Improved communication between regulators and applicants

In order to shorten the evaluation process and to avoid the preparation and submission of unnecessary data by the industry, there is a need for further communication between regulators and applicants. This can be achieved e.g. by arranging pre-submission meetings. In these, applicants and evaluators gain a better understanding of the substance and of the procedures relevant for its evaluation, and clarify which data are likely to be required during the evaluation. Many countries have established pre-submission meetings as a routine. This is for instance the case within the UK PSD and their experiences are positive throughout. Applicants avoid producing unnecessary data, and regulators save time, because dossiers better address those points which the regulators consider important. However, also further increase in the communication is needed later on in the evaluation process, e.g. during expert meetings.

REBECA proposals:

- Pre-submission meetings shall be established as a routine in all EU member states.
- Applicants should for each application prepare a pre-submission information package
- Applicants should have the opportunity of attending part time at evaluation/experts meetings

Improved communication between regulators

There is a lack of expert groups on BCAs in the EU regulatory system. REBECA propose that one expert group is established for each of the following types of active substances: microbials, botanicals and semiochemicals. An expert group on microbials does exist already, however, it needs to be enlarged and formalised, and meetings need to occur more regular. The purpose of this proposal is to increase the communication, harmonization and consistency between member states as well as to facilitate and speed up procedures.

For each expert group, one member state/expert or EFSA expert is appointed as chair. The chair/EFSA facilitates a high level of information exchange and is responsible for the coordination of regular meetings. The groups comprise a representative from the Commission, a minimum of one EFSA expert, national regulatory authorities including national experts with experience in evaluating the particular type of active substances. The expert meetings should be hosted and financed by the EFSA. The minutes of the meetings should be made available to all MS (and should be reported at meetings of the WG legislation).

The groups will discuss various issues (ecotox/fate/human health, etc.) in plenum, without splitting into subgroups, which is normal practice for chemical active substances. The purpose of the expert groups is to discuss risk assessment and risk management issues for the specific group of BCAs. Discussions in these groups will facilitate the peer-review process. The groups will also develop draft guidance documents, which are subsequently discussed and finally agreed upon by all MS. To

reduce travel expenses, the expert groups should try to organize their meetings jointly with other meetings. Conference calls /video conferences and e-mail discussions may also be useful tools.

REBECA proposal:

- Establishment of EFSA expert groups for three groups of BCAs: Microbials, botanicals and semiochemicals.

Guidance documents

A large number of microbials, semiochemicals and botanicals are currently under EU review in the so called 4th stage. When this process has been finalized, the EU regulators will have obtained more experience in assessing these kinds of substances. In a number of reports/draft guidance documents on "lessons learned from the 4th stage" regulators could summarize their experiences with these substances. Of course, data protection has to be respected. For micro-organisms the production of such documents has already been discussed. The lessons learned documents could be used for various purposes, as suggested in proposal A and B below.

The «lessons learned documents» should be used by applicants and regulators in general and in particular during future pre-submission meetings to determine data requirements/waivers for new substances in analogy to substances evaluated during the 4th stage. In the pre-submission meeting, it must be clarified in which way the applicant has to address the data requirements.

Further more the lessons learned documents could be used to justify a generic approach for certain groups of BCAs and as a basis for determining generic safety profiles.

REBECA proposal:

- Development of lessons learned guidance documents to be used in pre-submission meetings to determine data requirements/waivers and generic safety profiles

Fees and financial support

The regulatory authorities normally take fees for carrying out the risk assessment of BCAs and for authorising plant protection products. The size of the fee varies greatly among member states. The highest fee taken so far for a micro-organism is just above 200.000 €. Microbials, botanicals and semiochemicals are in most cases niche market products. In addition, most of these products have very low risk profiles and are therefore particularly in line with relevant EU Policies. This justifies indirect subsidies in the form of reduced registration fees, as is already the case e.g. in Canada, USA and many EU member states, or other means of support/subsidies. Registration fees can make up a significant proportion of the total costs for product development.

Many BCAs are developed by SMEs who do not have any or very little experience in applying for product authorisations. The process of generating an EU dossier and national applications for authorisations of their products is very complex and time consuming. Most SMEs ask consultancies for help in this process. However, it would

reduce the cost for product development and result in faster procedures if regulatory authorities would help the SMEs through the registration process. In addition it would certainly help the SMEs if they would be financially supported for the registration process. Funding could come from various sources, such as rural development actions, IPM and organic action plans, promotion of SMEs or taxes on pesticides. In The Netherlands, the project GENOEG has used such an approach with success. In the UK the Biopesticide scheme provides guidance to applicants.

REBECA proposals:

- National registration fees as well as fees for Annex I inclusion to be lowered substantially for microbials and semiochemicals.

- SMEs applying for registration of new microbials, botanicals or semiochemicals should be financially supported by specific programmes and should be given detailed guidance by the regulatory authority.

Generic approach in risk assessment

The 'precautionary principle' is a fundamental element of Directive 91/414. Its assumption is that all potential risks have to be excluded, before a substance can be included into Annex I of the directive. A practical consequence in the registration of micro-organisms is that most often data are required at the strain level, and not at the species level. In areas other than plant protection, other strategies of risk management are discussed. For micro-organisms entering the food chain, EFSA considers the «QPS» (Qualified Presumption of Safety) concept. QPS is based on scientific evidence and experience. Wherever possible, a more generic approach is taken instead of a full case-by-case assessment. It allows the generic listing of micro-organisms, provided that certain criteria are met, e.g. absence of acquired antibiotic resistance factors. QPS should be similar in concept and purpose to the GRAS (Generally Recognised As Safe) concept used in the USA, but is not identical to GRAS.
Experience gained during the EU evaluation of the micro-organisms in the 4th stage of re-evaluation may be taken as a basis to determine in which cases a generic approach is justified. For instance it might be possible evaluating certain micro-organisms at species level and evaluate other substances as groups as well (e.g. certain botanicals and semiochemicals). However, this approach can only be followed if there is enough experience/scientific evidence about a certain group

REBECA proposal:

- Establish risk management strategies taking a generic approach wherever possible, and restricting case-by-case evaluations to those cases where this is necessary and justified.

Strict and short timelines

Most applicants of BCAs are SMEs and they only have resources to apply for national provisional authorisation of their products in very few (1-2) member states

during the process of Annex I inclusion of their BCA. However, due to the large investments in the preparation of the dossier etc., it is crucial for the industry to reach the market as soon as possible, either by provisional authorisations, or by obtaining authorisations right after the Annex I inclusion. It is thus important for the applicants that the Annex I inclusion is obtained as fast as possible.

In the past, Annex I inclusion of micro-organisms has taken several years. This is a hurdle for the industry. In the USA and Canada, strict timelines are in place for the registration of BCAs. Strict and short timelines would provide better predictability on the length of the evaluation/registration process.

REBECA proposal:

- Strict and short timelines for the EU risk assessment as well as for national registrations should be included in the EU regulation. The timelines should be as short as is practicable to enable the appropriate risk assessments to be checked, and to ensure they have been supported by robust information.

Specific data requirements for each group of BCAs

Some stakeholders believe that even though it has been attempted, the Directive 91/414 it is still not adequately adapted to the special properties of microbial biocontrol agents and semiochemicals, which have completely different modes of action than the conventional pesticides, as well as completely different modes of production, methods for characterization and environmental and human health risk profiles. Proper evaluation of microbials and semiochemicals requires a different approach with different data. However, microbials and semiochemicals also differ greatly from each other. For these reasons, separate legislation or at least new and revised specific set of data requirements should be developed for those two groups.

REBECA proposal:

- Generate new guidance documents with new specific data requirements for microbials and semiochemicals.

Efficacy evaluation

Compared with conventional chemical substances, many BCAs have a lower level of efficacy. There is some uncertainty as to what levels of efficacy are required for BCAs. In addition, many BCAs have a different mode of action as conventional chemical substances, which may make it necessary to adapt trial protocols. This is particularly the case for semiochemicals, where it is often impossible to use replicated trial designs.

It should be noted that efficacy is currently only an issue at member state level, not in the EU review system for Annex I listing. However, efficacy may become an EU issue with the revision of Directive 91/414.

REBECA proposals:

- Introduction of efficacy into EU evaluation need to be accompanied by guidance on evaluation criteria
- Authorities should accept modified trial protocols, provided that the applicant can justify the modification

- Products with minor beneficial effects should be acceptable
- No efficacy evaluation prior to a 5 year registration period, however, data should be collected over the first five years of market use.

Proposal for alternative regulation strategies

Based on a comparison of the history of regulation of synthetic compounds and biological control agents (BCAs) it becomes obvious that regulation procedures for BCAs in EU have not been introduced based on reports of damage, nor have they been a result of a gradual evolution in cooperation with industry and other stakeholders. The REBECA Action therefore proposes to continue the dialogue between stakeholders, which has been initiated by the Action, in order to develop innovative and more balanced approaches for the regulation of BCAs, which are more cost-effective and will accelerate market introduction of BCAs. A detailed analysis of the communication of the European Commission on the precautionary principle revealed that the rules laid down have not been applied to BCA regulation. Since BCAs have a in contrast to chemicals a history of safe use, a more balanced regulation procedure would be appropriate. REBECA support the Parliaments view of the European Parliament, which proposes a separation of the legislation from synthetic compounds, because of the potential advantages for the market assess of low risk plant protection products. However, REBECA is aware that this would be long term project and the problems for BCAs might remain unsolved. The Commission in its communication on the precautionary principle demands a re-examination of regulation measures based on new scientific results. Innovative and balanced regulation of BCAs will consider the real risks and allow for fast track systems for low risk products. Many registration requirements introduced for synthetic compounds might not be necessary for BCAs. A re-evaluation process should be accompanied by research projects to produce more data on the risks and safety aspects of BCAs. Finally it is outlined that current Common Agricultural Policy (CAP) promotes the reduction of pesticide use but does not consider BCAs as an alternative, although the potential for plant health and protection is immense. More biological products come to the market than synthetic compounds and their share is increasing yearly. A promotion of biological control concepts must focus on the financial support of R&D in the evaluation of safety and risks and support SMEs in their attempts to register new BCA products.

The REBECA community has identified the regulatory requirements for BCAs as one of the major hurdles preventing the access of further of these generally safer PPPs to the market. Alternative measures are therefore urgently needed which

- are better adapted to carry out risk assessments for the specific risks of BCAs
- are more efficient for assessment of the real risks
- reduce costs related with the registration process
- accelerate the registration process

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

Reviewing the Commission´s communication of the precautionary principles the REBECA consortium proposes to

● treat BCAs in a non- discriminative way
● considering their lower risk compared to 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.

In order to avoid unnecessary over-regulation and related costs the REBECA consortium proposes to

● analyse costs and benefits prior to introduction of new regulation demands
● take into account trade-off effects of regulation
● minimize trade-off effects and maximize efficiency of regulation
● develop cost-effective procedures and accelerate the registration process.

In order to promote the further introduction of biological control strategies, the REBECA consortium proposes to

● reduce consensus finding costs
● equip registration authorities with skilled personnel
● consider expert knowledge in the regulation process
● not allow abuse of registration system to protect markets
● waive fees for registration of BCAs
● support production of safety data.
● acknowledge the lower risk of BCAs in the development of new rules
● consider the possibilities to separate legislation of BCAs from synthetic compounds
● develop more flexible risk assessment procedures
● produce definitions for low risk
● introduce fast track systems for low risk products
● support development of risk assessment guidelines
● support closure of knowledge gaps on risks related with the use of BCAs
● take into account BCAs as potential substitutes for synthetic compounds
● focus on introduction of BCAs in reduction programmes
● support farmers during introduction of BCAs into IPM systems
● support knowledge transfer on BCA concepts to the farmers (from lab to farmer to fork).

For more detail see deliverable 29

Microbials

Introduction

Microbial biological control agents (MBCAs, covering viruses, bacteria and fungi) used in plant protection in the EU are regulated according to the EU Council Directive 91/414/EEC. This Directive was amended by the Commission Directive 2001/36/EC regarding the data requirements for the Annex I inclusion of micro-organisms as active substances and national authorisation of products (Annex IIB and IIIB in the directive respectively). The Uniform Principles for evaluation and authorisation of plant protection products containing micro-organisms are laid down in the Council Directive 2005/25/EC.

The industry complains that the current registration system for MBCAs in the EU is costly and time-consuming. Long registration periods (Tab. 1) are a severe problem, because they delay the onset of the returns for the investments made during research and development. In addition, longer registration periods result in shorter periods of sale under data protection.

Table 1: Time periods for selected microbial BCAs between submission of the dossier and Annex I inclusion in the EU. The period is indicated from the month of dossier submission to the month of inclusion on Annex I of Directive 91/414/EEC, or granting of national registration. Some of the products have obtained provisional registrations and were already on national markets before the active ingredient was listed in Annex I.

Organism - Product	Period (month.year)	Annex I inclusion time frame (months)
Paecilomyces fumosoroseus - Preferal®	5.94 – 6.01	85
Coniothyrium minitans - Contans®	11.98 – 8.03	57
Pseudomonas chlororaphis - Cedomon®	1.96 – 4.04	99
Ampelomyces quisqualis - AQ10®	2.96 – 10.04	104
Gliocladium catenulatum - Prestop®	3.99 – 10.04	67
Bacillus subtilis - Serenade®	5.00 – 2.07	81
Spodoptera exigua NPV - Spodex®	7.97 – 8.07	121
Average time frame		87.7

Reasons for the long lasting registration process for MBCAs are among others the unique regulation system in the EU involving now 27 Member States and missing experience with the registration of microbials on the regulator and industry side (see ‘comparative studies on the current regulation practice’, deliverable 8). Proposals for improvements on these points are reported in the section on ‘general proposals for improvements of the current regulation practice’ (deliverables 27 and 29).

The data requirements and methodology for the risk assessment were derived from the assessment system of chemicals. Even though, the Commission puts effort into the development of better adapted data requirements for MBCAs (Directives 2001/36/EC and 2005/25/EC), the current procedures can be still judged as not appropriate. Some data requirements seem to be unnecessary and the risk assessment methodology based on the assessment of chemicals is not properly adapted and validated for microbials.

Many micro-organisms are human, animal and plant pathogens and they are known to produce toxins and antibiotics. Therefore, a risk assessment of micro-organisms used in biocontrol is essential. However, humans and animals are regularly exposed to micro-organisms and the human community is spending many resources to identify human and animal pathogens. Therefore, on the basis of a proper identification of the microbials, public knowledge can be used to a great extent to assess the related risks. So far, no hazards have been posed by the use of MBCAs. In contrast to chemicals, MBCAs have a history of safe use. In consequence, a more balanced risk assessment for MBCAs is requested by the industry and supported by scientific experts in the field.

REBECA carried out 4 workshops on the risk assessment of MBCAs involving experts from science, regulatory authorities and industry (see deliverable 5). During these workshops the potential risks of MBCAs, the data requirements and the risk assessment methodology have been reviewed and knowledge gaps have been identified (deliverables 9, 10, 11). Furthermore, rationales for the identification of low risk products have been delivered (deliverable 12). REBECA developed proposals for a better adapted and more balanced risk assessment for microbials and the rationale for waivers on data requirements has been delivered (deliverable 10). Furthermore, research programmes were proposed in order to overcome major knowledge gaps hampering an adequate risk assessment of microbials so far (deliverable 11).

Review of potential risks

Baculoviruses

On the basis of current knowledge on the host specificity of baculoviruses, the use of these viruses in plant protection was identified as safe. Baculoviruses are pathogens of insects and highly host specific. In most cases, the host range is restricted to a few species within one genus, sometimes even to a single species. However, all viruses should be recognized as potential sensitizers and so far, no appropriate methods for micro-organisms exist for assessment of sensitization labelled in this manner. Potential risks of BCAs based on viruses can be due to co-formulants. Further more, since viruses are produced *in vivo*, there is a potential risk of sensitization or irritation due to insect hairs and microbial contaminations of the product. For more details see deliverables 9 and 10.

Bacteria and fungi

Micro-organisms are a very heterogeneous group and need to be assessed usually case-by-case. However, with regard to the effects on soil microbiota and on earthworms, the related risks are in general negligible. Earthworms are exposed to

high levels of many different micro-organisms and therefore highly resistant. Earthworm pathogens are not known. Changes in the soil microbiota are regularly occurring, particularly in agricultural soil ecosystems. Severe impacts on the composition and quantities of soil micro-organisms are observed during irrigation, tillage, application of organic or synthetic fertilizers or simply by crop rotation. Agricultural measures with negative impacts on the functional soil characters are not regulated, but are more severe than the release of microbial plant protection organisms.

Most of the micro-organisms used in biocontrol are very common in nature and therefore, a regular exposure of humans and animals can be presumed. Nearly all microbial BCAs originated or can be isolated from the soil and from plants, including food and feed. Consequently, the absence of hazard reports for those micro-organisms in the scientific literature is a strong indication that they pose only low risks.

REBECA developed a proposal for an environmental 'risk indicator' published in 2008 by Tobias Laengle (Pest Management Centre, Agriculture and Agri-Food Canada) & Hermann Strasser (LFU, Austria), allowing a comparative assessment of biological and chemical plant protection products and the identification of low risk products (see deliverable 28: Specification of low risk products). This risk indicator is a refinement of earlier models. However, the proposed model is the first indicator allowing a direct numerical comparison of relative environmental risks posed by microbials and conventional chemical pesticides. Five basic components have been proposed for the calculation of the overall environmental risk score: persistence of the substance, dispersal potential, range of non-target organisms that are affected, direct and indirect effects on the ecosystem and risks to vertebrate non-target species. This system was applied to a number of well-studied biological control agents and selected chemical products used for similar purposes. Indices were calculated using open literature and published regulatory documents. The organisms with the lowest risk index were soil applied fungi with very narrow host ranges applied to environments to which they are native. These organisms consistently scored low in all categories. Biocontrol agents with broader host ranges delivered by spray application typically had a higher dispersal potential and also scored higher under direct and indirect effects, but remained about one order of magnitude or more below their conventional chemical alternatives

For more details see deliverables 9, 10 and 28.

Proposals for improved regulatory procedures for microbial BCAs

Baculoviruses

The high similarity between baculoviruses justifies a general assessment at the level of the family *Baculoviridae*, considering species-specific information where necessary. REBECA recommends listing the family *Baculoviridae* on Annex I. Several experts recommend limiting the inclusion into Annex I to "all Lepidoptera-specific Nucleopolyhedroviruses and Granuloviruses". A consensus view of representatives from regulation was that this could save resources for applicants and

MS without reducing safety for humans, animals and the environment. However, some representatives of regulatory authorities favour the inclusion at the level of individual species. This was supported as well by the industry for commercial and data protection reasons.

A facilitated procedure for the registration of new species or isolates can be performed similarly to the procedure for “equivalence of technical material“, as applied to chemically active substances for plant protection products. This necessitates the submission of an application for national authorisation of a plant protection product containing the new isolate at member state level. After national approval the MS reports to the Commission with a proposal for an inclusion of the new isolate in the review report of the equivalent isolate already included in Annex I.

Formally, each data point for the active substance and the product has to be addressed. However, most of the formally required data are published and equal for all baculoviruses, already assessed by MS and EU authorities and therefore, data on the isolate or species level are not mandatory. Product-specific data - according to Annex III data requirements - have to be provided, including the production method (medium components, larvae hairy or not), information on the amount of non-pathogenic and pathogenic bacteria and fungi, and composition of the product. Data on toxicology and ecotoxicology should be based on the composition of the product.

The proposed procedure to include baculoviruses at species level was adopted by the member states and the Commission in 2007 when the first baculovirus species was included in Annex I.

Bacteria and fungi

In order to simplify the registration procedure it is recommended to summarize the available data and to discuss relevant data requirements in a pre-submission meeting with the Rapporteur MS prior to submission of the dossier. The decision on the relevant data to be provided shall be based on the following information, which can be derived from the applicant's data and/or published literature:

- identification and taxonomic position of the MBCA
- natural distribution of the species, in particular on food and feed and in agriculture environments
- modes of action and host range
- toxicity data
- metabolites produced by the MBCA
- intended use of the product (target organisms)
- formulation of the product
- site and method of application
- health and medical reports
- absence from the list provided in Dir. 2000/54 EC concerning worker’s protection from micro-organisms
- maximum growth temperature
- list of available effective antibiotics.

The data provided shall be the basis for a decision on the provision of additional data in the dossier and the definition of waivers. These data might be sufficient to estimate a risk indicator as proposed in the REBECA deliverable 28 in order to identify low risk products.

Proposed waivers for data requirements:

- Data requirements on effects on earthworms and soil microbiota should be generally waived because hazards are very unlikely.
- Infectivity studies should be waived when all of the following requirements are met: no clinical reports, not listed in 2001/54 EC, humans and animals are already regularly exposed to the micro-organism, susceptibility against antibiotics.
- Data requirements regarding the instability of genetic traits affecting the efficacy of the product should be waived or removed because this will be checked by quality assurance.
- Data requirements on fate and behaviour in the environment should be waived for micro-organisms which are already part of the background population.

For more details see deliverable 10.

Knowledge gaps and proposed research programmes

REBECA carried out 5 workshops on microbial risk assessment and regulation, primarily in order to develop proposals on improvement of the current system. However, it became clear in early stages of this action that the development of proposals improving the current system is hindered by:

- significant lack on validated risk assessment methods for microbials
- knowledge gaps on natural exposure of humans and other non-target organisms
- missing definitions allowing the identification of low risk products.

This is hampering an adequate and balanced risk assessment of microbial plant protection products.

The current risk assessment for microbial biological control agents (MBCAs) is mainly based on whole animal test systems developed for chemical pesticides according to Directive 91/414 and the problems regarding the applicability of these methods for microbials are well known. Nevertheless, validated alternative methods for MBCAs are not available. The availability of high throughput and low cost alternatives to animal test systems will encourage the generation of innovative new products. Better adaptation of the test systems for microbials will improve the obtainable safety by the risk assessment of microbial pesticides, biocides and food additives. Potential alternatives to the current methodology are described in deliverable 11.

The Commission should set up a call in the 7th Framework programme for the development of better adapted risk assessment methods and the reduction of animal testing. The envisaged research programme should focus on studies with the

potential to refine or replace the animal tests commonly required by regulatory authorities. The validation of alternative test systems for microbials and the development of standard protocols and guidelines should be considered as important tasks. For that purpose, industry, regulatory authorities, the 'European Centre for the Validation of Alternative Testing Methods (ECVAM)' and the OECD biopesticide steering group should be involved.

Knowledge on the natural distribution of MBCAs or potential MBCAs and the related natural exposure of humans and animals will support a balanced risk assessment. Most of the micro-organisms used in biocontrol are very common and therefore, a regular exposure of humans and animals can be presumed. However, data on background and natural exposure levels are often not available. Such data will help to estimate the risks caused by an application of MBCAs to the environment, and to identify low risk agents, and can deliver the rationale for waivers on data requirements regarding infectivity, toxicity, non-target effects and fate in the environment. However, the biocontrol industry depends on public research in this field, as they usually do not have the human or monetary resources for such investigations.

The general applicability of the risk indicator model proposed by Laengle & Strasser needs to be validated on a broader basis with different kinds of plant protection products and may need to be refined further. The EU should support the further development of the proposed risk indicator model, also in view of the need for a comparative risk assessment of plant protection products which is included in the proposal from the Commission on a new regulation of plant protection products (2006/0136 COD).

Botanicals

Introduction

In this document, the term 'botanical' is used to describe active substances made from plants. Plants, and particularly plant extracts, have been used for plant protection for a long time. Extracts can range from crude to highly purified substances. Quantitatively, the most important botanical is pyrethrum, followed by neem, rotenone and essential oils. Ryania, nicotine, sabadilla, garlic oil and *Capsicum* oleoresin have limited use. Typical uses are: insecticides (e.g. pyrethrum, rotenone, rape seed oil, quassia extract, neem oil, nicotine); repellents (e.g. neem); fungicides (e.g. laminarine, fennel oil, lecithine); herbicides (e.g. pine oil); nematicides (e.g. neem); sprouting inhibitors (e.g. caravay seed oil); adjuvants such as stickers and spreaders (e.g. pine oil); allelopathy. Plant extracts and other materials of plant origin are also used for purposes not covered by Dir. 91/414, such as fertilizers and soil conditioners (e.g. green waste compost, seaweeds and seaweed extracts, sawdust, wood chips, composted bark, bark of hemlock pine [iron micronutrient fertilizer]); biocides (e.g. pyrethrum, azadirachtin as insecticides, citronella as repellent). Some plant products which are mainly used as foods or spices also have a secondary use in plant protection, e.g. rape seed oil, lecithine, garlic, mustard powder, fennel and caraway. Thus, botanicals are an extremely heterogeneous group of substances, which makes it necessary to define the data requirements case by case (see also deliverable 14).

Current regulatory situation

Plant extracts or 'botanicals' are not defined in the EU legislation, and no separate data requirements exist in Directive 91/414. Reduced data requirements are described in the SANCO draft working document 10472. However, this document is not legally binding. Regulators and applicants have little experience with this document, since it was published quite recently (see also deliverable 14).

Summary of activities

During several REBECA workshops and conferences, a separate working group discussed issues relating to the regulation of botanicals. The group met on the following occasions (see deliverable 5):

- Workshop in Brussels (Belgium) in June 2006 to discuss the risks of botanicals, and to outline proposals for improvements of the current regulation practice.
- Further elaboration of proposals for improvements of the current regulation practice, in the framework of the First REBECA Conference (C1) at Salzau Castle (Germany) in September 2006.
- Discussion on advantages and disadvantages of the proposals for improvements of the regulation practice (SWOT analysis) during the workshop on Risk-Benefit Analysis in Porvoo (Finland) May 2008.
- Workshop in Brussels (Belgium) in June 2007 to elaborate improved regulatory systems for botanicals in detail.
- Presentation of the proposals on the first day of the Final REBECA Conference (C2) in Brussels (Belgium) in September 2007. On the second day of the Final Conference, the working group met to make final, minor improvements of the proposals. In this workshop, candidate "low risk" botanicals were identified, and the effect of the proposed improvements was estimated for these case studies (SWOT analysis).
- In between all workshops, documents were circulated to the members of the working group for comment. FiBL organized, prepared and chaired all workshops and prepared the minutes and reports.

Summary of results

All REBECA proposals on botanicals described below are listed and further justified in deliverables 16 and 17.

Further development of SANCO/10472

The REBECA project recommends that a comprehensive guidance document should be formally adopted for botanicals. This could be based on SANCO/10472, with some amendments.

REBECA proposals: Currently, SANCO/10472 covers only water and ethanol extracts, and a limited number of plant parts. Its scope should be broadened to cover all extraction methods and all plants and plant parts. As a result of the broadened scope, a tiered system will be needed. It is desirable to establish a system to identify

substances/extracts of low risk/concern at an early stage of the process. For these substances, only tier I data requirements apply. The document should contain a list of plants and/or combinations of plants and extraction methods which are recognized as of low risk/concern. This should be an open list which can be amended when new botanicals have been evaluated (taking into account issues of data protection). As a starting point, all substances which are currently listed in SANCO/10472, all substances on the «25b list» of the US EPA and all substances with GRAS status should be considered for such a list. For this task, support by an EU funded research project would be useful.

Identification and analytical methods

Plant extracts usually contain a multitude of chemical substances. Often, the «active substance» is a cluster of very similar substances. For example, pyrethrum contains three esters of chrysanthemic acid and three esters of pyrethric acid. Of these, pyrethrin I and II are the most abundant and account for most of the insecticidal activity. Neem contains more than a dozen azadirachtin analogues, but the major form is azadirachtin, and the other analogues contribute little to overall efficacy. Neem also contains other triterpenoids such as salannin, nimbin, and derivatives thereof. Their role has been controversial, but seems to be minor in comparison to azadirachtin. In summary, it is often impossible with botanicals to draw a clear line between active and inactive substances. However, it is usually possible to identify one or a few substances which are responsible for most of the activity of the extract.

Plant extracts almost inevitably contain a large array of highly diverse substances which are hardly or not at all responsible for the effect on the target pest. In terms of Dir. 91/414, they are considered as «by-products» or «impurities». Some substances may present a hazard to human or animal health or the environment: (i) certain plant metabolites with high toxicity, and (ii) microbial metabolites or decay products which may be formed before and during manufacture and (iii) process impurities. The presence of other plant metabolites is unavoidable (except if they can be eliminated by purification), while microbial contaminants and process impurities can be avoided with appropriate quality management.

REBECA proposals: Identification and analytical methods will be required for the active substance(s), or for those substances which are mainly responsible for the effects on the target pest. If these are not identified, it should be determined case-by-case whether one or several representative lead substances (markers) may be used instead. Identification and analytical methods will also be required for all impurities or other plant constituents of concern. The other plant constituents should be characterized (e.g. by group analysis for sugars, fatty acids, terpenoids), but identification and validated analytical methods are not required for each component present in quantities ≥1 g/. It is not feasible to achieve 98% of closure as required in conventional pesticides. However, the relevant components should be identified as far as necessary in order to ensure reproducibility of the product.

Description of manufacturing methods

The contents of metabolites in plants is subject to great quantitative and sometimes also qualitative variation. Variation occurs between different plant parts, different

physiological ages, different harvesting times, different growing conditions (e.g. nutrient, water or light availability), different regions and different genotypes. Due to this variability in the material of origin, the contents of the active substance(s) in plant extracts usually varies also to some extent. If plant material or extracts are stored inappropriately, hazardous microbial decay products may be formed during manufacture, e.g. mycotoxins.

REBECA proposals: The description of the method of manufacture should include information on the plant material of origin, such as the plant parts used, the physiological ages, harvesting times, growing conditions (e.g. nutrient, water or light availability), regions and genotypes/ chemotype (if known), and should indicate the range of materials used. If other plant material is used in the future, the applicant has to demonstrate equivalency of the technical material with the criteria outlined here. Greater variation in the composition should be acceptable for botanicals than for synthetically produced substances.

All measures taken to prevent the formation of hazardous microbial decay products during manufacture (according to HACCP procedures) should be described. The description should cover harvesting, storage and transport of plant material, and manufacture and storage of the plant protection product. If the formation of hazardous decay products/microbial contamination is expected to occur in the materials of origin, analytical/microbiological data for these substances have to be provided.

Identification of low risk/concern substances

Regulators have pointed out that according to the precautionary principle, an assessment is needed to determine whether a substance is ‘low risk’. For botanicals, the normal data requirements would therefore apply.

REBECA proposals: The REBECA project recommends a system in which botanicals of low risk/concern are identified early in the process, and are subject to reduced data requirements.

Risk assessment for substances with a long history of safe use

Some plant extracts have been used in plant protection or for other purposes without evidence of adverse effects.

REBECA proposals: If a plant extract has been used in plant protection or for other purposes without evidence of adverse effects, its history of safe use shall be adequately taken into account. This includes the use of information from the literature and from other public sources, and its history of safe use. Details of a ‘safe use’ such as the concentration and level of exposure have to be considered. Which data requirements can exactly be fulfilled by such data should be determined in a pre-submission meeting. Bridging of information from similar extracts should be encouraged, but the relevance must be justified by the applicant in each case. The following table provides some guidance on how safe use should be considered in risk assessment. Applicants should provide reasoned cases based on exposure, dose, natural background levels, and application pattern:

Safe use in …	May provide justifications to replace some or all studies in the following areas:
Human nutrition	oral toxicity, residue studies
Animal feeding	oral toxicity, residue studies
Cosmetics	dermal irritation/sensitization, oral toxicity
Agriculture (e.g. fertilizers)	ecotoxicology, environmental fate (needs to be verified case-by-case)
Occurrence in nature (e.g. nettle)	ecotoxicology, environmental fate (needs to be verified case-by-case)
Pharmacopoeia*	must be determined case-by-case
Biocide	must be determined case-by-case
Technical use	must be determined case-by-case

* called «traditional use» in this context

Efficacy evaluation

The use of botanicals can involve specialized techniques, which require modification of trial protocols (e.g. plot size, replicates). Botanicals may be more variable in their performance than conventional chemical pesticides.

REBECA proposals: requirements for efficacy data should be flexible. Even products with only minor beneficial effects should be acceptable, provided that it is reproducible and the label accurately reflects the likely benefits. Introduction of efficacy into EU evaluation needs to be accompanied by appropriate guidance on evaluation criteria. Selectivity tests should be included in efficacy tests.

Candidate «low risk» botanicals

The REBECA project cannot establish the low risk/concern status of a substance, but can only indicate candidate substances. The following groups of substances were identified as candidate low risk botanicals: (i) Edible parts of plants used for human nutrition or animal feed (as listed in SANCO/10472); (ii) Parts of plants authorized as herbal drugs (as listed in SANCO/10472); (iii) Plant extracts classified as Minimal risk pesticides («25b list» of the US EPA); (iv) Plant extracts classified as GRAS (21 CFR 184.1400).

Semiochemicals

Introduction

Semiochemicals are chemicals emitted by plants, animals, and other organisms – and synthetic analogues of such substances – that evoke a behavioural or physio-

logical response in individuals of the same or other species. They include pheromones and allelochemicals. Pheromones modify the behaviour of other individuals of the same species, while allelochemicals act on different species. Most semiochemicals used in plant protection products are «straight-chained lepidopteran pheromones» (SCLPs), which have their natural function as sexual pheromones.

In the «mating disruption» technique, the pheromone is artificially applied in excess, so that no gradient from a 'calling' female can be built up. Therefore, males are no longer able to find females, resulting in unfertilized females and a reduction in offspring. Besides mating disruption, semiochemicals can also be used for mass trapping, monitoring and «attract and kill». In mating disruption and mass trapping, semiochemicals are considered as pesticides. In monitoring and attract and kill, they are not considered as pesticides, and are therefore exempt from registration.

Semiochemicals present a particular case among active ingredients used in plant protection products, as they are the only pesticides not intended to kill the pest organism. Semiochemicals have a high specifity for the target species.

Current regulatory situation

In the EU legislation, no separate data requirements for semiochemicals exist in Directive 91/414.

The OECD 12 consensus document provides the following rationale for reduced data requirements: Semiochemicals are generally effective at very low rates, comparable to levels that occur naturally. They are generally volatile and usually dissipate rapidly in the environment. In addition, many end use products are formulated in passive dispensers (hollow fibres, tapes) that present little direct exposure to humans or non-target organisms. Furthermore, they are usually not directly applied to the crop. In this case, exposure is limited to localised areas where the dispensers are placed (note: exposure may be higher in the case of direct application). All these factors minimise the risk of adverse effects from the use of semiochemicals (see also deliverable 14). OECD no 12 concludes that SCLPs in particular have a low toxicity, and that arthropod semiochemicals in general have a low exposure potential. These findings have been supported by experience of the US EPA, resulting in a recent proposal for relaxed registration requirements for semiochemicals.

Summary of activities

During several REBECA workshops and conferences, a separate working group discussed issues relating to the regulation of semiochemicals. The group met on the following occasions:

- Workshop in Brussels (Belgium) in June 2006 to discuss the risks of semiochemicals, and to outline proposals for improvements of the current regulation practice.
- Further elaboration of proposals for improvements of the current regulation practice, in the framework of the First REBECA Conference (C1) at Salzau Castle (Germany) in September 2006.

- Discussion on advantages and disadvantages of the proposals for improvements of the regulation practice (SWOT analysis) during the workshop on Risk-Benefit Analysis in Porvoo (Finland) May 2008.
- Workshop in Brussels (Belgium) in June 2007 to elaborate improved regulatory systems for semiochemicals in detail.
- Presentation of the proposals on the first day of the Final REBECA Conference (C2) in Brussels (Belgium) in September 2007. On the second day of the Final Conference, the working group met to make final, minor improvements of the proposals. In this workshop, candidate "low risk" semiochemicals were identified, and the effect of the proposed improvements was estimated for these case studies (SWOT analysis).
- In between all workshops, documents were circulated to the members of the working group for commenting. FiBL organized, prepared and chaired all workshops and prepared the minutes and reports.

(See deliverable 5)

Summary of results

All the REBECA proposals on semiochemicals described below are listed and further justified in deliverables 16 and 17.

Re-evaluation of SCLPs

A number of semiochemicals are subject to re-evaluation under the 4th stage of the review programme under Directive 91/414. The Rapporteur Member State is Austria. Among these, the 'straight-chained lepidopteran pheromones' (SCLPs) make up a very homogenous group of substances. Not only single substances were notified, but also blends of substances. Most of the SCLPs were notified with the 'single evaluation dossier' prepared by the IBMA task force. The REBECA project anticipates that the review will result in Annex I inclusion of all SCLPs, whereby each SCLP could be listed separately, or SCLPs could be listed collectively as a group of homogenous substances.

REBECA proposals: In case of positive evaluation in the 4th stage, SCLPs should be listed collectively in Annex I.

Low risk active substances

The proposed new pesticide Regulation contains some facilitations for «low risk active substances» (Art. 22 and 46).

REBECA proposals: When the new pesticide Regulation is in force, all SCLPs should be treated as low risk substances. Clarity and predictability of low risk status would benefit all stakeholders and would lead to cost and time reductions for all parties. Note: This proposal reflects current opinions, but will depend on the finalized and agreed definition of «low risk» in the revised Directive, and on the outcome of the re-evaluation of the SCLPs.

Analysis of impurities

In the case of SCLPs, two types of impurities occur: (i) other SCLPs and (ii) unrelated contaminants. Other SCLPs are typically stereo-isomers of the active substance, or closely related molecules which differ from the active substance in the position/orientation of a double bond, alcohol, acetate or aldehyde group. These occur mainly because a small proportion of the material does not undergo the synthetic pathway completely. There is no indication that these substances are of toxicological concern and if present in low quantities, they do not adversely affect efficacy (in mass trapping, higher purity may be needed than in mating disruption). Because of their chemical similarity, removal of other SCLPs is neither economically feasible nor necessary. Unrelated contaminants may be of toxicological concern, and they may affect effectivity. Manufacturers use HACCP procedures to avoid the formation of other contaminants. Information on the manufacturing process is likely to be useful to identify the potential for the formation of substances of toxicological concern.

REBECA proposals: Information on the manufacturing process should be used to determine the likely identity of impurities. For impurities which are SCLPs or structurally similar substances, validated analytical methods shall only be required if they are present in quantities ≥20 g/kg. For other impurities, validated analytical methods shall be required if they are present in quantities ≥1 g/kg.

Number of samples to be analyzed

According to the survey in OECD 12, analyses from 5 batches are requested in the EU if feasible, while only 3 are requested in the USA, Canada and Switzerland. For some pheromones not produced every year, multiple analyses are essentially pseudo-replicated analyses of same sample.

REBECA proposals: For rarely produced pheromones (e.g. 1 batch/3 years), it should be acceptable to present analytical results from fewer batches. In this case, additional analyses must be provided as soon as additional batches have been manufactured.

Risk assessment

SCLPs have been intensively studied and are widely used in plant protection. The currently available knowledge shows that the lepidoptera have pheromones with very similar structure and function, and with very similar safety profiles. The pheromones of other arthropods are much less studied. Nevertheless, several other taxonomic groups of arthropods also have pheromones which are structurally very similar within one taxonomic group, e.g.:

- beetles (coleoptera): pheromones based on terpenoids,
- midges (diptera): pheromones based on diacetoxy alkanes,
- pentatomides (heteroptera): pheromones based on alkene esters.

REBECA proposal concerning risk assessment of SCLPs: If SCLPs are used in quantities comparable to natural emission (up to 375 g/ha per year) no data shall be required for OECD sections 3 – 6 (human health; residues; fate and behaviour in soil,

water, air; effects on non-target organisms). If SCLPs are used in quantities higher than natural emission or above 375 g/ha per year, data may be required for OECD sections 3 – 6 (human health; residues; fate and behaviour in soil, water, air; effects on non-target organisms) case-by-case.

REBECA proposal concerning risk assessment of other semiochemicals: For semiochemicals other than SCLPs, the following data requirements shall be used for the moment: OECD sections 3 and 4 (human health; residues): data requirements shall be determined case-by-case in a pre-submission meeting, taking into account natural emissions and the history of exposure to the substance. OECD sections 5 and 6 (fate and behaviour in soil, water, air; effects on non-target organisms): if application rates are comparable to natural emissions, no data shall be required. Otherwise, data requirements shall be determined case-by-case.

As soon as 3 – 5 structurally similar semiochemicals are listed on Annex I, the Commission and the RMSs for these semiochemicals shall decide whether the number of substances and their similarity is sufficient to justify a more generic approach.

Efficacy evaluation

The use of semiochemicals can involve specialist techniques, which require adapted trial protocols. Authorities should not be too prescriptive concerning trial protocols, but it is important that the rationale for the trial protocol is justified by the applicant. Pheromones applied in dispensers need to be applied to large areas and therefore, the requirement for crop destruction would cause very high costs (ca 160'000 EUR per trial), which would effectively preclude doing a trial.

Semiochemicals acting through mating disruption do not directly affect the population size of the treated generation, but rather the following generation. Therefore, a comparison with chemicals for short-term effects on population size is not appropriate. Evaluation and approval may be based largely on demonstrating a reduction of crop damage. Long term effects accumulating over several seasons could also be taken into account, and information on factors such as numbers of overwintering larvae provide very useful support on the longer term effects. Even if these effects are frequently observed, they are difficult to quantify.

REBECA proposals: Requirements for efficacy data should be flexible and adapted to the special properties of semiochemicals. For pheromones used in mating disruption and autoconfusion, PSD efficacy draft guideline 220 on mating disruption products could be used as a guideline. If semiochemical products are not directly applied to crops, there should be no requirement for crop destruction.

Products with minor beneficial effects should also be acceptable, provided that they can be demonstrated and the label accurately reflects the observed benefits.

Efficacy data from all areas of the EU or from outside the EU should be acceptable, if they have been generated under comparable conditions. Reasoned cases justifying the comparability of such data should be based on issues such as pest biology, climatic conditions, number of generations, formulations and label claims, and must

take into account potential differences in agricultural practices, average field size, and shape and size of trees/vines.

Harmonization of registration for semiochemicals

In the working group of semiochemicals, some applicants reported the experience that the registration of pheromones as biocides is far more expensive than the registration as PPP. This is due to higher registration fees and lesser flexibility (e.g. SCLPs cannot be submitted in a joint dossier).

REBECA proposals: REBECA recommends that the registration requirements for semiochemicals used particularly as biocides, but also for human and veterinary medicine, are harmonized with those for PPP. In particular, joint dossiers should be permitted for the inclusion on Annex 1 and registration of SCLPs, and the registration fees should be lowered proportionately to the volume of work necessary.

Candidate «low risk» semiochemicals

The REBECA project cannot establish the low risk/concern status of a substance, but can only indicate candidate substances. The SCLPs were identified as candidate low risk semiochemicals.

Note: The REBECA project assumes that many non-lepidopteran pheromones have similar safety profiles as the SCLPs, and suggests similar, relaxed registration requirements, as soon as this assumption is confirmed. At the moment, however, these pheromones are not well known from a regulatory point of view, and have to be evaluated on a case-by-case basis.

Macrobials

Introduction:

Invertebrate biological control agents (IBCAs) have been used in arthropod (insect and mite) pest management for over 100 years, with remarkably few reported negative environmental effects. The use of non-native - and in some cases native – control agents is subject to well established systems of regulation in different parts of the world, most notably, USA, Canada, Australia and New Zealand.

The use of invertebrate biocontrol agents in Europe is not regulated by any directive such as EU Council Directive 91/414/EEC that applies to the use of microorganisms, botanical substances and semiochemicals as plant protection products. As a result, there is a ‘patchwork of regulation’ of IBCAs across Europe, in which some countries have strict controls on the import of non-native species enshrined in national legislation, and other countries, sometimes directly neighbouring countries, have no restrictions on the import and release of so-called ‘exotic species’. As insects used in biocontrol are sometimes highly mobile, it is possible, perhaps likely, that an

organism will migrate from a country where it has been released without regulation to a different country where its import and release may have been prohibited.

The absence of any EU-wide regulation of non-native IBCAs can be viewed as having both advantages and disadvantages. As an example, the absence of regulation has been cited as one of the main reasons for the success of IBCA-based biocontrol in Europe, and it is the case that there have been relatively few reports of any negative environmental effects arising form such unregulated releases. By contrast, the fact that countries with regulation have different 'information requirements' within their permit application forms means that companies have to produce separate dossiers for each country to which an application is made. Additionally, the recent rapid spread through Europe of the predatory ladybird *Harmonia axyridis* and concerns about possible local declines in native coccinellid populations has raised awareness among regulators, the biocontrol industry and governmental and NGOs responsible for environmental protection, of the need to ensure the safe release of non-native species. At an administrative level, the lack of any coordinated regulation across Europe means that there is no forum for discussion or information exchange among regulators operating under national legislation.

Prior to the REBECA Action, various organizations (FAO, EPPO, OECD) had produced recommendations and guidelines on the environmental risk assessment (ERA) of non-native biocontrol agents. The content of these documents was recently reviewed by the IOBC-WPRS 'Commission on the harmonization of invertebrate biological control agents' (CHIBCA), which produced an updated review 'Guidelines on Information Requirements for Import and Release of Invertebrate Biological Control Agents in European Countries', published in *Biocontrol News and Information* (Bigler *et al;* 2005). Most of the regulators, representatives of industry and scientists who had contributed to the CHIBCA review became participants in the REBECA project, thus providing a continuity of knowledge.

Guidelines for a hierarchical regulatory (risk assessment) system for macrobial (invertebrate) BCAs

In EU countries that regulate the import and release of non-native (and sometimes native) biological control agents, the dossier that companies are required to submit to seek a permit (licence) for release has various information requirements. Whilst much of this information is routine and primarily for administrative purposes, the section on the environmental characteristics of the species is crucially important as it contains the data on which regulators conduct an analysis of the environmental risk assessment. The REBECA Action recommends that the tests conducted within an ERA for a novel biocontrol agent should follow a hierarchical approach as a key component of a balanced regulatory system, with the aim of minimising the costs for industry and avoiding the need for unnecessary tests. Also, whilst there is a logical order of tests (establishment, host range and dispersal), this can be modified depending on the characteristics of the agent, target pest and intended area of release. The overall framework is designed to incorporate evidence-based waivers

(exemptions) based on discussions between industry and regulators. For more details see deliverable 19.

Description of research methodologies to underpin proposed regulatory (risk assessment) system for macrobial BCAs

Whilst the principles of a hierarchical ERA are well understood, the REBECA Action recognised that for some aspects of the proposed ERA (e.g. establishment) there were no recommended methods in the published literature, whilst in other areas (e.g. host range) there was a need to refine current ideas and develop a consensus on approved methods. The outcome of this objective describes current best practice in terms of methods that should be used to acquire data for an ERA, where this is necessary. Where possible, these methods have been tested experimentally, and then simplified to reliable formats that allow industry to conduct their own research. For more details see deliverable 20.

Criteria for inclusion of species of macrobial BCAs on a 'Positive List' of 'safe species'

The EPPO 'List of biological control agents widely used in the EPPO region' ('EPPO Positive List') was first published in 2002 to facilitate decisions by national regulatory authorities on the import and release of invertebrate biological control agents (IBCAs) within EPPO countries. Because the listing of agents is based on an expert judgement of available information, other EPPO countries may presume with some confidence that these agents can be introduced and used safely. However, the REBECA Action has highlighted the fact that national EU regulators are not using the Positive List as an advisory tool because it was considered to be in need revision and updating. The REBECA Action has produced a set of proposals on the criteria and format for inclusion of IBCAs on a revised Positive List, which also enables 'risky' species to be removed from the existing list. Looking to the future, the REBECA Action endorses the plan for EPPO and IOBC to establish a joint 'Expert Group' to update and maintain the Positive List. Further, REBECA recommends that this body should also provide advice on request to national regulatory authorities on the environmental safety of IBCAs proposed for introduction (first release) into EU and EPPO countries.

REBECA established a link with EPPO early in the project and encouraged EPPO to reactivate its panel on the 'Safe use of biological control agents – Positive List'. EPPO responded positively to this idea and has now established a joint Expert Group with IOBC to revise and update the Positive List. The joint panel will meet for the first time in March 2008 in The Netherlands, with representatives from 14 EPPO countries and the IBMA together with representatives from IOBC. At the meeting, the REBECA request for this panel to also offer advice on request to EU and EPPO countries on the first release of non-native biocontrol agents will be discussed.

For more details see deliverable 21.

Evaluation of options for implementing a pan-European regulatory system for macrobial BCAs

In the absence of an EU directive for macrobial agents, it is evident that any pan-European system has to operate on a voluntary basis. With this in mind, REBECA recommends that an Expert Group could provide valuable advice on the safety of novel agents to countries both with and without existing national regulatory systems; and that achievement of this goal would be greatly aided by the Europe-wide adoption of standardized documents (Application Form, Guidance Document and description of methods for risk assessment). The REBECA Action has therefore produced these documents, and they have been immediately adopted in some EU countries. However, REBECA recognizes that the wider and longer term success of the proposed regulatory system would be aided by other developments including, the translation of the documents into national languages, and a forum for the communication of information between IBCA regulators in different EU countries. For more details see deliverable 22.

Testing of proposed regulatory system and ERA guidelines for macrobial BCAs based on retrospective case studies

The REBECA Action has recommended a hierarchical system for the ERA testing of novel biocontrol agents, described current best practice in methodology, and recognised the need to incorporate appropriate waivers, as fundamental requirements of a balanced regulatory system, with the dual aims of minimising the costs for industry without compromising environmental safety. A retrospective analysis of the proposed application process and ERA has been applied to selected macrobial biocontrol agents that have been widely used in a number of EU countries. These analyses indicate that the recommended methods of the proposed ERA are able to identify risks of establishment, and characterise host range and dispersal abilities, provided that adequate data are available, either from the literature or by experimentation.

In summary, Work Package 5 has: compared regulatory systems operating in EU member states with those used in the USA, Canada, Australia and New Zealand; produced a standardised 'Permit (Licence) Application' form; written an accompanying 'Guidance Document'; devised a hierarchical ERA with details of methods; made recommendations for updating and maintaining the EPPO Positive List; set out options for implementing a balanced regulatory system in Europe; and shown by retrospective case studies that the proposed ERA is robust and effective.

For more details see deliverable 23.

Impact on industry

The REBECA Action maintained intensive contacts with industry and industry stakeholders throughout the period of the Action. The outcome of the Action and the

interactions initiated between the stakeholders were of major benefit for the biocontrol industry. The Action has had significant positive impacts on the European and International biocontrol industry.

Cooperation with IBMA

The biocontrol industry is represented by the International Biological Manufacturers Association (IBMA). At the IBMA's annual meeting in Paris in December 2005, the REBECA co-ordinator Ralf-Udo Ehlers presented the objectives of the Action. At the IBMA's annual meeting in Paris in December 2005, the REBECA co-ordinator Ralf-Udo Ehlers presented the objectives of the Action. At this meeting one company representative doubted whether the Action would have any benefit for his company. The representative questioned why it should be easier for other companies when his enterprise 'had already gone through the treadmill. Despite this comment, many of the attending industry representatives expressed their interest in the Action.

Four IBMA heads of the professional groups attended at the first Action Steering Group meetings as well as a number of the REBECA workshops: microbials (Guido Sterk, Biobest, B), invertebrates (Richard Greatrex, Syngenta Bioline, UK), semiochemicals (Robin Sheppard, IMBA, UK) and natural and biochemical products (Denise Munday,Valent Bioscience, USA). In 2007, IMBA hired a specialist in registration aspects, Ulf Heilig, to represent IBMA in Brussels. The REBECA Action asked him to also represent IMBA in REBECA; however, IMBA asked for a per diem salary of his contribution to the Action, which was had not been included in the REBECA budget. Despite this problem, Ulf Heilig attended the Salzau meeting out of his own interest and was reimbursed for his travel expenses by REBECA. In general the input of IMBA to the REBECA Action was based on the personal attendance of active members of the professional groups. Ulf Heilig in cooperation with the co-ordinator prepared the industry stakeholder meeting and led the discussion. This meeting elaborated the view of IMBA and industry based on the White Paper of the IMBA, which had been produced by Bernard Blum.

In October 2006 IBMA organized a meeting and fair (Annual Biocontrol Industry Meeting; ABIM) in Lucerne, CH, which was attended by the co-ordinator who explained in detail the objectives and the outcome of the first year activities in a 2 hour presentation and discussion together with Ulf Heilig. On the second IBMA meeting in October 2007 the coordinator gave a short presentation of the final results of the Action.

General benefits

If the proposals of the REBECA Action is implemented by legislation and put into practice by regulatory authorities, the biocontrol industry would have the opportunity to deliver more products on to the market, sales would increase and the industry will continue or even accelerate its annual growth rates. More importantly, the increased use of BCAs would be in line with EU agricultural and environmental policies. It would certainly also have benefits for the farmers, which will have a competitive advantage over producers from outside of the EU by providing more residue-free agricultural produce. Currently, world market prices often are lower than production costs within

the EU. If farmers have more biocontrol products available, they would be able to justify higher prices for their products. Industry would also benefit from support for the further development of guidance documents and for research projects dealing with the assessment of relevant risks and filling of knowledge gaps.

Personal contacts

In general, companies received considerable benefits from REBECA through the opportunity to discuss aspects of registration, safety aspects and risk management with regulators, without direct reference to an application file or dossier. This opened possibilities to exchange views and results and helped to develop personal relations with regulatory personel.

Information exchange

For smaller enterprises, attendance at REBECA meetings was often the first time they became aware of the procedures for regulation and registration. However, also for larger companies, the meetings were a forum to exchange ideas and discuss problems. During the REBECA Action many companies had pending applications for new active ingredients and several companies had formed task forces for the re-registration of their products. The REBECA meetings helped to gather and exchange information on safety data and administrative aspects and they were an active forum to improve organisation and networking within the task forces.

Dissemination of results

The webpage www.rebeca-net.de is a compilation of documents on safety, guidelines and legislation for the main groups of biocontrol agents and products discussed during the Action. According to the documentation of this website this page was and still is, often and continuously used by biocontrol industry. The network also helped industry to identify officials in charge of the registration in different MS and rapporteur countries, enabling contacts to be made for support and possibly for pre-submission meetings. Contacts were also made available to industry regarding service companies and scientists who can help to produce safety data and support the organisation of the registration procedures.

Impact for SMEs

With few exceptions (e.g., Syngenta Valent BioSciences, Koppert), biocontrol enterprises fall within the category of SMEs. Their interest in low registration hurdles is high as many have products in the pipeline, but fear that high costs related to the production of safety data and registration procedures may inhibit the further development and marketing of these novel products. Many of these companies attended the meetings to learn about the registration procedures and gather further information. SMEs usually have one person in charge of registration, who also have other duties within the enterprises. Any kind of improvement of regulation procedures to reduce time and costs are beneficial for SMEs. The SMEs might be among the major beneficiaries of the Action, should the various proposals made by REBECA be transferred into legislation or new practice. However, even if the REBECA proposals

are not transferred into regulation or practice, the SMEs have at least been able to identify their position within the process and have learned how to estimate the economic risks related to the registration of biocontrol agents. They can make informed decisions on whether the application process can be afforded or whether R&D activities should be curtailed.

During the period of the REBECA Action it became obvious that SMEs were usually not able to articulate and professionally represent their interests during the meetings. One reason was that members of these enterprises had less knowledge and experience in the subject and thus did not always take an active part in the discussions. Another reason was that these companies do not have an effective network among themselves. Consequently, no general position was developed that relates specifically to the position of SMEs and they were generally less well represented.

Interests of non-SMEs

Larger companies have departments which have the sole responsibility to deal with registration aspects or to sub-contract this area to specialized services to organise the registration process for them. Those companies which had products listed on Annex 1 were less interested in lowering standards for registration. Many products based on biological control agents contain ingredients of natural origin or comprise of living organisms, which cannot easily be protected by patent application. Thus regulation is an appropriate tool to protect markets.

Structural deficits

As the biocontrol industry is comparably young it has not yet fully developed well defined principles in relation to competitors, separating areas of common interest and areas of competition. This might have been a reason why proposals from industry were rare and often did not go beyond the IBMA White Paper, which had already been published in December 2005.

Impact on different product groups

Microbials

The OECD guidance document on the risks of baculoviruses was generally accepted by participants. The decision to propose the inclusion of baculoviruses on Annex 1 would immediately open a market for many SMEs to start *in vivo* mass production of granulosis and nucleopolyhedrosis viruses against lepidopteran pest insects in horticulture. The producers of virus products can already benefit from the REBECA action. The REBECA proposal for a simplified inclusion of baculovirsus on the species level into Annex I was adopted by the European regulatory authorities already in 2007.

If the REBECA proposals for the risk assessment of bacteria and fungi are transferred into practice and published data on the risks of micro-organisms according to Dir. 2000/54 EC more regularly accepted, the costs for production of safety data would be reduced significantly. Currently, only very few products based

on micro-organisms are considered for registration in Annex 1. A large number of products remain on the shelves of academia and industry to be exploited for plant protection. For instance, the MASE and DOM project supported by the Swedish organisation MISTRA have gathered data on the potential of micro-organisms for plant protection for almost a decade. Such scientific and technical progress will only be transferred into practice by industry when the costs for their registration are significantly reduced. Otherwise, industry will re-orientate their R&D activities on products considered easy to register (botanicals, food compounds), and not focus on the exploitation of the potential of microbial products. Most of these microbes will not be exploited unless the data requirements are changed or financial support is made available for the production of risk assessment data and/or for scientific investigations related to the risks of microbial metabolites. Many industry representatives think that metabolites should be ignored as they are biodegradable and produced in very low quantities. Other experts believe metabolites are the most risky part of the registration process. The metabolite issue needs to be resolved to make sure that further microbial products will be developed.

Botanicals

The production and discussions on the SANCO draft guidance document 2003/10472 was very helpful for industry. The list of acceptable plant ingredients was enlarged. The borderlines between risky and less risky botanicals were better defined and guidelines for risk assessment were improved. These steps enable industry to better define requirements for potential new products and estimate costs.

Semiochemicals

The REBECA Action proposes to include the Straight-Chained Lepidopteran Pheromones (SCLP) as a group in Annex 1. These products are currently a major focus in plant protection for mating disruption of lepidoteran insects in orchards, vegetables and stored products. The SCLPs are toxicologically of remote or no risk and lack a killing mode of action, which is why many experts consider that these products should not be subject of regulation. In trapping for monitoring purposes no authorisation is required. Any further steps to ease the market excess will accelerate the use of these valuable control measures.

Macrobials (Invertebrates)

Compared to other products such as micro-organisms and botanicals, the risks of this group seem to be low. However, industry accepted and even supported the idea of a regulation process on condition that risk assessment procedures would be easy to conduct and could be performed in-house as well - advantages seemed to out-weigh the disadvantages of a regulatory procedure. In general, all stakeholders agreed that a risk assessment of indigenous species is not necessary, but their commercialisation should be documented. The definition of necessary data requirements was agreed with industry. We have now reached a very favourable outcome for all parties: if a MS wishes to regulate the use of invertebrate biocontrol agents, the procedures, necessary guidelines and standardised dossier application forms are now available through the REBECA Action. This was made possible because discussions on the risks related to the use of invertebrates had been

instigated prior to the start of the REBECA Action and steps toward harmonisation had been mapped out by a range of stakeholders, all of whom participated in REBECA. Thus industry now hopes that MS will use the standardised documents to reduce bureaucratic paper work for companies. It is generally accepted that invertebrates should not be subjected to any registration procedure comparable to the Dir. 91/414 EC. However, a voluntary EU-wide scheme could be coordinated by EPPO and the IOBC, and this avenue is currently being explored. As a consequence, companies will have to apply for permits in individual MS, but the use of standardised documentation provides the opportunity for mutual recognition, and information exchange between countries. The implementation of the REBECA proposals for the regulation of invertebrate BCAs holds advantages and disadvantages for the industry. The intended harmonisation, mutual recognition and the delivered standard forms and guidelines will reduce efforts for product registrations in different EU-countries. On the other hand, in consequence of this harmonisation regulation of invertebrates might be installed in MS which did not regulate these BCAs before (e. g. Belgium, France, Greece, Italy, Poland, Portugal). It remains to be seen how the REBECA proposals will finally influence the availability of macrobial BCAs in Europe in future.

Impact on science

Many researchers developing BCAs at scientific institutions are not very much aware of regulation tasks. This situation could be improved by the activities of the REBECA Action. The project partners of the Action gave presentations at 12 national and international scientific meetings on biocontrol in order to introduce that topic (see dissemination of results). Safety and other regulation tasks (costs, time frame) should be always taken into account from the beginning in a BCA product development. Better awareness of researchers regarding that points can lead to a more purposive research in products which will have the potential to reimburse the registration efforts and it might improve the availability of safety relevant data for BCAs in future. On the other hand the awareness on the currently high registration hurdles, especially the related costs and time frames for BCAs can discourage researches and investors developing innovative low risk products in future.

In case the proposals of the REBECA action will be adopted by the EU and MS authorities, reduced costs and time frames for registration will give BCA products a better chance to reach the market. This would give the development of and the research in low risk plant protection products a positive impetus, including the research on risk assessment tasks.

REBECA demands public research in the development of better adapted risk assessment methods for microbial BCAs and the reduction of whole animal testing systems (deliverable 11). The proposed research programmes will not only improve the risk assessment methodology for microbial BCAs. This research will also improve the risk assessment of microbial biocides and foot additives. Alternative methods to whole animal testing developed for the toxicity, sensitisation and irritation assessment of microbials might be also transferable to the assessment of chemicals.

There is also a demand on public research regarding the natural distribution of micro-organisms used as BCAs and natural exposure of humans and animals. This research will help to estimate the risks caused by artificial application of micro-organisms as plant protection products or biocides.

Further on, research is needed delivering a clear and practicable definition for low risk plant protection products. Such a definition would enable a more systematic support of such products in the development and regulation process. REBECA proposed a risk indicator model for that purpose which may needed to developed further.

Exploitable knowledge and its Use

It was not the aim of the REBECA Action to produce knowledge with any potential for industrial or commercial application in research activities or for developing, creating or marketing a product or process or for creating or providing a service.

Plan for implementation of results

Proposals for microbials, botanicals and semiochemicals

In order to obtain implementation of the many REBECA proposals a number of partners needs to be involved in the implementation process. Deliverable 30 presents a table listing all the proposals, it describes the measures to obtain implementation and the partners involved/responsible for securing an implementation.

The main partners are:

- The European Commission, DG SANCO
- The European Food Safety Authority (EFSA)
- All of the EU member states (politicians as well as regulatory authorities)
- OECD-BioPesticide Steering Group
- BCA Industry/applicants
- Academia
- Grower and consumer organisations (national as well as international)

EFSA and expert groups

For a successful implementation of a number of REBECA proposals it will require EFSA to play an active role. The most important and first task for EFSA will be to establish 4 expert groups with participation from a number of member states. An expert group on microbials has already been established by the Commission, however, the EFSA will have to take over the lead of this group and establish a formal group in which further experts should be encouraged to join. Further more an expert group on botanicals as well as one on semiochemicals should be established as soon as possible. Finally an expert group on efficacy should be established.

EFSA will be responsible for inviting these groups for regular meetings.

The three expert groups on microbials, botanicals and semiochemicals will together with EFSA be responsible for the development of lessons learned guidance documents as well as other types of guidance documents e.g. on waivers, specifications of existing data requirements and drafting revised or new sets of data requirements for BCAs. The three groups will also discuss which level the active substances should be included to Annex I and give guidance to EFSA and the Commission on these and other issues.

The efficacy expert group will also be responsible for the development of a number of guidance documents for each of the types of BCAs. These documents should describe efficacy data requirements and criteria for BCAs.

The Commission, DG SANCO
The main tasks for the Commission will be to initiate the development of a guidance document that will describe the process of pre-submission meetings which shall be established as a routine in all EU member states. Such guidance document will also include a detailed description of which information should be required in a pre-submission information package.

Regulatory authorities in EU member states
Regulators including internal and external affiliated BCA experts will have to play an active role: in the EFSA expert groups; in the development of guidance documents; in revising data requirements; in establishing increased communication with EU colleagues, OECD colleagues and with applicants/industry.

Politicians in EU member states
Politicians will have to give priority to BCAs by: securing adequate funding which can be used to lower the fees, financial support for generation of data and for regulatory authorities to give better guidance to applicants. Politicians should also secure short timelines in the authorisation process by providing adequate resources for the regulatory authorities.

OECD-BioPesticide Steering Group
In order to obtain further harmonisation in data requirements and in particular in the risk assessment of BCAs the OECD-BioPesticide Steering Group will have to play an active role. The group should initiate the development of OECD guidance documents and discussion papers.

BCA Industry/applicants
Not only the regulatory authorities are responsible for an increased communication between them and the applicant. The applicant as well should play an active role in communication with the regulators in the process of submitting applications. They should ask for pre-submission meeting(s). The industry should be better organised e.g. in IBMA and use this organisation in putting pressure on politicians in order to obtain advantages for their industry. IBMA should take active part in the demand for further communication between industry and regulators, e.g. by playing an active role in the OECD-Biopesticide Steering Group and by inviting regulators for their IBMA meetings.

Academia
Researchers should keep on carry out research on BCAs and should invite other stakeholders to their scientific conferences in order to increase communication among the partners. They should give input to specific part of new or revised data requirements and waiver guidelines.

Grower and consumer organisations (national as well as international)
Grower organisations should play a more active role in initiating national as well as international political awareness on the potential of BCAs and the problems related to the lack of such products on the market.

For further details see deliverable 30

Proposals for invertebrates

Regulation of macrobial biocontrol agents across Europe is patchy, with well organized systems in some EU countries, and no regulation in others. Whilst this situation allows biocontrol in some countries 'without restriction', it also has some disadvantages, most notably, the inability to prevent the spread of potentially harmful species to countries where they were never licensed for release; additionally, the lack of any consistency in the information requirements in those countries with regulation requires industry to prepare separate dossiers for each country. In the absence of any EU directive for macrobial agents, it is evident that any pan-European system has to operate on a voluntary basis. With this in mind, REBECA recommends that an Expert Group could provide valuable advice on the safety of release of novel agents to countries both with and without existing national regulatory systems – and achievement of this goal would be greatly aided by the Europe-wide adoption of the standardized 'Dossier Application Form', 'Guidance Document' and 'ERA Methods' produced by REBECA (deliverable 22). It would be desirable for the Expert Group to be coordinated by an organization based in Europe and with an international reputation. REBECA therefore supports the initiative of EPPO and IOBC to form a joint Expert Group. Further, the success of the proposed regulatory system would be aided by other developments, including, the piloting of the new documentation in some member states, the translation of the documents into national languages, and a forum for the communication of information between regulators in different EU countries. For further details see deliverable 22.

Dissemination of knowledge

Action taken

Actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible /involved
February 2006 - December 2010	Project web-site	General public	World wide	4000	CAU
May 2006	Presentation Joint Organic Congress, 30 - 31 May 2006 in Odense, Denmark	Research, Agriculture	Europe	200	FIBL
September 2006	Presentation, REBECA Conference, Salzau, Germany	Research, Industry, Regulation,	Europe, USA, Canada, Australia, New Zealand	120	CAU LFU FIBL UOB UHEL DEPA GAB CABI
September 2006	Presentation, 55. German Plant Protection Conference, Göttingen, Germany	Research	Germany	1400	CAU

Actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible /involved
October 2006	Presentation, 1st Annual Biocontrol Industry Meeting Lucern, Schweiz	Industry	Europe	200	CAU
November 2006	Press release, Agrow, World Crop Protection News, 508	Research, Industry, Regulation, Agriculture	World wide	No data available	CAU
January 2007	Press release, IPMnet Newsletter, Issue no. 152, ISSN: 1523-7893, www.ipmnet.org	Research, Industry, Regulation, Agriculture	World wide	No data available	CAU
April 2007	Presentation, XII International Symposium on Biological Control of Weeds, La Grande-Motte, France	Research	Worldwide	100	CAU
May 2007	Presentation, International Symposium on Crop Protection (Ghent, Belgium, 21-23 May 2007),	Research	Worldwide		UOB
June 2007	Presentations, 11th European Meeting of the IOBC/WPRS Working Group "Insect Pathogens and Insect Parasitic Nematodes" and the EU COST Action 862 “Bacterial Toxins for Insect Control”, Alés, France	Research	Europe	150	CAU LFU GAB
July 2007	Publication Journal of Applied Entomology, Blackwell, Berlin	Research Regualtion	Worldwide	unknown	CABI
in press	Publication Biopesticides d’origine végétale (seconde édition). Regnault-Roger, C., Philogène, J.R. and Vincent, C. Tec et Doc. Lavoisier, Paris.	Regulation Research	Europe	unknown	CAU FIBL GAB
August 2007	Presentation, 40th Annual Meeting of the Society for Invertebrate Pathology, Quebec, Canada	Research Regulation	Worldwide	250	LFU
August 2007	Presentation, Symposium on Insect-Plant relationships (Uppsala, Sweden), July 29 to August 3, 2007	Research	Europe		UOB

Actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible /involved
October 2007	Presentation, 2nd Annual Biocontrol Industry Meeting Lucern, Schweiz	Industry Research	Europe, Turkey, USA	100	CAU UHEL
October 2007	Presentation, Applied Biology workshop on 'Advances in Pest Management' (Warwick, UK) on 11 October 2007.	Research	United Kingdom		UOB
September 2007	Presentations, REBECA Conference on 'Balanced Regulation for Biological Plant Protection Products', (Brussels, Belgium)	Research BCA Industry Regulation Agriculture Policy Food Industry NGOs	Europe, Canada, USA	145	CAU LFU FIBL UOB UHEL DEPA GAB CABI
November 2007	Presentation, IOBC-WPRS meeting of Council and Convenors in Barcelona on November 22-23, 2007	Research			UOB
November 2007	Presentation, 25. Tagung des DPG und DGaaE Arbeits-kreises „Nutzarthro-poden und Entomo-pathogene Nematoden"	Research	Germany	30	CAU

Additional to the listed activities the REBECA internet page was used for the dissemination of results. In an average about 500 different users visited the page monthly in 2006 and about 1000 in 2007. From 2006-2007 the page was visited more than 25,000 times.

Publishable results

Publications:

- Hunt E. J., Kuhlmann U., Sheppard A., Qin T.-K., Barratt B. I. P., Harrison L., Mason P. G., Parker D., Flanders R. V. & Goolsby J., 2007. Review of invertebrate biological control agent regulation in Australia, New Zealand, Canada and the USA: recommendations for a harmonized European system. J. Appl. Entomol. 132, 89–123.

- Hauschild R., Speiser B., Tamm L. & Ehlers R.U. (in press). Réglementation et homologation des produits phytopharmaceutiques à base d'extraits végétaux dans la législation de l'Union Européenne (UE): présent et perspectives d'évolution. In:

Biopesticides d'origine végétale (seconde édition). Regnault-Roger, C., Philogène, J.R. and Vincent, C. Tec et Doc. Lavoisier, Paris.

- Laengle T. & Strasser H., submitted. Developing a risk indicator to comparatively assess environmental risks posed by microbial and conventional pest control agents.

The publication of all REBECA results in a monograph is envisaged for 2008. The publisher Springer (Heidelberg) shows already interest in publication of the book.

Title: "Regulation of Biological Control Agents in Europe"

Chapters General Aspects

- Biocontrol: Economic and Perspectives
- History of BCA regulation
- Risks and trade-off analysis of regulation
- Cost-benefit analysis of regulation
- Stakeholders and policy aspects
- A Comparative analysis of regulation practice in the EU and other OECD countries
- Proposal for a Regulation of the European Parliament and of the council concerning the placing of plant protection products on the market
- Regulation practice with invertebrate biocontrol agents in inundative and classical biological control
- Regulation in organic farming

Chapters: Risks and risk assessment

- Microbial BCAs and risks
- Bacterial ecology and risk aspects
- Toxicology of fungal metabolites
- Potential risks related to the use of botanicals and semiochemicals
- The Harmonia invasion

Chapters: Proposals for innovative regulation procedures

- Baculoviridae
- Bacterial and fungal BCAs
- Semiochemicals
- Botanicals
- Macrobials
- Proposals to accelerate EU regulation