

**A comparison of legislation and current practise regarding
evaluation and registration of plant protection products
based on micro-organisms, plant extracts and pheromones
in the EU, USA, Canada and Australia**

Report prepared in the course of WP 2 of the REBECA project

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1. Introduction

Invertebrate and microbial biocontrol agents, plant extracts, and semiochemicals (here collectively called BCAs) are interesting alternatives to conventional pesticides for the control of plant pests and diseases. Their use is in most cases safer to humans and the environment when compared to conventional plant protection products.

Nevertheless, the industry complains that the current registration system for BCAs in the EU is costly and time-consuming. For the industry, long registration periods 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 patent protection. A comparison between the time needed for evaluation for microbial BCAs in the EU and the USA is very difficult because of differences in the procedures. The fact that the time needed for listing in Annex I of Directive 91/414 in the EU was longer than product registration in the USA is only one aspect (Table 1A). Times summarized in the table include both times needed for evaluation of the dossier by authorities and for the generation and provision of additionally required studies or information by applicants. Provisional national registrations can be applied for and granted before Annex I listing. So some of these products were already on the market in some member states before Annex I inclusion. Times required to obtain provisional national registrations differ considerably between member states and products, and no complete detailed information could be obtained. On the other hand, not all member states granted provisional registrations before Annex I inclusion so far. Originally, it was assumed that longer registration periods reflect greater data requirements and thus higher costs for dossier preparation.

Table 1A: Time periods for selected microbial BCAs between submission of the dossier and Annex I inclusion in the EU or national registration in the USA. 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. In the EU, times needed to generate further studies and provide them by the applicants is included.

Organism - Product	EU period (month.year)	EU Annex I inclusion time frame (months)	USA registration time frame (months)
<i>Paecilomyces fumosoroseus</i> - Preferal [®]	5.94 – 6.01	85	60
<i>Coniothyrium minitans</i> - Contans [®]	11.98 – 8.03	57	15
<i>Pseudomonas chlororaphis</i> - Cedomon [®]	1.96 – 4.04	99	-
<i>Ampelomyces quisqualis</i> - AQ10 [®]	2.96 – 10.04	104	?
<i>Gliocladium catenulatum</i> - Prestop [®]	3.99 – 10.04	67	13
<i>Bacillus subtilis</i> - Serenade [®]	5.00 – 2.07	81	14
<i>Spodoptera exigua</i> NPV - Spodex [®]	7.97 – 8.07	121	12
Average time frame		87.7	16.2

Long registration periods are considered to affect the availability of BCAs in Europe. To date (November 2007), **7 micro-organisms** are listed in Annex I of Council Directive 91/414/EEC. Another 8 micro-organisms (strains) are being evaluated as new substances. About 30 strains belonging to 16 species are now being evaluated as “existing active substances” and

plant protection products containing these micro-organisms are still on the market. An overview on the number of microbial strains used in plant protection products in the EU, USA, Canada, and Australia can be found in Table 1B.

Comparisons between the EU and the USA, Canada, or Australia for the products containing micro-organisms that are available on the market are extremely difficult for several reasons: Names for the same product may differ between countries. Product availability changes for economical reasons (supply, distribution). Not all products that are registered are currently available. On the other hand, products used to control plant pests or pathogens may still be on the market under different labelling. Furthermore, a national registration in a single EU member state would not be comparable to a national registration in e.g. the USA with regard to market size.

Table 1B: Number of strains available in Plant Protection Products in different countries. Differences between strain numbers for Annex I inclusion and for strain numbers available in products is due presence or absence of provisional national registrations during the Annex I evaluation process. Some strains registered in the US for use in plant protection products are commercialised in Germany as Plant resistance improvers (PRI, cp. Point 6.5) and included in the number for EU member states. In the USA, no distinction is made like in the EU between plant protection products and biocides. Strains only used in products considered to be biocides are not included in the list.

EU Annex I (strains)		EU member states (strains available in products)	USA	Canada	Australia	New Zealand
Included	7					
under evaluation as old substances	30	42	70	17	24	22
under evaluation as new substances	8					

Till today, only one **botanical** is included in Annex I of Directive 91/414: Laminarin is a purified substance from brown algae (*Laminaria sp.*). Plant extracts like pyrethrum, quassia, neem or rotenone, extracts from tea tree, Equisetum, or Garlic, plant oils like Citronella oil, Clove oil, Rape seed oil, Spearmint oil; or pepper are at present under the 4th stage of re-evaluation as (so-called "List 4 substances") with products containing these active ingredients still on the market.

16 **semiochemicals** are currently under evaluation as existing active substances. The corresponding products are still on the market. No semiochemical is listed in Annex I so far.

The list of biochemical pesticides in the USA currently includes 160 registered products, with most of them pheromones (50), followed by repellents (29, some of them are not considered as plant protection products in the EU, but as biocides), plant growth regulators (phyto-hormones, 21), and attractants for traps (14). 18 products are intended for insect, nematode, or plant pathogen control based on physical modes of action. None of these products are or contain classical plant extracts.

The objective of the REBECA project is to accelerate the regulation process for BCAs and to make it more cost-effective without compromising the level of safety. To this end, this report contains a description of the registration system in the EU, with emphasis on aspects which could be improved. Where adequate and available, the EU system is compared with non-EU systems. The main focus is on registration of active ingredients under Directive 91/414/EEC, resulting in inclusion in Annex I. However, some attention is also given to registration of plant protection products, which is under national authority. Invertebrate biocontrol agents are not

discussed in this report, but a similar study has been prepared within the REBECA project (see www.rebeca-net.de).

2. Methodology and Terminology

This report is based on a review of data requirements inside and outside the EU. In addition, the practical experience of the industry and regulators is also considered. The report covers microbial biocontrol agents (fungi, bacteria, viruses), plant extracts (crude, purified), microbial extracts, and pheromones. These products do not have much in common except that all of them are of natural origin and that all of them are very different from the typical, synthetic pesticides.

The following legislation was considered for the comparison of data requirements:

EU: Council Directive 91/414/EEC, with the Commission Directive 2001/36/EC, and Commission Directive 2005/25/EC for “Uniform Principles for Evaluation” included in the Council Directive .

USA: Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); Code of Federal Regulations (40 CFR 158). In addition to the data requirements for the USA, differing requirements according to a new proposal (Federal Register, Part III, Environmental Protection Agency, 40 CFR Parts 158 and 172, Pesticides; Data Requirements for Biochemical and Microbial Pesticides; Proposed Rule, March 8, 2006) are included in the comparison. These regulations cover also uses that are not considered as plant protection in the EU, e.g. insect repellents for humans or biocides.

Canada: Regulatory Directive DIR 2001-02 (Guidelines for the Regulation of Microbial Pest Control Agents and Products) and Regulatory Directive DIR2002-02 (The PMRA Initiative for Reduced-Risk Pesticides).

Australia: “Manual of Requirements and Guidelines” and “Guidelines for the Registration of Biological Agricultural Products” from the Australian Pesticides and Veterinary Medicines Authority.

Switzerland: Data requirements in Switzerland are regulated by Pflanzenschutzmittelverordnung (PSMV, SR 916.161, published 18 May 2005). These data requirements are identical to those in the EU and are therefore not mentioned explicitly in this comparison.

New Zealand: In New Zealand, data requirements for microbial plant protection products are not separated from those for chemical plant protection products, and are defined case-by-case according to the particular micro-organism, the product, and the uses.

3. Legal framework and regulatory procedures

3.1 Regulatory procedures in the EU

In Europe, registration of active substances and plant protection products is performed in a two-step system. The **active substance** first has to be evaluated at EU level. The dossier containing all information on the active substance and on at least one representative product and one representative use is submitted to a member state, the designated Rapporteur Member State (RMS). Authorities of the RMS first check the completeness of the dossier, then evaluate the dossier and distribute the Draft Assessment Report (DAR) to the other member states, the applicant, and EFSA. EFSA, the European Food Safety Authority, is a decentralized agency of the European Union, financed by the Community budget. EFSA provides risk assessments and risk communication on all matters related to food safety, including plant protection products and their residues. A peer review process is then initiated which involves all member states and EFSA. This process includes a written procedure as well as meetings. Following this evaluation, an EFSA scientific report with conclusions of the

peer review is released. Finally the EU Commission (DG SANCO)¹ prepares inclusion (or non-inclusion) directives of the active ingredient into Annex I of Directive 91/414/EEC, for which the Member States vote in a committee. When all the existing active substances have gone through the EU re-evaluation process, this annex will contain the active ingredients for all plant protection products registered in the EU. No guarantee is given regarding the length of the evaluation process. Annex I inclusion is valid for 10 years.

Plant protection products are regulated at the national level of member states. Formally, applications for provisional national registrations can be submitted when the dossier for Annex I inclusion is declared complete by all RMS and when completeness is published. In some member states, especially if application for product evaluation is made to the RMS, evaluation of the dossiers for Annex I inclusion and for national registration can be treated in parallel, which accelerates the process for national registration. However, in the past some member states refused provisional registrations and awaited Annex I inclusion before they evaluated the dossier for national registration.

In addition to a complete Annex II+III dossier, data on efficacy have to be provided in most member states of the EU for national registration of a plant protection product. In case the application concerns a product for field application, the efficacy data have to be specific for the country or at least the climatic zone. This restriction is normally not relevant for products that are only intended for use in greenhouses. Efficacy data for biological plant protection products are in some countries reduced when compared to the requirements for chemical plant protection products. This reduction refers both to the number of successful studies that have to be submitted and to the extent of efficacy obtained in the trials.

In addition, specific forms, most frequently in the national language have to be filled in. In some member states, summaries in the dossier (Documents M and N) have to be submitted in the national language, in others only parts of the dossier (e.g. Document N). In practice, the national distributor for the product prepares the required documents in the national language.

The organisation of the regulatory bodies within the member states varies greatly. In some member states, the regulation is mainly carried out within the ministry of agriculture, in others within the ministry of environment or health, or related agencies. Often, several regulators from several ministries or agencies are involved in the evaluation of the active substances and the plant protection products. In several member states both the risk assessment and risk management part is carried out within the regulatory agencies. However, in many other member states external experts are involved or even responsible for the risk assessment. Some, but not all, member states have pre-submission meetings with applicants.

3.1.1 Fourth stage of re-evaluation

Substances which were already registered in an EU member state when Dir. 91/414 came into force can stay on the market, but are subject to re-evaluation. The re-evaluation was divided into four stages. The 4th stage comprised among other groups microbials, plant extracts and semiochemicals. Commission Regulation 1112/2002 required that substances had to be notified by autumn 2002. Commission Regulation 2229/2004 assigned the notified substances to RMS. Dossiers had to be submitted to RMS by 30 June / November 2005. Currently, evaluations within the 4th stage are ongoing. Cooperation between RMS is working well for microbials and less pronounced for botanicals. All semiochemicals are reviewed by one RMS, Austria. The 4th stage is expected to be completed in 2008.

¹ DG Sanco is the Health and Consumer Protection Directorate General

3.2 Regulatory procedures outside the EU

3.2.1 Regulatory procedures in the USA

Contrary to the practice in the EU, both the active substance and the end use product are being evaluated by a centralised authority in the USA. US pesticide regulation is under the authority of the US Environmental Protection Agency (EPA; registration) and the US Food & Drug Administration (FDA; MRL enforcement). After a pesticide is registered by EPA, states can register pesticides under specific state pesticide registration laws. A state may have more stringent requirements for registering pesticides for use in that state. States may also register an additional use of a federally registered pesticide product or a new end-use product to meet special local needs. EPA reviews these registrations and may disapprove them under certain circumstances. In practise, additional data are mainly required by authorities in California.

The Biopesticides and Pollution Prevention Division was founded in 1995 within the EPA Office of Pesticide Programs. It comprises the Microbial Pesticide Branch (20 staff, responsible for microbial pesticides and plant incorporated protectants, foreign genes introduced in transgenic plants) and the Biochemical Pesticide Branch (23 staff).

The «Biochemical Classification Committee» was formed in 1995. It decides if an active substance can be classified as a Biochemical Pesticide, based on literature, SAR analysis, whether or not it is a significant food component or if it has other uses, etc. The Committee has the options to decide that an active substance (1) is a biochemical pesticide, (2) is not a biochemical pesticide, but eligible for review using the reduced data set, (3) is a conventional chemical pesticide, (4) is not a pesticide. The Committee has evaluated 212 chemicals, classifying 42 as conventional pesticides.

Prior to submission of a dossier, the US Environmental Protection Agency (EPA) invites applicants to one or more pre-submission meetings, during which the applicant is advised which studies are necessary for the particular product in question based on the applicant's preliminary identification of the product and whatever data is available from the literature or other sources. The applicant then submits a summary of the meeting to the agency for comment and approval. The dossier has to contain all the required studies, but no summary dossier is requested in the US.

Since the implementation of the Pesticide Registration Improvement Act (PRIA) of 2003, which established fees for registrations, time limits are set to process a registration application. US EPA is supposed to register a microbial pesticide in 16 months from receipt of a complete application. Therefore, inadequate applications are often denied unless negotiations with the company will allow them to be delayed to wait for additional data. Registrations can be granted as "conditional" registrations (1 year), if data are missing or classified as "supplementary", and the risk is low enough to market the product (e.g. field testing to verify lack of effects on non-target organisms). Data submitted later will be classified as confirmatory data. Unconditional registrations are valid forever, but re-examined every 15 years to ensure that the original assessment is still valid (re-registration).

Biopesticides (USA)

Biopesticides are divided into two groups: **Microbial pesticides** include microbial entities such as bacteria, fungi, viruses, and protozoans. **Biochemical pesticides** include, but are not limited to, products such as semiochemicals (e.g. insect pheromones), hormones (e.g. insect juvenile growth hormones), natural plant and insect regulators (attractants, repellents), and enzymes. Biochemical and microbial pesticides are generally distinguished from conventional chemical pesticides by "their unique modes of action, low use volume, target species specificity or natural occurrence". This definition was written about 30 years ago and has now been revised to better describe how it has always been interpreted for biochemical pesticides (see "proposed new rule", below).

Financial aspects: Grants for research projects needed for the registration of biopesticides, especially for minor uses, can often be obtained from the US Department of Agriculture's IR4 program. Small businesses and government are exempt from fees paid to EPA for review (PRIA). The new pesticide data requirement rule attempts to reduce the number of studies and data waiver paperwork needed for biopesticides.

Proposed new rule: Since the 1970's, the US EPA encourages the registration of BCAs through exemptions, explicit footnotes, tiered data tables and by facilitating data waivers. After two decades' experience, data requirements have been revised. The new proposed data requirements are included in Federal Register, Part III, Environmental Protection Agency, 40 CFR Parts 158 and 172, Pesticides; Data Requirements for Biochemical and Microbial Pesticides; Proposed Rule. The new rule formalizes pre-submission meeting to reach agreement on what data is needed and to provide EPA assistance on data waivers. The NAFTA procedures for joint review of biopesticides describe how the US-EPA and the Pest Management Regulatory Agency in Canada will coordinate the joint pre-submission consultation to agree on data needed. Exemptions are based on the following legislation: *40CFR 152.20*: All Biocontrol organisms except microbial pesticides & plant incorporated protectants (nematode symbiont policy: exempt, unless bacteria grown separately and/or genetically engineered). *40CFR 152.10*: Products to attract pests for survey or detection and physical barrier products. *40CFR 152.500*: Devices. *40CFR 152.25*: Specific exemptions for: (1) pheromones used in pheromone traps, (2) «foods» used to attract pests, (3) «natural cedar» chips, panels, etc, (4) «Minimal Risk Pesticides» (see below).

The proposed new rule contains revised definitions for microbial and biochemical pesticides that better describe the established interpretations of the old definitions. A biochemical pesticide is characterized as follows: (1) It is a naturally-occurring substance or structurally-similar and functionally identical to a naturally-occurring substance; (2) it has a history of exposure to humans and the environment demonstrating minimal toxicity, or in the case of a synthetically derived biochemical pesticide, is equivalent to a naturally-occurring substance that has such a history; and (3) it has a non-toxic mode of action to the target pest(s). Non-toxic modes of action include: (i) lures, attractants, repellents, irritants; (ii) systemic acquired resistance induction; (iii) growth/developmental changes (IGRs, PGRs); (iv) physical modes of action (suffocation, desiccation, coatings). The naturally-occurring part of the definition allows for pre-registration analysis of the product to determine if any adverse effects have been identified as a result of its human and environmental exposure. The non-toxic mode of action makes it less likely that the more toxic naturally-occurring chemicals, might not have sufficient data submitted to support an adequate risk assessment. The Biochemical Classification Committee is authorized to accept well known substances with toxic modes of action for review using the biochemical pesticide reduced set of data requirements if it can be justified as appropriate for that chemical, but those are not allowed to be called "biochemical pesticides".

Minimal Risk Pesticides

In the USA, there is a list of substances that can be used as pesticides without any registration, although they still need a residue limit, or exemption, for food or feed uses. These substances are called Minimal Risk Pesticides, as described in the US Code of Federal Regulation, 40CFR 152.25(f). The list contains many essential oils². All inerts must be on EPA's 4A inert list, all ingredients must be identified on the label, and the label may not contain false or misleading claims. This regulation was developed by an EPA workgroup in

² Currently, the list includes the following substances: castor oil, cedar oil, cinnamon and cinnamon oil, citric acid, citronella and citronella oil, cloves and clove oil, corn gluten meal, corn oil, cottonseed oil, dried blood, eugenol, garlic and garlic oil, geraniol, germanium oil, lauryl sulfate, lemongrass oil, linseed oil, malic acid, mint and mint oil, peppermint and peppermint oil, 2-phenethyl propionate (2-phenylethyl propionate), potassium sorbate, putrescent whole egg solids, rosemary and rosemary oil, sesame (includes ground sesame, plant) and sesame oil, sodium chloride (common salt), sodium lauryl sulfate, soybean oil, thyme and thyme oil, white pepper and zinc metal strips.

1994 and revised in accordance with public comments for a final Federal Register publication in 1996 (61 FR 8878, March 6, 1996). A public petition that expresses concern about the potential lack of efficacy for some of these ingredients when used as public health pesticides (which would be classified as biocides and not plant protection products in the EU) has recently been submitted to EPA and is under review. Another enforcement problem has been with identifying exactly what chemical substances are included under the names listed. Currently, CAS numbers are used to describe the substances on the EPA inert substance classification lists.

3.2.2 Regulatory procedures in Canada

In Canada, applicants are asked to meet with the authorities before the submission of a dossier, to define data requirements applicable for the active ingredient and the product. Canada accepts dossiers in their own PMRA format as well as in US EPA or OECD formats. The dossier is evaluated by the Pest Management Regulatory Agency (PMRA) and is scheduled to be finished within 12 month. Additionally, a 52 days front-end and a 30-75 days tail-end administrative phase has to be considered, resulting in a maximum time between receipt of the application and the decision of 16 months. If data are incomplete and additional information is requested, the “review clock” is reset to 0, starting with the submission of the additional information. Full registration is granted for 5 years, with the possibility for 2 renewal periods of 5 years. After 15 years, the product is subject to re-evaluation. Temporary or conditional registrations are possible to allow the applicant to collect further data required for full registration.

Reduced-Risk Pesticides Initiative

The Canadian Regulatory Directive DIR2002-02 is the basis for the «PMRA Initiative for Reduced-Risk Pesticides». This initiative is not restricted to a particular group of substances, but may apply to all groups of products including chemicals, botanicals, micro-organisms and semiochemicals. Data are required for the technical active ingredient and at least one product. Data requirements are very similar to those for «biochemicals» in the USA. In this initiative, there is emphasis on the replacement of more risky plant protection products by reduced-risk plant protection products.

3.2.3 NAFTA joint review process

If applicants apply in both the USA and Canada, these countries may use a joint review process starting with a joint pre-submission meeting to determine the actual data requirements. For microbials, the initial evaluation is based on the taxonomy and a literature research. Evaluation of the active ingredient and the product are done in parallel. The evaluation period normally takes 12 months, with additional national administrative periods. Using this procedure, applicants simultaneously get access to both markets.

3.2.4 Regulatory procedures in Australia

Pre-submission meetings are recommended to determine the applicable data requirements. For microbials, the taxonomy and a literature search on possible risks are used for initial evaluation. Time frames are set to proceed the evaluation within 12 months, but missing data can delay the process.

4. Analysis of formal data requirements

4.1 Formal dossier requirements

The authorities in the EU now require dossiers according to the OECD format. Dossiers are organized in 7 sections (see Table 2) and include Tier I, Tier II, and Tier III summaries for studies, literature information and risk assessments for toxicity and the environmental impact. These summaries and risk assessments are not required in the USA and Australia. In

Canada, formal requirement for summaries is quite recent, but dossiers without summaries are equally accepted. Most dossiers are submitted in “national” formats, but the OECD data format is generally accepted in USA and Canada.

Summary documents are highly appreciated by regulators because information concerning the data point from literature or studies is presented in a short and compact form. All essential literature can be revised and summarized. Detail information in publications can be pointed out by the applicant and is thus more easily accessible to the evaluators. These presentations can lead to considerable time savings for evaluating authorities, but it has to be taken into account that the applicant needs sufficient expertise to provide these summaries.

Dossiers for national registration of plant protection products in some EU member states must be submitted in the national language. At least specific forms have to be provided. In some member states, summaries in the dossier (Documents M and N) have to be submitted in the national language, in others only parts of the dossier (e.g. Document N).

Table 2: Dossier organization according to the OECD Guidance Document

Section #	Active Agent – Annex II	Formulation – Annex III
Section 1	Identity, Biological Properties/ Physical-Chemical Properties	Identity, formulation
Section 2	Analytical Methods	
Section 3	Human Health	
Section 4	Residues	
Section 5	Fate and behaviour in the environment	
Section 6	Effects on non-target organisms	
Section 7	-	Efficacy

4.1.1 «Waivers»

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. However, the summaries in the M-Documents give space for the same scientific argumentation to fulfil the data requirement using published literature and data from the applicant instead of a study. No formal waiver is necessary in the EU to replace a study with a «reasoned case» based on existing, public or non-public, information. 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.

At the scientific level, the arguments why a study is not necessary in a particular case are very similar in the EU and the USA, but the formal procedure is different. For reasons of simplicity, the term «waiver» is used in this document for all systems.

4.2 Data requirements for microbials

“Microbials” are a heterogenous group including fungi, bacteria, viruses, and protozoans used in biological plant protection products. Data requirements are formulated to account for

all groups, even if some points are not applicable for particular groups (e.g. metabolite production for baculoviruses).

4.2.1 Definitions of micro-organisms

EU: A “micro-organism” according to the Council Directive 91/414/EEC is defined as “A microbiological entity, cellular or noncellular, capable of replication or of transferring genetic material. The definition applies to, but is not limited to, bacteria, fungi, protozoa, viruses and viroids.”

USA current version 40 CFR 158.65 (p. 86): Biochemical and microbial pesticides are treated together: “Biopesticides include naturally occurring substances (biochemical pesticides), micro-organisms (microbial pesticides), and pesticidal substances produced by plants containing added genetic material (Plant-Incorporated Protectants, PIPs).” Only living entities are considered as microbial pesticides, while dead micro-organisms are included in biochemical pesticides. In contrary to the EU, genetically modified plants are as well covered by this regulation.

- Microbial pesticides consist of a micro-organism (e.g., a bacterium, fungus, virus or protozoan) as the active ingredient.
- Plant-Incorporated-Protectants (PIPs) are pesticidal substances that plants produce from genetic material that has been added to the plant. The protein and its genetic material, but not the plant itself, are regulated by EPA.
- Biochemical pesticides are naturally occurring substances that control pests by non-toxic mechanisms. Biochemical pesticides include substances such as insect sex pheromones as well as various scented plant extracts that attract insect pests to traps.

USA new proposal: (the microbial pesticide definition in this proposed rule will be slightly reworded and improved in accordance with public comments when published in the final rule in late 2007). Biochemicals are separated from microbials. Extracts from plants or from micro-organisms with toxic properties continue to be treated as conventional chemicals. “Microbial pesticides” includes all living or dead microbial pesticides: “*Microbial pesticide* is a microorganism intended for preventing, destroying, repelling, or mitigating any pest, or intended for use as a plant regulator, defoliant, or dessicant, that

- is a eucaryotic micro-organism including, but not limited to, protozoa, algae, and fungi;
- is a procaryotic micro-organism, including, but not limited to, bacteria; or
- is an autonomous replicating microscopic element, including but not limited to, viruses.”

Canada: In Canada, a “microbial pest control agent” is defined as “a micro-organism (bacterium, alga, fungus, protozoan, virus, mycoplasma or rickettsia and related organisms) and any associated metabolites, to which the effects of pest control are attributed.”

Australia: In Australia, microbial plant protection products are classified as “Biological agricultural chemical products”. “A biological agricultural chemical product is an agricultural chemical product where the active constituent comprises or is derived from a living organism (plant, animal, micro-organism, etc), with or without modification.” Micro-organisms are included in Group 3: “microbial agents (e.g. bacteria, fungi, viruses, protozoa)”. Biological agricultural chemical products include, among others, also natural chemicals (pheromones, hormones etc., Group 1), plant extracts and oils (Group 2), and microscopic insects (Group 4). Decisions on actual data requirements are made on a case-by-case basis; special emphasis is on environmental expression and suppression of indigenous species. Five micro-organisms are excluded from the requirements of APVMA approval as constituent in plant protection products: *Helicoverpa zea* NPV, *Metarhizium anisopliae*, *Paecilomyces lilacinus* strain 251, Rabbit calicivirus, and *Trichoderma harzianum* Rifai strain T-39.

Regulation of micro-organisms is done on strain level in all regulatory systems. Each „new“ variety, subspecies, or strain of an already registered microbial pest control agent must be evaluated. In the EU, strains can be treated together, if they are “similar”. In the USA and

Australia, non- indigenous micro-organisms are subject to additional data requirements. All regulatory systems follow a case-by-case approach in the evaluation of micro-organisms for the use in microbial plant protection products.

In all regulatory systems, additional data have to be provided for genetically modified organisms (GMOs). In the EU, GMOs are evaluated also under the Council Directive 2001/18/EC. On the other hand, no GMOs are expected for the use in plant protection products in the EU in the near future as they will not be accepted by the market. Therefore, GMOs are not further considered in this comparison.

4.2.2 Data requirements for the active ingredient, the micro-organism (MPCA)

Section 1

According to the OECD numbering system, the identity of the micro-organism including criteria for the identification have to be described under point 1. This includes literature information and identification studies on the species and the strain and represents the central information for evaluation of all aspects considered in the application. The question whether the organism is indigenous or not to the area of application is required in the EU, USA, Canada, and particularly pointed out in Australia. The composition of the technical grade of the active substance (the micro-organism after fermentation) and of the material used for manufacture of the end use product is required in all systems. Production methods and quality control data are demanded as well. Differences occur for Point IIM 1.4.5 "The formation, presence, and/or impact of unintentional ingredients": a "theoretical discussion" on impurities and other unintentional ingredients on human health or product quality, and appropriate quality criteria have to be provided in the USA and Canada, but not in the EU and Australia. Likewise, physical and chemical properties of the technical product are required if the manufacturing product is stored before formulation of end-use products in the USA and Canada. The international regulatory status is to be provided in Australia and Canada. Samples of the micro-organism and analytical standards have to be provided on request in the EU, USA, and Australia. Additionally, reference substances for relevant impurities may be required in the EU. The patent status of the MPCA is only required in Canada.

Under Point IIM 2, biological properties of the micro-organism shall be described in a very similar way in the EU, USA, Canada, and Australia. For all regulatory systems, information is to be provided on strain level where possible. A point that is particularly important for bacteria and fungi is the potential of the micro-organism to produce metabolites which are of concern for human health and/or the environment. This information is required in the EU, Canada (with a special emphasis on toxins and genotoxins), and Australia. Information on physiological properties and on genetic stability of the micro-organism have to be provided in the EU and Canada, but not in the USA and Australia. The USA and Canada ask for a description of extrachromosomal elements involved in pesticidal activity, pathogenicity, or toxicity. This information is in practice also required in the EU, if extrachromosomal elements are involved in the mode of action. Information on resistance or sensitivity of the micro-organism to antimicrobial agents is required in the EU, Canada, and Australia, but not the USA. Only in Canada, the relationship of the MPCA to known human dermatophytes has to be discussed.

Under Point IIM 3, information on function, mode of action and handling of the micro-organism is summarized. Data requirements are again similar, with differences for the information on resistance or cross-resistance (only required in the EU and Australia). Material Safety Data Sheets and procedures for the decontamination of water are only required in the EU and Canada, while measures to render the MPCA harmless are only required in the EU.

Section 2

Data demanded in Section 2 “Analytical methods” are very similar for maintenance of the master seed stock, the production processes, and methods of detection, differentiation between similar strains, and the determination of contaminants, pathogens, or metabolites. However, post registration monitoring methods to determine and quantify residues from different matrices are only required in the EU if residues are considered to be relevant.

Section 3

Section 3 comprises “Toxicological and Exposure Data and Information on the Microbial Pest Control Agent”. In general, a tiered test system is applied in all systems. Testing is started with basic studies (acute testing) and, if negative effects occur, continued with further tests. These depend on the outcome of the tests where negative effects were observed.

A summary on the potential of the microbial pest control agent to be hazardous to humans with consideration of its pathogenicity, infectivity and pattern of clearance, and its toxicological effects is demanded in the EU, in Canada, and in Australia, but not in the USA. Occupational health is a central point in all regulatory systems and reports on sensitisation, allergies, or hypersensitisation, especially of workers, have to be provided. Similarly, information on persons with increased susceptibility and literature information on clinical cases has to be supplied. However, the sensitisation properties of micro-organisms are still a matter of debate. As tests systems used for determination of dermal and inhalative sensitization of chemicals are not appropriate for microbials, no proper test system is available. In the EU and in Canada, tests are therefore not required. In the EU, “all micro-organisms should be regarded as potential sensitisers” until appropriate test methods are available (Commission Directive 2001/36/EC, p.13). However, applicants may submit data to demonstrate that the micro-organism does not have a sensitizing potential. In the USA, studies on the sensitization properties are “required if commonly recognized use practices will result in repeated human contact by inhalation or dermal routes”. According to the new USA proposal a skin sensitisation study is not required, but hypersensitivity incidents have to be reported.

Studies on acute infectivity, toxicity, and pathogenicity have to be performed for oral, intratracheal or inhalative, and intravenous or intraperitoneal administration in the EU, USA, Canada, and Australia. In these studies, effects on the test animals as well as the clearance have to be determined. The US guidelines define the requirements in more detail: oral tests have to be performed with the manufacturing product and technical active ingredient. In the new proposal only studies for the technical active ingredient, but not for the end-use product or manufacturing product are required.

“Acute intratracheal/inhalation infectivity, toxicity and pathogenicity” in the USA has to be covered by studies only if a possibility of inhalation exists. Methods for the determination of intravenous/intraperitoneal infectivity are detailed according to the nature of the micro-organism: the administration should be intravenous for bacteria and viruses (no longer required for viruses in the new proposed rule), intracerebral for viruses and protozoa (but the intracerebral route is no longer required in the new proposed rule), and intraperitoneal for fungi or protozoa. In Canada and Australia, intravenous administration is recommended for bacteria and viruses, and intraperitoneal for fungi or protozoa. Additionally, in Australia intracerebral studies are required for neurotropic agents. All studies shall be performed as single studies with a single high dose. Further studies are required if negative effects are observed.

The genotoxic potential has to be determined in the EU for purified metabolites if the micro-organism produces exotoxins, or for the entire micro-organism. If production of exotoxins is not known, expert judgement is advised to decide on the necessity of a test with broken cells of the micro-organism. Information requirements include bacterial gene mutation assays (Ames test), clastogenicity tests, and gene mutation tests in mammalian cells. The risk of insertional mutagenesis has to be discussed for a virus. In Canada, an appropriate and sensitive analytical test (e.g. HPLC) must be performed to detect the presence of possible genotoxins in the technical product, if a related fungus or actinomycete produces a genotoxin. In the USA, genotoxicity tests are only currently required in Tier II and have been

deleted in the new rule. Genotoxicity testing on appropriate extracts of the micro-organism is also required in Australia.

Cell culture studies have to be provided in the EU in Tier I for micro-organisms which are able to replicate intracellularly. In the USA, tissue culture studies with the TGAI are only necessary for virus products. In Canada, cell culture assays are required in Tier I for virus only. Studies have to be performed to assess infectivity and toxicity in a human cell line, a primary cell type, or a primate continuous line. If infection occurs and the virus is replicated in the mammalian system, a cell transformation assay is required.

Information on short-term toxicity is required in the EU unless the information already provided is sufficient to assess human health effects. A study is not necessary if it can be explained why there is no risk, e.g. exposure is not likely to occur, and if there is enough information for a proper risk assessment. The route of administration depends on the exposure for humans. In a short-term toxicity study (28 days minimum) pathogenicity and infectivity have to be assessed and clearance from different organs must be determined. Similarly, short-term studies are also required in Australia. In the USA and Canada, short term toxicity studies are only required in Tier II, if significant negative effects were detected in Tier I acute studies. Toxicity assays on toxins can be demanded in all systems in Tier II, if concerns arise in acute toxicity tests. If needed, also further toxicity studies may be required if concerns arise from Tier I studies.

Section 4

Information on “Metabolism and Residue Studies on the Microbial Pest Control Agent” is summarized in Section 4. In the EU, no studies are required if literature data are available and if no negative effect on human health is known. Information on persistence of the micro-organism or relevant metabolites after application has to be provided. If significant persistence above naturally occurring levels occurs, the full data set as for chemicals may be required. In the USA and Canada, residue data are only necessary if Tier II or Tier III toxicity data are required. Studies are not necessary for indigenous species. If toxins are produced by the micro-organism, the same residue testing scheme as for chemicals is applicable. In Australia, residue data are generally not necessary for microbials, but information has to be provided on the natural occurrence.

Section 5

In Section 5 “Fate and Behaviour Studies on the Microbial Pest Control Agent in the Environment”, the information requirements can normally be covered using literature information. Studies are only needed if mammalian toxins are produced or if studies on toxicity, pathogenicity, infectivity, or on ecotoxicology showed adverse effects. In the EU, mobility studies for the micro-organism are required if negative effects were observed in toxicology studies.

Section 6

Section 6 includes “Ecotoxicological Studies on the Microbial Pest Control Agent (Effects on non-target organisms)”. In the EU and Canada, studies listed according to the OECD numbering scheme are required unless certain non-target organisms are not exposed. In the USA, the extent of ecotoxicity testing depends largely on the use of the product and thus on exposure of potential non-target organisms, and conditions under which studies are required are explicitly defined. For Australia, studies have to be provided and the host range for the micro-organism must be described. Studies are not required if the micro-organism does not survive in the Australian environment, if certain non-target organisms are not exposed, or if high host specificity is demonstrated. Higher Tier tests are required if negative effects on the test organisms are observed.

In particular, data requirements differ for avian toxicity. In the USA, oral and injection tests are required, except if the product is only applied in greenhouses. In the new proposal for USA, the avian injection test is replaced by an inhalation test, which is only required if there is any indication that the microbial pesticide or its toxins may be pathogenic to birds. Canada requires toxicity tests on birds by oral and pulmonary (inhalation or injection) administration,

whereas in the EU, only a study using oral administration is required. Toxicity tests with wild mammal species are only required in the USA, Canada, and Australia, and only if tests conducted on laboratory animals to assess human toxicity, pathogenicity, and infectivity, are inadequate or inappropriate for assessment of hazard to wild mammals.

Studies assessing the effect of the micro-organism on algal growth are required in the EU and Australia, but not in the USA and Canada. Studies using aquatic plants or terrestrial plants have to be provided alternatively in the EU. Aquatic plants have to be tested in Canada and in Australia if aquatic exposure is anticipated, but not in the USA.

Effects on terrestrial plants have to be assessed in USA and Australia. In Canada, this test has only to be provided if the MPCA is related to a plant pathogen (this is also the condition in the new proposal in USA).

Effects of the micro-organism on bees and other terrestrial arthropods have to be tested in all systems, but not for greenhouse use in USA. In the new USA proposal this requirement is reduced, and arthropod tests are only required if the micro-organism acts through infecting insects. Effects on earthworms need to be determined in the EU and Australia, but not in Canada and the USA. Studies on effects on other terrestrial invertebrates have to be provided in Canada only if the micro-organism is intended to control non-arthropods, and in Australia. Effects on soil micro-organisms have to be assessed in the EU and Australia, and can be required in Canada, depending on the micro-organism. Generally, the strategy in USA and Canada is directed towards a maximum hazard testing, whereas in the EU effects and exposure are evaluated. The exposure is calculated and a risk assessment is provided by the applicant (cp Annex III data requirements below).

4.2.3 Data requirements for the product (MPCP)

Section 1

Information on the product as required in Section 1 include the identity, physical, chemical, and technical properties of the product, and data on application. Data requirements are widely the same for the EU, USA, Canada, and Australia.

Section 2

Data demanded for methods of analysis, manufacturing, and quality control are again the same in all systems and equivalent to the data required in Annex II. Methods for the determination of residues, if relevant, are only required in the EU, and are in most cases identical to the information for the determination of the micro-organism provided in Annex II.

Section 3

“Toxicological Studies and exposure data” required in Section 3 are similar between the EU, the USA, Canada, and Australia. Acute oral and dermal (percutaneous) toxicity tests using the formulated product are required in the EU unless justification is provided, in the USA and Australia. In the new USA proposal, acute oral toxicity tests are no longer required for the end-use product or manufacturing product, but may be combined with the limit dose infectivity/pathogenicity testing for the technical active ingredient. Acute inhalation toxicity studies are demanded generally (Australia), or conditionally if inhalative exposure can occur (EU, USA). The new USA proposal specifically recognizes that all the acute toxicity tests on the end-use and manufacturing products can be waived if the inerts are not likely to pose significant risk. Skin and eye irritation studies are as well required, unless the micro-organism or formulants are already classified as “sensitizing”. For details on irritation, refer to Annex II information. Monitoring data for operator and bystander exposure are always demanded.

Section 4 and Section 5

Information on residues and on fate and behaviour in the environment can be based on published literature. Studies are only required if negative effects were observed in toxicology or ecotoxicology studies. In most cases residues only derive from the micro-organism and not from other ingredients. Therefore the argumentation is in general similar to that in Annex II.

Section 6

Ecotoxicity tests are frequently performed with the unformulated micro-organism or the technical product. Therefore, testing of the formulated product is in most cases only necessary if the formulation is suspected to modify the effect on non-target organisms. Point IIIM 11 “Summary and evaluation of environmental impact” includes a summary of all data relevant to environmental impact and an environmental risk assessment. For this risk assessment, effects of the micro-organism on different non-target organisms as determined in the studies required in Annex II are compared to application rates for the product under the appropriate conditions of use. This summary with the risk assessment is to be provided by the applicant in the EU, but not in the USA, Canada, and Australia.

Section 7

“Efficacy Data and Information (including Value Data) for the Microbial Pest Control Product” is not required in the EU for listing of active substances in Annex I of Commission directive 91/414. However, these data are necessary for national registration of the product in most EU member states. Efficacy data are as well required in Canada and Australia, but are not required to be submitted for review in the USA. Efficacy data are only required for review in the USA if the product is to control a public health pest, but these products are considered to be biocides and not plant protection products in the EU.

4.2.4 Differences between data requirements in the EU and in non-EU countries

The major differences in formal data requirements for micro-organisms as active ingredients in plant protection products concern methods for residue analysis if relevant metabolites are expected, the demand for information on short-term toxicity, infectivity, and pathogenicity (justifications based on lack of relevant exposure can be accepted for not providing a study), and some ecotoxicity tests. For a summary of the main differences, please refer to Table 3. It should be realised that in the EU the data requirements ask for information, which can be provided from published literature, internal information from the applicant, or from studies. A justification for not submitting a study can always be submitted. The acceptance of such justifications differed in some cases between different member states, but is expected to be better harmonised by the different Member States within the EU based on the experiences with the 4th list substances (see also 5.2)

Table 3: Summary of the major differences in the formal data requirements between the EU, the USA, Canada, and Australia.

Section	Subject	Major differences
2	Analytical methods	Methods for the determination of residues are only required in the EU if relevant residues are expected
3	Human health	Information on short term-toxicity in Tier I is required in the EU and Australia, not in the USA and Canada.
4	Residues	EU: general information is required on persistence, multiplication, population dynamics, mobility (soil/water/air) of the microorganism and eventually occurring metabolites. Information can be derived from published literature. USA/CAN: data are only required if toxicology or ecotoxicology studies showed negative effects. Australia: no data required.
6	Effects on Non-Target Organisms	USA: Tests depend on application of the product. EU: Effects on non-target organisms have to be determined, if these are exposed. Evaluation of exposition and effects, calculation of exposure, risk assessment. Studies to assess effects on birds are required in the EU, USA and Canada, but not in Australia.
7	Efficacy	Information is required for national registration in member states of the EU, in Canada, and Australia, but not required to be submitted and reviewed in the USA

4.2.5 Proposed revision of data requirements in the USA

In the USA, data requirements are currently being revised. New proposed data requirements are included in “Federal Register, Part III, Environmental Protection Agency, 40 CFR Parts 158 and 172, Pesticides; Data Requirements for Biochemical and Microbial Pesticides; Proposed Rule, 8 march 2006”. Major differences to the existing rules are more flexible data requirements depending on the use of the product, the group of micro-organisms, and the particular species or strain. In particular, toxicity tests are further adapted to the MPCA. The hypersensitivity studies are no longer required, but hypersensitivity incidents have to be reported. Avian inhalation tests are only conditionally required if the presence of toxins is suspected. Studies on the toxicity to plants are only required if the MPCA is related to a plant pathogen.

4.3 Data requirements for botanicals

“Botanicals” include a vast diversity of substances or mixtures. Plants used for the extraction of “botanicals”, might be known for food, feed, or medicinal uses, or are restricted in their use to plant protection purposes. Extraction methods and the extent of purification can vary as well, from crude extracts to purified single substances. Active constituents may be well-characterized or unknown. In addition, as for any biological products, variation occurs from one batch to another. “Botanicals” also differ in their modes of action. In general, substances with direct toxicity to the target pest are treated as conventional chemicals. Modes of action include induction of systemic resistance, repellence and growth regulation. Definitions differ between the regulatory systems considered in this comparison

4.3.1 Definitions

EU: Plant extracts or “botanicals” are not defined in the EU legislation, and no separate data requirements exist. Therefore, the situation is different when compared to micro-organisms. Formally, they have to be registered like chemicals according to the data requirements outlined in Directive 91/414. Reduced data requirements are described in a SANCO Draft guidance document (SANCO Draft 10472/2003/rev.5), but this document covers only a small proportion of plant extracts. The SANCO draft document includes a reference list of plants for which these reduced data requirements shall apply. This list is based on experience with these plants in food or feed use, or as herbal drugs in European pharmacopeia. The document is furthermore restricted to water and ethanol extractions. Extracts derived from plants which are not mentioned in the document, or which are extracted with other solvents are treated like conventional chemicals. All data points have to be addressed, but information does not necessarily have to be provided by studies, but might be presented from published literature. In the comparison below, data requirements in the SANCO draft document and in the Directive 91/414 are considered.

USA: In the USA, naturally occurring substances are treated as “biochemicals” if they have a non-toxic mode of action. If Tier I testing shows toxic effects, the substance may be treated like a conventional chemical. “Biochemical and microbial pesticides are generally distinguished from conventional pesticides by their unique modes of action, low use volume, target species specificity or natural occurrence. Biochemical pesticides include, but are not limited to, products such as semiochemicals (e.g., insect pheromones), hormones (e.g., insect juvenile growth hormones), natural plant and insect regulators, and enzymes.”

The **new proposed regulation in the USA** separates biochemicals from microbials and presents a new definition: A biochemical pesticide is a pesticide that...

- (1) is a naturally-occurring substance or structurally similar and functionally identical to a naturally-occurring substance;
- (2) has a history of exposure to humans and the environment demonstrating minimal toxicity, or in the case of a synthetically derived biochemical pesticides, is equivalent to a naturally-occurring substance that has such a history; and

(3) has a non-toxic mode of action to the target pest(s).

Extracts from plants or from micro-organisms with toxic properties are treated as conventional chemicals.

Canada does not have a particular set of data requirements for plant protection products based on plant extracts. However, for many plant extracts the “PMRA Initiative for Reduced-Risk Pesticides” (Regulatory Directive DIR2002-02) with reduced data requirements when compared to “conventional” chemicals might be applicable. “Reduced Risk” criteria are applicable for all other groups of products, including chemicals, micro-organisms, and semiochemicals. Data are required for the technical active ingredient and at least one product. Data requirements are very similar to those for “biochemicals” in the USA.

In **Australia**, plant protection products containing plant extracts and oils as active ingredients are classified as Group 2 “Biological agricultural chemical products”. Decisions on actual data requirements are made on a case-by-case basis. Biologically derived chemicals that have direct toxicity to the target species are exempted from reduced data requirements and treated like chemicals. Unpurified or purified plant extracts can be included, as long as purification is incomplete and composition not fully characterised. Examples are “Pyrethrum”, consisting of a mixture of related pyrethrins, and “Neem oil” and “Neem extract”, consisting of mixtures of characterised and uncharacterised components. If purification and full identification of a plant-derived substance is possible, these substances are as well treated as conventional chemicals and not as biological agricultural products (examples: nicotine, strychnine and ivermectin). Several plant extracts are excluded from the requirements of APVMA approval as constituents in plant protection products: Cabbage extract, Canola oil, Capsicum oleoresin, Chilli extract, Citronella oil, Cypress wood oil, Derris dust, Eucalyptus oil, Garlic extract, Garlic oil, Lanolin oil, Lavender fragrance, Lime oil, Orange oil, Pine oil, Pyrethrins, Pyrethrin I, Pyrethrin II, Quassia, Rotenone, Salicylic acid, Sesame, Tea tree oil and Thymol.

4.3.2 Data requirements for the active ingredient and the plant protection product

Requirements for plant extracts according to the SANCO Draft 10472/2003/rev.5 concerning information on toxicology and effects on non-target species are similar to the data requirements for micro-organisms. Data requirements refer to the active substance (if it can be purified at all) and to the plant protection product.

If other components than the active substance(s) are not considered to affect human or animal health, environmental behaviour, or effects on non-target species, data requirements for sections 2 and 3 to 6 can be covered using information on the active substance.

Section 1

According to Directive 91/414/EEC, the SANCO draft document, and to US/Canada and Australian data requirements the active ingredient has to be described. As a starting point, the plant species and cultivar as well as growth region and conditions, the plant organ and growth stage, have to be specified. If any substance has been identified, its chemical name according to IUPAC, CAS Number, structural formula, and ISO name have to be provided. For the description of physical-chemical properties vapour pressure, partition coefficient, hydrolysis, and photolysis have to be determined. The composition of the extract has to be described as far as possible. Concentration ranges have to be provided for all known substances included in the extract. Maximum limits have to be given for any substances that are relevant for human or animal health and the environment. If the active substance(s) is (are) not identified, a representative marker, i.e. a chemical naturally present in a known proportion in the plant extract has to be defined in order to identify the plant protection product. Five production batches collected over several periods have to be analysed for their contents. Mode of action and specificity as well as likely biological effects arising from use have to be declared. In Australia, special emphasis is on natural occurrence and distribution

of the source organism in Australia, on the natural occurrence of the chemical or relationship to the form occurring in an organism.

A full list of ingredients of the plant protection product has to be submitted, including a precise quantity or an upper and lower limit of the extract and other ingredients. The plant protection product's trade name, physical state and function must be specified. Physical and chemical properties of the plant protection product, data on application, and further information on the plant protection product have to be given as for all other plant protection products. Information on shelf-life is as well required.

Section 2

According to Directive 91/414/EEC, validated analytical methods have to be provided for the active ingredient and for all «impurities» present in quantities ≥ 1 g/kg. According to the SANCO draft document, validated analytical methods for the determination of contents of the active substances have to be provided if the substances are identified. If the active substances are not identified, a validated method of analysis of the marker in the plant protection product should be available. A validated method for analysing the active substance in water, soil and air is necessary. If exposure of the concerned compartment is not likely or the contribution compared to natural background levels is not substantial such methods do not need to be provided. If any substances that are relevant for human or animal health and the environment are detected in the plant protection product, validated methods of analysis must be provided.

Section 3

Council Directive 91/414/EEC requires thorough testing of the active substance and/or the product, including acute, short-term, and long-term toxicity, carcinogenicity, reproductive toxicity, and delayed neurotoxicity tests. According to the SANCO draft document, toxicology testing refers to the product rather than to the active substance, to take all possible impurities into account. Information is required for acute oral, dermal, and inhalation toxicity, skin and eye irritation, and skin sensitisation in the form of studies or literature data. Oral toxicity studies may be waived if the plant is also used for food or feed. Risk assessments for the operator and worker must be addressed. Further toxicological testing is needed, if effects are observed in first tier studies.

In the USA, data on acute oral, dermal, inhalation toxicity, cutaneous and eye irritation and genotoxicity are required. Further toxicological testing is needed, if effects are observed in Tier I studies. In Australia, data on acute oral, dermal, and inhalation toxicity, genotoxicity, and short-term toxicity are required. Furthermore, information is required on Occupational Health and Exposure.

Section 4

The data requirements in section 4 are similar between Directive 91/414/EEC and the SANCO draft working document.

Data on residues in or on treated products, food and feed are required according to the exposure to the plant extract's components due to the use as plant protection product, and have to be compared to the exposure due to consumption of the plant itself or to natural exposure to the plant itself. Residue data are required, if human exposure to residues from products based on plant extracts is higher than from consumption of the plant itself. Supervised field trials only have to be carried out if human health or ecotoxicology are concerned. This requirement is different from microbials, where residue trials are in general not necessary. US EPA demands residue data depending on the use rate of the product. If the application rate is below 0.7 ounces active substance per acre (corresponding to 52.5 mL/ha), no residue studies are required. However, the proposed new rule requires residue data for biochemical pesticides only if Tier II or Tier III toxicology data were required. In Australia, residue studies are normally not required, and information demands can be covered using published literature.

Section 5

According to Council Directive 91/414/EEC, pathways and kinetics of degradation, adsorption/desorption, and mobility in soil have to be determined. Data on abiotic and biotic degradation in water, on volatility, and on photolytic degradation are required to assess the persistence of the substance in water and air.

The SANCO draft document and USA/Canada, Australia demand provision of available information from literature on natural background levels if, depending on the use of the product, exposure of water, soil or air is likely to occur. More information may be required based on expert judgement, if there is a substantial increase.

Section 6

According to Directive 91/414/EEC, the effects of the active substance and/or the product have to be determined on terrestrial vertebrates (acute, short-term dietary, and long-term reproductive toxicity to birds and mammals), aquatic organisms (acute, short-term, chronic toxicity to fish, invertebrates, sediment dwelling organisms, and algae, bioaccumulation), arthropods (acute oral and contact toxicity to bees and other arthropods depending on the use of the product), earthworms (acute and reproductive toxicity), and soil microorganisms according to Council Directive 91/414/EEC. SANCO/10472 only requires submission of "all available ecotoxicological information" which might primarily be based on published literature. If classification as dangerous substance according to Directive 67/548/EEC or 1999/45/EC is applicable, the following studies must be provided: acute effects on fish, daphnia and algae. Depending on the use, non-target arthropod testing is needed for those groups that are exposed to the product. In the USA, information is required on effects on birds (acute oral and dietary exposure), fish, and freshwater invertebrates. Depending on the use, nontarget arthropod testing is needed. Data required in Australia depend on the use of the product.

Section 7

Efficacy data have to be submitted for national registrations of plant protection products in EU Member States, Canada and Australia, but are not required to be submitted for review in the USA. In case the application concerns a product for field application, the efficacy data have to be specific for the country or at least the climatic zone. This restriction is normally not relevant for products that are intended for use in greenhouses. Efficacy data for biological plant protection products are in some countries reduced when compared to the requirements for chemical plant protection products. This reduction refers both to the number of successful studies that have to be submitted and to the extent of efficacy obtained in the trials.

4.3.3 Proposed revision of data requirements in the USA

The new proposed rule in the USA suggests changes to define when a data point is applicable.

Toxicology testing is dependent on the expected human exposure through the use of the product. Exposure data have to be provided and hypersensitivity incidents have to be reported (which are new requirements). Data requirements for genotoxicity testing are more clearly described. Residue data are required depending the use of the product (and no longer the use rate).

4.4 Data requirements for semiochemicals

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 can be used for (i) mating disruption, (ii) mass trapping, (iii) monitoring and (iv) attract & kill. Semiochemicals are considered as pesticides in the first two uses. In the last

two uses, they are not considered as pesticides, and are therefore exempt from registration. This section deals only with the use for mating disruption.

Semiochemicals have a high specificity for the target species. Their efficacy is not related to population effects, which makes assessment of efficacy difficult. One problem in fulfilling formal data requirements are the low production rates of most substances. Some substances are not even produced once every year, thus request of data from a 5-batch analysis is very difficult to fulfill. On the other hand, exposure for applicators, bystanders and the environment is very low, because the released quantities are very low when compared to chemicals. One group among semiochemicals is particularly well characterised: the Straight Chained Lepidopteran Pheromones (SCLPs). SCLPs represent a homogenous group with low toxicity to non-target (and target-) organisms including mammals.

4.4.1 Definitions

EU: Formally, there are no separate data requirements for semiochemicals in the EU, thus they have to be registered according to the data requirements outlined in Directive 91/414. The OECD developed the 'Consensus Document No 12' on "Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control". Many EU member states choose to implement OECD 12. This document defines semiochemicals as follows: "Semiochemicals are chemicals emitted by plants, animals, and other organisms - and synthetic analogues of such substances - that evoke a behavioural or physiological response in individuals of the same or other species. They include pheromones and allelochemicals. This report pertains only to semiochemicals that affect the behaviour of arthropods".

USA: Semiochemicals are included in the group of "Biochemicals" according to 40 CFR 158. Data requirements are therefore formally the same, but vary according to the uses. For the definition, refer to Point 4.3.1.

Canada: Registration of products containing semiochemicals as active substances is possible as reduced-risk pesticide (Regulatory Directive DIR2002-02: The PMRA Initiative for Reduced-Risk Pesticides). Data are required for the technical active and at least one product. Synthesized pesticides can be considered as pheromone or other semiochemical pesticides, if it is demonstrated that they are structurally similar and functionally identical to a naturally occurring pheromone or semiochemical. Data are required according to OECD 12.

In **Australia**, semiochemicals in plant protection products are classified as Group 1 "Biological agricultural chemical products". Decisions on actual data requirements are made on a case-by-case basis; special emphasis is on environmental expression and suppression of indigenous species. Most pheromones are exempted from data requirements for the active ingredient for chemistry, manufacture, and biological properties. Metabolism and kinetics data are only required if the concentration of the active ingredient results in levels that can be differentiated from background levels. Residue studies are usually not required. Environmental studies have to be provided as for chemicals, but the actual requirements are determined case-by-case. The following semiochemicals are excluded from the requirements of APVMA approval as active constituents (Pheromone use only): 4-(p-acetoxyphenyl)-2-butanone (Cue-lure), 4-(p-hydroxyphenyl)-2-butanone (Frambinone), 8,10-Dodecadiene-1-ol, 8-Dodecen-1-ol, 8-Dodecen-1-ol acetate (cis-isomer), 8-Dodecen-1-ol acetate (trans-isomer), German Cockroach Pheromone, Isomate LBAM, Isomate OFM Rosso, (E)-2-Octadecenal, (E,Z)-2,13-Octadecadienal, and (Z)-9-Tricosene.

4.4.2 Data requirements for semiochemical active ingredients and products

Date requirements as in OECD 12:

Sections 1 and 2

According to OECD 12, the mode of action of a semiochemical product should be explained in terms of its function in modifying the behavior of the target pest, and information should be provided to support the claim that the active ingredient is a naturally occurring arthropod semiochemical. Qualitative information is required on the pest species life cycle, and the nature and extent of damage it causes. Other useful information includes the compatibility of semiochemicals with IPM programs and their contribution to risk reduction.

Identification of the active ingredient has to be provided as well as specific physical and chemical characteristics. Identity data are used to determine whether an active ingredient is identical or structurally similar to another active ingredient or a naturally occurring substance. The manufacturing process has to be described with the starting materials. The possible formation of impurities has to be discussed and upper and lower certified limits for each active ingredient component, and upper limits for impurities have to be given. Supporting analytical data including component identity confirmation are required.

For the characterisation of the product, identification of the active ingredient, formulants, and impurities of toxicological concern in the plant protection product has to be provided. Starting materials and the formulation are to be described including upper and lower certified limits of the technical grade active substance and formulants. An enforcement analytical method for each active ingredient component has to be provided. If the formulation process introduces or enhances the presence of impurities of toxicological concern, this must be identified along with upper limits and a corresponding enforcement analytical method.

Section 3

Sufficient information to identify potentially hazardous products is always required, including information on irritation, dermal sensitisation, acute toxicity, mutagenicity, and medical data. Studies of teratogenicity and subchronic exposure can generally be waived if long-term exposure above background levels can be excluded, or if a substance is a member of a well-characterized group, such as SCLPs, for which toxicological concerns have already been addressed. Less information is available on the toxicity of other forms of semiochemicals containing ketone, epoxide, lactone, terpenoid, pyrazine, pyran and other aromatic structures. If they have the toxicological characteristics of other chemicals with these substructures or functional groups, they may be more toxic than the SCLPs and might potentially require long-term tests.

Section 4

For semiochemicals, residue data may not be required, if detectable residues on the consumable commodity are unlikely to occur, if residue levels are unlikely to exceed natural background levels during outbreaks of the pest, or if residues are not toxic. In Canada and the EU, applicants are encouraged to provide a scientific rationale for waiving residue data based on the low potential risk of any residues on a treated crop.

The US EPA has established an exemption from the requirement of a food tolerance (i.e., MRL) for most uses of arthropod semiochemicals, namely

- in retrievably sized polymeric dispensers used at a rate no more than 375 g a.i./ha/year;
- at a rate of no more than 50 g a.i./ha per application regardless of formulation, provided no potentially adverse effects are observed during the tier I toxicity testing;
- SCLPs at rates up to 375 g a.i./ha/year, regardless of the mode of application.

Sufficient information is required to characterize occupational and bystander exposure potential. This would include consideration of application method and rate and appropriate physical-chemical properties. For those substances with significant exposure potential and for those with toxicological concerns, additional exposure data would be required. In the EU, the USA and Canada, residue studies are conditionally required if toxicity data indicate concern. In contrast to this, residue data are generally not necessary for semiochemicals in Australia.

At EU level the exemption from MRLs setting is foreseen (not implemented so far) and exempted substances will be listed in Annex IV of Regulation 396/2005 on residues. Semiochemicals are among the candidates to be listed there.

Section 5

According to the OECD document, assessment of the environmental fate of a semiochemical (e.g., stability in air and water) is required, based on available information. Test data on a compound will only be required if its use will result in environmental contamination exceeding natural background levels. Application rates of up to 375 g SCLP/ha/year are generally understood to result in exposure levels that are comparable to natural emissions and safe for nontarget species. This threshold may or may not be applicable for other kinds of semiochemicals; applicants are invited to request waivers of environmental testing, based on information that indicates that application rates are comparable to natural emissions. If ecotoxicity data or public literature indicate a hazard to biota, data on the persistence of a semiochemical and its transport from the site of application to another site or medium may be required.

If the data indicate that significant persistence and transport of these agents occurs in any part of the environment such that significant exposure to nontarget organisms could be expected, then additional environmental testing will be necessary.

Determination of the estimated environmental concentration (EEC) is performed with a simple mass-balance analysis of the pesticide, taking into consideration

- the pesticide application parameters (i.e., rate, frequency, and site of application)
- initial tests that measure transport properties (volatility, dispenserwater leaching, vapour pressure, and water solubility).
- persistence testing (hydrolysis, aerobic soil metabolism, aerobic aquatic metabolism, soil photolysis, aquatic photolysis, adsorption–desorption, and octanol–water partition coefficient), each of the transformation processes should be expressed as a half-life for the particular environment, or as a rate constant for the environmental process, depending on the test.

Estimated environmental concentrations can then be calculated for different times using these data and the field application rate of the pesticide. Aquatic use patterns and non-dispenser pesticides will require mass-balance analysis following persistence tests.

Section 6

Fewer tests are required for semiochemicals when compared to chemical pesticides, and the number of organisms per test is reduced because of the non-toxic mode of action of semiochemicals and limited exposure of non-target organisms. Avian dietary toxicity is only of concern for formulations that might be ingested, e.g., granules. No wild mammal testing is required. Non-target terrestrial plant studies would only be required if effects are suspected. Aquatic invertebrate and fish toxicity data are required for direct application to aquatic sites for all semiochemicals. One species of fish (rainbow trout), an aquatic invertebrate (*Daphnia magna*), and (in Europe) an algal species should be tested. Aquatic testing is not required for fixed-point dispensers applied over land. Non-target arthropod testing is not required if no adverse effects were observed during efficacy testing (in particular on predators or parasites of the target organism, closely related species and pollinators). Following OECD 12, and depending on the use also in the USA, testing of effects on bees and terrestrial arthropods other than bees is required, while effects on earthworms and soil micro-organisms only have to be determined according to OECD 12, if the product is applied to the soil and can accumulate in soil. It is only required if the exposure exceeds natural background levels (e.g. at >375 g ai/ha/yr for SCLP). Available information has to be provided and discussed. Ecotoxicity data are generally not necessary for semiochemicals in Australia.

Section 7

In the EU (only for national registrations, not for Annex I listing) and Canada, data from scientifically conducted efficacy trials are required to support pest control claims on the product label and to demonstrate how a product may be used most effectively. Sufficient efficacy data are required to confirm the performance. At least one study should evaluate a range of rates to demonstrate the lowest effective rate of application. In conjunction with the efficacy trials, information on any adverse effects on the crop or site should be reported, including phytotoxicity and effects on non-target arthropods.

Because the use of semiochemicals can involve specialist techniques, they require adapted trial protocols. The UK PSD has recently developed draft efficacy guideline 220 on efficacy testing of mating disruption products. This has been submitted to the EPPO fungicides and insecticides panel as a draft guideline for discussion.

4.4.3 Proposed revision of data requirements in the USA

The new proposed data requirements according to the “Federal Register, Part III, Environmental Protection Agency, 40 CFR Parts 158 and 172, Pesticides; Data Requirements for Biochemical and Microbial Pesticides; Proposed Rule, 8 march 2006” introduce a change for semiochemicals: No toxicity data are required for SCLPs, and no nontarget organism and environmental fate data are required for all arthropod pheromones, if they are applied at less than 360,66 g/ha.

5. Practical experience with the regulatory process

5.1 Case study: registration of *Paecilomyces lilacinus* in the EU and the USA

As an illustration of current regulatory practice, studies submitted for the registration of the plant protection product based on the micro-organism *Paecilomyces lilacinus* strain 251 in the USA and for the inclusion of the same strain in Annex I of Council Directive 91/414/EEC were compared. Both applications regarded the same use of the product. As the same studies were available for both dossiers when initial applications were submitted, most of the submitted studies were identical. Some studies already existed, and were therefore submitted even if they might not have been necessarily required. It must be emphasized that this section is based on the experiences with a single micro-organism, and not on a representative sample of substances.

Data requirements: Data submitted in the EU but not in the USA include studies on the genotoxic potential and a cell culture study. In the EU, a study to assess acute intratracheal/inhalation infectivity, toxicity and pathogenicity of the formulated product including analysis of the clearance of the micro-organism was additionally requested during the evaluation process. Furthermore, studies on effects on terrestrial arthropods other than bees and on effects on earthworms were additionally demanded.

Waivers: No studies to assess short-term toxicity, pathogenicity, or infectivity were submitted in any of the two systems, because no signs of acute toxicity, pathogenicity, or infectivity were observed in acute tests. Furthermore, no data were submitted on effects of the micro-organism or the formulated plant protection product on birds, aquatic and terrestrial plants, and bees, because these non-target organisms are not exposed to the micro-organisms with the intended uses.

Time for registration: The comparison of the time needed for registration in the USA and for Annex I listing in the EU is extremely difficult. The time needed by the applicant to generate data that were additionally requested in the EU is counted as well as the time needed by authorities (RMS, other member states, and EFSA) for the evaluation. Evaluation in the USA took 21 months starting from the submission of the dossier to the registration of the product. A provisional national registration for the product BioAct was obtained in Italy before Annex I listing of *Paecilomyces lilacinus* in December 2005. The application for the inclusion of *P. lilacinus* strain 251 into Annex I was submitted in April 2002 and is expected to be completed in early 2008.

5.2 Data requirements and «waivers»

Whether specific data or studies are required or whether a data requirement can be waived is better defined in the USA and in the Canadian system than in the EU. Also, the industry reports that the registration authorities in the EU are in general less willing to accept «waivers» than the authorities in the USA. The background for this is that (i) in the EU, the registration authorities take more responsibility when they register a substance, while in the USA, the responsibility stays largely with the applicant; (ii) within the US EPA, a separate unit of staff is concerned exclusively with the registration of «biopesticides», and has built up expertise with this kind of substances. Also, many biopesticides have been applied for in the USA which has given the US EPA a large experience in assessing these kinds of products. In the EU few applications for active substances and products were submitted and evaluated under the current legislation before the EU review program. Furthermore, these applications have been assessed by different RMS (producing the DAR). Therefore, the registration authorities within each RMS have build up less experience with such products. With this background of knowledge, the US EPA can accept waivers more easily than their European counterparts. (iii) Even if the RMS accepts a waiver, a study may later be requested, when the other member states and EFSA are evaluating and giving comments to the DAR. It is possible that some RMS rather require the maximum number of studies which might be required, in order to avoid such requests in the commenting phase. The 4th stage of re-evaluation will give the European regulators' community a chance to collectively improves their expertise in evaluating BCAs, and to harmonize their interpretation of data requirements in this field. This experience is expected to result in a number of EU guidance documents/"lessons learned documents", which will facilitate the application process for future registrants as well as the future assessments carried out within the regulatory authorities.

USA

In the USA, more BCAs are registered than in the EU (see Table 1B), and registration is faster (see Table 1A). Given the aims of the REBECA project, the US system is successful. This is only partly due to lower data requirements than in the EU (for details see section 4). However, other factors contribute equally to the success of this system. (i) The process is organized much simpler than in the EU, with only one authority in charge of registration (except for some states that require separate registration). (ii) There are strict timelines for registration. (iii) Within the EPA, a separate unit is concerned with biopesticides, thus building up expertise with this kind of products.

US EPA recently conducted a survey on the data that were effectively required for the evaluation of 9 different bacteria and 11 fungi for the use in microbial plant protection products between 1997 and 2004. Data on chemical identity and technical properties were required in all cases. No data on residues or methods for residue analysis were required. For assessment of toxicity, acute studies were required, but cell culture studies or studies on subchronic toxicity / infectivity / pathogenicity were not demanded. Studies on ecotoxicity (non-target-organisms) were limited to organisms that were apparently exposed or at risk. No data on environmental fate and behaviour were required. Data requirements for the only baculovirus that was evaluated during the selected timeframe were limited to information on chemical identity and technical properties, a study on acute oral toxicity / pathogenicity, acute inhalation toxicity, and acute eye irritation. Further information on toxicity, ecotoxicity or residues was not required.

During recent evaluation of 5 different Straight Chain Lepidopteran Pheromones (SCLP) by the US EPA, data on chemical identity and technical properties were required. However, no data on residues or methods to determine residues, no toxicity studies, and no studies on ecotoxicity and environmental fate and behaviour were required. No comparable survey is available for the EU, Canada, or Australia.

Microbial pesticides: 78 microbial pesticides are currently registered: bacteria: 17 *Bacillus thuringiensis* subspecies, 10 other *Bacillus* species, 10 *Pseudomonas* species, 2 *Agrobacterium* isolates; 29 fungi; 7 baculoviruses; 2 yeasts; 1 protozoan.

Biochemical pesticides: 160 biochemical pesticides are currently registered: 50 semiochemicals (pheromones), 4 insect growth regulators (e.g. azadirachtine), 21 plant growth regulators (e.g. indole-3-acetic acid), 3 herbicides (e.g. corn gluten meal), 29 repellents (e.g. capsaicin from red pepper), 14 floral attractants and plant volatiles, 18 products for insect & nematode control (e.g. soybean oil) and 21 products for plant pathogen & microbial control (e.g. sodium bicarbonate).

The registration procedures in the USA for the registration of BCAs are more predictable than those in the EU. This results in a much larger number of products registered in the USA (see introduction). The proposed new rule, which is based on long-term experience with a large number of products, will formalize the current practice of the US EPA. This procedure applies to biochemicals, microbials, semiochemicals, but also to chemicals if certain conditions are fulfilled. Likewise, applications restricted to minor uses can be treated as reduced risk pesticides.

EU

No comparable survey is available for the EU, Canada or Australia. However, in the EU a similar survey will be carried out for all the 4th list micro-organisms (approximately 30 strains belonging to 16 species) and is expected to be finalized during 2008. This survey will also include information regarding studies being accepted even though they were performed on closely related strains and not the specific strain in question. However, from such surveys it is not possible to see if some studies were submitted even though maybe a waiver would have been accepted. In the EU, practice demonstrates that assessment of clearance in studies on acute toxicity, pathogenicity, and infectivity in many cases is only required for one out of the three studies. In many cases, these studies and studies on non-target organisms only have to be performed with the active ingredient or the formulated product and not with both. Furthermore, short-term toxicity studies were only required for a smaller part of micro-organisms already listed in Annex I. Tier II toxicity tests are normally not required, as results with micro-organisms in Tier I tests do not raise concern for human or environmental aspects.

So far, relatively little experience exists with the current European data requirements. Since the first micro-organisms were evaluated as “new active substances” for inclusion in Annex I, data requirements have been amended (Commission Directive 2001/36/EC) and the uniform principles for evaluation were defined (Commission Directive 2005/25/EC). The so called “old active substances”, including micro-organisms, which were used in plant protection products before 1993, are subject to the 4th stage of re-evaluation. As this is still ongoing and is expected to be finalised during 2008, there is no experience with the 4th stage available.

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 have chosen to submit «minimum data packages», in order to save costs for studies which might not necessarily be required. This has led to demands for further studies not initially considered, which has considerably lengthened the process. Such studies are especially expensive and time consuming, if new methods have to be developed.

Little experience exists with the registration of botanicals in the current system. To date (July 2007), only one botanical has been evaluated in this system and is included in Annex I of Directive 91/414. The active substance, Laminarin, is a polysaccharide purified from the brown algae *Laminaria* sp.. Due to the chemical properties and the indirect mode of action of Laminarin towards fungal plant pathogens, only a reduced set of data when compared to chemical substances was required during evaluation the active substance and a corresponding product for inclusion into Annex I. Data requirements were reduced for human

health, environmental fate and behaviour, and ecotoxicology. Other plant extracts, some of them with direct effects on the target organisms, are now under evaluation as List 4 substances.

Also for semiochemicals, relatively little practical experience exists regarding the applicability of the data requirements in the EU. EU evaluation of the so called “old substances” including the majority of semiochemicals that are used in plant protection products is still ongoing.

5.3 Experience with the structure of the registration process in the EU

The registration process under Directive 91/414 is structured in a complex way and involves a large number of authorities, such as The European Commission (mainly DG SANCO, who is responsible for the coordination of the process and the legal aspects), the registration authorities of the Rapporteur Member State (RMS) and the European Food Safety Authority (EFSA) which is responsible for coordinating a peer review process of the active substances (see Figure 1). This process takes time. In addition, this structure is intrinsically conservative and may in many cases hinder the acceptability of waivers, since even though accepted by some member states, others may not accept the waiver during the peer review process. In some cases, RMS have to request data even if they do not consider them essential for the evaluation themselves. Compared with the EU system, the registration processes in the USA, Canada, Australia, or Switzerland are more simple, mainly because they involve only one country.

The current registration procedure has grown historically. Originally the plant protection products were only regulated by the national authorities in each of the member states. In 1991, Directive 91/414 established an EU-wide system for registration of active substances. The EFSA was created in 2002.

The Commission's proposal for revision of Dir. 91/414 of 12.07.2006 contains other important changes such as the transition from a Directive to a Regulation, and mutual recognition of plant protection product registration within each of three climatic zones.

Conclusions: The current EU registration system is complex. It reflects the structure of the political organization of the EU, which is a compromise between central administration and independence of member states (subsidiarity). The system is dynamic and likely to change in the future. However, changes cannot be made solely from a technical and practical viewpoint, but must be embedded in a wider political context.

5.4 Time span for registration

As the examples in Table 1A show, it takes much longer for an active substance to be included in Annex I of Directive 91/414, than it takes for a substance and the corresponding product to be registered in the USA. Furthermore, in most EU member states Annex I inclusion must be followed by registration of plant protection products at national level, before commercialization can begin. However, some member states have given provisional authorisation of products prior to Annex I inclusion. In the USA, the registration process is at present guaranteed to be completed within 18 months. As can be seen from Table 1A this was not always possible in the past.

For the industry, long registration periods 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 patent protection.

Conclusions: The length of the registration period in the EU is one of the main obstacles for the industry to obtain registration of their products. The long process is mainly caused by the complicated structure of the decision-making process.

5.5 Fees

Fees demanded by the authorities vary widely. EU fees for evaluation of dossiers for substances of the 4th list varied between 11,600 € and 215,000 € (information was not available for all MS). In most member states, fees for BCAs were considerably reduced compared with the fees demanded for conventional chemicals as active substances. In some MS, fees are intended to recover the costs for evaluation, but in others, fees are lower than actual costs.

The fees for new active substances also differ between member states (0 € - 42,000 €). Some countries do not require any fees for new substances, e.g. if a national registration of a product is applied for simultaneously (which also applies for new chemical substances).

In Canada, no cost recovery-fees are demanded for the evaluation of microbial plant protection products, in order to encourage the registration of biological control products. Only a label review fee of 252 CDN\$ is requested. In the USA, fees for products containing microbials are 25,000 US\$, but fees can be reduced or waived for small enterprises. In Australia, fees depend on the data that are actually required, since the fee has to cover the costs for evaluation.

5.6 Pre-submission meetings

Pre-Submission Meetings between the applicant and the evaluating authorities are formally recommended in the USA, in Canada, and Australia and proved to be very effective. They are also informally recommended in the EU. Practice in the EU demonstrated that these meetings were in some cases not offered by the authorities or not used by the applicants. The structure of the registration process sets a limit to pre-submission meetings in the EU: Besides the rapporteur member state, other member states and EFSA are later on also involved in the evaluation of an active ingredient, but they do not participate in pre-submission meetings.

In pre-submission meetings, the substance is briefly discussed and it is outlined what kind of data are likely to be needed, and where waivers are likely to be acceptable. Applicants can thereby better target their application dossiers to the requirements of the authorities, and save expenses on the production of unnecessary data and consequently speed up the preparation of the dossier. Authorities report that the improvements of dossier quality save labour during evaluation.

5.7 EU harmonization with biocide regulation

Some BCAs, mainly pheromones and botanicals, can be used both as plant protection products and as biocides. The industry reports that the two registration processes are non-harmonized to a large extent. For example, dossiers normally have to be presented in different formats. Regulatory fees are higher for biocides than for plant protection products (authorization & evaluation of dossiers) in all EU member states. However, the data requirements for microbial biocides were recently revised mainly in order to harmonise these with the data requirements for microbial plant protection products (the biocide data requirements can be found in Commission Directive 2006/50/EC and further information can be found in the Technical Notes for Guidance). Also, the Uniform Principles of the microbial plant protection products have been used as a basis when a similar and nearly identical document was recently prepared for the biocides.

Conclusions: BCAs are highly specialized products, of which the evaluation methodology differs greatly from conventional pesticides. Thus, the plant protection and biocide use of a specific substance (e.g. a certain lepidopteran pheromone) share many common aspects. The evaluation of plant protection and biocide uses should be harmonized as much as

possible, to avoid further fragmentation of the regulatory community, and to save costs on unproductive tasks such as reformatting of dossiers. The REBECA project is focused on improvements in the registration of plant protection products and not of biocides. Nevertheless, increased harmonization has the potential to benefit the use of BCAs in both areas.

5.8 Level of Annex I inclusion

In workshops on semiochemicals which were held during 2006 in the framework of the REBECA project, the question was raised how the active ingredients will be listed in Annex I. Listing could be in one of the following ways:

- «Straight-Chained lepidopteran Pheromones» (SCLPs) could be listed collectively, or
- each substance could be listed separately, or
- each blend of substances, with their proportions, could be listed separately.

The mode of listing will influence the registration requirements for future applications. In particular, it determines whether or not the active ingredient must be registered. Under the first option, new plant protection products based on old and on new SCLPs would not require Annex I inclusion, but only national registration of the plant protection product. Of course, the data of the SCLP notifiers in the 4th stage re-evaluation would have to be protected. Under the second option, new plant protection products based on old SCLPs would not require Annex I inclusion, while new SCLPs would require Annex I inclusion. Under the third option, even new blends of old SCLPs would require Annex I inclusion. Industry would prefer one of the first two options, because this facilitates the development of new end-use products.

Plant extracts are complex mixtures of numerous substances, which can be characterized to a variable degree, but rarely to 100 %. Therefore, similar problems may arise with the listing of plant extracts in Annex I.

Micro-organisms are listed in Annex I at strain level. A working group within the framework of the REBECA project has proposed facilitations in the registration of plant protection products containing baculoviruses. Based on conclusions of the "OECD Consensus document No 20 on information used in the assessment of environmental applications involving baculoviruses" (see 6.1.1), on the high host-specificity of baculoviruses, and on the high similarity of baculoviruses with regard to effects on humans, the environment, or non-target organisms, the authors propose to include members of the family *Baculoviridae* on the level of species.

5.9 Efficacy data

For Annex I inclusion of the active substance, efficacy data are not required. For registration of the plant protection product, efficacy data must be submitted for all uses applied for. By contrast, efficacy data are not required for registration in the USA under the present legislation, but will be required under the proposed new rule.

Not all EU member states require efficacy data, and EU member states differ in their practice how easily they accept efficacy data from other countries. Also, the practice for issuing experimental permits and the requirements for crop destruction differ across the EU.

Experimental permits: Practice for issuing experimental permits differs widely in member states, in terms of crop destruction and area that can be treated. No mechanism is foreseen to harmonize experimental approval systems, and there is no legal basis for this. However, industry and Member States could take the initiative for harmonization.

Conclusions: These aspects are under national authority and therefore cannot be harmonized with EU legislation at the moment. Nevertheless, the costs related to submission

of efficacy data are often high, and add to the total costs for market introduction of a new BCA and should therefore be kept as low as possible. Currently, there are plans for mutual recognition of registration within climatic zones. If this concept will come into force, such problems would be greatly reduced.

6. Initiatives taken to facilitate the registration of BCAs in the EU

Section 6 of this report contains an inventory of documents, initiatives and concepts aiming to improve the registration of BCAs. These include guidance documents at EU and OECD level (section 6.1), legislation and regulation at national level and national initiatives for supporting SMEs in the registration of BCAs (sections 6.2 – 6.6). This section also briefly discusses the new categories of 'low risk substances' and 'basic substance' mentioned in the Commission's proposal for a new Directive on plant protection products, as well as new concepts for risk assessment (sections 6.7 – 6.9). These initiatives act at different levels. Some of these documents, initiatives and concepts may serve as models or as inspirations for improvements of the registration process in the EU.

6.1 Guidance documents

6.1.1 Baculoviruses: OECD 20

The "OECD Consensus document No 20 on information used in the assessment of environmental applications involving baculoviruses" dates from January 2002. With respect to human health, it is stated that «Baculoviruses are naturally occurring pathogens of arthropods. Their host range is exclusively restricted to arthropods. No member of this virus family is infective to plants or vertebrates» and it concludes that «No adverse effect on human health has been observed in any of these investigations indicating that the use of baculovirus is safe and does not cause any health hazards.»

6.1.2 Botanicals: SANCO/10472

The draft guidance document SANCO/10472/2004 proposes data requirements for some plant protection products based on plant extracts. Data requirements are described in detail under 4.3.2. The data requirements apply only to plant protection products made from the edible parts of plants used for animal or human feed, from parts of plants mentioned explicitly, or from parts of plants currently authorised as herbal drugs in European pharmacopoeia and known traditionally for plant protection properties (also listed explicitly). Further, the data requirements apply only to plant extracts made with water and/or ethanol. For plant protection products made from other plants or plant parts or with other solvents, data requirements will be established case-by-case in a pre-submission meeting, based on the available information.

As pointed out in Chapter 4.3, the document is still a draft and is not legally binding. During a REBECA meeting a working group on botanicals recommended that SANCO/10472 should be reviewed and amended, based on the experience of applicants and regulators involved in the 4th stage re-evaluation.

- The document should also include extracts prepared with other extraction methods, such as CO₂, pressure or food-grade oils.
- The list of plants in the annex should remain indicative («plants such as»).
- The definitions for 'products' and 'extracts' need specification and should be used consistently throughout the document.

- The working group recommended to encourage purification of plant extracts, but to allow declaration of a range of composition for actives and 'impurities'. The degree of detail required should be justified by toxicological relevance.
- At the moment, there is still very little experience with this document. With more experience, the document should become an official guidance document.

6.1.3 Semiochemicals: OECD 12

The OECD Consensus document No 12 on "Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control" dates from February 2002. The document suggests reduced data requirements, particularly for straight-chained lepidopteran pheromones (SCLPs). Data requirements are presented in detail in Point 4.4.2. The rationale is that

- The application rate is typically low and probably comparable to natural emissions.
- Volatility and rapid environmental transformation minimise residues in crops and exposure of non-target organisms.
- SCLPs are of low toxicity to mammals.

Although it has no official status within the EU, several registration authorities are ready to use it as a basis for evaluation. The working group «semiochemicals» suggested to formalize its use within the EU, and also to adopt its use for registration under the biocide directive 98/8.

6.1.4 Plant strengtheners (EU Draft working document)

There have been attempts to elaborate data requirements for plant strengtheners at EU level. Draft working document SANCO/1003/2000 rev.3, 21/06/2001 was intended to be a guidance for a reduction in data requirements for "low risk products", when compared to data required for chemicals according to Council Directive 91/414/EEC. The document refers to products which are expected to be "low risk" for humans, animals and the environment from their composition and their uses.

During the drafting of "Commission Regulation (EC) No 2229/2004 laying down further detailed rules for the implementation of the fourth stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC" Guidance Documents were developed on Plant extracts (Sanco 10472/2003-rev. 5; 6.7.2004) and Chemical substances (Sanco 10473/2003-rev. 4; 6.7.2004). In a certain sense these documents replace the working document on plant strengtheners. The document on Plant Strengtheners was not followed up.

As active substances are not characterised or cannot be purified for many plant strengtheners, data requirements refer basically to Annex III data. Evaluation follows a tiered approach. If during evaluation of Tier 1 data it turns out that the product is not "low risk", the full data requirements are applicable. Requirements are similar to those for microbials, with some exceptions.

Sections 1 and 2

Information on the identity and composition of the product, methods of manufacture, its physical-chemical and technical properties, and application is required. For plant extracts, details on the origin of the plant, harvest season, plant parts, extraction methods and main components are demanded. In addition to data required for micro-organisms, a method to qualitatively identify the characteristics of the extract is required for plant extracts. On the other hand, analytical methods for determination of residues are not required.

Section 3

Acute toxicity studies are required for the product as for products containing micro-organisms. Short term toxicity studies and genotoxicity testing are also required. A literature summary on operator exposure based on available information has to be provided. Assessment of bystander and worker exposure is not considered to be relevant.

Sections 4 and 5

No data are required.

Section 6

Data requirements are identical to those for micro-organisms.

Section 7

Efficacy data are limited to qualitative effects and possible long-term effects. Information can be derived from literature.

6.2 GENOEG (NL)

The «GENOEG» (Gewasbeschermingsmiddelen van Natuurlijke Oorsprong Effectief Gebruiken) project was initiated in the Netherlands in 2002. Its aim was to get more natural pesticides registered, to learn about their low risk profiles and to apply this knowledge for registration purposes. The project is funded by the Dutch Ministry of Agriculture, Nature and Food Quality and the Product Board for Horticulture. It is carried out in collaboration between the Board for Authorization of Pesticides (CTB), the Plant Protection Service, the Agricultural University, the Dutch Organisation for Agriculture and Horticulture (LTO), the National Institute for Public Health and the Environment (RIVM) and CLM.

Applicants were supported in registration procedures and financially by partial funding of the costs required for generation of data and for registration (co-financing of up to a maximum of 50%, with a limit of EUR 100,000). Furthermore, scientific and administrative expertise was provided to facilitate registration.

Initially, potential “low risk profile” of the products was evaluated by experts based on information provided by the applicants. Products were also selected according to their use, efficacy, and relevance for particular growing conditions in integrated agriculture in The Netherlands. Evaluation was done in contact with the applicants. Data requirements were partially answered with statements based on literature, expert judgement, or information from registration procedures in other countries for matters of identity of the active ingredient, residues, ecological effects, and efficacy. Basic information that has to be provided is the composition of the product, the application rates and frequencies, and toxicology studies. Administrative procedures were facilitated by guidance through the registration process. Despite this support, the main responsibility remained with the applicant.

Economic risks for registration remained high due to unpredictable time scales for registration. At the same time, the market for biological pesticides is still very small, as the use of these products requires adapted culture conditions for many crops. Experience with biological pesticides is increasing among regulatory bodies. During the project, risk assessment and evaluation were adapted to biological pesticides and statements were accepted more frequently. Case-by-case evaluation again turned out to be essential for biological pesticides. By using statements instead of performing studies, costs could be saved. From the project, the following steps were considered necessary: a reduction in formal data requirements, taking into account the specific risk of biologicals, predictable registration costs, and improved communication between applicants and authorities

Since 2002, GENOEG has supported the registration of two plant protection products with active ingredients in the 4th stage of re-evaluation (Trianum [*Trichoderma harzianum*]; Botanigard [*Beauveria bassiana*]), one product with the active ingredient listed in Annex I (Preferal [*Paecilomyces fumosoroseus*]) and of two new substances, the registration of which is not yet completed. All 5 initial applicants claimed that they would have withdrawn their applications if they had not been supported by GENOEG. In 2004, this activity was scaled up with 10 new products. For more information, see www.genoeg.net. Source of information: «Five case studies on the registration of natural pesticides in The Netherlands», GENOEG, March 2006.

6.3 RUB (NL)

The Dutch pesticide law recognizes the so-called «Regulation Exemption Pesticides» (Regeling Uitzondering Bestrijdingsmiddelen, abbreviated «RUB»). RUB are products with such a low risk for man and environment that the usual procedures for authorization are considered unnecessary. Contrary to the other procedures where the decisions on authorization are taken by the CTB (on behalf of the government), the government itself decides about RUB authorizations, advised by the CTB. Examples of RUB: milk as a viricide and against mildew in courgette, sugar as a fungicide against a specific disease in arboriculture and several plant oils against pests and diseases, potassium phosphonate as a fungicide in glasshouse culture. Sometimes, authorization is only given for a specific application method. For example, heavy oils like coconut oil and sunflower oil are allowed for spraying, while lighter, volatile oils may only be used for dipping and pouring. A number of fourth list substances have been registered under the RUB procedures in the past years. However the RUB procedure will no longer apply when the substances of the fourth list have been evaluated.

Source of informations: R. Boeringa and M. Trapman (2004) «Plant protection products in organic farming in the Netherlands». In: Current Evaluation Procedures for Plant Protection Products Used in Organic Agriculture. Proceedings of a workshop held September 25–26, 2003 in Frick, Switzerland.

Conclusions: Given that the low-risk status of a plant protection product is established, the RUB procedures allow fast registration. A number of substances have been registered under the RUB procedures in the past years, demonstrating that this pragmatic approach is effective in practice. The RUB procedure might be taken as a blueprint for similar procedures in other countries, and possibly also at EU level.

6.4 PSD pilot scheme and biopesticide scheme (UK)

In June 2003, the UK Pesticides Safety Directorate (PSD) introduced the «pilot scheme» for BCAs. The overall aim was to increase the availability of BCAs in the UK. Within this programme, recommendations and guidance were given to applicants, starting with support early in the product development. Data requirements were not modified, but the procedure was facilitated. Pre-submission meetings were held to create confidence between the authorities and the applicants, and to increase the awareness of the regulation process among the applicants. Fee structure and success rate depend on dossier quality. An identification of «low risk» profile was done beforehand in initial pre-submission meetings. An authorisation within 42 weeks after completeness is guaranteed. Within the pilot scheme, 'Exosex CM' (Codlemone, under evaluation for Annex I inclusion as existing substance), 'Curbit' (Zucchini Yellow Mosaic Virus; ZYMV, under evaluation for Annex I inclusion as new active substance) and 'Contans WG' (*Coniothyrium minitans*, included in Annex I) were registered, and several other biologicals are at various stages of evaluation.

On the 1st of April 2006, the pilot scheme was completed and the «Bio-pesticides Scheme» was launched as its successor. It comprises the following categories: semiochemicals, micro-organisms (bacteria, fungi, protozoa, viruses), natural plant extracts and «other novel

products» on a case-by-case basis. Fees are £22'500 for biologicals/plant extracts, £13'500 for semiochemicals plus £ 7'500 for EU consideration (Annex I listing). A biopesticide «champion» is assigned to act as contact point for general enquiries. Pre-submission support and advice on the registration process and data requirements are free. Close contact and cooperation between the applicant and the authorities shall be maintained throughout the evaluation. Special guidance can be given by specialists. An internal biopesticides e-mail group was established, to keep awareness of current issues and to disseminate information, and an area for biopesticides was dedicated on the PSD website.

Source of informations: L. Moakes: «Experience with the UK pilot scheme and consequences for the biopesticide scheme». In: Review of potential risks of botanicals and semiochemicals. Minutes of a workshop held on 13 – 14 June 2006 in Brussels.

6.5 Plant resistance improvers (DE)

Plant resistance improvers (PRI) – sometimes also called plant strengtheners (literal translation of the German term «Pflanzenstärkungsmittel») – make their own category of products in Germany. They are regulated by the German Plant Protection Act. Plant resistance improvers are defined in Article 2 no. 10 as substances which are

- solely intended to enhance the resistance of plants to harmful organisms, or
- intended to protect plants against non-parasitic impairments, or
- intended for use on cut flowers.

This means that plant resistance improvers may not have any biocidal effects nor effects that are covered by the definition of a plant protection product (e.g. as growth regulators or repellents). The mode of action should be induction of systemic resistance, increase in nutrient uptake resulting in reduced susceptibility towards pests or parasites, or competition between the active ingredient and the parasite. A product which primarily increases growth and not resistance of the plant is classified as a fertilizer. Active agents in PRIs may be micro-organisms, plant extracts, organic or inorganic compounds.

The indirect mode of action of a micro-organism used in PRIs implies that this micro-organism is not infective towards other organisms, including man and other non-target organisms and that it does not produce harmful metabolites. Likewise, lack of a direct effect on pests and parasites from a plant extract or a chemical is assumed to imply a lack of detrimental effects on humans or the environment. The risk assessment in the course of the listing procedure is based on material safety data sheets for all the ingredients and additional data given by the applicant, and follows the pathway of answering the questions: is there any risk inherent in one of the substances or in the product? (1) The environmental risk assessment furthermore gives special interest to the predicted concentration of the substances in the environment. If certain applications are too risky to the environment, they might be excluded. But, unlike for plant protection products, no sophisticated risk management is accepted for plant resistance improvers, i. e. the use has to be safe without risk mitigation. Otherwise a listing of such a product is not feasible. (2) For the risk assessment in toxicology, the criteria are similar to those for home and amateur gardening, i. e. toxic substances are not allowed in plant resistance improvers. The use of irritant products is restricted to professional users (only very few, exceptional cases). For products containing micro-organisms, the criteria of the directive 91/414/EEC are adopted. (3) The assessment in efficacy covers mainly the question whether any of the ingredients acts as an active substance in the sense of a plant protection product with the exception of products for use on cut ornamental flowers: they may contain plant hormones. Only the plausibility of the mode of action is checked, but studies on efficacy are not required.

Recently, data requirements were changed for PRI containing living micro-organisms. Data required for the evaluation of health effects for plant protection products and biocides containing micro-organisms are now as well required for PRI containing micro-organisms. The applicant has to prove that the micro-organism does not produce and secrete toxic metabolites, and has to provide a literature research proving that the micro-organism has no

deleterious effects on human health. Information on the identity of the strain and production of mycotoxins is required as well as data on exposition of users, workers and bystanders, medical data, toxicity, pathogenicity, infectivity, and the sensitization potential of the micro-organism. Furthermore, information on viable or non-viable residues on treated plants is required. A description of the production process has to be provided including information on quality control during production and determination of contaminants and content of the active ingredient. For the assessment of toxicity, pathogenicity, infectivity, and the sensitization potential of the micro-organism, information from animal experiments is currently not required and data may be derived from published literature.

The majority of microbial strains used in plant protection in Germany are listed as PRI, and a minority are registered as plant protection products (Table 5). Listing as a PRI represents an interesting alternative to registration as a plant protection product, provided that

- it has an indirect mode of action against the pest or parasite, and
- production of toxic metabolites can be excluded.

However, determination of the mode of action is often difficult, particularly for living organisms. For further information on listed products, the listing procedure and the application form please see: www.bvl.bund.de.

Table 5: Strains of micro-organisms in plant protection in Germany, under plant protection products and plant resistance improvers. V = virus, B = bacterium, F = fungus.

Group	Species	strain	target pest / use
Strains registered as plant protection product			
V	<i>Adoxophyes orana</i> GV	Swiss	<i>A. orana</i>
B	<i>Bacillus subtilis</i>	QST713	<i>Venturia</i> spp.
B	<i>Bacillus thuringiensis</i> ssp. <i>aizawai</i>	ABTS-1857	Lepidoptera
B	<i>Bacillus thuringiensis</i> ssp. <i>kurstaki</i>	HD-1	Lepidoptera
B	<i>Bacillus thuringiensis</i> ssp. <i>tenebrionis</i>	NB 176	<i>Leptinotarsa decemlineata</i>
F	<i>Coniothyrium minitans</i>	CON/M/91-08	<i>Sclerotinia</i> spp. / <i>Sclerotium</i> spp.
V	<i>Cydia pomonella</i> GV	Mexican	<i>Cydia pomonella</i>
B	<i>Pseudomonas chlororaphis</i>	MA 342	<i>Fusarium</i> spp., <i>Pyrenophora graminea</i> , <i>P. teres</i> , <i>Septoria nodorum</i> , <i>Tilletia caries</i> , <i>T. foetida</i>)
Strains listed as plant resistance improver			
F	<i>Aureobasidium pullulans</i>		<i>Erwinia amylovora</i>
F	<i>Aureobasidium pullulans</i>		foliar fungal pathogens
B	<i>Bacillus subtilis</i>		<i>Erwinia amylovora</i>
B	<i>Bacillus subtilis</i>	FZB-24	soilborne fungi
B	<i>Bacillus subtilis</i>	B2g	soilborne fungi
B	<i>Pseudomonas</i> sp.		soilborne fungi
F	<i>Pythium oligandrum</i>		soilborne fungi
F	<i>Trichoderma harzianum</i>	T-22	soilborne fungi
F	<i>Trichoderma harzianum</i>		increase of resistance, abiotic diseases
F	<i>Trichoderma harzianum</i>		soilborne fungi
F	<i>Trichoderma harzianum</i>	T 39	<i>Botrytis</i> spp.
F	<i>Trichoderma harzianum</i>		soilborne fungi
F	<i>Trichoderma harzianum</i> + <i>T. polysporum</i>		soilborne and floral fungi
F	<i>Ulocladium oudemansii</i>		<i>Botrytis</i>

Germany is the only EU member state with separate legislation for PRI, but PRI listed in Germany can be marketed in Austria as well (where they are considered to be fertilizers). As mentioned in 6.1.4, there have been attempts at EU level to define data requirements for plant resistance improvers with low risk profile (Draft working document SANCO/1003/2000 rev.3, 21/06/2001). However, these activities have been discontinued. Plant resistance improvers are products of low risk, but they are not congruent with the planned low risk category of the Directive 91/414/EEC.

6.6 Italian Presidential Decree 290 (IT)

In Italy, Presidential Decree 290 dated April 23rd 2001, established a general, simplified procedure for authorization of plant protection product and adjuvants. Specifically, Article 38 dealt with substances for organic and biodynamic agriculture. It allowed the commercialization and use of several products traditionally used in organic farming but not registered/authorized in Italy (e.g. oils, lecithine, herbs, quassia). These substances could only be marketed under the technical name of the active ingredient, but not under a brand name. Source of information: C. Micheloni, 2004: Plant protection products in Italy. In: B. Speiser & O. Schmid, Current evaluation procedures for plant protection products used in organic agriculture. Proceedings of a workshop held September 25-26, 2003 in Frick, Switzerland. The Presidential Decree 290 is not in force any more.

6.7 QPS

The development of a «QPS» (Qualified Presumption of Safety) concept was initiated in 2003 by a working group consisting of members of the former (EC) scientific committees on animal nutrition, on food and on plants. It is now continued within an EFSA working group involving the panels on micro-organisms used in animal feed, on preservation of animal feed, on plant protection products, on novel foods regulation and on GMO. The aim is to develop a scheme that would make the approval procedure for micro-organisms more consistent. For this, a more generic approach instead of a full case-by-case assessment is envisaged. This could allow 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 not identical to GRAS. A further aim is the harmonisation of the safety assessment of micro-organisms throughout the food chain, making better use of assessment resources by focussing on those organisms that present greatest risk or uncertainties, and which would need a case-by-case risk assessment. A **major advantage** of the QPS status for the notifier may be the ability to change production conditions (media etc.), with only a requirement for notification rather than generating a need for an additional full safety assessment.

The EFSA Scientific Committee recommended that EFSA should develop a strategy for the introduction of an assessment system based on the QPS concept. As a first step, this should be limited to micro-organisms deliberately introduced into the food chain or used as production strains for food/feed additives. If the robustness and value of such a system has been shown in practice, its application to micro-organisms used in plant protection products may be considered. The Committee recommended to consider non-spore forming gram positive bacteria, *Bacillus* spp., yeasts and commonly encountered filamentous fungi. The conclusions of the working group should be made available for public consultation.

A consultation on documents for the four groups of organisms took place during February 2007. The documents made available for consultation suggested that all strains belonging to the *Bacillus cereus sensu lato* group (e.g. *Bacillus thuringiensis*) should not be given a QPS status, since it is known that the vast majority of strains within this group are toxin producers and thus can not meet the required qualifications. In the document regarding filamentous fungi (which includes e.g. *Trichoderma*) it is concluded that no filamentous fungi can be

proposed for a QPS status. The main reason is the difficult taxonomy of these fungi and the lack of knowledge concerning production of toxic compounds

Bacteria directly consumed by humans only qualify for QPS status, if they are free of acquired resistance to antibiotics of importance in clinical and veterinary medicine. Furthermore, all bacteria capable of toxin production should be demonstrated to be free of any toxigenic potential. It is important to stress that QPS would carry no legal status.

QPS status of an organism should be established by risk assessors, as a result of an assessment. Establishment of QPS lies on four pillars: (1) taxonomy, (2) familiarity and body of existing knowledge, (3) pathogenicity to humans and animals, (4) end use. Some safety issues like carrier, particle size and dust need to be addressed at product level case-by-case, while hazards like sensitisation are more amenable to a generic approach. The assumption could be that all products are potential sensitisers, unless otherwise demonstrated. There should be no implication that micro-organisms considered unsuitable for QPS status are less fitted for introduction into the food chain.

Taxonomy: QPS should be sought at the highest taxonomic level that is practicably possible by using the mechanism of qualifications to exclude undesirable strains. If the identity of a micro-organism cannot be established, a full assessment is required.

Body of knowledge/familiarity: The body of knowledge of the group of organisms seeking QPS must be sufficient to provide adequate assurance that any potential adverse effects in humans, livestock or the wider environment is understood and predictable.

Pathogenicity: Any grouping of micro-organisms in which the *majority of members* produce any form of adverse effect would automatically be excluded from consideration for QPS status. In case only few strains produce adverse effects, there is the option to use qualifications to exclude the undesirable strains, provided the means exist to do so (e.g. *B. subtilis*).

End use: The end use determines, to which degree end users come into contact with the micro-organisms (intended to enter food chain / not intended to enter food chain, but possibility of unintentional introduction [plant protection product] / production strains [end product free of micro-organisms]). This will influence the nature and extensiveness of the body of knowledge needed to determine whether the taxonomic unit is suitable for QPS status. The body of knowledge made available for QPS status for one use may not be sufficient to be able to extrapolate and give QPS status for another use.

The **following data would be required** for organisms within a taxonomic unit with QPS status: (1) identity, (2) evidence that strains are not excluded by any of the qualifications imposed for the particular taxonomic unit, (3) product-specific safety data.

Source of information: A. Fjelsted: «QPS – Qualified Presumption of Safety». Presentation at the 1st REBECA conference, 18 – 22 September 2006, Kiel.

Conclusions: QPS might in the future be a useful tool during the risk assessment and registration process of plant protection products based on well-known micro-organisms. However, it is not applicable if the micro-organisms belong to novel groups.

6.8 Proposed new regulation for low risk and commodity chemicals

The Commission's proposal for a new pesticide Regulation (2006/0136 [COD]) contains separate paragraphs relating to «low-risk» and «basic» substances. Article 22 extends the period of approval to 15 years for low risk active substances. Article 23 provides a definition for basic substances and extends the period of their approval to an unlimited time. Article 28 states that plant protection products containing basic substances exclusively need not be authorized. Article 46 sets timelines for the authorization of plant protection products based on low risk substances.

The proposal does not contain a definition for low risk substances. However, such a definition is needed. It is expected though that most microbials, some botanicals and/or many SCLPs will fall into this category.

The category of basic substances is relevant for some botanicals, e.g. lecithine, and for some other substances such as kaoline. These are often also low-risk substances.

6.9 History of safe use

During the REBECA meetings, it was repeatedly stressed that many BCAs have a long history of safe use in food or feed, in pharmacopoea or cosmetics, or as PRI or plant protection product. Other substances have a long history of safe co-existence in the environment (e.g. pheromones). It was stressed that such «history of safe use» should be accepted as an argument instead of a study in the data requirements on human health and environmental safety.

Table 6: Overview of different approaches which may facilitate registration of BCAs.

Approach	Examples
Scientific argumentation to justify non-submission of data	<ul style="list-style-type: none"> For baculoviruses: OECD Consensus document No 20 on information used in the assessment of environmental applications involving baculoviruses For semiochemicals, particularly for SCLPs: OECD Consensus document No 12 on Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control
Reduced data requirements	<ul style="list-style-type: none"> For semiochemicals, particularly for SCLPs: OECD Consensus document No 12 on Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control For plant extracts: SANCO/10472 (draft proposal) For low-risk substances: RUB (no longer applicable after the end of EU review program) For plant resistance improvers (PRI): German PRI regulation For micro-organisms: QPS (under development, not yet to be applied to plant protection products, but to other uses)
Maximum timelines for registration	<ul style="list-style-type: none"> Germany, for plant resistance improvers (4 months; but additional requirements reset the clock to 0) USA & Canada for biopesticides National reg. of plant protection products containing low-risk AI, according to SANCO proposal for new Regulation
Reduced registration fees (in some cases only for SMEs)	<p>Fee structure is variable across the EU. Examples are:</p> <ul style="list-style-type: none"> Cancelling of fees for new active substances (e.g. Germany, Denmark) Reduced fees for certain categories of products (e.g. microbials in Belgium and Sweden, biopesticides in the UK, Austria, USA and Canada) Lower fees related to separate legal categories (plant resistance improvers in Germany)
Financial support for dossier preparation and/or registration fees	<ul style="list-style-type: none"> GENOEG

Approach	• Examples
Increased time, before re-evaluation is required	<ul style="list-style-type: none">• Low-risk substances, according to SANCO proposal for new Regulation (15 years)• Basic substances, according to SANCO proposal for new Regulation (unlimited)
Application can be submitted by any interested party or by a member state.	<ul style="list-style-type: none">• Basic substances, according to SANCO proposal for new Regulation (unlimited)
No national registration of plant protection products required.	<ul style="list-style-type: none">• plant protection products containing basic substances, according to SANCO proposal for new Regulation
Pre-submission meetings or other support with dossier preparation	<p>Occurs in a number of EU member states and other countries, for example</p> <ul style="list-style-type: none">• GENOEG in the Netherlands. Here, the support comes in part from an institution which is independent of the regulatory agencies.• UK for biopesticides• USA for biopesticides

7. Overall conclusions

In conclusion, this study shows that

- 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 and Canada, this requires a formal **waiver**. In the EU, a scientific argument in the M Documents – without a formal waiver – serves the same purpose.
- **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 reports and monographs, 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.
- The registration process in the EU has a **different structure** from all other systems. Registration is divided in two parts (Annex I inclusion of active substance, registration of plant protection product), while such a division does not exist outside the EU. 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 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, 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 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, DAR), but may be extended, if additional information is required. In the later steps of the evaluation strict timelines are missing in the EU. Experience with registration in the EU shows that the time effectively needed for registration is much longer than in the USA.

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