ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Annex to the Report of the 8th Biopesticides Steering Group Seminar on Niche Uses of Highly Specific Biocontrol Products

Series on Pesticides
No. 95

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Presentation on the OECD and the work of OECD-EGBP and general introduction to the seminar on ‘Niche Uses of Highly Specific Biocontrol Products’

Jeroen Meeussen (EU Minor Uses Coordination Facility)

SEMINAR ON “NICHE USES OF HIGHLY SPECIFIC BIOCONTROL PRODUCTS”

26 June 2017, OECD, Paris
OECD Expert Group on BioPesticides

Jeroen Meeussen
Chair of the OECD Expert Group on Biopesticides

My Background

- Until October 2010: Ctgb
- October 2010 – July 2015: DG Sante
- Since September 2015: EUMUCF
- Since 2005: Chair of the EGBP

Unclassified
OECD

- A few words about OECD
- OECD Work on (Bio)Pesticides
- Today’s seminar: purpose, scope and structure

A few words about OECD

OECD: The Organisation for Economic Co-operation and Development
OECD

- Started after World War II
- Transformed in 1961 into the Organization for Economic Co-operation and Development with trans-Atlantic and then global reach
- Today the OECD has 35 member countries
- More than 70 developing and transition economies are engaged in working relationships with the OECD (Brazil, Russia, India, China and South Africa)

OECD – What is OECD?

A forum in which governments work together to:
- Co-ordinate and harmonise policies;
- Discuss issues of mutual concern;
- Work together to respond to international problems.

A provider of comparative statistics and economic and social data with more than 250 publications per year.
OECD – How do pesticides fit in all this?

One of the fields in which OECD is actively involved is the sustainability of agriculture.

OECD-WGP (Working Group on Pesticides)

The OECD work on agricultural pesticides aims to help member countries:
- improve the efficiency of pesticide control;
- share the work of pesticide registration and re-registration;
- minimise non-tariff trade barriers;
- reduce risks to human health and the environment.
OECD

• A few words about OECD

• OECD Work on (Bio)Pesticides

• Today’s seminar: purpose, scope and structure

OECD-BPSG

• The BioPesticides Steering Group (BPSG) was established by the WGP in 1999 to help member countries to harmonise the methods and approaches used to assess biological pesticides.

• New name: Expert Group on BioPesticides (EGBP).
**OECD-EGBP**

**Biological Pesticides:**

- Macro-organisms
- Microbial pesticides
- Semiochemicals
- Plant extracts/Botanicals

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**OECD-EGBP**

The first tasks of the BPSG consisted of:

- reviewing regulatory **data requirements** for three categories of biopesticides;
- developing **formats for dossiers and monographs** for microbials, and pheromones and other semio-chemicals.
OECD-Publications (I)

Registration requirements:

• for pheromones (Series on Pesticides, No. 12, 2001) under revision
• for microbial pesticides (Series on Pesticides, No. 18, 2003)
• for invertebrate biocontrol agents/IBCAs (Series on Pesticides, No. 21, 2004)

OECD-EGBP

The EGBP then decided to concentrate its efforts on science issues that remain as barriers to harmonisation and work-sharing.
OECD-Publications (II)

• Working Document on the Evaluation of Microbials for Pest Control (Series on Pesticides No. 43, 2008)

This document is essentially a set of examples/case studies aimed at helping the regulatory authorities to deal with these issues in the safety assessment of microbial pesticides.

OECD-Publications (III)

• Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products (Series on Pesticides No. 65, 2011)

• Guidance to the Environmental Safety Evaluation of Microbial Biocontrol Agents (Series on Pesticides No. 67, 2012)

• Guidance Document: Outline on Pre-Submission Consultations for Microbial Pest Control Products
OECD-Publications (IV)

- Guidance Document on Storage Stability of Microbial Pest Control Products (OECD Series on Pesticides No. 85, 2016)
- Report of a Survey on the Need for Further Guidance on Data Requirements and Updated Test Guidelines to Support the Assessment of Microbial Pesticides (OECD Series on Pesticides No. 87, 2017)

OECD-Publications (V)

- Guidance Document on Semiochemical Active Substances and Plant Protection Products (DRAFT)
- Guidance document for the assessment of the equivalence of technical grade active ingredients for identical microbial strains and isolates (DRAFT)
Workplan 2013-2016 and 2017-2020

- Promote communication and exchange of information among regulatory authorities of participating countries

- Organise seminars and workshops on topics of common interest

OECD-Seminars (I)


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**OECD-BPSG workshops**

- Workshop on the Regulation of Biopesticides: *Registration and Communication Issues*; 15-17 April 2008, EPA, Arlington, USA

- Workshop on Microbial Pesticides: *Risk Assessment and Risk Management*; 17-19 June 2013, Saltsjöbaden, Sweden
OECD

- A few words about OECD
- OECD Work on (Bio)Pesticides
- Today’s seminar: purpose, scope and structure

Seminar on Niche Uses of Highly Specific Biocontrol Products

The topic “Niche Uses of Highly Specific Biocontrol Products” was selected based on the discussions that the usage of some invertebrates and pheromones can be highly specific and that it should be clarified what the requirements should be for their registration.

Focus of the seminar is to present highly specific biological solutions and to illustrate the hurdles and issues which must currently be faced, as well as to work towards the delivery of workable solutions to bring highly specific biological plant protection solutions to farmers.
Seminar - Scope

Discussion on:
- What are possible solutions to overcome regulatory hurdles?
- The more specific a product is the less impact it has on the environment.
- The more specific a product is the smaller the size of the market, but the higher the impact of regulatory costs.
- The use of highly specific biological products is even more restrictive for speciality crops where markets are limited.
- The availability of highly specific biological products is essential for IPM programmes.

Seminar - Structure

Presentations focussed on:
- government, research and stakeholder experience and perspectives,
- followed by discussion after each set of presentations.
Seminar - Results

With the focus on “niche uses of highly specific biocontrol products”, the goals of this seminar are

1. for participants to promote a dialogue, and

2. to initiate a process to make recommendations for improvements to the registration of highly specific biocontrol products.

Seminar on Niche Uses of Highly Specific Biocontrol Products

I wish you an interesting and useful seminar!
Overview of Niche Uses of Highly Specific Biocontrol Products: How to bring solutions to farmers

David Cary (International Biocontrol Manufacturers Association)

Greening policies

- FAO
  - Sustainable Development Goals
  - 5 Principles of Sustainable Food and Agriculture
- OECD
  - Green Growth and Sustainable Development
  - Sustainable Agriculture
- China
  - China’s No. 1 Central Document
- USA
  - Green Chemistry Awards
  - Better for the Environment
- EU
  - Sustainable Uses Directive
  - EU Sustainable Agriculture Group 40 point implementation plan
What is wrong with the current agricultural system?

Surface look
- Plentiful food since 1st green revolution
- Good quality food
- More reliability of production
- Cheap food
- Plentiful choice of food

In depth look
- Resistance development
- Increase of invasive pests and diseases
- Pendulum of pest and disease occurrence
- Imposed produce quality standards
- Direct costs only accounted for
- Loss of PPPs due to multifactorial issues
- Failure to accommodate new PPP solutions

Problem solving needs to change

Incident based problem solving

Holistic problem solving
Characterisation of agricultural inputs

Why do niche products need to be treated differently?

• Cost of developing and registering traditional PPPs was estimated at $286M* in 2014
• Time to market for traditional PPPs in 2014 was 11.3 years*
• It is no wonder the number of R&D companies producing PPPs is now reduced from 15 pre 2000 to the top 6 companies having >75% market share in 2005 and by end of 2017 2 of those will have merged leaving 4
• PPPs have had to be blockbusters or silver bullets for economic prudence as they are only viable on the big crops in the big markets
• Highly specific tools and tools for niche markets often produced by SMEs cannot come to the market using this model forced on us by regulation and the resultant structure of the Agchem market

* Phillips McDougall Agri Futura Magazine April 2016 No. 198
The products: “innovative green tools” of the Biocontrol industry

**Macrobials**
- Predators, parasites & nematodes
- Living organisms found to naturally protect crops

**Microbials**
- Viruses, Bacteria & Fungal Pathogens
- Found naturally in soil, used in food, feed & end unregulated uses

**Semiachemicals**
- Pheromones, Plant volatiles
- Communication tools found in nature with no killing effect

**Natural Products**
- Botanicals & Other Natural substances
- Products derived from nature

Not usually regulated as PPPs
Regulated as PPPs
All groups can have niche solutions

Specificity

- What do we mean by specificity
  - Species specific products
    - Pheromones
    - Baculoviruses
    - Weak strains of host specific viruses
  - Invertebrate Biocontrols, Specific uses, Bacteriophages, etc.
Unique attributes

- Activity on non-target species
- Corrective technologies without impacting other control mechanisms
- A part of agroecology
- Often without major uses

Who can/need to help with the issue

- Policymakers
- Regulators
- Researchers
- Industry
- Farmers
- Food value chain
What are possible solutions

- Global or regional positive list
  - EPPO list for IBCAs
  - FAO list of MBCAs
  - EU 2003/2003 proposed list of microbial biostimulants
- No renewal requirement
- Notification only procedure for a.s. ie EU and SCLPs
- No requirement for product authorisations or a single regional product authorisation
- Ability to allow a minor use without needing a major use
- Concurrent a.s approval and a regional product authorisation in a single step
- Think outside the box!!!

Engagement during the seminar

- Understand the type of products that have already been lost
- Understand what solutions are available
- Understand the specificity / niche markets
- Understand that if we are to bring such products to the farmer and make agriculture more sustainable - the system and how we apply it has to change
- Understand if we don’t apply a system designed for these specific solutions that in the main they will not be available and they are arguably because of the specificity the most sustainable tools we could use
- Think of ways we can work together to solve this common issue
Holistic Agriculture

- Prevention of pest & disease explosion
- Use of all available tools
- Minimise risk to human health and the environment

Only through use of true IPM

A new true green revolution

Thank you for attending now is time for us all to actively participate in this seminar and only then can we solve our dilemma together
Presentation 3

Niche Uses of Semiochemicals
Vittorio Veronelli (CBC Europe, Italy)
Semiochemicals an established technology

USA vs EU available formulations

NEW PHEROMONES

USA time to registration
4-6 months
Free Experimental use up to 200 Ha

EU time to registration
3-5 years
Free Experimental use not available

Almost 40 Years Passed!!
World use of SCLP in 2017

Vine: 360,000 ha
Forestry: 250,000 ha
Pome: 250,000 ha
Stone: 135,000 ha
Nuts: 90,000 ha
Vegetables: 20,000 ha
Total: ~1,105,000 ha

Share of SCLP formulations

Passive Reservoir: 598,000 ha (54%)
Sprayable: 285,000 ha (26%)
Active Reservoir: 200,000 ha (18%)
Female like: 22,000 ha (2%)
Total: ~1,105,000 ha

Unclassified
Identification of Semiochemicals

Pherobase > 8,000 Pheromones & Semiochemicals

Market available Semiochemicals

- >8,000 semiochemicals identified
- large majority are SCLP
- Roughly 200 produced (g/kg scale)
- mostly for monitoring traps
- About 50 available at Kg level
- all SCLP for Mating Disruption
- ONLY 20 widely applied
- on world basis
- JUST 5 covers 80% of world uses
- only fruit and forest
- 150 SCLP formulations registered
- 40% are just for one pest & one crop
Sex Pheromones specificity

- **Species specific**
  Sex pheromones are specific to species, and the pheromones produced by individual males
  and females are almost unique for each species and function to locate a partner for mating.

- **Non-killing mode**
  Sex pheromones have no direct impact on the target insect; they do not kill the insect.

- **Only for adult stage**
  Sex pheromones are only effective for adult insects, not for larvae or pupae.

- **Crop specific**
  Sex pheromones are specific to the host plants, and some may be specific to certain crops.

- **Volatilization**
  Sex pheromones are volatilized into the air, and the males can detect the pheromones from a distance.

- **Consider the pest size**
  The size of the pest population can influence the effectiveness of sex pheromones.

- **Preventive approach**
  Sex pheromones can prevent damage by reducing the population size of pests.

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Sex Pheromones characteristics

### Straight Chained Lepidoptera Pheromones

<table>
<thead>
<tr>
<th>Insect Species</th>
<th>Pheromone Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Synanthedon tipuliformis (Currant moth)</em></td>
<td>CH₃(CH₂)₉CH=CH(CH₂)₉CH=CH(CH₃)OOC(CH₃)₃</td>
</tr>
<tr>
<td><em>Lecisia botanica (Grapevine moth)</em></td>
<td>CH₃CH₂CH₂CH₂CH(CH₂)₇CH=CH(CH₂)₇COCH₃</td>
</tr>
<tr>
<td><em>Grapholitha molesta (Oriental fruit moth)</em></td>
<td>CH₃CH₂CH₂CH₂CH₂CH=CH(CH₂)₇CH=CH(CH₂)₇COCH₃</td>
</tr>
<tr>
<td><em>Cydia pomonella (Codling moth)</em></td>
<td>CH₃CH₂CH₂CH₂CH₂CH=CH(CH₂)₇CH=CH(CH₂)₇COCH₃</td>
</tr>
</tbody>
</table>

### Fatty Acids

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleyl alcohol</td>
<td>CH₃(CH₂)₉CH=CH(CH₃)OH</td>
</tr>
<tr>
<td>Z9-octadecanol</td>
<td>CH₃(CH₂)₆CH=CH(CH₂)₂CH(CH₂)₂COOH</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>CH₃(CH₂)₆CH=CH(CH₂)₂CH(CH₂)₂COOH</td>
</tr>
<tr>
<td>Z,Z-9,12-octadecadienoic acid</td>
<td>CH₃(CH₂)₆CH=CH(CH₂)₂CH(CH₂)₂COOH</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>CH₃(CH₂)₆CH=CH(CH₂)₂CH(CH₂)₂COOH</td>
</tr>
<tr>
<td>Z9-octadecenoic acid</td>
<td>CH₃(CH₂)₆CH=CH(CH₂)₂CH(CH₂)₂COOH</td>
</tr>
</tbody>
</table>
Pheromones facts

**Grape Moths Areawide Pheromone Mating Disruption helps reducing insecticides achieving best control**

*Trentino – Italy*

Data courtesy of Messacrona Winery

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Pheromones facts

**Grape Moths Areawide Pheromone Mating Disruption helps reducing insecticides achieving best control**

*Carinena – Spain*

Data courtesy of Grandes Vinos y Vinedos technical department
**Pheromones facts**

2016 Harvest infestation with project strategy in South France

- Very low (0-5%)
- Low (6-15%)
- Medium (16-25%)
- High (>25%)

**2015 Harvest - Standard vs. Area Wide**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Non Area Wide</th>
<th>Area Wide</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLOT CHECKED</td>
<td>50</td>
<td>52</td>
<td>159</td>
</tr>
<tr>
<td>AVERAGE TREATMENT</td>
<td>G1: 2</td>
<td>G2: 3</td>
<td>G3: 4</td>
</tr>
<tr>
<td></td>
<td>2 to 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TREATMENT PER PLOT</td>
<td>0.1</td>
<td>0.8</td>
<td>0.6</td>
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<tr>
<td></td>
<td>1.8</td>
<td></td>
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</tr>
<tr>
<td>AREA WIDE</td>
<td>0.1</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
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</tbody>
</table>

**European Grapevine Moth Eradicated from California**

Release #16-000 Sacramento August 16, 2016

Agricultural officials confirm eradication of grape pest, lift quarantine restrictions

“Eradicating EGVM has been a top priority for USDA-APHIS, and together with industry, state and local officials, growers, university scientists and extension services, we were able to successfully invest in and implement the right tools to safeguard California grapes. The collaborative strategies used by the EGVM eradication project will be a model for addressing future pest incursions.”

(Among other measures up to 9,000 Ha of vineyards applied pheromones during the program from 2011 to 2015)
G. funebrana in plums - Holland
Plums are grown on about 20 hectares in Holland. G. funebrana is a key pest, as it is in most of European orchards in Europe. A well-known moth for which pheromone MD is applied in many European countries since a decade on several thousand hectares. The grower's cost for the product is about 160 Euro/ha/season. A total market of 3,000 Euro a year.
Producers association (NPC) wanted to get the product authorized, but the MR process from Germany (same zone) cost 12,000 Euro which would take a decade to be recovered. It was supported by growers but yet an annual tax of 1,300 Euro has to be paid to Dutch authorities.

Leafrollers in Cherry - Denmark
Leafrollers is a generic name given to a large number of moths due to their behavior. Very often they share a number of common components in their pheromone blends though in different proportions, but can be disrupted by using mixed blends of mimics. Typical species are A. orana, R. heparana, A. pedana, A. jungiana etc. Danish growers had problems in 2016 on Cherries and advisors requested a label extension of another product authorized on Apples and Pears for Leafroller. It was granted this year with fees 1,500 Euro? Market?

Casius cassin (European Goat Borer)
a secondary pest wood borer attacking several trees including Cherry, Pear and Apple. It is occasional, but difficult to control because larvae are in the wood. Pheromone is known and available, MD can be a good option...but registration?

S. sesamoides - stone fruit; S. myopaeformis - apple; S. luteolus - persimmon three wood borers that can cause high damages to orchards trees. The occurrence is occasional and limited. MD is good solution as for most borers moth, but...

Zeuzera pyrina – (Leopard moth)
a big moth wood borer, originally affecting pear trees but recently found on olive carob, hazelnut, pomegranate, mainly favored by irrigation. MD was registered on pear and olive, it works very well, but how to predict where the pest will move next?..Label extension...?
Pheromone minor uses (3)

- *Coccocimorpha pronubana* (Carnation tortrix)
  a pest originally of flowers, but recently found on soft fruits (blackberry), again MD works well and is ready available because in Japan another species, pest in tea orchards, has same pheromone blend. But market is too small for the registration hurdles...

- *Pandemis heparana, Adoxophyes orana* (Leafrollers)
  typically secondary pest in apples, but in southern areas found in peaches and plums. In apple orchards they are associated with *Cydia pomonella* (Codling moth) and MD dispensers have been developed combined for all pests, but in peach and plums there is no Codling moth. Separate dispensers are required, but... another registration...

- *Epiphysas postvittana* (Light Brown Apple moth)
  a moth originally of Australia and New Zealand, spread to California and lately UK. Damaging grapes and berries. MD was developed in Australia and successfully applied. Would be ready for Europe except for the Regulation hurdle...

Pheromones and invasive pests

- **The Tuta absoluta (SA Tomato moth) case**
  landed in Europe (Spain) in 2008, pheromone first identified in 1996, mimic pheromone and MD dispenser completed development in 2009, dossier application in 2010, FIRST EU REGISTRATION (Protected Crops) granted January 2016 in Italy. Not yet available in all EU Member states due to lengthy MR procedures. MD efficacy very high, reduction of standard insecticides very high. Tomatoes in greenhouse is minor crop in all EU.

- **The Tecia solaniivora (Potato tuber moth) case**
  first detected in Europe (Spain, Galicia) in September 2015. Field and storage pest exclusively of potato. Sex pheromone first identified in 1995. Dispenser formulation ready developed and tested in Colombia in 2004. Can prevent spreading of pest, but inclusion and full registration will take 5-6 years... could be too late to control. Meanwhile only conventional insecticides are applied...
Pheromone present and future contribution

- **Apple, Pear**
  25 years of use in *C. pomonella* and leafrollers in all countries of EU have reduced the insecticides use. In northern areas some species of leafrollers are different and rotating seasonally. Technically easy to include their pheromones in the dispensers, but not easy for Regulation...

- **Grape**
  25 years of use in EU on *L. botrana, E. ambigua* and *A. lilaugiana* brought to more than 250,000 ha of grape with virtually no chemical spray. Other secondary pest appear and need to be controlled in some way to keep the insecticides at lowest level, again the Regulation will slow the solution.

- **Bell peppers**
  *O. nubilais* (European Corn borer) was originally developed for corn but found use in bell peppers greenhouses production to support IPM with beneficial insects for a zero residue production. Use could be extended to other crops...

- **Rice**
  *C. suppressalis* in Spanish rice fields is controlled without insecticides...

Limits of current Regulation

- **Target pest can affect different crop**
  In pheromones crop relevance is little, as mode of action is interference to adult mating. However pest are typically polyphagous and can adjust to a variety of plants. No phytotox (for passive dispensers) and no residues is expected. Crop label extensions should be flexible and easier.

- **A crop in specific Country is minor or very minor**
  MR or Authorization process and fees do not take this into account. When a product is registered and widely applied in one States should be facilitated in another especially if the border is practically just administrative like in EU.

- **Invasive species affecting crops**
  Pests are moving across borders, MD already registered in other Countries in the world can help preventing the pest expansion in fast way if Regulation would support fast adoption.
Molecular factors defining specificity and host range of baculoviruses
Johannes A. Jehle, Jörg T. Wennmann (Julius Kühn-Institute (JKI), Darmstadt, Germany)
Characteristics of Baculoviruses

- rod shaped virions embedded in an occlusion body
- > 120 Baculovirus genomes fully sequenced
- dsDNA genome, 80 - 180 kb, 100 - 150 genes
- from more than 700 insect species isolated
- huge undiscovered diversity expected
- specific for Lepidoptera, Diptera, Hymenoptera
- Specific for single species

Host Range of some Baculoviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Insect species</th>
<th>Insect families</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Autographa californica</em> MNPV (alfalfa looper)</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td><em>Mamestra brassicae</em> MNPV (cabbage moth)</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td><em>Helicoverpa zea</em> SNPV (corn earworm)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td><em>Cycia pomonella</em> GV (codling moth)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><em>Cryptophlebia leucotreta</em> GV (false codling moth)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Spodoptera exigua</em> MNPV (beet army worm)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

www.julius-kuehn.de
Why are they so specific?

It’s their biology!

The Occlusion Body (OB)
The OB – a natural Formulation

Provides protection against physical (shearing, UV, heat, pH) and chemical (detergents, enzymes) factors

www.julius-kuhn.de

Baculovirus Infection of Insect Larvae
example: nucleopolyhedrovirus

midgut (pH > 10)

ODV = occlusion derived virus
PM = pentroptic membrane
epithelial cell of the midgut
primary infection

BV = budded virus
systemic infection
secondary infection
### One Life Cycle – Two Virus Phenotypes

<table>
<thead>
<tr>
<th>EM</th>
<th>Phenotype</th>
<th>Biological function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occlusion Derived Virus (ODV)</td>
<td>- environmental persistence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- peroral (= primary) infection of midgut</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- horizontal transmission from insect to insect</td>
</tr>
<tr>
<td></td>
<td>Budded Virus (BV)</td>
<td>- secondary infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- transmission from cell to cell</td>
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</tbody>
</table>

**Baculovirus-Infected Codling Moth Larvae**

- Healthy
- Infected L1 larva
- Infected L4 larvae

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Unclassified
Baculovirus Gene Regulation

What makes Baculoviruses different from other Invertebrate Pathogens?

- Not toxigenic
- No secondary metabolites
- Highly conserved infection process adapted to different host species
- Small genomes, strains well described
- Strain variability considerably low
- No potential to harm or grow on mammals
- QPS (Qualified Presumption of Safety) Status by EFSA
- EU: Registration on species level not on strain level
- EU: Potential of being considered as low-risk product
What is needed to make a successful Infection?

Factors defining Host Specificity

1. pH in Midgut lumen >9
2. PIF Proteins on ODV
3. Apoptosis
4. Viral Transcription
5. DNA Replication
6. ...

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**Peritrophic Matrix and Midgut Milieu**

GV: $300 \times 500 \text{ nm}$
NPV: $1-5 \mu\text{m}$

30–60 nm x 250–300 nm

Increasing time of incubation at pH 9

PM: Chitin microfibrils and proteins, Sieve <100 nm

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---

**Per os infectivity Factors (PIFs)**

- Localized in membrane of ODFs
- Binding and Fusion Proteins
- Interact with cellular receptor in midgut
- Loss of PIFs = Loss of infectivity
- Crucial for host range

Slack and Arif, 2007
Baculovirus Inhibition of Apoptosis

Robust pro-apoptotic response

Delayed/interrupted pro-apoptotic response

Programmed cell death
- Development (metamorphosis)
- Malfunction of cell cycle (DNA damage,
- Unscheduled DNA replication and RNA synthesis
- Anti-viral mechanism

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Baculoviruses express Inhibitors of apoptosis
a) p49/p35
b) IAPs

Inhibits crucial steps in apoptosis
Allows virus replication

Without:
- Sloughing and cleaning of infected midgut cells

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Baculoviral RNA Polymerase

Viral RNA Polymerase
Consists of several subunits (p74, p16.4, p16.8, p19.9)
Recognizes specific baculoviral promoters
Transcription of late and very late proteins

Change of virulence by Change of Helicase

<table>
<thead>
<tr>
<th></th>
<th>Sf9</th>
<th>BmN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcMNPV</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>BmNPV</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AcMNPV + signatures of BmNPV helicase</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- AcMNPV and BmNPV 93% identical genome sequence
- Val561Leu, Ser564Asn, Phe577Leu in Helicase extends host range to BmN cells
- AcMNPV helicase toxic to BmN cells?
Summary and Conclusion (I)

- Baculovirus host specificity is unique
- Host specificity is the consequence of 140 Million years of coevolution with insect hosts
- No related viruses out side arthropods
- Host specificity and host range depend on successful virus-host interaction during replication
  1. pH in Midgut lumen >9
  2. PIF Proteins on ODV
  3. Apoptosis
  4. Viral Transcription
  5. DNA Replication

Many factors needed for a successful infection
One factor missing results in block of replication

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Summary and Conclusion (II)

- The narrower host range the smaller the market
- Most baculoviruses are single pest applications
- Discrepancy between ecological benefits and commercial value
- Absolutely safe to humans and mammals
- Reptetions of Ecotox and human Tox studies still necessary?
- Several pre-Directive 91/414 products are still missing
- Harmonization impeded local solutions
- Discrepancy between registration expenses and market value
- Further facilitation of registrations for small markets needed

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Presentation 5

Niche Uses of Baculoviruses
Philip Kessler (Andermatt Biocontrol, Grossdietwil, Switzerland)

where Nature leads Innovation

Niche Uses of Baculoviruses
Philip Kessler
Director International Market Development, Andermatt Biocontrol AG
OECD 8th BPSC Seminar on “Niche Uses of highly Specific Biocontrol Products”
Paris 26. June 2017
Baculoviruses – Mode of action

Primary infection (of the host from external source)
1. dissolving of protein capsule in the midgut, releasing of virions
2. virions infect the larva through the midgut cells
3. forming of new occluded viruses
4. death of the larva and releasing of occluded viruses to the environment
5. migration of occluded viruses by the larva

Secondary infection (within host, cell to cell)
6. virus replication inside the host and infection of new host cells

Toxicology and Ecotoxicology

Only found in insects (mainly lepidopteran species)

OECD Consensus Document No 20
- Safe for user and consumer
- No effects to plants, mammals or aquatic organisms
- Narrow host range, no adverse effects on beneficial insects
- No production of metabolites or toxins
Toxicity of different active substances

Beneficial insect | Antagonist of
---|---
Predatory mites<br>Spider mites | Spiders<br>Mites<br>Ants<br>Nematodes
Predatory bugs<br>Spider mites | Spiders<br>Mites<br>Ants<br>Nematodes
Lacewings<br>Ants<br>Aphids<br>Mealybugs | Spiders<br>Mites<br>Ants<br>Nematodes
Ladybirds<br>Aphids<br>Mealybugs | Spiders<br>Mites<br>Ants<br>Nematodes
Parasitoids<br>Wooly apple aphids<br>Apple aphids<br>Mummies<br>Mealybugs<br>Beetles | Spiders<br>Mites<br>Ants<br>Nematodes
Damsel bugs | Spiders<br>Mites<br>Ants<br>Nematodes
Water organisms | Spiders<br>Mites<br>Ants<br>Nematodes

Maximal percent of population reduction per application
- 0% non-toxic
- 40% slightly toxic
- 60% moderate toxic
- 100% highly toxic

Source: Adaptation GO all effects

Benefit using baculovirus for pest control

- Control of a key pest
- High efficacy
- Low residue requirements
- No side effects on beneficial insects
- Occurrence of resistant pest populations towards chemical pesticides
- Resistance management
Baculoviruses - Challenges

Virus biology
- Narrow host range
- Slow speed of kill
- UV sensitivity

Production (in vivo)
- Labor intensive
- Consistent product quality

- Target key pests
- MRL issue
- Resistance management

Reliable instructions
- Logistics and storage

Distributor

End user (farmer)

Uses of baculoviruses

- 1970s first use of NPV
- 1987 first registration of GV
- Today
  - More than 50 baculovirus products, of which ca. 24 HaNPV and 16 CpGV products
  - >180 registrations worldwide
  - >30 countries

- Main producer:
  - AgBioTech (AU), Andermatt Biocontrol (CH), Arysta (FR), Biofepp (CA), Certis (USA),
    Henan Jiyuan Balyun Industry (CN), Kanya Biologics (KE), River Bioscience (ZA),
    Serdios (IT), further Indian and Chinese producers

Unclassified
Adoxophyes orana granulovirus (AoGV)

Adoxophyes orana GV: Timelines
- Dossier submitted to RMS in 2004
- Conclusion for Annex-I inclusion by EU COM in 2012
- Eight years after application for Annex-I inclusion, application for mutual recognition in MS can be submitted

Adoxophyes orana GV: Costs
- Registration costs up to 1 Mio € (fees, consultants, studies and field trials)
- Fluctuating market for CAPEX
- Estimated annual turnover of 50’000 to 200’000 €

Return of investment, when CAPEX (AoGV) already needed to be re-registered. Why to register CAPEX in the EU?

Spodoptera exigua MNPV: used in IPM in protected pepper production in Spain

SeMNPV used in IPM to control Spodoptera exigua in protected pepper production in Almeria, Spain
- 2007: SeMNPV F1 - first inclusion in Annex-I
- 2010: 2 new isolates of SeMNPV on Annex-I
- Since 2009: applications of three SeMNPV products submitted to Spain (Spod-², Spexx², Vrex²)
- Since 2009: Emergency authorisations issued yearly limited to the Province of Andalucía
  - Too late in the season
  - No marketing strategies possible
- Remaining a spot business
- 2013 Renotification for SeMNPV necessary: SeMNPV not notified by Aldermatt for Annex-I renewal of SeMNPV in 2017
- 2016 National approval for Spexx in Spain
Photorimae opercula GV

- BIOCOMES
- EU funded project 2012-2017
- Development of new biocontrol tools
- PnPGV against tomato leaf miner (Tuta absoluta)
- TLM x Tomato -> Niche market
- Regulatory hurdle for market entry

BIOCOMES
New biological control products for sustainable farming and forestry

Consensus Document on Information used in the Assessment of Environmental Applications involving Baculovirus

Baculoviruses are safe and do not cause hazards to human health and to the environment
- EU: mainly accepted
- USA: partly accepted
  - Cell-culture studies
  - Non-target studies
- Canada: mainly accepted
- Australia: partly accepted
  - Non-target studies on indigenous leps
  - Caddies flies
- Japan, South Korea: no experience
- Brazil (non-OECD): not yet accepted
  - New specific studies

OECD Environment, Health and Safety Publications
Harmonization of Regulatory Oversight in Biotechnology No.20

Unclassified
To take the hurdles

Leaders
- CpGV, HaNPV, CitcGV

Struggling or failed ...  
- AoGV, SeMNPV, SpliNPV, SINPV, MbNPV, AgpNPV, AcMNPV

On the start
- PxGV, SINPV, EppoNPV, PhopGV; Ld11NPV, more?

How we can improve

- Harmonize dossier formats (e.g. accept OECD data format)
- Harmonize and adjust data requirements (e.g. for microbial a.i.)
- Accept available guidance (e.g. from OECD)
- Accept scientific rationales
- Adjust fees for niche market products
- Prioritise assessment of low risk products
- No re-registration procedures of low-risk products

Global organisation such as OECD, FAO, etc. can give valuable guidance
Presentation 6

Niche Uses of Bacteriophages
Roma Gwynn (Rationale, United Kingdom)

Niche uses of bacteriophages
Roma L Gwynn

Bacterial phytopathogens – economically important

- 85% plant diseases caused by fungi – rest bacteria, viruses
- Bacterial phytopathogens = 35 species (approximately)
- Bacterial diseases cause economic losses in cultivation and storage

Israel, soft rots in potato: yield reduction 24–25%
### Bacterial phytopathogens – seed borne

<table>
<thead>
<tr>
<th>Crop</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td><em>Pseudomonas syringae</em> pv. syringae, <em>Xanthomonas campestris</em> pv. translucens</td>
</tr>
<tr>
<td>Maize</td>
<td><em>Pantoea stewartii</em> subsp. stewartii, <em>Clavibacter michiganensis</em> subsp. Nebraskensis</td>
</tr>
<tr>
<td>Rice</td>
<td><em>X. oryzae</em> pv. oryzae, <em>X. oryzae</em> pv. oryzae, <em>Acidovorax oryzae</em></td>
</tr>
<tr>
<td>Bean</td>
<td><em>P. syringae</em> pv. phaseolicola, <em>Curvibacter flavumfaciens</em> pv. flavumfaciens, <em>Xanthomonas campestris</em> pv. phaseoli and <em>X. tucanae</em> var. <em>tucanae</em></td>
</tr>
<tr>
<td>Soybean</td>
<td><em>P. syringae</em> pv. glycinea</td>
</tr>
<tr>
<td>Chicory</td>
<td><em>Rhodococcus fascians</em></td>
</tr>
<tr>
<td>Cereals; grasses</td>
<td><em>Rathaybacter sp.</em></td>
</tr>
<tr>
<td>Alfalfa</td>
<td><em>C. michiganensis</em> subsp. <em>insolens</em></td>
</tr>
<tr>
<td>Tomato, pepper</td>
<td><em>Pseudomonas syringae</em> pv. <em>tomato</em> (tomato), <em>P. syringae</em> pv. <em>syringae</em>, <em>Xanthomonas sp.</em> , <em>Clavibacter michiganensis</em> subsp. <em>Michiganensis</em></td>
</tr>
<tr>
<td>Carrot</td>
<td><em>Xanthomonas campestris</em> pv. <em>cardiae</em></td>
</tr>
<tr>
<td>Onion</td>
<td><em>Pantoea ananatis</em>, <em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td>Crucifers</td>
<td><em>Xanthomonas campestris</em> pv. <em>campestris</em>, <em>P. syringae</em> pv. <em>alkalinos</em> (broccoli), <em>Pseudomonas spp.</em> (crucifers)</td>
</tr>
<tr>
<td>Cucurbits</td>
<td><em>P. syringae</em> pv. <em>lachrymans</em>, <em>Acidovorax citrull</em></td>
</tr>
<tr>
<td>Lettuce</td>
<td><em>Xanthomonas campestris</em> pv. <em>vitians</em></td>
</tr>
</tbody>
</table>

### Bacterial phytopathogens – vegetative transfer

<table>
<thead>
<tr>
<th>Crop</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrus</td>
<td><em>Candidatus Liberibacter</em> asiaticus, <em>Xylella fastidiosa</em> subsp. <em>paucia</em>, <em>Xanthomonas citri</em></td>
</tr>
<tr>
<td>Strawberry</td>
<td><em>X. fragariae</em></td>
</tr>
<tr>
<td>Grape, almond</td>
<td><em>Xylella fastidiosa</em> subsp. <em>fastidiosa</em>, <em>Pectobacterium amylovora</em></td>
</tr>
<tr>
<td>Pear, apple, quince</td>
<td><em>Pectobacterium amylovora</em></td>
</tr>
<tr>
<td>Sugarcane</td>
<td><em>Leifsonia xyli</em> subsp. <em>xyli</em>, <em>Xanthomonas albilineans</em></td>
</tr>
<tr>
<td>Cassava</td>
<td><em>Xanthomonas campestris</em> pv. <em>cassavae</em></td>
</tr>
<tr>
<td>Banana</td>
<td><em>X. campestris</em> pv. <em>musacearum</em></td>
</tr>
<tr>
<td>Roses, ornamentals</td>
<td><em>Agrobacterium tumefaciens</em></td>
</tr>
</tbody>
</table>

- Propagation production systems offer ideal conditions for bacterial reproduction and spread
Bacterial phytopathogens - products

Number of diseases for which there are biocontrol products

Fungal diseases  |  Bacterial diseases
0  |  0
20  |  5
50  |  100
120  |  150

From BCPC Manual of biocontrol agents

Bacterial phytopathogens - biocontrol products

Number of Biocontrol Products

Fungal diseases  |  Bacterial diseases
0  |  0
100  |  200
300  |  400
500  |  500

From BCPC Manual of biocontrol agents
Bacteriophage – biology

- The most abundant organisms in the world ($10^{31}$ on Earth)
- Abundant in wide range of ecological niches such as soil, water, plants and animals
- Act as antibacterial agents, with different bacteriophage being specific to different hosts
- For almost every bacterial species - at least one bacteriophage that can specifically infect that particular bacterial group

Bacteriophage – bacterial viruses

![Diagram of bacteriophage](image)
Bacteriophage – Life cycle

Bacteriophage – current taxonomic situation

Bacteriophage taxonomy is complex & continually evolving:
- ICTV (International Committee of Taxonomy of Viruses): use virion properties & nucleic acid (not fully agreed approach)
- Alternative: classification according to morphotype, host genus & pathogenicity (approach accepted by PMRA, Canada)

>96% bacteriophage ‘tailed’ with double-stranded DNA (order Caudovirales)
Bacteriophage – key aspects for products

- High virulence
- High specificity to host
- Rapid mode of action
- Short persistence without host

Bacteriophage - commercialisation

Mainly applications to food of animal origin against human pathogens (e.g., Listeria, Salmonella spp.)

- Listax P100 (Micros, The Netherlands): approvals in the US, Canada, New Zealand, Australia & The Netherlands for use on meat, fish, vegetables and cheese
- ListShield, SalmoFresh & EcoShield (Intralytics, USA)

One bacteriophage plant protection product approved in Canada (PMRA) and USA (IR4 supported):

- AgriPhage-CMM (Omnilystics): Bacteriophage of Clavibacter michiganensis (subsp. michiganensis) in tomato
Bacteriophage – commercialisation - regulation

Conclusion of PMRA review of bacteriophage of Clavibacter michiganensis (subsp. michiganensis)

- By nature, bacteriophage are viruses that are only capable of infecting bacteria.
- Bacteriophage are not capable of infecting animals, plants, or fungi and are not capable of producing any toxins outside their hosts because they are not metabolically active. Bacteriophage rely on the bacterial host's metabolism for reproduction and survival. Bacteriophage themselves are not considered to be toxic.
- Also, since the host bacterium, C. michiganensis subsp. michiganensis, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of Clavibacter michiganensis (subsp. michiganensis) will not alter the bacterial population in a way that could be harmful to humans.
- Although the relative exposure of people to bacteriophage of Clavibacter michiganensis (subsp. michiganensis) may increase from the use of AgriPhage-CMM, there have been no reports of adverse effects or incidents resulting from the direct exposure to naturally occurring bacteriophage.

Bacteriophage – common approach to production

[Diagram showing the process of bacteriophage production]

Unclassified
Bacteriophage – why are they niche products?

Specificity of bacteriophage to disease

- Market potential limited as product highly specific
- Specific to disease strains – need mixture of phage genotypes
- Disease strains vary geographically – may need to tailor phage strain mixture to geography

Large-scale production

- Production only on host bacteria – host may not be amenable to in vitro cultures
- Bacterial hosts often disease complexes – need to produce several host bacteria
- Production only on host bacteria – double cultivation in production
- Must clean-up plant pathogen from active substance – ultra filtration needed
Bacteriophage – why are they niche products?

Delivery to target on plants

- Delivery of product to plants – need host disease – may limit bacteriophage persistence
- Bacteriophage susceptible to environmental conditions - on-plant persistence can be short
- Diseases often within plants – specific inoculation to get phage to disease sites?
- Bacterial soft rots – in root zone – difficult delivery

Bacteriophage – regulatory aspects

Aspects of biology and ecology

- Specificity of relationship between bacterial host strain and bacteriophage genotype
- Specificity of disease complex to crop(s)
- Need mixtures of multiple bacteriophage which may need to be altered regionally
- Bacteriophage specificity and mode of action = good safety profile for humans and environment
- Need bacteriophage with lytic life cycle for PPP
- Lysogenic cycle confirm absence of potential virulence factors and/or antimicrobial resistance genes in both host bacteria and bacteriophage
Bacteriophage – regulatory aspects

Aspect of commercialisation

- *In vitro* production
- Need to produce mixed strain/genotype cultures
- Cultured on host diseases – must remove for market acceptability
- Downstream processing removes host bacteria and all other microorganisms - active substance is only bacteriophage culture – no contaminants
- Usually formulated in buffer solution – simple formulation
- Long-term storage – low temperature, distribution – room temperature
- Need balance between market size and regulatory costs

Bacteriophage – regulatory aspects

Aspect of regulatory procedures

- Virus of microorganisms – new PPP technology
- Bacteriophage are not specifically referred to in any PPP regulations
- Use of bacteriophage as PPP for agriculture and horticulture is a relatively new technology - no guidance documents to allow interpretation of the data requirements
- Closest parallel in biocide regulation – baculoviruses?

[Image of bacteriophages]
Presentation 7

Two examples of fungal biopesticides that disappeared from the EU market
Willem Ravensberg (Koppert Biological Systems, Berkel en Rodenrijs, The Netherlands)

Two examples of fungal biopesticides that disappeared from the EU market

Willem Ravensberg, PhD
Koppert Biological Systems
The Netherlands
OECD EGBP, 26 June 2017, Paris
Seminar on “Niche Uses of Highly Specific Biocontrol Products”

Mycotal and Vertalec

- Mycotal and Vertalec are bio-insecticides based on the entomopathogenic fungus Verticillium lecanii

- Vertalec: strain Ve2 - for control of aphids

- Mycotal: strain Ve6 - for control of whitefly and thrips
Vertalec

- Developed in the 1970’s in the UK at the Glasshouse Crops Research Institute (GCRI) and Tate and Lyle as manufacturer, from 1985 on Koppert
- Targeted at aphid species in cucumber, tomato, peppers, chrysanthemum
- *Myzus persicae, Aphis gossypii, Macrosiphoniella sanborni, Macrosiphum euphorbiae*
- First bio-insecticide registered in the UK in 1979
Mycotal

- Developed in the 1970’s in the UK at the Glasshouse Crops Research Institute (GCRI) and Tate and Lyle as manufacturer, from 1985 on Koppert
- Targeted at whitefly and thrips species in cucumber, tomato, peppers, etc.
- Triauleurodes vaporariorum, Thrips tabaci, Franklinsiella occidentalis a.o.
- Second bio-insecticide registered in the UK in 1981

Registration

- One dossier of Mycotal and Vertalec based on the species Verticillium lecanii and the two strains
- Some studies based on Ve6, some on Ve2, some on both
- Efficacy generated per product
- Applications per product
- Approvals per product
- Vertalec: registered in UK, North Ireland, Finland, Denmark, Switzerland, Norway and Japan
- Mycotal registered in UK, North Ireland, Netherlands, Finland, Denmark, Greece, Italy, Austria, Switzerland, Turkey, Kenya, New Zealand and Japan
Re-registration

• Application for approval within EG 91/414 and List 4 procedure (Reg. 112/2002)
• RMS- Netherlands
• One dossier submitted for both strains
• Taxonomy changed: 2 new species
  – Mycotal strain Verticillium lecanii Ve6 → Lecanicillium muscarium
  – Vertalec strain Verticillium lecanii Ve2 → Lecanicillium longisporum

Re-registration

• One dossier submitted for both strains
• Ctgb refused the joint application and required two new dossiers
• Not acceptable for Koppert due to registration history, and other comparable submission: Trichoderma harzianum Task Force dossier with 4 strains that also ended up in a new taxonomic classification as 3 species.
Re-registration

- Koppert withdrew Vertalec application
- And continued with Mycotal only
- Main reason: extra burden in terms of money and time to large for Vertalec
- Vertalec annual turnover € 50,000 due to niche market
- Versus total costs € 2-300,000 to register

Vertalec

- Due to loss of product in EU, remaining market even smaller, ultimately we stopped production and withdrew from Japan, Switzerland, etc.
- Request from PMRA and growers to register in Canada, several times, but could not honoured
- Small market also due to high RH requirement of Vertalec
- Still growers ask for Vertalec, it was/is the only effective entomopathogen against aphids in many minor (protected) crops
Biochon

- Biochon is a fungus causing wood rot through wounds in trees and shrubs: silverleaf
- Ubiquitous fungus *Chondrostereum purpureum*
- Considered sometimes as a disease in apple, pear
- Used to control American black cherry tree *Prunus serotina*, an invasive weed in Dutch forests
- Also potential for control of other deciduous trees
- To prevent regrowth after cutting, stump re-sprouting

Biochon

- Over 10 years of research in Wageningen UR and Dutch Forestry Department, and Koppert
- Application method: brushing mycelial suspension on freshly cut stump
- Product development: Koppert
- Formulation: freshly delivered product on demand
- Results: very effective
- Tree (90%) dies in a two-three years
Biochon

- Biochon market very small, NI and Germany
- Only target: Prunus serotina
- Nature reserves, etc.; treatment partly subsidized
- Placed on market as wood rot promotor
- Registration as a herbicide to costly
- Also request from water authorities: willows, alder, populars

Biochon

- Market less than € 30,000 per annum
- Used during 1997-2001
- Ctgb required registration as herbicide
- Costs-benefit and ROI negative
- Withdrawal from the market
Similar products

• Mycotech Paste – from Myco-Forestis Corporation Canada
  – Registered in Canada in 2002 - 2008
  – Registered in USA in 2005 (?)

• Chontrol Paste – from MycoLogic inc.
  – Registered in USA in 2004
  – Registered in Canada in 2007

Solution for EU market

• Vertalec: accept closely related and similar entomopathogenic strains through read-across

• Sprouting inhibitor: accept sprouting inhibitor product approval from USA and Canada through mutual recognition
Niche Uses of fungi
Christina Donat (Bio-Ferm GmbH, Tulln, Austria)

Niche Uses of fungi in biocontrol

Example: *Aureobasidium pullulans* strains DSM14940 and DSM14941 against fire blight in pome fruits

Christina Donat

The main players are…
*Aureobasidium pullulans*, DSM 14940 and DSM 14941
Aureobasidium pullulans

- Ascomycete with asexual, yeast-like reproducing cells (blastospores)
- Natural occurrence in the environment (soil, plant surface)
- Well adapted, resistant to drought and UV radiation

Aureobasidium pullulans under the microscope, on an agar plate and dried to granules

History:
1989 University Konstanz, Chair of Phytopathologie:
about 500 microbial isolates: Schiewe und Mendgen 1992; Falconi 1993; Schiewe 1993; Falconi und Mendgen 1994, ...

1996: End of the research projects at Uni-Konstanz; strains were stored frozen

1998-2001: Research project fire blight (BBA Darmstadt, governmental research institute, BMBF Bundesministerium für Bildung und Forschung) – among others also A. pullulans tested

2001: Bio-Protec GmbH founded, Konstanz, further development of Aureobasidium pullulans strains
Further 5 years research funded by Baden Württemberg till 2005
- Blossom Protect™

BÖLW fire blight project University of Konstanz: 2004-2011 field trials
- 6 pack Tox, field trials Germany, first emergency use registrations

2004: bio-ferm GmbH, founded by the Erber Group in Tulln, Austria: production, registration and marketing of A. pullulans products
Global Presence
~1400 employees in more than 120 countries. Own Business Units in 37 countries

ERBER Group

Analytic test systems
Biochemicals, Mycotoxins, Allergens, Residues

Biological plant protection
Fungicides, Fruits

Animal health
Animal husbandry

From Field to Plate

Basic research

Environmental protection

ERBER Group is a group of healthy and profitable businesses which are aligned for organic growth on a global scale and show a strong ability to innovate.

Science cluster Tulln:
2005: Start with the dossier for Annex I inclusion – 1.5 employees
Emergency use permits in several EU countries
Tox, Ecotox, Fate, Field trials

2007: submission of the dossier Blossom Protect™, start development Botector®

2009: Provisional registration of Blossom Protect™ and Botector® in Austria

2012: Registration and entry into the U.S. market

2014: USA: Blossom Protect™ on 6,000 ha in use

2014: Cooperation with Nufarm in Australia, France, Portugal, Canada

2017: 8 employees (+ Erber group in the back)
Blossom Protect™ against fire blight: 110 trials 2003-2016
Scale up the production:

Marketing:

Europe

< 2014  Provisional Registrations (Art. 8(1)) Dir. 91/414 and Emergency Use Permits (Art. 53) Reg. 1107/2009) Final registrations (not EU)

2014-01 EU Approval of A. pullulans

2014-07 Final Registrations (zonal procedure; pending in C-EU and S-EU)

Transition period:
Provisional Registrations remain valid until final registration (e.g. Austria, Belgium, Netherlands, Poland, Portugal...)
Emergency Use Permits
Conclusion:
Fire blight is a tricky pathogen:


  some million € governmental foundation, some million € industry investment
Niche Uses of Invertebrate biocontrol agents
Lieselot van der Veken (Biobest, Westerlo, Belgium)

Biocontrol’s (BC) offer:
IBMA: 4 professional groups according to product categories

- **Macrobials**
  - Predatory mites
  - Insects
  - Nematodes

- **Microbials**
  - Viruses
  - Bacteria
  - Fungi

- **Semiochemicals**
  - Pheromones
  - Plant volatiles

- **Natural and Biochemical Products**
  - Plant extracts
  - Seaweed products
  - Basic chemical substances

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**IBCA’s**

- Invertebrate Biological Control Agents include insects, entomopathogenic nematodes and predatory mites

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Unclassified
The cradle of commercial biocontrol

1967
- Jan Koppert- cucumber grower
- Chemical PPPs gave health and resistance problems
- Looking for alternatives
- *Phytoseiulus persimilis* against spidermite (CH)
- *Encarsia formosa* against whitefly
- Positive results and effects

Why BC solutions are highly specific and often restricted to niche use

- High costs compared to market potential
- Economic potential of single products often does not exceed € 0,2 mio
- 1107/2009 EC regulated products often do not make the cut when registration costs come in the picture
- Imidacloprid turnover 2003: 590 mio € (Agrow 2004) commensurates with estimated registration cost of chemical PPPs (€ 200 mio),

- Is this the case for any BCA?

Ehlers, 2011
Why IBCAs are highly specific and often restricted to niche use

- 2000: BC market share were 55% IBCAs and 26% Microbials
- Economic potential of single products often limited
- Host specificity of IBCAs (e.g. *Phytoseiulus persimilis* vs. *Tetranychidae*, parasitoids)
- Successful introduction is highly depended on technical support
- Limited shelf life requires high demanding distribution logistics
- Regulatory hurdles: Convention of BioDiversity CBD

Ehlers, 2011

Predatory mites most important IBCA’s

<table>
<thead>
<tr>
<th>Predator</th>
<th>Bar Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amblyseius swirskii</td>
<td>65%</td>
</tr>
<tr>
<td>Phytoseiulus persimilis</td>
<td></td>
</tr>
<tr>
<td>Neoseiulus californicus</td>
<td></td>
</tr>
<tr>
<td>Macrolophus pygmaeus</td>
<td></td>
</tr>
<tr>
<td>Encarsia formosa</td>
<td></td>
</tr>
<tr>
<td>Orius laevigatus</td>
<td></td>
</tr>
<tr>
<td>Nesidioconus tenuis</td>
<td></td>
</tr>
<tr>
<td>Neoseiulus cucumeris</td>
<td></td>
</tr>
<tr>
<td>Eretmocerus rermicus</td>
<td></td>
</tr>
<tr>
<td>Aphidius colemani</td>
<td></td>
</tr>
</tbody>
</table>

Top-10 of biocontrol agents used in greenhouses (turnover)

J Klapwijk
Phytoseiulus persimilis against spidermite in tomato and strawberry

Source: Biobest

Unclassified
Highly specific uses of IBCAs in niche markets

Source: Entocare

Regulation of IBCAs

International Convention of Biodiversity (CBD 1992)

Ratifications: (# 194) Almost all EU countries, S-AM, (USA)

1 Conservation of Biological diversity
   “prevent the introduction of all alien species and, when prevention fails, to control as far as possible species that threaten indigenous ecosystems, habitats or species”

2 Sustainable use of biological components

3 ABS (Access and Benefit Sharing)
SUD EC 128/2008

• Art. 14 ‘Member States shall take all necessary measures to promote low pesticide-input pest management, giving wherever possible priority to non-chemical methods so that professional users of pesticides switch to practices and products with the lowest risk to human health and the environment among those available for the same pest problem’

IBCA Regulation history:

• 1996 FAO ISPM 3 (IPPC)
• 1997 EPPO / CABI on Safety and Efficacy of Biological Control in EU: endorsement ISPM 3
• 1999 EPPO Guidelines for the first import of exotic BCAs for research under contained conditions
• 2000 EPPO Guidelines for import and release of exotic BCAs
• 2002 EPPO positive list with IBCAs widely used in the EPPO region
• 1998-2002 ERBIC; detailed criteria for RA and IBCA ranking (safety)
• 2003 OECD Guidance for information requirements for IBCAs
• 2003 IOBC/WPRS Commission for the Harmonisation of Regulation of IBCA’s
• 2005 FAO: revised version of ISPM 3
• 2006 Bigler et al. 2006: book as framework for ERA of IBCAs
• 2006-2008: REBECA (EU Policy Support Action)

(Ehlers, 2011)
How to perform ERA for IBCAs?

Identify risks of introducing exotic natural enemy

- **Establishment** and/or **dispersal** in non-target habitat
- Non-target **host range**
- (In) direct effects on **non-target organisms**

Determine likelihood and magnitude of each of the risks
Quantify risk and apply cost-benefit analysis (**also for other control methods!!!**)

(Van Lenteren, 2006)

Stepwise risk assessment: from 5 to 1 scheme

- Clearly good or bad species are discovered early in evaluation (saves resources)
- Only doubtful species go through whole evaluation
- Useful for quick scan or comprehensive evaluation

Van Lenteren, 2006
import and release of non-indigenous biological control agents

Introduction

Invasive species, including biological control agents, are a major threat to biodiversity and ecosystem services. The European Union (EU) has recognized this threat and established the Invasive Alien Species (IAS) Directive (2000/29/EC) to control the spread and establishment of invasive alien species and to minimize their impact on biodiversity. This Directive sets the framework for Member States to develop and implement national plans of action to control invasive alien species. The Directive also requires Member States to monitor the occurrence of invasive alien species and to report on their management activities.

Specific Scope

The current guidelines for the import, usage and import analysis process for non-indigenous biological control agents are:

- Specific approval and amendment
- Specific scope and measurement
- Specific approval and amendment

Key Words

- Invasive alien species
- Screening
- Management
- Reporting

Status of national regulation in European countries:

- Implemented (16)
- In preparation (2)
- No regulation
International Regulation

- NAPPO region: NAPPO application: US, CAN and MEX
- Rest of the world: country specific (often PRAs) ISPM 3

Bottlenecks

- Lack of taxonomic reports
- All IBCA’s are seen as potential IAS
- Variability in experience with authorities
- Procedure not transparent
- Responsibilities of dossier evaluation unclear
- Product specific regulation with biopesticide-like procedures
- Subspecies interpretation of native
- Lack of full implementation of EPPO guidelines
- Different formats of (EPPO) application form
- Lack of clarity about host range testing protocols
1 Interpretation of native below species level

‘National biodiversity’

Considerations

- Added value for environmental safety?
- How to define ‘national’ species?
- Cut off criteria to distinguish based on molecular data?
IBMA position paper on the interpretation of ‘native’ is available

Position paper on the interpretation of ‘native’ in invertebrate biocontrol agent regulations

IBMA member companies produce a broad range of solutions for the biological control of pests and diseases. These products provide ecologically compatible alternatives to the use of Plant Protection Products, and as such generate considerable ecological benefits. As an ecologically responsible industry it is obviously vital to us that our products have low environmental impact. For this reason, IBMA has engaged early-on with academic experts in the field of biocontrol to pro-actively develop stringent guidelines for ecological impact assessment of non-native species. These guidelines were published as EPPO standards PM 8/3(1) First impact of exotic biological control agents for research under contained conditions and PM 8/2(2) Import and release of non-indigenous biological control agents. Our Industry has complied with these standards to validate the ecological safety of our natural pest control solutions.

We only produce and market natural species, using material for our ensuing as it has been collected from nature. Our Industry has an excellent record in providing environmentally benign and acceptable solutions for crop protection. By providing alternatives for registered plant protection products, important ecological benefits have been realized.

In various European countries we work together with the authorities to develop appropriate and workable regulations that allow for a sound environmental impact assessment, without generating unnecessary hurdles to making our ecological solutions available to farmers. As such we offer to work with national authorities in order to avoid the potential risks associated with the use of non-native species.

2 Studies on request for non-native species

- Efficacy data for new applications: TBD
- No adoption of the EPPO positive list as such
3 Procedural hurdles

- Efficacy data per crop
- Invertebrate registration falls under national plant protection law and is treated in a biopesticide-like manner
- Procedures overshadow the fairly feasible content of a dossier

4 Good practice

- Balanced registration application; based on EPPO list (PM 6/3)
- Clear procedures
- Open Communication with evaluators
- Application dealt with in timely matter
Prospectives

- Harmonized IBCA regulation within an ecological zone context (relevant abiotic parameters limiting species distribution)

Species distribution or environmental niche = abstract multidimensional space, in which a set of biotic and abiotic conditions allow a species to maintain a viable population (Hutchinson, 1957; Schnitzler et al., 2012).

EPPO standard PM 6/3: ‘Positive list’

List of biological control agents widely used in EPPO region, created in 2001

- Facilitates decisions on import/ release of BC agents within EPPO
- First listings based on expert judgement: Quick scans
- Joint EPPO-IOBC panel: updating of list
- Criteria:
  - Native in large part of EPPO region or
  - used in 5 EPPO countries for at least 5 years with
    - no reported negative environmental effects or significant non-target effect
- Removal of species when it does no longer meet criteria (Appendix 3, documented!)
• Use EPPO list as a positive list with safe IBCA’s

• Risk categories: ranking according to risk:
  • Develop tools based on these categories: the safer the category, the lesser assessment required
    ➢ For specialist parasitoids less data required as for generalist predators

• Expected vs perceived risk

Positive list and harmonized application format in agro-ecological zone context with relevant (a)biotic parameters limiting natural species distribution according to regional IPPC offices:
• NAPPO
• OIRSA, CA, COSAVE,
• EPPO
• NEPPO, IAPSC
• PPPO, IAPSC, APPPC

Species distribution or environmental niche = abstract multidimensional space, in which a set of biotic and abiotic conditions allow a species to maintain a viable population (Hutchinson, 1957; Schnitzler et al., 2012).
Best way to meet CBD goals?
conservation of biodiversity
sustainable use of biological components

Diverse portfolio for key pests
Position paper: Why ‘national species’ do not make sense in case of IBCA’s

• 1. Widespread genetic exchange (highly mobile insects)
• 2. No added protection to the national flora and fauna
• 3. Seriously hamper the development of clean and safe alternatives for crop protection
• 4. Unfeasible to have production plant in each country
• 5. Unconstitutional in terms of European laws on free trade to favor national producers over other EU producers.
Presentation 10

The US approach to the registration of highly specific biocontrol products
Shannon Borges (Environmental Protection Agency, Washington DC, United States)

The U.S. Approach to Registration of Highly Specific Biocontrol Products

June 26, 2017
The 8th Expert Group on BioPesticides Seminar
Paris, France

Shannon Borges
Senior Scientist
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency

Biopesticides in the U.S.

- Biopesticides are derived from natural materials
- In the U.S., biopesticides fall into three main categories
  - Microbial Pesticides
  - Biochemical Pesticides
  - Plant Incorporated Protectants (PIPs)
Microbial Pesticides

- Microorganisms with pesticidal effect
- Consist of:
  - Eukaryotic microorganisms (e.g., protozoa, algae, fungi)
  - Prokaryotic microorganisms (e.g., bacteria)
  - Autonomous replicating microscopic elements (e.g., viruses)
- Target various pests
  - Insects
  - Bacterial and fungal plant diseases
  - Plants
  - Nematodes

Examples of Microbial Pesticides:

**Bacteria**
- *Bacillus thuringiensis* subspecies
- Other *Bacillus* species
- *Pseudomonas* species
- *Streptomyces* species
- *Agrobacterium* isolates

**Fungi**
- *Beauveria bassiana*
- *Trichoderma* species
- *Clonostachys rosea*

**Baculoviruses**
- *Helicoverpa zea* NPV
- *Cydia pomonella* GV

**Plant viruses**
- Tobacco mild green mosaic tobamovirus (TMGMV)

**Yeast**

**Protozoa**

**GE microbes**

**Products of microbes**
Biochemical Pesticides

- Naturally occurring substance or synthetically derived equivalent
- History of human exposure with minimal toxicity
- Non-toxic mode of action to target pest(s)
  - Desiccant
  - Suffocating agent (e.g., soybean oil)
  - Abrasive agent (e.g., diatomaceous earth)
- Determined by Biochemical Classification Committee

Biochemical Pesticides

Examples of Biochemical Pesticides:

**Semiochemicals (Pheromones)**
- n-Tetradecyl acetate – a mating disruptor for codling moth

**Insect growth regulators**
- Azadirachtin

**Herbicides**
- Vinegar (acetic acid)

**Repellents**
- Coyote and fox urine – repel deer and other animals
- Capsaicin – repel birds, mammals

**Floral attractants and Plant Volatiles**
- 1-Octen-3-ol attractant in electric bug traps

**Insect & Nematode Control**
- Soybean oil

**Plant pathogen & Microbial Control**
- Potassium silicate (induces Systemic Acquired Resistance)
- Laminarin (induces Systemic Acquired Resistance)
Highly Specific Biopesticides

- Biopesticides can be highly specific
  - Pheromones
  - Certain baculoviruses
- Others are more “broad spectrum”
  - Fungal entomopathogens
  - Biochemical insecticides (e.g., neem oil, diatomaceous earth)
- Others can be somewhere in the middle
  - *Bacillus thuringiensis* — subspecies can target specific insect orders, but within those orders there are nontargets of concern
- In general, the more targeted the biopesticide for the intended pest, the more targeted the data requirements
  - Must be supported

How EPA Views Benefits of Biopesticides

- Generally pose fewer risks compared to other types of pesticides
- Low environmental persistence leading to reduced potential for exposure
- Can be target specific
- When used as part of IPM program, can decrease use of conventional pesticides
- When used in rotation with conventional pesticides, can reduce incidence of resistance development
- Often require reduced restricted entry interval and have no pre-harvest interval – greater flexibility for growers
- May address minor crop or obscure pest control needs that are not addressed by conventional pesticides
BPPD’s Role Within OPP

- Biopesticides and Pollution Prevention Division - created to facilitate registration of biopesticides to help bring them to the market
  - Microbial Pesticides Branch
  - Biochemical Pesticides Branch
  - Environmental Stewardship Branch
- Committed to encouraging development and use of low risk biological pesticides as alternatives to conventional pesticides
- Employs multiple measures to facilitate application process
  - All science and registration activities are performed within BPPD
  - Shorter registration timelines
  - Targeted data requirements
- Promotes IPM initiatives and coordinates Pesticide Environmental Stewardship Program

Pesticide Registration – Primary Statutes

- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
  - Legal standard: No unreasonable adverse effects to man or the environment
  - Considers both risks and benefits
  - Lower toxicity, targeted efficacy = reduced risks, increased benefits
- Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Legal standard: Reasonable certainty of no harm
  - Establishes tolerances (maximum residue level) in or on food or animal feed
  - Most biopesticides are granted tolerance exemptions
- Pesticide Registration Improvement Act (PRIA) and extensions
  - Establishes deadlines for registration
  - Requires fees for registration activities
  - Biopesticides – fees are reduced, timelines shorter
  - Small business fee waivers allowed
Pesticide Data Requirements

• Product Characterization
  • Identity of the active ingredient (a.i.), product formulation, discussion of formation of impurities, manufacturing process, analysis of samples, physical and chemical characteristics

• Human Health
  • Acute and subchronic toxicity, pathogenicity (microbial pesticides), developmental toxicity, mutagenicity
  • Food safety assessment (residue data or tolerance exemption)

• Environmental
  • Nontarget organism toxicity, pathogenicity (microbial pesticides)
  • Environmental fate
  • Endangered species

Unclassified
Microbial Pesticide Data Requirements

- Human Health Tier I
  - Tox/Path (TGAI) and Toxicity Studies (Product)

- Human Health Tier II
  - Acute Tox. and Subchronic Tox/Path

- Human Health Tier III
  - Long-term Tox. and Infectivity Analysis

- NTO* Tier I
  - NTO Tox/Path Testing

- NTO Tier II
  - Environmental Expression

- NTO Tier III
  - Chronic and Mesocosm Testing

- NTO Tier IV
  - Simulated/Actual Field Studies

NTO = Nontarget Organism

Biochemical Pesticide Data Requirements

- Human Health Tier I
  - Acute, Subchronic, Developmental Tox., Mutagenicity (in vitro)

- Human Health Tier II
  - Mutagenicity (in vivo), Prenatal Development, Immunotox., User Exposure

- Human Health Tier III
  - Chronic Tox., Companion Animal Tox.

- NTO* Tier I
  - NTO Acute Tox. Testing

- NTO Tier II
  - Environmental Fate and Nontarget Plant Testing

- NTO Tier III
  - Simulated/Actual Field Studies

NTO = Nontarget Organism

Unclassified
How To Satisfy Data Requirements

- Conduct a study in accordance with EPA guidelines
- Cite a study from the literature
- Cite existing data from similar active ingredients/products (“bridging” rationale or studies may be needed)
- Provide a scientific rationale to address the requirement
  - Cite scientific literature or other sources of data
  - Physical and/or biological characterization of the active ingredient and product formulation
  - Lack of exposure
- Many data requirements can often be addressed by means other than conducting a guideline study

Conclusions

- In the U.S., biopesticides includes microbial and biochemical pesticides (also PIPs)
- Many biopesticides have niche uses
- EPA recognizes the benefits of biopesticides, including that they generally have a low risk profile
- EPA’s approach to regulation of biopesticides is aimed at facilitating and streamlining their registration
  - Lower registration fees; shorter time frames
  - Reduced, more targeted data requirements
  - Pre-registration consultations provide a.i.- and product-specific advice on data requirements
- [https://www.epa.gov/pesticides/biopesticides](https://www.epa.gov/pesticides/biopesticides)
The Ctgb approach to the registration of highly specific biocontrol products
Jacobijn van Etten (Board for the Authorisation of Plant Protection products and Biocides (Ctgb), Ede, The Netherlands)

Highly specific biocontrol
- Less risk
- Fit for IPM
- Contribute to diversity of modes of action
- Small markets
- Relative high burden of development and regulatory cost
Highly specific biocontrol

- Highly desirable,
- in line with EU and national politics, consumer wishes, grower needs

Increase feasibility
- Orphan drug law?
- New procedure for tiny uses?

Ctgb experience niche products

Three examples:
- Dutch trig
- Mild Pepino Mosaik virus VC1 and VX1
- Semiochemicals (SemiosNET)
Dutch Trig

- protective agent based on *Verticillium albo-astrum* to prevent the Dutch elm disease.
- injected into the trunk of the tree using a special tree-injection-device
- no exposure
- no studies required for fate, ecotox and human tox
- sound justification for the waivers

Mild Pepino Mosaik virus *VC1 and VX1*

- an inoculant that induces resistance to prevent the infection by virulent PepMV in tomatoes in greenhouses
- CtgB RMS of substances
- Full data package for human tox
- proposed use of direct rubbing of leaves of plants within a greenhouse
- exposure to the environment is not relevant.
Mild Pepino Mosaic virus VC1 and VX1

- The host range of PepMV is mainly restricted to plant species of the Solanaceae family.

- Question: we had to justify that the (plant!) virus could not be transmitted to humans and animals.

Semiochemicals

- Feromones generally effective at very low rates, often comparable to levels that occur naturally.
- New guidance makes it possible to do a very limited evaluation.
- Non-testing strategies if the applicant can provide a justified rationale.
- Read-across.

SemiosNET
- SCLP group.
- Highly specific; very limited assessment.
Lessons highly specific products

- Explain the mode of action: exposure, extrapolation
- Understand biology: GreenTEAM
- Be pragmatic were possible, justified with sound science and/or long term experience
- Do we need new procedures for tiny uses (specific, low risk)?

Experience from the Green Deal

Aim:
- To stimulate sustainable growth by collaboration between all stakeholders
- To resolve obstacles in the authorisation process
- To have more “green” products available for Dutch growers
Experience from the Green Deal

Activities

- Pilot assessments of biopesticides
- Adapt organisation of Ctgb (GreenTEAM for intake and assessment)
- Contribute to harmonisation in EU

Results Green Deal

- Decision taken on 6 product dossiers, important steps in two substance dossiers
- A successful workshop on human toxicology "micro-organisms in PPP's" >> guidance by COM
- A harmonizing workshop on efficacy for biopesticides organised together with EPPO and NPPO >> New EPPO guidance (sept 2017)
- Evaluation manual Biopesticides
Lessons learned Green Deal

- A Pre Submission Meeting is important to clarify possibilities and difficulties
- High quality dossiers support speedy assessments
- A specialised “greenTEAM” of assessors for intake and assessment
- Efficacy assessment should be in line with nature of products
- Tailor made solutions for dossiers

How to get your business case right?

*for green innovation*

outside 1107/2009
- Biostimulants
- Basic substances
- Illegal use

within 1107/2009
- Low Risk
- Specific guidances for biocides
- New procedural solutions needed??
Concerns

• 1107/2009 should enable green innovation
• Large differences in regulatory requirements of biostimulants and low risk products

Solutions (?)

• 120 days for zonal low risk product dossiers
  > criteria are clear
  > development of guidance
• Highly specific biopesticides with low risk profile (tiny uses) might ask for different requirements
• Enforcement of non-authorised products