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

# REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS - ANNEX 6 (PRESENTATIONS - PART 2/3)

**Series on Pesticides**
**No. 76**

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This document contains part 2/ 3 of the Annex 6 of the REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS. Annex 6 includes slides of all presentations made during the seminar.

The main part of the seminar report, as well as Annexes 1-5, is published under the reference ENV/JM/MONO(2014)2.

**PART 2 OF 3**

# COMPILATION OF PRESENTATION SLIDES PRESENTED AT THE OECD/KemI/EU WORKSHOP on Microbial Pesticides: Assessment and Management of Risks

*17-19 June 2013*
*Vår Gård, Saltsjöbaden, Sweden*

**Organised jointly by:**
**OECD (Organisation for Economic Cooperation and Development)**
**KemI (Swedish Chemicals Agency)**
**European Commission**

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***EFSA's role in the peer review process within the EU: Experience of concluding for each organism, using the information provided against the EU data requirements, with the existing guidance.***

***By Christopher Lythgo***
***Team Leader, Environmental Exposure, Peer Review, EFSA***


ANNEX 6: SLIDES FOR PRESENTATIONS

## EFSA's origins

efsa European Food Safety Authority

- Formally set up in January **2002** as an independent source of scientific advice and communication on risks associated with the food chain

  •(REGULATION (EC) No 178/2002 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety)

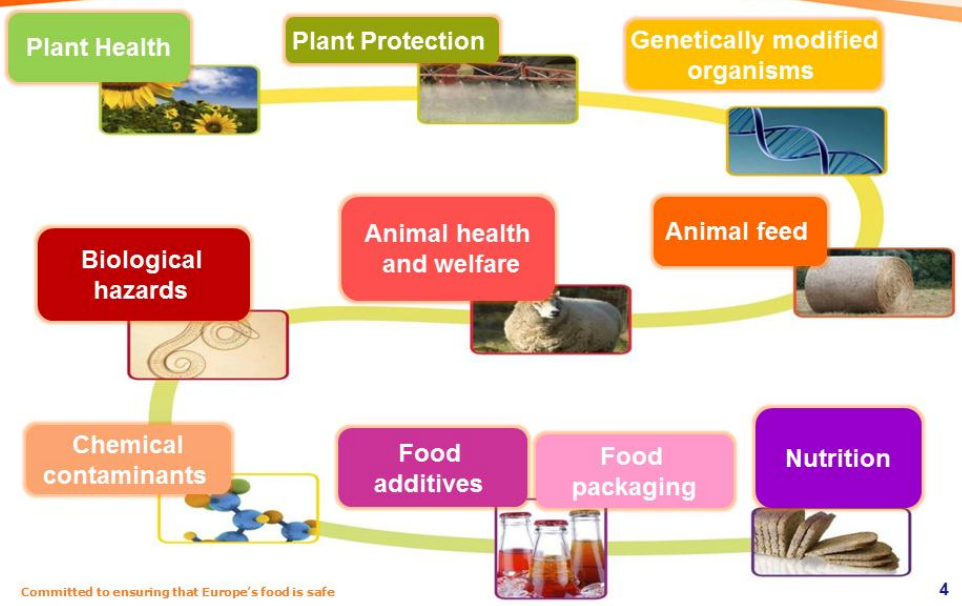
- Created as **part of a comprehensive programme** to:

  •improve EU food safety
  •help ensure a high level of consumer protection
  •restore and maintain confidence in the EU food supply
  •provide (scientific) evidence based risk assessments

Committed to ensuring that Europe's food is safe 3

## Scientific advice from farm to fork

efsa European Food Safety Authority

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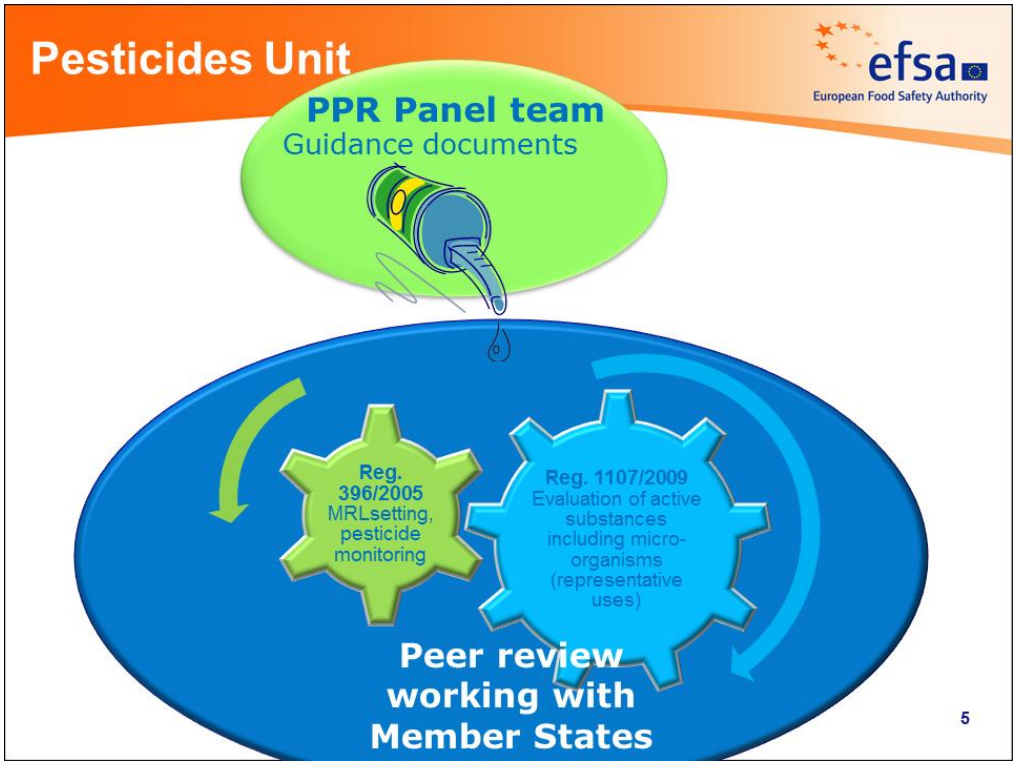


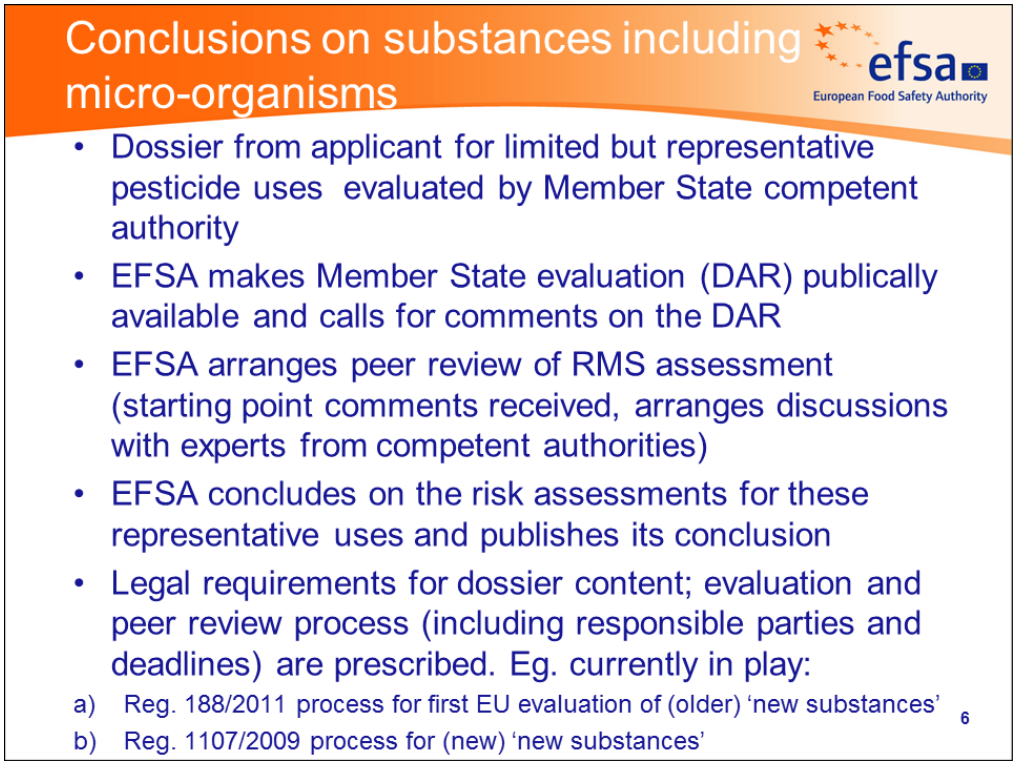

## Experience of concluding for each organism, using the information provided against the EU data requirements, with the existing guidance.

Guidance available that should be followed / is accepted:

- OECD issue paper on microbial contaminant limits for microbial pest control products Series on pesticides No. 65 ENV/JM/MONO(2011)43 12-Oct-2011
- European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

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## Guidance available that gives pointers and approaches that can be followed / have been accepted by the peer review in selected cases:

- OECD guidance to the environmental safety evaluation of microbial biocontrol agents Series on pesticides No. 67 ENV/JM/MONO(2012)1 17-Feb-2012

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## Peer reviewed scientific literature

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- Systematic review of the available literature has to be provided for the organism strain and any metabolites that this literature indicates that the strain or species might produce, following the EFSA guidance
- Other peer reviewed scientific literature can be provided on other strains of the same species or related species where the applicant wishes to use this evidence to address individual data requirements
- When evidence from the peer reviewed literature is cited, the paper with the observation or measurement providing the evidence, should be included in the dossier. Quotes and opinions that just originate from authors in their introduction or discussion sections, should not be considered good evidence

## Data gaps / issues identified in EFSA conclusions:

efsa European Food Safety Authority

- Methods for identity of the strain, best available technology, how to assess if the test procedures presented are appropriate
- Level of evidence to demonstrate relationships to / lack of relationships to known pathogens (EFSA considers evidence of systematic literature review is needed) and how to distinguish from related pathogens
- Information on production of metabolites including other strains of the species, conditions of production, evidence of absence of these from the product
- Insufficient characterisation / evidence / information / measurement that metabolites are not formed at relevant (as described in the data requirements) levels in environmental compartments following application

ANNEX 6: SLIDES FOR PRESENTATIONS

## Data gaps / issues identified in EFSA conclusions:

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- Lack of assessment of the potential for transfer of genetic information to other species (primary concern usually plasmids between bacteria species)
- Information not provided on absence of interference of organism on prescribed methods of analysis for pathogens in drinking water
- Insufficient information on competitiveness / multiplication to conclude if the organism will decline to background levels within a year
- Effects studies provided for characterising environmental risk can be too short to conclude lack of pathogenicity or infectivity to non target species. Ensure that information on the biology of the active organism strain / species is considered when designing tests, particularly test duration

## Conclusion

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- There is a need for guidance, on practice for risk assessment for micro-organisms when used in plant protection products, against the EU regulatory framework (data requirements and uniform principles for product decision making)
  - ➢ EFSA's PPR panel could do this, once the relevant EFSA procurements for systematic review of the literature are finalised, to any priority that was agreed by EFSA's pesticide steering committee (Network of member state competent authorities), subject to resource availability
  - ➢ Alternatively a member state competent authority (or small group of authorities) could initiate work on a document, that EFSA's panel might subsequently be mandated to give an opinion on

ANNEX 6: SLIDES FOR PRESENTATIONS

***Basic strategies in risk assessment – comparison with chemicals***

***By Kersti Gustafsson***
***Swedish Chemicals Agency***


## Similarities and differences

- Same/similar regulations
- Same/similar purpose – to kill/to repel harmful organisms
- Same/similar use – the application methods can be quite similar

- Biology is the difference

## Basis in risk assessment for pesticides including biocides

**Micro-organism** *natural occurring, mutant or GMO*

- Identity
- Biological properties including pathogenicity
- Contaminants
- Human health effects and exposure
- Environmental effects and exposure
- Metabolites
- …

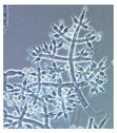
**Chemical** *natural occurring or synthetic*

- Identity
- Physical / chemical properties
- Contaminants
- Human health effects and exposure
- Environmental effects and exposure
- Metabolites
- …



## Risk assessment - same basic outline as for chemicals

**Micro-organism**



***Biological properties***

- Identity
- Life cycle and nutritional / environmental requirements
- Mode of action
- Metabolites

***Effects***

**Non-target organisms**

**Human health**

- Lethality
- Patogenicity
- Toxicity

***Fate and behaviour***

**Ecosystem**

**User, worker, by-stander, general public**

- Use / GAP / scenarios
- Proliferation

## Naturally occurring micro-organisms
## ≠
## no hazard and no risk

- *Bacillus anthracis*
- *Bacillus thuringiensis israelensis*
- Baculovirus
- *Clostridium botulinum*
- EHEC
- *Escherichia coli*
- *Candida albicans*
- *Saccharomyces cerivisiae*
- ..

**Nature is neither kind nor evil, just is**

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Kemikalieinspektionen
Swedish Chemicals Agency

## What have we done -SE?

- SE as EU MS taken part in development of
  - data requirements;
  - uniform/common principles for product authorisation;
  - guidance documents;
- SE / NL Lead Country EU draft assessment reports for active micro-organisms
- SE microbial ~4% of the total number of pesticide products
  - 21 plant protection products
  - 2 biocidal products

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## What can we do – EU/OECD?

- Interpretation / improvement of regulations
  - knowledge compilations – Science / Industry
  - guidance documents – Authorities
- Development/improvement of test methods
- Development of decision criteria for active micro-organisms
- Development of exposure scenarios
- Improve general knowledge about biopesticides
- Communication – expert networking
- Facilitate the process – Industry / Authorities

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## In summary

- As chemicals have been assessed much longer and for many more active substances – take note of valuable experiences
- Interpret/improve the data requirements with detailed guidance and improve the assessment of the biological aspects
- Take special consideration to that micro-organisms are living organisms and improve the exposure assessments based on that

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***Feedback from survey on test guidelines and data requirements***

***By Marloes Busschers***
***CTGB, the Netherlands***

# BPSG Questionnaire

Test guidelines for microbials, 2013

Marloes Busschers
Ctgb, the Netherlands

## BPSG meeting June 2012

- To promote harmonisation:
  - *- table indicating available test guideline per data requirement, interpretation and deficiencies and problems.*
  - *- this will help priority list for development of new test guidelines*
  - *- questionnaire on issues and problems with test guidelines*

## Questionnaire

- Table with all OECD data requirements for microbials (MPCA and MPCP)
- Indicate deficiencies/problems with test guidelines or any other problems
- E.g. lack of test guideline, different interpretations of guideline or of data point

## Questionnaire

Input from:

11 regulatory bodies:

- 7 EU (Austria, Sweden, Germany, Denmark, United Kingdom, Belgium, Netherlands)
- Canada
- USA
- Japan
- Australia

IBMA (10 biocontrol companies/consultants)

## Main issues MPCA

- Identity (IIM 1)
- Biological properties (IIM 2)
- Further information (IIM 3)
- Analytical methods (IIM 4)
- Toxicology (IIM 5)
- Metabolism and residues (IIM 6)
- Fate and behaviour (IIM 7)
- Ecotoxicology (IIM 8)

## Main issues MPCP

- Identity (IIIM 1)
- Phys-chem properties (IIIM 2)
- Data on application (IIIM 3)
- Analytical methods (IIIM 5)
- Efficacy (IIIM 6)
- Toxicology (IIIM 7)
- Residues (IIIM 8), see IIM 6
- Fate and behaviour (IIIM 9), see IIM 7
- Ecotoxicology (IIIM 10), see IIM 8

## Main issues: general

- Metabolites
- Data needed on species or strain?
- Strain characterisation
- Impurities, pathogens, quality control data
- Analytical methods
- Fate and behaviour
- Ecotoxicity

## Consensus

- **Identity: scientific name**
  - strain level
  - names will change based on modern taxonomy methods
  - no further guideline seems to be needed

(identification methods are however in need of guidance)

## Consensus

- **Mamm tox: short term tox testing**
  - no test protocol
  - tier 2 or waiver usually accepted

## Problematic

- **Toxins/metabolites**

➢ "their presence is *suspected*"? "known mammalian toxin"?

➢ Which metabolites need to be assessed?

➢ Theoretical vs practical relevance.

➢ How much of concern? How much data needed to assure this fact? Non-presence is difficult to prove

➢ Insufficient guidance; highly variable between dossiers. Area frequently ignored by applicants.

## Problematic

- **Microbial impurities, human/mammalian pathogens**
  - Insufficient guidance
  - OECD Issue Paper on Microbial Contaminant Limits (ENV/JM/MONO(2011)43)
  - Highly variable between dossiers. Often applicants devise their own quality control testing based on their own experiences.
  - GLP?

## Problematic

- **Characterisation: Best available technology**
  - (No) guidance on methods and degree of strain differentiation
  - Genetic techniques for microbial identification are constantly advancing
  - Acceptable molecular identification methods? Different regulatory authorities don't accept the same data
  - Applicants using outdated methods

## Problematic

- **Related to characterisation is Bridging:**
  - Closely related strains and species
  - It is not clear how much information is required
  - Different interpretations about degree of similarity. No clear rules

## Divergence

- **Toxins/metabolites**
  - CAN/USA: clear guidance, but frequently ignored by applicants. No/little information/discussion provided for metabolic by-products or toxins.

## Divergence

- **Analytical methods**
  - Simple plating techniques:
  - CAN/USA: Standardisation and validation rarely required
  - EU: validation, linearity, accuracy and specificity required. GLP? Criteria needed.

## Divergence

- **Sensitisation**
  - CAN: No study, only incidents reporting
  - USA: Study and incidents reporting
  - EU: No study, only incidents reporting. Some countries accept negative study.

Question: is there an acceptable study for microbials to prove non-sensitiser?

## Divergence

- **Tox: Acute tox/infect/path studies**
  - OPPTS most often used
  - However, might need update
  - Is lacking positive control (Bc: human pathogens, but no effects in oral rat study)
  - Necessary if microbe does not grow >30°C?
  - Intratreacheal: unspecific effects/mortality?

## Divergence

- **Fate and behaviour**
  - EU:
    - tier 1 requirement
    - no guidelines
    - OPPTS not often used, or different interpretation
    - interpretation in relation to background?
  - CAN/USA: Tier 2 data

# Divergence

- **Ecotoxicity**

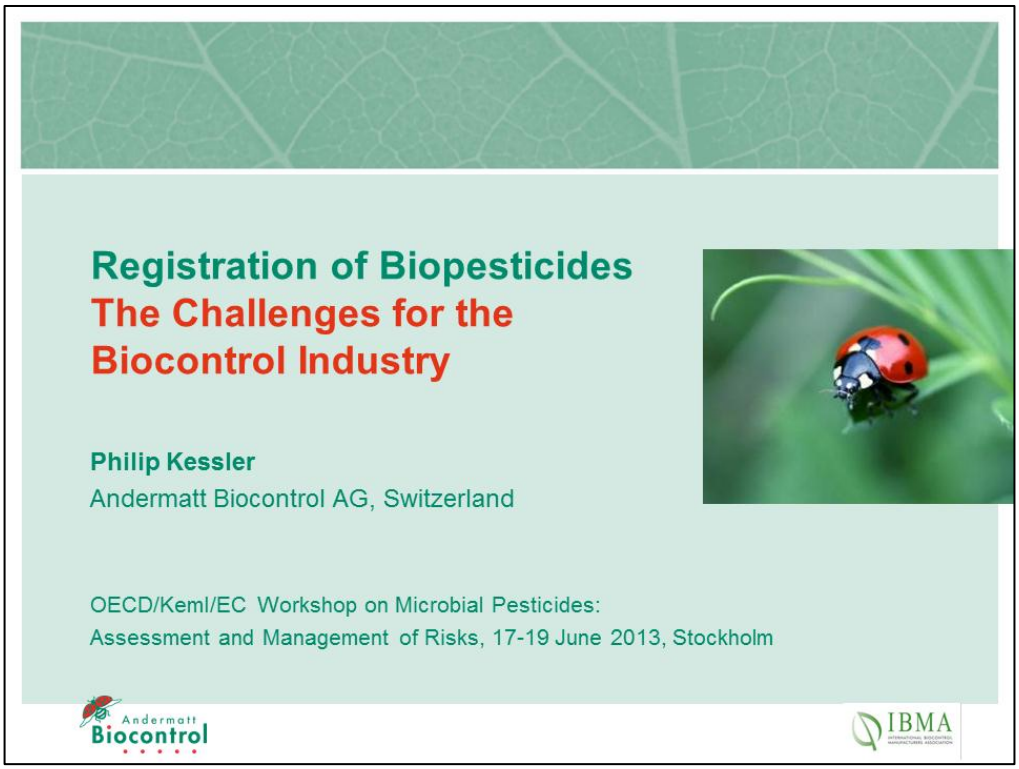
- CAN: GD EPS1/RM/44 or OPPTS
- USA: OPPTS
- AUS: tailoring data req. by radial taxonomy
- Some OPPTS quite brief, update?

- JP/EU: OECD (=Chemical protocols)
- EU data requirements too strict? (e.g. infectivity/pathogenicity in arthropods)

**Industry/Consultant Views**

***Registration of Biopesticides: Challenges for the Biocontrol Industry***

***By Philip Kessler***
***Andermatt Biocontrol AG***



## The Challenges for the Biocontrol Industry

- How the Biocontrol industry is challenged by regulatory framework
- Experience with OECD guidelines and data requirements
- How the new EU regulation 1107/2009 impacts the Biocontrol Industry
- Lessons learned and future considerations

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## Registration of Biopesticides

**Biopesticides need to be regulated**

- ensure safety of the products
- ensure quality of biopesticides (avoid bad reputation, "snake oils")
- protect R&D investment of the industry

- Registration requirements need to be adapted to special characteristics of micro-organisms
- Registration costs need to be reasonable, especially because most biopesticides have a smaller market potential due to their high specificity to their target organisms (narrow host range)

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## Registration of Biopesticides under 91/414

**Registration of a biopesticide in the EU under 91/414/EEC**

- Investment in a full OECD compatible data package (data requirements according to Annex II and III part B)
- Existing study guidelines often not appropriate for micro-organisms.
- Communication possibilities with EFSA and other authorities would improve registration process
- Unpredictable time period for the Annex-1 inclusion and national authorisations
- High registration fees (for RMS, and MS for national registration
- Efficacy data for each MS

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## Registration of Baculoviruses under 91/414

| Active substance<br>PRODUCT | submitted | Annex-1 | status |
|---|---|---|---|
| *Cydia pomonella* granulovirus<br>MADEX | 2005 | 2009 | old a.s., list 4<br>green track , EFSA |
| *Adoxophyes orana*<br>granulovirus<br>CAPEX | 2004 | 2012 | Approved in DE after NPA |
| *Helicoverpa armigera*<br>nucleopolyhedrovirus<br>HELICOVEX | 2006 | 2013 | NPA in IT (2010) and GR (2011), |
| *Spodoptera littoralis*<br>nucleopolyhedrovirus<br>LITTOVIR | 2007 | 2013 | NPA in IT (2012) |
| *Spodoptera exigua*<br>nucleopolyhedrovirus<br>SPEXIT | 2008 | 2010 | SANCO 0253/2008<br>No MS approval yet!<br>Emergency approval for Andalucía (ES) |

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## Main Hurdles and Challenges

1. Unknown or inappropriate data requirements
2. High and unpredictable costs for data packages
3. Lack of experience of authorities
4. Lack of knowhow within biocontrol industry
5. Unreasonable delays in the evaluation procedure
6. Too high registration fees

**High investments and uncertainties are killing factors to register a biopesticide for niche markets**

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## Registration of CAPEX

**CAPEX**

- Baculovirus product based on *Adoxophyes orana* granulovirus
- Biological control of summer fruit tortrix (Adoxophyes orana)

**Why to register CAPEX in the EU?**

- Fluctuating market for CAPEX
- Estimated annual turnover of 50'000 to 200'000 €
- Registration costs of 650'000 to 750'000 €
- Registration process more than 8 years
- ROI when CAPEX already need to be re-registered?

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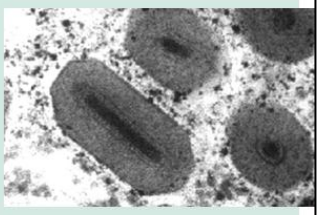
## OECD Consensus Document Nr. 20 (2002)

**Consensus Document on information used in the risk assessment of environmental applications involving Baculoviruses**

- occur only in arthropods, predominantly in the insect orders
- specific pesticidal agents: host range limited to one or a few species of the same genus.
- Effects on non-target species can be excluded
- not infective for mammals and no replication in mammalian cells.
- Not pathogenic, genotoxic, mutagenic, or carcinogenic
- produce no metabolites or toxins



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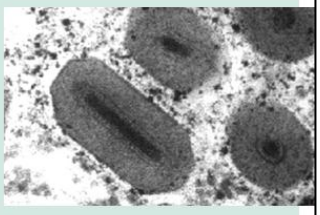
## OECD Consensus Document Nr. 20 (2002)

**REBECA → SANCO 0253/2008**

- Assessment of new isolates of baculovirus species already included in Annex I of 91/414/EEC
- New isolates for *Cydia pomonella* granulovirus (CpGV) quickly authorised, after Annex I inclusion of reference isolate (CpGV-M)
- Make new CpGV products available to bring solutions against CpGV-M resistance



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## OECD Consensus Document Nr. 20 (2002)

- However….!

| Country (OECD) | Request for additional studies |
|---|---|
| Italy | non-target studies on honey bees, *Typholodromus pyri* and *Aphidius rhopalosiphi* |
| EFSA | non-target studies on earthworms |
| Australia | non-target studies on caddiesflies (Trichoptera) |
| USA | Human toxicology: cell culture study |

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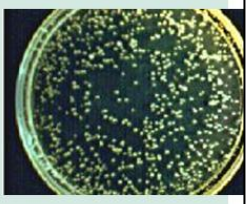
## OECD Guidance Document Nr. 65 (2011)

**OECD issue paper on microbial contaminant limits for microbial pest control products**

- Guidance on acceptable levels of microbial contaminants
- EU: Thresholds have been accepted by EFSA during evaluation of baculoviruses
- How other OECD countries will implement OECD conclusions (USA, Canada, Australia, ..) ?



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## 1107/2009 : Experience with Biopesticides

| Adapted data requirements? | | Experience |
|---|---|---|
| Pre-Submission meetings | can help to avoid incomplete or inappropriate data packages at submission | It can be difficult that MS agree to set a date for these meetings |
| draft Registration Report | should help MS to assess submitted data more efficiently | Template has been just recently developed and accepted for micro-organisms |
| Requirements for studies | No changes in data requirements compared to 91/414 (Annex II and III Part B) | Cost for data packages are actually still at a too high level |
| Data requirements for efficacy data | GEP status and EPPO guidelines | For many biopesticides guidelines are not available or not appropriate , GEP trials are expensive |

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## 1107/2009 : Experience with Biopesticides

| Reduced cost for the application? | | Experience |
|---|---|---|
| draft Registration Report | Conversion of the AIII data package into dRR format | Additional costs |
| Zonal approach | Should reduces the volume of efficacy trials within a zonal application | 1107/2009-zones and EPPO zones are not congruent. Many MS still ask for MS-specific data |
| Adapted fees for biopesticides | Many MS grant special fees for biopestiicdes, but no harmonisation between MS | Focus on a few preferred, in-expensive MS to be zRMS<br>In some cases reduced fees are not granted |
| Mutual Recognition | No separate national applications necessary anymore | Costs registration through mutual recognition are lower, but are still at too high level for niche markets |

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## Further Difficulties with Study Requirements and Methodology

- Storage stability studies: Request for new testing of products containing a new baculovirus isolate, but with identical formulation to already approved products.
- GLP studies for quality tests and storage stability studies: Bioassays
- EPPO guidelines for many microorganisms not appropriate

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## 1107/2009 : Experience with Biopesticides

| Quicker registration process? | | Experience |
|---|---|---|
| Strict timelines | Quicker process, help to predict the marketing for new products | Time gaps between submission and actual start of evaluation of several months.<br><br>MS do not stick to timeframes |
| Mutual recognition | Faster authorisation of a PPP within a zone | So far no experience how smooth cMS are accepting decision by zRMS |
| Resources in MS | Increased workload in some MS | Waiting list before new dossier will be accepted by the preferred zRMS<br>or shift to new zRMS. |

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## Lessons learned and Future Considerations

**Consideration of the Biocontrol Industry**

- The investment of registration of a new biopesticide in the EU may have less priority
- Focus registration for alternative markets (e.g. USA, South America, Asia, South Africa)
- Different focus of R&D investment for biopesticides with markets outside EU

➡ EU growers will lack of new innovative environmental friendly biopesticides in the future, especially in the niche markets

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## Lessons learned and Future Considerations

**Demand for improved registration process, especially for biopesticides**

- Reduce time frame for registration process
- More transparency in the procedure
- Data requirements need to be adapted and predictable
- Increase the experience for assessment of biopesticides
- Reduced fees, especially for products with limited market size

These are not new demands, but we need these improvements **NOW**

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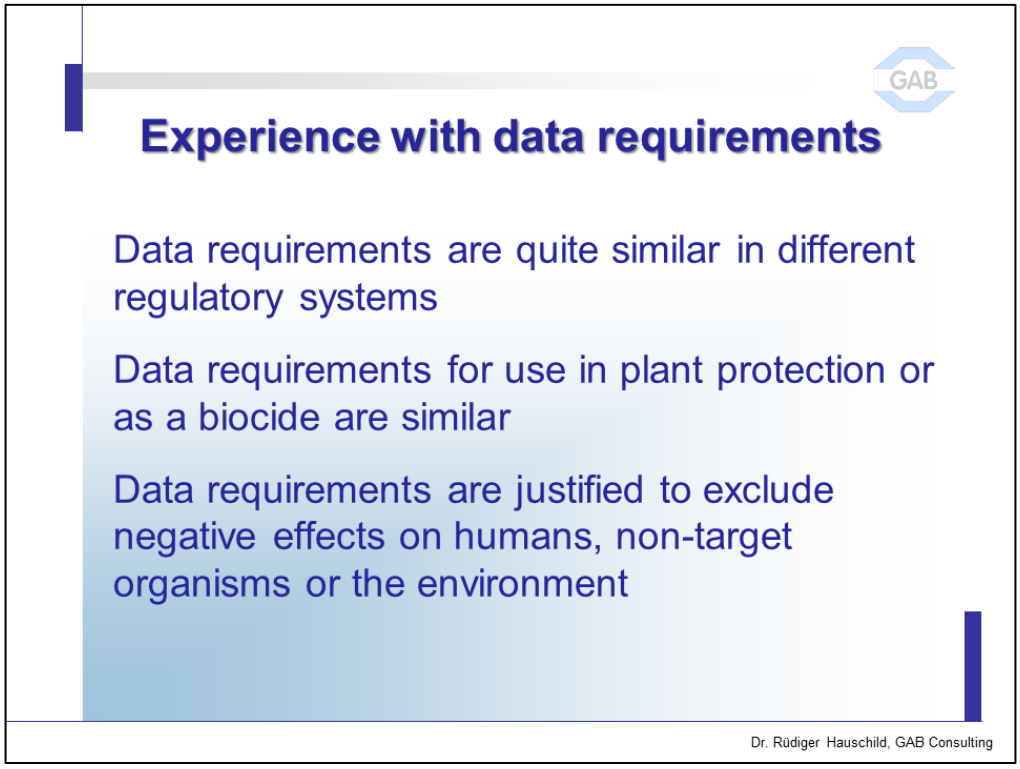
*Experiences with data requirements*

*By Rüdiger Hauschild*
*GAB Consulting*

## Experience with data requirements

Differences exist in the interpretation of data requirements

Which requirements need to be addressed by strain-specific studies and which can be covered using published literature?



## Experience with data requirements

Most microorganisms used in biological control are scientifically well known

*Bacillus*, *Pseudomonas*

*Trichoderma*, *Verticillium*, *Beauveria*

Baculoviruses

Very little information on negative effects of microorganisms used for biocontrol

## Experience with data requirements

One Example:

1. Evaluation of microbial metabolites



## Assessment of Microbial Metabolites

Microorganisms can produce and secrete metabolites in the environment

Chemical properties differ considerably:

- difference in molecular weight
- biosynthetic pathways
- chemical composition

## Assessment of Microbial Metabolites

Possible properties of microbial metabolites:

- inhibitory to fungi
- inhibitory to bacteria
- toxic to insects
- induction of resistance in plants (SAR/ISR)
- toxic to non-target organisms

Metabolites can be involved in the mode of action

- alone
- in combination with other mechanisms

Dr. Rüdiger Hauschild, GAB Consulting

## Assessment of Microbial Metabolites

Ecological functions of microbial metabolites:

- facilitation of attachment to surfaces
- inhibition of competitors (fungistasis)
- inactivation of hosts (parasitism)

Production and secretion of metabolites:

- losses in energy and nutrients
- production in nutrient rich media in vitro
- produced during exponential growth

Dr. Rüdiger Hauschild, GAB Consulting

## Assessment of Microbial Metabolites

Identification of microbial metabolites:

- Literature information on the species or the genus
  - which metabolites can occur?
  - which of them ore potentially harmful to non-target organisms?
- Strain specific data
  - determination and quantification of potentially harmful metabolites in the product
  - analysis of genes encoding potential toxins or enzymes of their biosynthetic pathway



## Assessment of Microbial Metabolites

Occurrence of microbial metabolites:

- contained in the product
  - determination and quantification may be possible
  - potential effects can be assessed using safety studies with the product
- synthesized by the microorganism after application of the product
  - identification is not possible
  - quantification is possible for some compounds, difficult in many cases, and may be impossible at all

## Assessment of Microbial Metabolites

Synthesis of microbial metabolites after application of the product:

- some metabolites need to be synthesized as they are part of the mode of action
- mainly produced during the interaction of the BCA with its host
- accumulation may occur in infested host insects
- exponential growth rarely occurs under environmental conditions
- accumulation in soil was never demonstrated



## Assessment of Microbial Metabolites

Under which conditions do microbial metabolites represent a risk to humans, non-target organisms or the environment?

1. metabolites are toxic
2. metabolites are contained in the product
3. metabolites are produced and accumulated after product application
4. accumulation occurs at sites that are exposed to non-target organisms

Only in case points 1 and (2 or 3+4) are fulfilled, further analysis is required

# Experiences with data requirements Summary

## Assessment of Microbial Metabolites

Most microorganisms used in biocontrol are well known

Some metabolites are synthesized as part of the mode of action

Metabolites can be contained in the product

Synthesis occurs often during interaction with the host

Accumulation of microbial metabolites with harmful effects on non-target organisms in the environment is unlikely to occur and was never observed

Evaluation can be based on product data and published literature



# Many Thanks!

Rüdiger Hauschild
GAB Consulting
D-21769 Lamstedt
ruediger.hauschild@gab-consult.de

***Experiences with compilation of dossiers etc. where there is a need for more guidance and criteria, obstacles***

***By Mark Whittaker***
***Biosphere Biopesticide Consulting***

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# ECOTOXICOLOGY AND MICROBIAL BIOPESTICIDES

**Dr Mark Whittaker** MBPR (Hort)
Managing Director
**BIOSPHERE BIOPESTICIDE CONSULTING**

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# INTRODUCTION

## INTRODUCTION

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- Biological crop protection industry
  - Consultant Entomologist
  - Research & Regulatory Affairs Manager
  - General Manager (UK)
- EU regulatory affairs consultancy
- BIOSPHERE BIOPESTICIDE CONSULTING



## ENTOMOLOGY AND MICROBIOLOGY FOR THE CROP PROTECTION INDUSTRY

APIS
APPLIED INSECT SCIENCE

- A GLP lab specialising in microbial biopesticides

- 5-batch analysis
- Phys-chem studies
- Storage stability
- Terrestrial ecotox
- Microbiology for acute tox studies

## ECOTOXICOLOGY

- Expertise from some of the best ecotoxicologists in Europe
- High quality, bespoke studies
- Basic limit tests through to field scale studies
- Aquatic ecotox undertaken at local CRO (no vertebrate studies undertaken in-house, hence no fish, and thus no *Daphnia* & algae)
- Analytical dose verification undertaken for all aquatic studies

## Ecotoxicology and microbial pesticides

- For microbial substances, studies are routinely requested on:
  - Aquatic ecotoxicology
  - Avian toxicity
  - Earthworm toxicity
- Waiver arguments may be accepted by RMS, but in many cases the safest approach is to conduct the study

## OECD vs OPPTS guidelines

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- OECD guidelines poorly adapted to microbial substances
- OPPTS guidelines quite severe in terms of animal usage in vertebrate studies
- A compromise position is often required

**More fundamental issue:**

Are these studies required at all for microbial substances?

## Cost vs benefit

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- Toxicity studies with microbial substances require a full investigation of pathogenicity, infectivity and clearance
- This adds considerably to the cost of studies, and provides little genuinely useful information

| Study | Cost (including P, I & C) |
|---|---|
| Fish | £10,000 - £15,000 |
| Daphnia | £6,000 - £10,000 |
| Algae | £6,000 - £10,000 |
| Avian toxicity | £15,000 - £25,000 |
| Earthworm reprotox | £9,000 - £12,000 |
| **TOTAL** | **£46,000 - £72,000** |

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# AQUATIC ECOTOX



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- Aquatic systems are continually exposed to microbial agents through run-off and surface deposition from the air
- Aerobic microorganisms don't proliferate in water: poor nutrient status, insufficient organic carbon *etc*
- Where effects are reported they tend to be sub-lethal effects on Daphnia and algae, and are usually attributed to physical rather than toxic effects

DAR risk assessment conclusions

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## Aquatic ecotox

| Active Substance | Fish | Daphnia | Algae |
|---|---|---|---|
| *Ampelomyces quisqualis* | ✓ | ✓ | ✓ |
| *Aureobasidium pullulans* | ✓ | ✓ | ✓ |
| *Bacillus amyloliquefaciens* | ✓ | ✓ | ✓ |
| *Bacillus firmus* | ✓ | ✓ | ×[1] |
| *Bacillus pumilus* | ✓ | ✓ | ✓ |
| *Bacillus subtilis* QST713 | ✓ | ✓ | ✓ |
| *Bacillus thuringiensis Aizawai* ABTS1857 | ✓ | ✓ | ✓ |

**Notes**
1. Adverse effect reported on algae due to turbidity in test system.

DAR risk assessment conclusions

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## Aquatic ecotox

| Active Substance | Fish | Daphnia | Algae |
|---|---|---|---|
| *Bacillus thuringiensis Aizawai* GC-91 | ✓ | ✓ | ✓ |
| *Bacillus thuringiensis Israelensis* AM-6552 | ✓ | ✓ | ✓ |
| *Bacillus thuringiensis Kurstaki* ABTS-351 | ✓ | ✓ | ✓ |
| *Bacillus thuringiensis Kurstaki* PB-54 | ✓[1] | ✓[1] | ✓[1] |
| *Bacillus thuringiensis Kurstaki* SA-11 *et al.* | ✓[1] | ✓[1] | ✓[1] |
| *Bacillus thuringiensis Tenebrionis* NB-176 | ✓ | ✓ | ✓ |
| *Beauveria bassiana* ATCC 74040 | ✓ | ✓ | ✓ |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

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## Aquatic ecotox

| Active Substance | Fish | Daphnia | Algae |
|---|---|---|---|
| *Beauveria bassiana* GHA | ✓ | ✓ | ✓ |
| *Candida oleophila* strain O | ✓[1] | ✓[1] | ✓[1] |
| *Lecanicillium muscarium* Ve6 | ✓ | ✓ | ✓ |
| *Metarhizium anisopliae* | ✓ | ✓ | ✓ |
| *Paecilomyces fumoseroseus* | ✓[1] | ✓[1] | ✓[1] |
| *Paecilomyces lilacinus* 251 | ✓ | ✓ | ✗[2] |
| *Phlebiopsis gigantea* | ✓[1] | ✓[1] | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.
2. Slight adverse effect reported on algae due to nutrient competition.

DAR risk assessment conclusions

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## Aquatic ecotox

| Active Substance | Fish | Daphnia | Algae |
|---|---|---|---|
| *Pseudomonas chlororaphis* | ✓ | ✓ | ✓ |
| *Pseudomonas sp.* | ✓[1] | ✓[1] | ✓[1] |
| *Pythium oligandrum* | ✓[1] | ✓[1] | ✓[1] |
| *Streptomyces lydicus* | ✓ | ✓ | ✓ |
| *Trichoderma asperellum* | ✓[1] | ✓[1] | ✓[1] |
| *Trichoderma atroviride* IMI-206040 | ✓ | ✓ | ✓ |
| *Trichoderma atroviride* I-1237 | ✓ | ✓ | ✓ |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

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## Aquatic ecotox

| Active Substance | Fish | Daphnia | Algae |
|---|---|---|---|
| *Trichoderma harzianum* Rifai | ✓ | ✓ | ✓ |
| *Trichoderma polysporum* IMI-206039 | ✓ | ✓ | ✓ |
| *Trichoderma viride* ICC-080 | ✓ | ✓ | ✓ |
| *Verticillium albo-atrum* WCS-850 | ✓[1] | ✓[1] | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

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# AVIAN TOXICITY

DAR risk assessment conclusions

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## Avian toxicity

| Active Substance | Birds |
|---|---|
| *Ampelomyces quisqualis* | ✓ |
| *Aureobasidium pullulans* | ✓ |
| *Bacillus amyloliquefaciens* | ✓ |
| *Bacillus firmus* | ✓ |
| *Bacillus pumilus* | ✓ |
| *Bacillus subtilis* QST713 | ✓ |
| *Bacillus thuringiensis Aizawai* ABTS1857 | ✓ |

DAR risk assessment conclusions

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## Avian toxicity

| Active Substance | Birds |
|---|---|
| *Bacillus thuringiensis Aizawai* GC-91 | ✓ |
| *Bacillus thuringiensis Israelensis* AM-6552 | ✓ |
| *Bacillus thuringiensis Kurstaki* ABTS-351 | ✓ |
| *Bacillus thuringiensis Kurstaki* PB-54 | ✓[1] |
| *Bacillus thuringiensis Kurstaki* SA-11 *et al.* | ✓ |
| *Bacillus thuringiensis Tenebrionis* NB-176 | ✓ |
| *Beauveria bassiana* ATCC 74040 | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

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## Avian toxicity

| Active Substance | Birds |
|---|---|
| *Beauveria bassiana* GHA | ✓ |
| *Candida oleophila* strain O | ✓[1] |
| *Lecanicillium muscarium* Ve6 | ✓ |
| *Metarhizium anisopliae* | ✓ |
| *Paecilomyces fumoseroseus* | ✓[1] |
| *Paecilomyces lilacinus* 251 | ✓[1] |
| *Phlebiopsis gigantea* | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

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## Avian toxicity

| Active Substance | Birds |
|---|---|
| *Pseudomonas chlororaphis* | ✓ |
| *Pseudomonas sp.* | ✓[1] |
| *Pythium oligandrum* | ✓[1] |
| *Streptomyces lydicus* | ✓ |
| *Trichoderma asperellum* | ✓[1] |
| *Trichoderma atroviride* IMI-206040 | ✓ |
| *Trichoderma atroviride* I-1237 | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

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## Avian toxicity

| Active Substance | Birds |
|---|---|
| *Trichoderma harzianum* Rifai | ✓ |
| *Trichoderma polysporum* IMI-206039 | ✓ |
| *Trichoderma viride* ICC-080 | ✓[1] |
| *Verticillium albo-atrum* WCS-850 | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

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# EARTHWORM TOXICITY

## Earthworm toxicity

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- There are no reported pathogens of earthworms
- When one is found, it has a ready market in the amenity sector
- Worms live in constant contact with soil and have highly efficient immune systems
- Earthworms are used in vermistabilisation – removing dangerous pathogens from contaminated waste
- Where pathogenic effects have been reported they were either induced at rates greatly in excess of field application rates, or were due to something other than the toxicity of the MBCA

## DAR risk assessment conclusions

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BIOPESTICIDE CONSULTING

### Earthworm toxicity

| Active Substance | Earthworms |
|---|---|
| *Ampelomyces quisqualis* | No data[1] |
| *Aureobasidium pullulans* | ✓ |
| *Bacillus amyloliquefaciens* | ✓ |
| *Bacillus firmus* | ✓ |
| *Bacillus pumilus* | ✓ |
| *Bacillus subtilis* QST713 | No data[1] |
| *Bacillus thuringiensis Aizawai* ABTS1857 | ✓ |

**Notes**
1. Acute study with full histopathological investigation requested by RMS

DAR risk assessment conclusions

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## Earthworm toxicity

| Active Substance | Earthworms |
|---|---|
| *Bacillus thuringiensis Aizawai* GC-91 | ✓ |
| *Bacillus thuringiensis Israelensis* AM-6552 | ✓ |
| *Bacillus thuringiensis Kurstaki* ABTS-351 | ✓ |
| *Bacillus thuringiensis Kurstaki* PB-54 | ✓[1] |
| *Bacillus thuringiensis Kurstaki* SA-11 *et al.* | ✓[1] |
| *Bacillus thuringiensis Tenebrionis* NB-176 | ✗[2] |
| *Beauveria bassiana* ATCC 74040 | ✓ |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.
2. Lowest test concentration was 4 orders of magnitude greater than highest field concentration.

DAR risk assessment conclusions

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BIOPESTICIDE CONSULTING

## Earthworm toxicity

| Active Substance | Earthworms |
|---|---|
| *Beauveria bassiana* GHA | ✓ |
| *Candida oleophila* strain O | ✓[1] |
| *Lecanicillium muscarium* Ve6 | ✓ |
| *Metarhizium anisopliae* | ✓ |
| *Paecilomyces fumoseroseus* | ✓[1] |
| *Paecilomyces lilacinus* 251 | ✓ |
| *Phlebiopsis gigantea* | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

BIOSPHERE
BIOPESTICIDE CONSULTING

## Earthworm toxicity

| Active Substance | Earthworms |
|---|---|
| *Pseudomonas chlororaphis* | ✓[1] |
| *Pseudomonas sp.* | ✓[1] |
| *Pythium oligandrum* | ✓[1] |
| *Streptomyces lydicus* | ✓[1] |
| *Trichoderma asperellum* | ✓[1] |
| *Trichoderma atroviride* IMI-206040 | ✓[1] |
| *Trichoderma atroviride* I-1237 | ✓ |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

DAR risk assessment conclusions

BIOSPHERE
BIOPESTICIDE CONSULTING

## Earthworm toxicity

| Active Substance | Earthworms |
|---|---|
| *Trichoderma harzianum* Rifai | ✓ |
| *Trichoderma polysporum* IMI-206039 | ✓[1] |
| *Trichoderma viride* ICC-080 | ✓ |
| *Verticillium albo-atrum* WCS-850 | ✓[1] |

**Notes**
1. No data submitted. RMS concluded that it posed low risk on basis of evidence provided.

## Concluding remarks

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- Aquatic, avian and earthworm studies represent a considerable investment
- Requirement to reduce vertebrate testing
- Effects are rare, and when encountered are usually:
  a) Sub-lethal
  b) Induced at unrealistic rates
  c) Not attributed to the toxicity of the MPCA
- Are these studies required for microbial substances?

***Experiences with compilation of microbial dossiers: relevance of current data requirements***

***By Roma L Gwynn***
***Rationale***

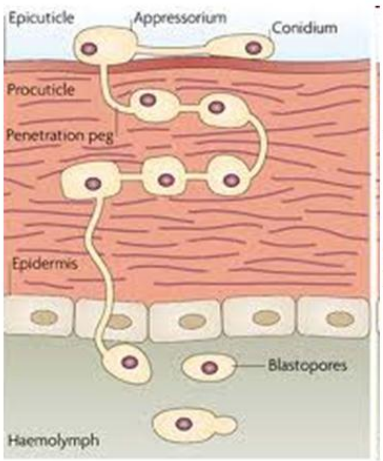
Experiences with compilation of microbial dossiers: Relevance of current data requirements

Roma L Gwynn

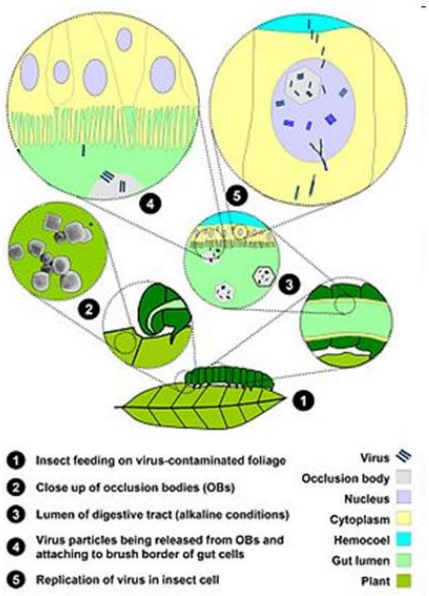
RATIONALE
BIOPESTICIDE STRATEGISTS

Microbial bioinsecticides – MoA

Entomopathogenic fungi



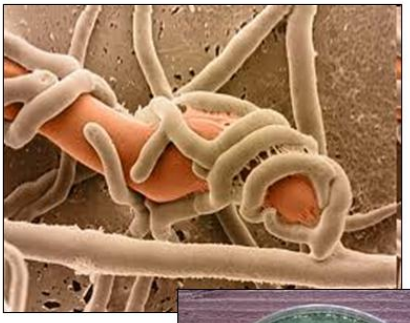

## Baculoviruses – MoA




RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial biofungicides – MoA

*Trichoderma* spp.



*Bacillus subtilis*

RATIONALE
BIOPESTICIDE STRATEGISTS

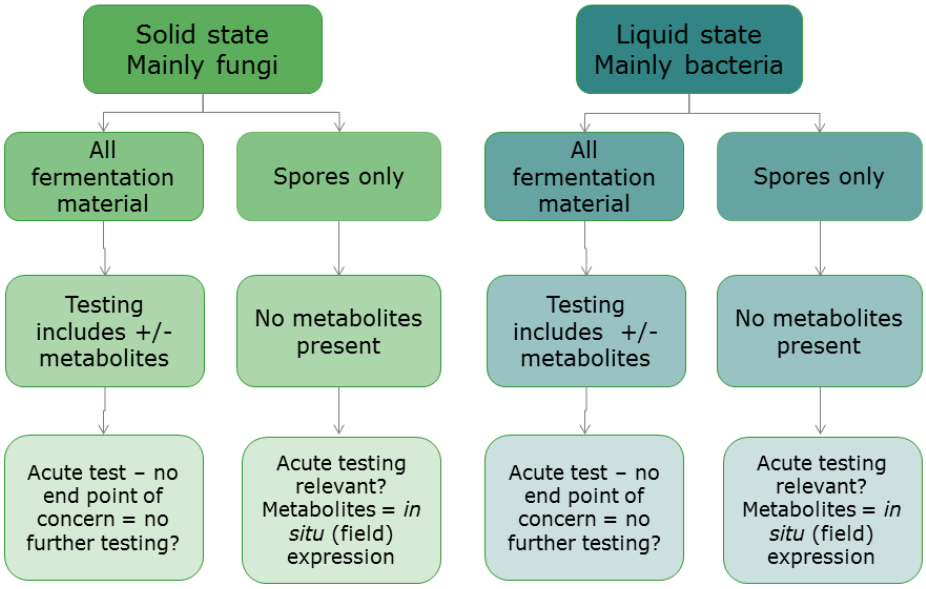
## Microbial Biopesticide production

RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial Biopesticide production

RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial production systems




## Microbial production systems

Solid state -mainly fungi

Liquid state -mainly bacteria

- Production systems often total systems → product
- TGAI or A.S. – often deliberate stop - specifically for sampling
- In product – micro-organisms in quiescent state – no growth

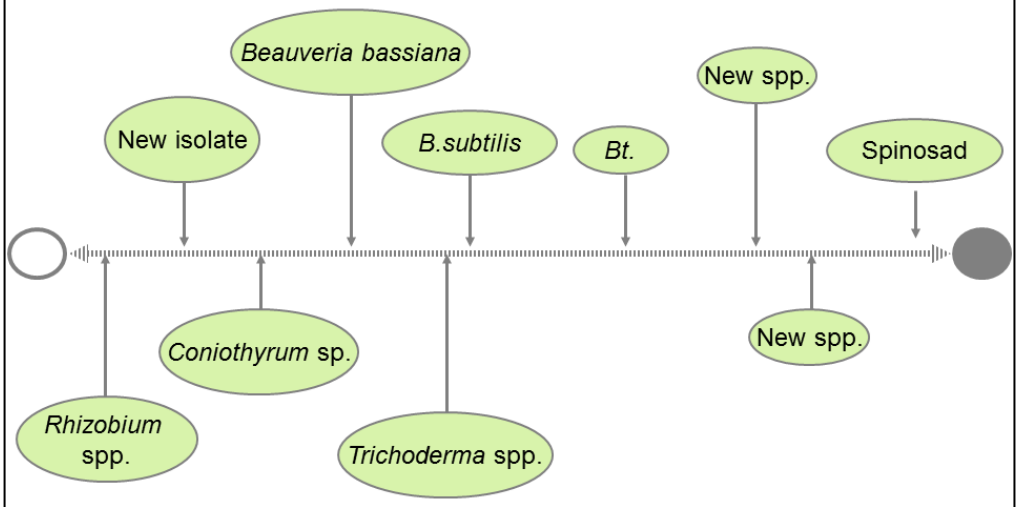
RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial – metabolites

- *Beauveria* spp. – produced in solid state fermentation – spore product
- Metabolites - in product
  - *in situ* expression post application
- Product:
  - not possible to test for all metabolites
  - from literature possibly 9 metabolites
  - beauvericin most common = representative
  - test for this and x 9 safety factor
  - No beauvericin found in product
- *In situ*
  - *Beauveria* spp. used for example against whitefly in greenhouse
  - Adult whitefly = 40 µg
  - Potential metabolites = max 0.002 µg per adult
  - Very low potential exposure

RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbials - types




RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial – toxicity, acute studies

- In EU: currently 37 microbials on Annex I – 28 dossiers
- In EU pending: 12 microbial a.s., 12 dossiers
- Sensitisation – agreement to have standard phrase 'may provoke sensitisng reaction'
- For all other acute tests – for cfu no end points of concern
- For metabolites – only 3 cases where metabolites considered significant - for each product, reasoned case possible to indicate not relevant in field
- No MRL
- Many other areas where study results always negative

RATIONALE BIOPESTICIDE STRATEGISTS

## Natural microbial infections

Natural declines in cotton aphid, *Aphis gossypii*, caused by the fungus *Neozygites fresenii*, in the southern USA

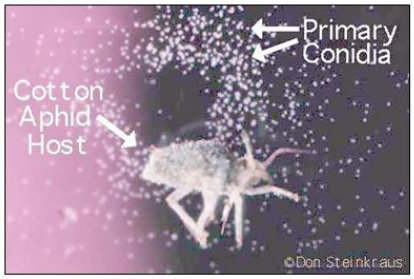
- Important cotton pest in USA since the 1980s.

Steinkraus, Arkansas University

- Caused by *A. gossypii* developing pesticide resistance.

RATIONALE BIOPESTICIDE STRATEGISTS

## Natural microbial infections




- *N. fresenii* started causing epizootics in *A. gossypii* on cotton in Mississippi Delta in 1989.
- Common, begin in July, occur at same time in the same region.
- Prediction service run by Uni. of Arkansas (Steinkraus *et al*.) - allows farmers to save insecticide sprays.
- Saves money and preserves other natural enemies.

Steinkraus, Arkansas University

RATIONALE BIOPESTICIDE STRATEGISTS

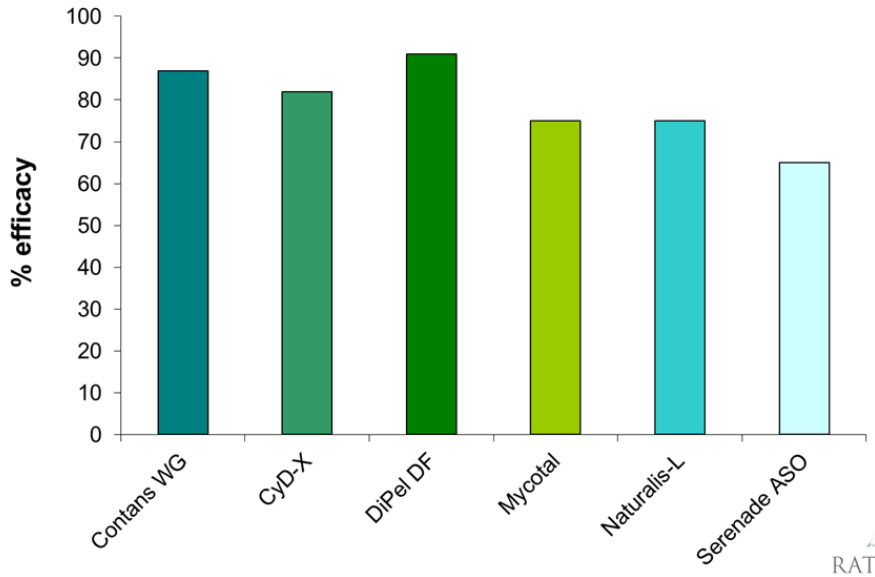
## Natural microbial infections

### Population dynamics

- When average prevalence of fungus reaches 15%, the aphid population will soon begin to decline.
- When this starts, the aphid population falls by 80% in 3 - 4 days.
- Fungus detectable up to 10 days before the aphid population starts to decline this rapidly.

RATIONALE BIOPESTICIDE STRATEGISTS

## Biopesticides – efficacy




RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbial – environmental persistence

- Consider application rates compared to background levels
- Product applied to disturbed agro ecosystem not natural ecosystem
- Cultivation more effect on microbial community that short perturbation caused by application of microbial
- Recent work demonstrating that in Denmark in one field – 14 species of *Metarizium* spp.
- 1 gram of soil, there may be 20,000 to 40,000 species of bacteria

| | |
|---|---|
| Bacteria | 3,000,000 to 500,000,000 |
| Actinnomycetes | 1,000,000 to 20,000,000 |
| Fungi | 5,000 to 1,000,000 |
| Yeast | 1,000 to 1,000,000 |
| Protozoa | 1,000 to 500,000 |
| Algae | 1,000 to 500,000 |
| Nematodes | 10 to 5,000 |

RATIONALE
BIOPESTICIDE STRATEGISTS

## Microbials – critical requirements for safety

Questions asked in current system: not specifically designed to assess safety of a microorganism – are they right Q's ?

1. Identity: taxonomic position = biology, ecology and specificity
2. More differences between isolates than between spp.
3. Ability to persist and spread – potential to disturb natural ecosystem
4. Efficacy
5. Test only product
6. ?

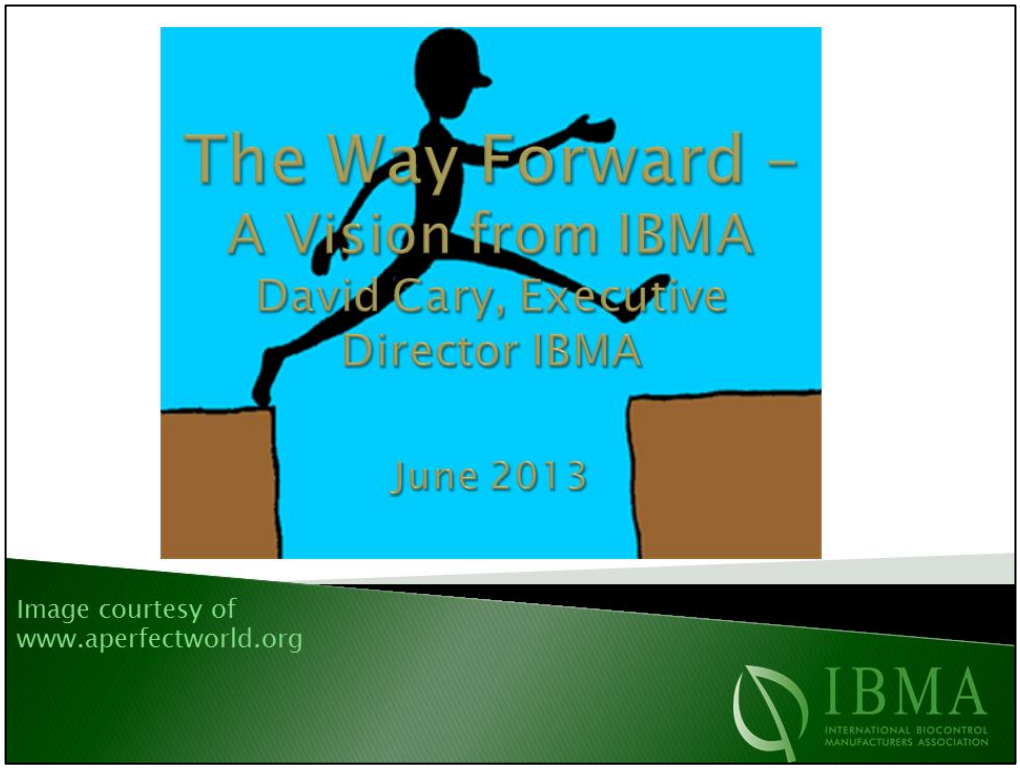
RATIONALE
BIOPESTICIDE STRATEGISTS

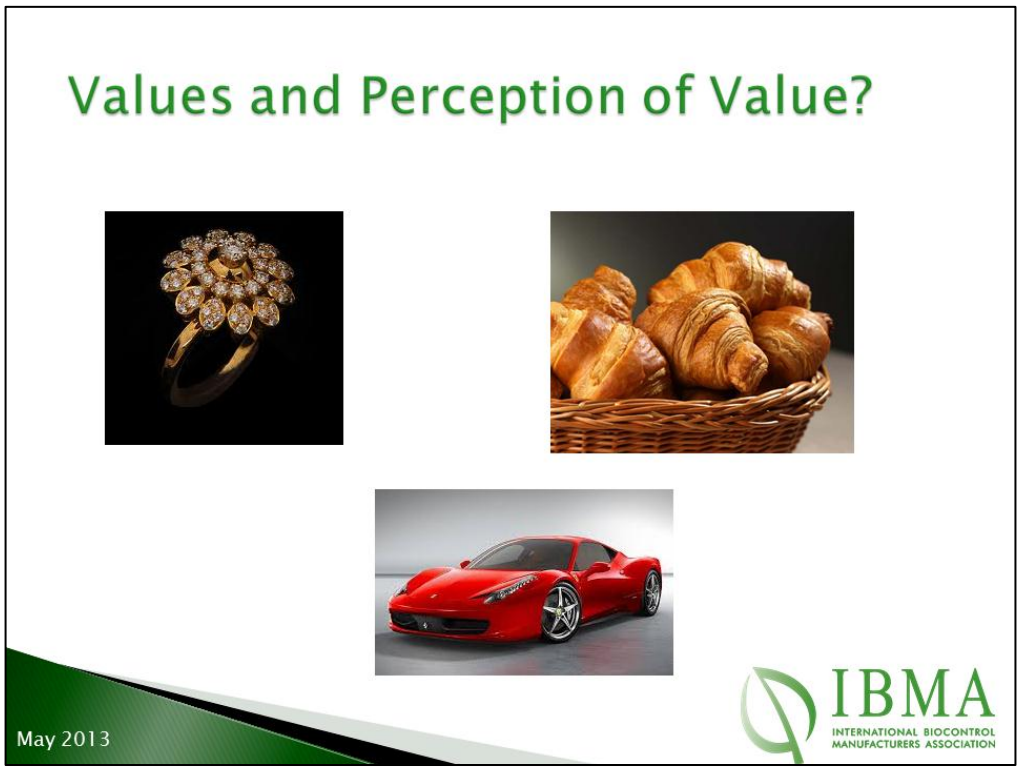
## Thank you for your attention

rgwynn@biorationale.co.uk

***The Way Forward – A Vision from IBMA***

***By David Cary***
***Executive Director, IBMA***



## OECD International Regulatory Co-operation – Addressing Global Challenges – April, 2013

- "The world is becoming increasingly global. This raises important challenges for regulatory processes which still largely emanate from domestic jurisdictions. In order to eliminate unnecessary regulatory divergences and to address global challenges pertaining to systemic risks, the environment, and human health and safety, governments increasingly seek to better articulate regulations across borders and to ensure greater enforcement of rules and their application across jurisdictions."



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## OECD Policy

- IRC – International Regulatory Co-operation
  - Growing regulatory co-operation
  - Layering of co-operation
  - Shift from complete harmonisation to more flexible regulatory co-operation mechanisms
    - Such as mutual recognition
  - Multiplication of state & non-state actors
  - Rise of soft law
    - Codes of conduct, guidelines & guidance
  - Increase in using intergovernmental organisations
    - OECD, FAO, etc..
  - Utilise formal regulatory partnerships where established
    - NAFTA, ECOWAS, CILWAS, etc..



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## What have we got with biopesticides?

- A system designed for substances presenting different risks to environment & health
- Lack of a system in many OECD & non-OECD Member States
- Restricted expertise in regulatory bodies
- Rapid global expansion in the industry
- Expansion of fraud and false practice
- Expansion & lack of clear boundaries with related industries
- Policy support for expanded use
- Support from Growers, NGOs, PMOs and Consumers
- Wide range & experience of actors

May 2013

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## Recommendation of the Council on Regulatory Policy and Governance – OECD 2012

http://www.oecd.org/gov/regulatory-policy/49990817.pdf

May 2013

IBMA INTERNATIONAL BIOCONTROL MANUFACTURERS ASSOCIATION

# How to proceed

- Clearly define all bio industries & propose proportionate legislation for all based on risk to human health & the environment
- Apply soft law
  - Guidance
- Recognise, Foster and Utilise formal regulatory partnerships or umbrellas
  - Use established groups and co-operations where possible
- Recognise and utilise the strengths and benefits of Intergovernmental Organisations – OECD & FAO

May 2013

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# Current tool categories available from the Biocontrol industry




| Microbials | Macrobials | Semiochemicals | Natural Products |
|---|---|---|---|
| Viruses, Bacteria & Fungal Pathogens | Predatory mites & insects, nematodes | Pheromones, Plant volatiles | Plant extracts, Seaweed products & Basic substances |

May 2013

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INTERNATIONAL BIOCONTROL MANUFACTURERS ASSOCIATION


A new global regulatory approach utilising FAO / OECD / Regional areas of expertise
OECD Guidance & Definitions
•Regional Representation
•BRIC participation
•EU involvement
•EPA & PMRA expertise utilised
Global evaluations
•EU centres of excellence
•Regional representation from LATAM, AF, Asia & Pacific
•Utilise US EPA expertise
FAO Global Regulatory Toolbox
•Adopt existing NAFTA / EU registrations into toolbox
•Available for cross adoption on a global basis
•Progressively incorporate new global reviews
May 2013
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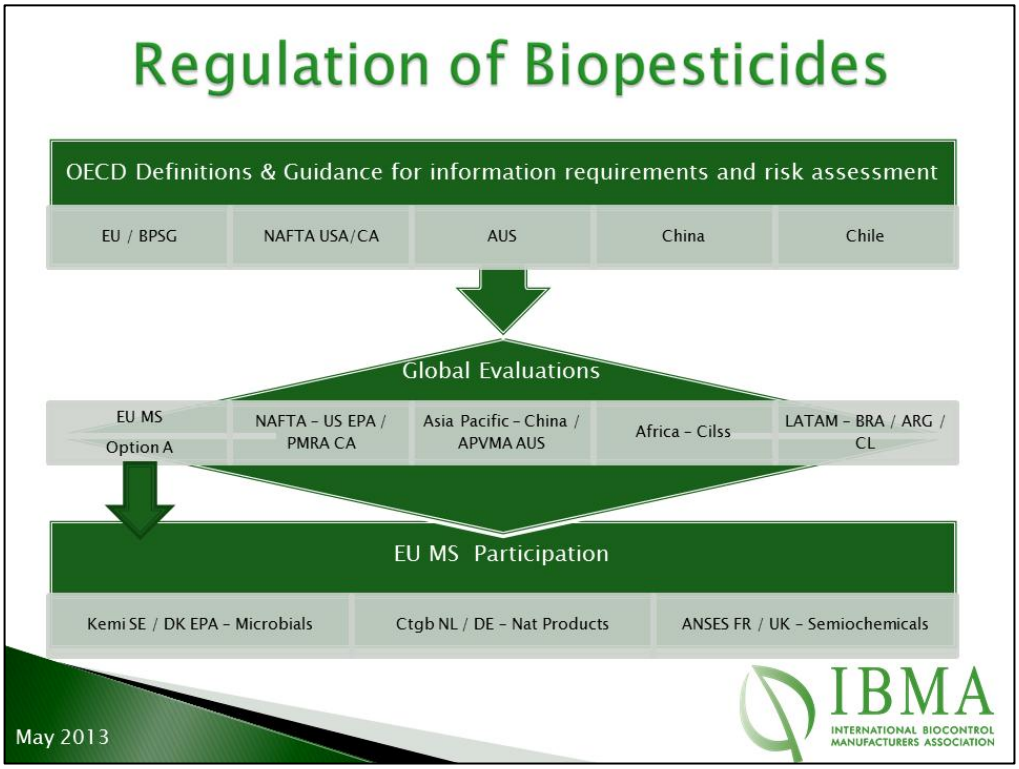
Regulation of Biopesticides
OECD Definitions & Guidance for information requirements and risk assessment
EU / BPSG
NAFTA USA/CA
AUS
China
Chile
Global Evaluations
EU MS Option A
NAFTA – US EPA / PMRA CA
Asia Pacific – China / APVMA AUS
Africa – Cilss
LATAM – BRA / ARG / CL
EU MS Participation
Kemi SE / DK EPA – Microbials
Ctgb NL / DE – Nat Products
ANSES FR / UK – Semiochemicals
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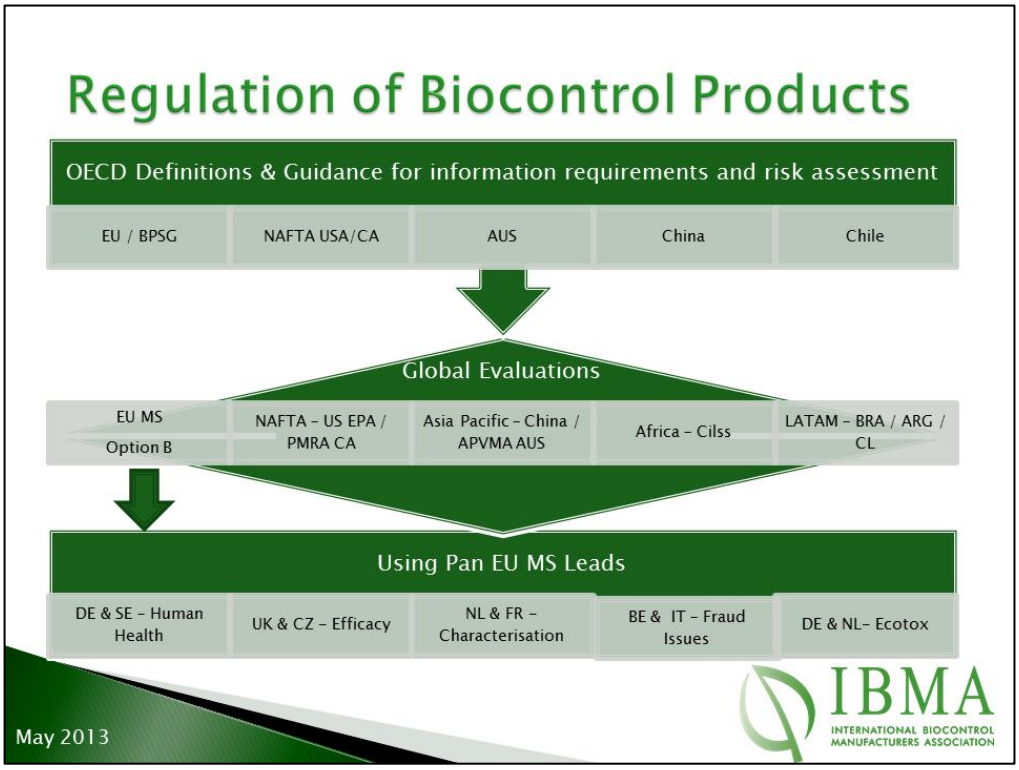
Regulation of Biocontrol Products
OECD Definitions & Guidance for information requirements and risk assessment
EU / BPSG
NAFTA USA/CA
AUS
China
Chile
Global Evaluations
EU MS
Option B
NAFTA – US EPA / PMRA CA
Asia Pacific – China / APVMA AUS
Africa – Cilss
LATAM – BRA / ARG / CL
Using Pan EU MS Leads
DE & SE – Human Health
UK & CZ – Efficacy
NL & FR – Characterisation
BE & IT – Fraud Issues
DE & NL– Ecotox
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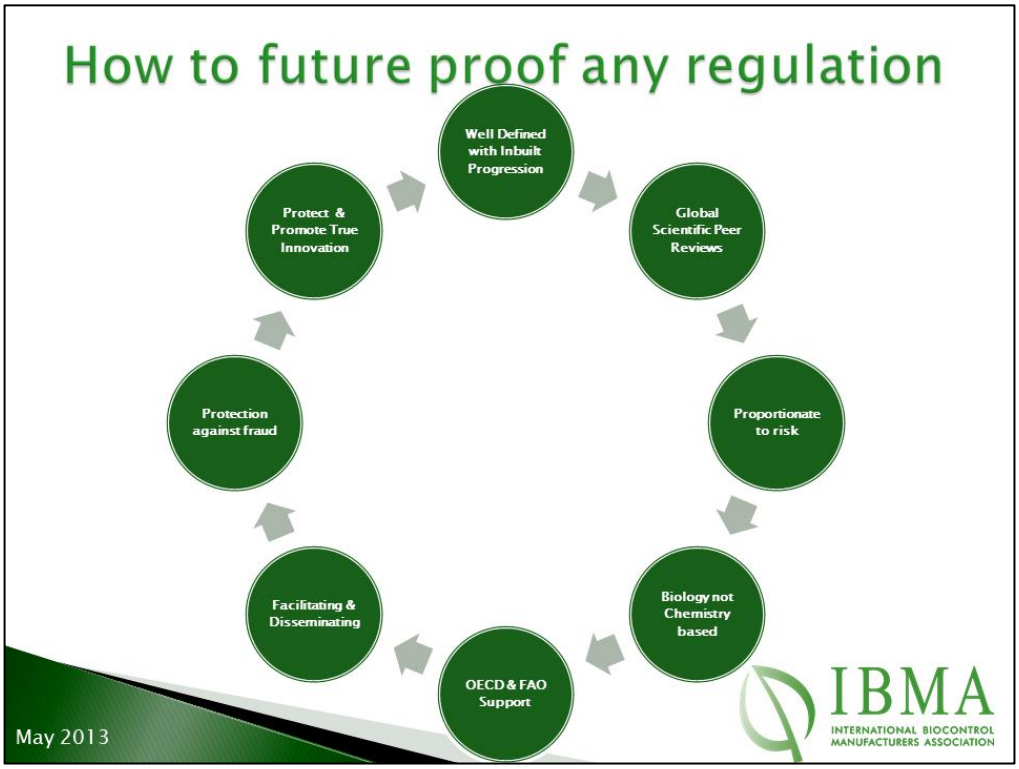
How to future proof any regulation
Well Defined with Inbuilt Progression
Global Scientific Peer Reviews
Proportionate to risk
Biology not Chemistry based
OECD & FAO Support
Facilitating & Disseminating
Protection against fraud
Protect & Promote True Innovation
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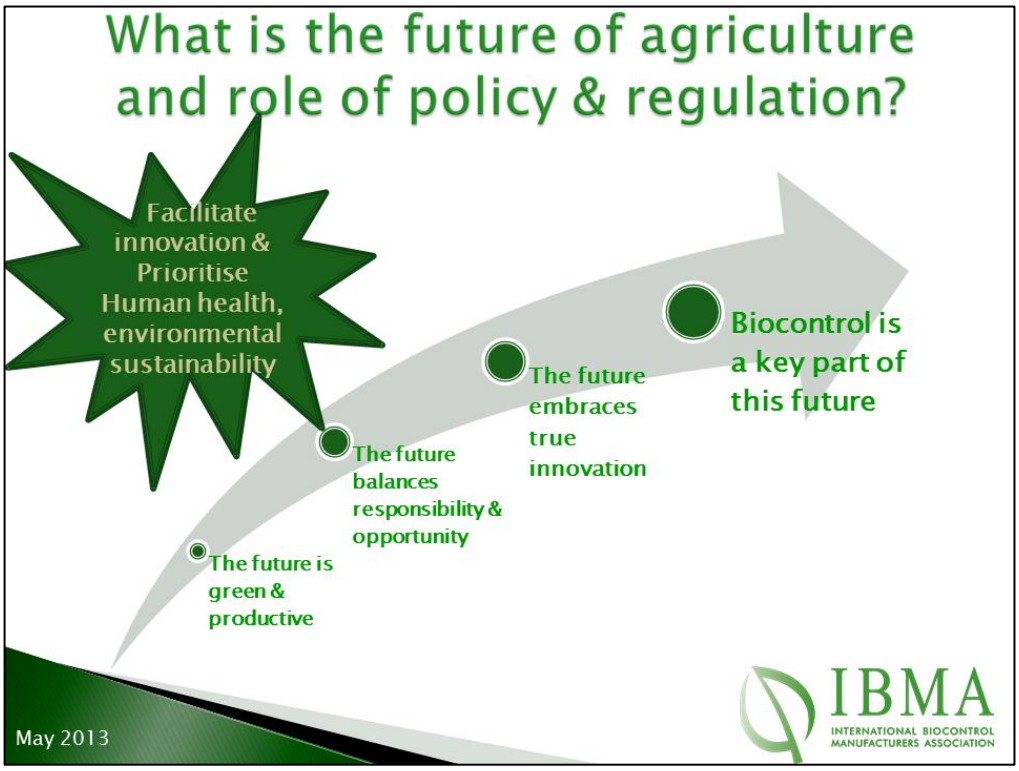
What is the future of agriculture and role of policy & regulation?
Facilitate innovation & Prioritise Human health, environmental sustainability
The future is green & productive
The future balances responsibility & opportunity
The future embraces true innovation
Biocontrol is a key part of this future
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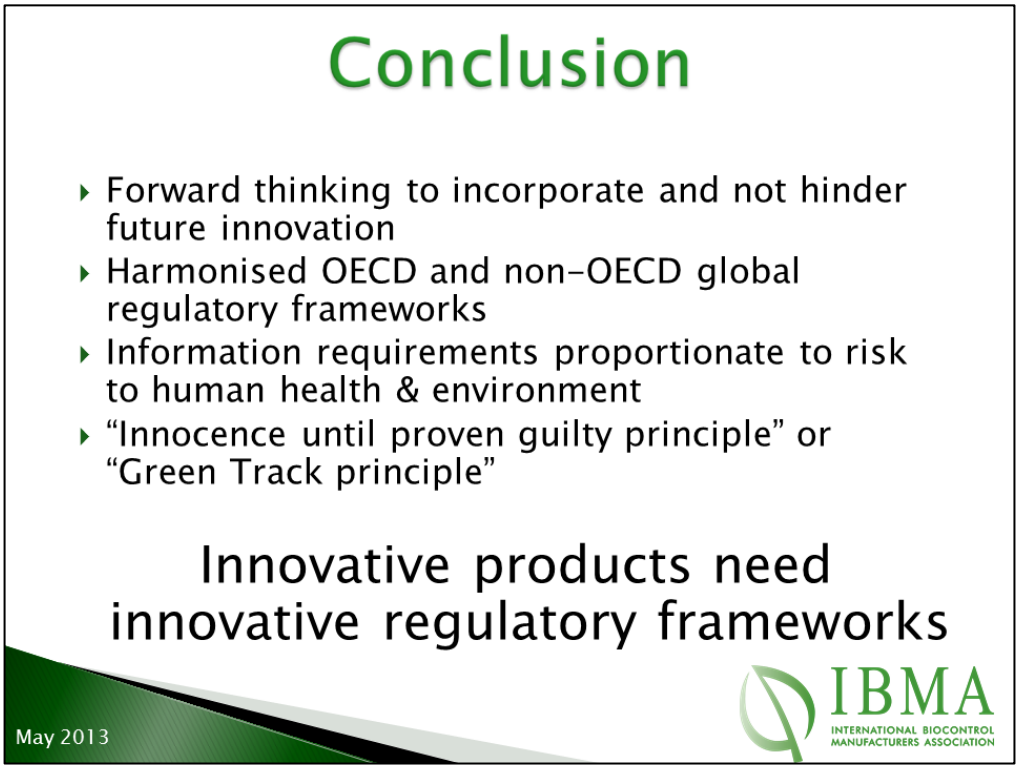
Conclusion
Forward thinking to incorporate and not hinder future innovation
Harmonised OECD and non-OECD global regulatory frameworks
Information requirements proportionate to risk to human health & environment
"Innocence until proven guilty principle" or "Green Track principle"
Innovative products need innovative regulatory frameworks
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