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# REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS

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# REPORT OF THE OECD/KEMI/EU WORKSHOP ON MICROBIAL PESTICIDES: ASSESSMENT AND MANAGEMENT OF RISKS

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
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The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

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## FOREWORD

This document is the report of the joint **OECD/KemI/EU Workshop *on "Microbial Pesticides: Assessment and Management of Risks"*** that took place between the 17th and 19th of June 2013 in Saltsjöbaden, Sweden. The workshop was hosted by KemI, the Swedish Chemicals Agency, and was chaired by Jeroen Meeussen of DG Sanco (European Commission) and Chair of the OECD BioPesticides Steering Group (BPSG). It was attended by about 80 participants, representing 22 regulatory authorities of OECD countries, regional and international organisations (including the European Commission (EC), the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), the International Biocontrol Manufacturers Association (IBMA), the Business and Industry Advisory Committee to the OECD (BIAC) representing the plant protection and biocide industry, and experts from academia).

The focus of the workshop was on i) identifying pragmatic approaches that can be taken now with information that was available during the workshop and ii) the elaboration of solutions for the future (e.g. to generate new guidance on how to address technical and scientific issues in performing studies and carrying out assessments) in the regulation of microbial pesticides, including biocides. In many regions and countries microbial pesticides are regulated in a similar way to chemical pesticides as they are used for the same purposes. Clearly the (biological) properties of living microbial pesticides differ from the properties of chemical pesticides, and based on these differences the type and level of regulatory requirements for microbial pesticides can be challenging.

The workshop consisted of plenary sessions with presentations (from regulators, industry and academics active in the area of microbial pesticides regulation, registration and research) and break-out groups in which participants discussed specific issues and tried to come up with solutions and to prioritise areas for further work. In a final plenary session, the results from the break-out groups were discussed and a consensus document was drafted that forms the basis of the conclusions and recommendations section of this report.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which agreed to its declassification on 31 March 2014.

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## 1. INTRODUCTION

This report presents the proceedings of the joint **OECD/KemI/EU Workshop *on "Microbial Pesticides: Assessment and Management of Risks"*** held in Saltsjöbaden, Sweden on the 17th – 19th June 2013. It includes the abstracts of presentations given at the workshop (presentation slides are available in a separate document), a summary of the workshop discussions and the overall workshop conclusions and recommendations. The purpose of the workshop was to develop recommendations to the OECD, its member countries and other interested parties on approaches in the regulation of microorganisms used as pesticides, so-called microbial pesticides, against both the background of relevant regulations that have been designed for chemical pesticides and the current available scientific, technical and regulatory knowledge on microbial pesticides. In this report, pesticide means any product used to control a pest and includes biocides (human health pesticides and other products with pesticide uses that do not involve agriculture and related areas) and plant protection products. The focus of the workshop was on identifying pragmatic approaches that can be taken now with available information and on the elaboration of solutions for the future (e.g. to generate new guidance on how to address technical and scientific issues in performing studies and carrying out assessments in the short, medium and longer term). Topics that were addressed included: identification of the microorganism and its biological properties, mode of action, infectivity, production of metabolites, analytical methods, efficacy, residues, effects on non-target organisms and persistence/propagation in the environment in the context of the natural presence of the microorganism, as well as a number of procedural and regulatory issues.

The workshop was planned as a joint event between the OECD, the Swedish Chemicals Agency (KemI) and the European Commission. A workshop organising committee consisting of representatives of the organisers (OECD, KemI, the European Commission), regulators from OECD member countries and industry participants was set up to develop the concept for this workshop, its overarching theme and its detailed programme. Within the OECD's work programme, the workshop falls under the BioPesticides Steering Group (BPSG), a sub-group of the OECD Working Group on Pesticides but is also closely related to the work of the OECD Task Force on Biocides (TFB).

The workshop was hosted by KemI, the Swedish Chemicals Agency, at the Vår Gård conference centre. It was chaired by Jeroen Meeussen of DG Sanco (European Commission) and BPSG Chair, and was attended by about 80 participants. Around half the participants were officials from 22 OECD country regulatory agencies. The other participants were representatives of regional and international organisations, including the European Commission (DG Sanco and DG Research), the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), the International Biocontrol Manufacturers Association (IBMA) and the Business and Industry Advisory Committee (BIAC) representing the pesticide and biocide industry, experts in the field of biopesticides from academia and the OECD Secretariat. The list of workshop participants is attached in Annex 1.

### *The increasing use of microorganisms as pesticides*

The use of microorganisms as agricultural pesticides and, to a lesser extent, biocides[1] has existed for many years. The last decade has seen a marked increase in the numbers and types of microbial pesticides and their uses, although they are still largely used as plant protection products as opposed to biocidal products[2]. This increase has come about as a result of innovations in the industry, probably largely driven by the need to produce more targeted ("smarter"), environmentally friendly and sustainable products and

[1] Biocides in this context include human health pesticides and other products with pesticide uses that do not involve agriculture and related areas, such as forestry or amenity uses

[2] In the EU, as of 2013, 54 microorganisms have been approved for plant protection use, compared with only one microbial biocide; however, many more applications of both types are in the approval and/or authorisation process.

technologies as alternatives to the broader spectrum of chemical products. In addition, the modes of action of microbial pesticides may provide new opportunities for resistance management. Resistance in the target organism is becoming an increasing concern for chemical agricultural pesticides.

***Regulating microbials: a challenge***

When innovative products are commercialized, regulation often struggles to keep pace. This seems to be the case for microbial pesticides, which are regulated in many regions and countries in a similar way to chemical pesticides as they are used for the same purposes. Clearly the (biological) properties of living microbial pesticides differ from the properties of chemical pesticides, not least because microorganisms have the capability of propagation. Based on these differences, the type and level of regulatory requirements for microbial pesticides can be challenging, particularly in the areas of:

- Identity, characterization and biological properties (including identification of the microorganism and differentiation from similar microorganisms, mode of action, metabolites and impurities, and stability of the end use formulation)
- Toxicological and environmental properties , in particular with respect to non-target organisms
- Residues on food crops (of both the microorganism and any produced metabolites)
- Level of efficacy

Although OECD countries have different regulations and see different uses of microbial pesticides, there are many similarities between countries in the way microbial pesticides are managed (for example, as shown by the EU REBECA project http://www.rebeca-net.de/?p=999). In addition, most countries/regions are facing similar problems around the registration and approval/authorisation of microbial pesticides. Legislation covering microbial pesticides in OECD countries tends to be originally designed for chemical pesticides although, in some cases, specific provisions have been added for microorganisms. This means that very often information requirements for microbials are the same or very similar as for chemical products; in many cases it is not clear how to test a microorganism for a particular endpoint, or how to assess it within the regulatory framework.

The regulations for chemicals have been further improved with guidance documents and criteria. This is also necessary for microorganisms. A lot has already been done but there is still need for further improvement. Especially there is a need to develop further guidance in detail and decision criteria that concern the fact that microorganisms are living organisms that can die, survive or proliferate. There is also a need to develop different exposure scenarios. The application of microbial pesticides may be performed with different techniques which give varying exposure to man and environment compared with chemical pesticides.

***Scope of the workshop***

Microorganisms in the scope of this workshop meant any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material (in accordance with the definition used in the European Union Regulation (EC) No 1107/2009). Products in the scope of the workshop include both agricultural pesticides as well as non-agricultural products (in some OECD countries this distinction is made by the terms pesticide and biocide, respectively).

## 2. WORKSHOP OBJECTIVES

The workshop had a number of objectives aimed at addressing issues concerning the regulation of microbial pesticides, as follows:

- to provide an overview of the current status of microbial pesticide regulation worldwide;

- to discuss technical, scientific and regulatory problems that countries' authorities face when assessing microbial `plant protection products and biocides;
- to identify technical and scientific solutions that are available now to those common assessment problems;
- to suggest harmonised solutions to facilitate the approval process including the need to adapt existing guidance or produce new guidance (for example on the interpretation of data requirements); and
- to draw conclusions and recommendations for further work for OECD, the governments of its member countries and identified stakeholders.

To meet these objectives it was essential to promote efficient use of the expertise on microorganisms within and between OECD member countries and organisations, including input from member country regulatory authorities and other national/regional organisations dealing with microbial pesticide approvals/authorisations, experts from industry dealing with microbial testing and registration, and experts from academia who conduct research into microbial pesticides.

It was envisaged that the workshop would provide conclusions and recommendations covering:

- a better understanding of data requirements for microbial pesticides;
- a better harmonisation of data requirements and their interpretation;
- an improved collaboration and communication;
- a better and more efficient use of knowledge on microbial pesticides within and between countries;
- improvement of the approval and authorization process for microorganisms within the legislative framework; and
- suggestions for development of OECD guidance documents.

## 3. WORKSHOP ORGANISATION

The 2.5-day workshop was organised in alternating plenary and break-out group (BOG) sessions, as described below. Plenary sessions consisted either of presentations, BOG feedback or discussion sessions amongst all delegates. Four BOGs met at three BOG sessions. The agenda for the meeting can be found in Annex 2. A background document with topics and questions was prepared by the organisers for use in BOGs (this can be found in Annex 3).

### *PLENARY SESSIONS*

The initial plenary session on the morning of day 1 included a welcome address by the workshop host KemI followed by presentations from the OECD Secretariat on the work of the OECD, the Chair of the OECD Task Force on Biocides (TFB) on the group's work, and the Chair of the OECD BioPesticides Steering Group (BPSG) on that group's work and how this workshop came about. The BPSG Chair was also the Chair of this workshop, and so gave an introduction to the aims of the workshop and its logistics. At the end of the first day there was a presentation by KemI.

The next plenary sessions were comprised of the following presentations:

- seven regulatory authorities in EU and non-EU countries shared their experiences and challenges in the assessment and approval of microbial pesticides.
- Three related presentations followed, covering: experiences from the European Food Safety Authority (EFSA), a comparison with the risk assessment of chemical pesticides, and feedback received on an OECD BPSG survey of test guidelines and data requirements as they relate to microbial pesticides.

- Five presentations of experiences in testing and registering microbial pesticides were given by industry representatives and consultants.
- Five presentations related to research on microbial pesticides, their risk assessment and test methods for metabolites.

There was a short period for questions and answers after each presentation.

Abstracts for all presentations can be found in Annex 5 and presentations' slides in Annex 6 (separate document), and section 4 of this report summarises some of the recurring issues that the talks highlighted as they relate to the background document (Annex 3).

At the end of the second day Chairs for each of the four BOGs gave their initial feedback orally in plenary, with a short period for questions and answers after each report. Then, at the beginning of the final morning of the workshop, the four BOG Chairs gave longer presentations on the discussion, conclusions and recommendations from their groups. Again, there was a short period for questions and answers with the audience after each presentation.

Finally, there was a two-hour plenary discussion which aimed to agree a written outline of the overall workshop conclusions and recommendations which had been developed from the findings of the four BOGs. The session was concluded by a short presentation on next steps and closing remarks by the workshop Chair and host.

***BREAK-OUT GROUP (BOG) SESSIONS***

During three break-out group (BOG) sessions that lasted for about six and a half hours in total, participants met in four BOGs of about 20 people each. Two BOGs were tasked with addressing the topics and questions given in the background document (see Annex 3) from an environmental perspective, whereas the other two BOGs were to address the topics and questions from a human health perspective. The membership of each BOG was tailored such that as far as possible any environment or human health specialists were assigned to the appropriate group, and so that each BOG had a mix of participants from regulatory authorities, industry and academia.

Each BOG produced a set of slides which their Chair presented in plenary on the last day of the workshop (see above), and from these slides and their notes of their sessions developed a report of their BOG discussions as follow up work to the workshop (please see Annex 4 for these BOG reports). The BOG reports formed the basis for the conclusions and recommendations described in section 5 of this report.

## 4. WORKSHOP ISSUES

The background document (Annex 3) was prepared before the workshop to aid discussions in the BOGs. It lists topics and, within each topic, questions which were felt to be the main technical, scientific and regulatory issues that should be addressed at the workshop.

The topics covered in the background document are as follows:

- Identification and biological properties, including
    - Identity
    - Phenotype/genotype and read across
    - Growth temperature
    - Infectivity

    - Mode of action
- Potential production of secondary metabolites
- Methods for counting of viable/non-viable cells and other test methods, including validation
- (Level of) efficacy and formulation, including label claims
- Production and quality assurance, including issues around equivalence and contaminants
- Residue requirements
- Effects on bees/pollinators and bee brood
- Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments
- Factors determining the persistence (or competitiveness) of microorganisms in the environment
- Risk assessment for organisms involved in biological methods for sewage treatment
- Risk and safety phrases
- Procedural/regulatory questions

The presentations (see separate Annex 6) made reference to many of these topics, covering some in more detail but also raising additional topics and questions that fed into the BOG discussions. These topics are dealt with in the individual sections in chapter 5.

## 5. WORKSHOP CONCLUSIONS AND RECOMMENDATIONS: "Biology is the difference"

This section of the report summarises the conclusions and recommendations that came out of the break-out group discussions and concluding plenary session of the workshop. The background document on discussion topics including questions for the break-out groups can be found in Annex 3. Where applicable, cross-references to the background document are made in the text below. Further detail on break-out group discussions can be found in the break-out group reports (see Annex 4).

The workshop first highlighted that "*Biology is the difference*" and developed a general introduction to its detailed Conclusions and Recommendations, as follows:

*Pesticides, including biocides, are used to control harmful organisms. Chemicals are the most commonly used pesticides; however the use of microorganisms as pesticides is increasing. In most jurisdictions, these microorganisms are regulated with the same regulations and in a similar way to conventional chemical pesticides. Microorganisms differ from chemicals especially because they are living organisms with biological properties.*

*The basis for the risk assessment of chemicals is knowledge of the intrinsic properties and knowledge of the exposure to humans and to the environment. The same is valid for microorganisms.*

*The difference between chemicals and microorganisms is biology, including the property to proliferate. As living organisms microorganisms respond to the environment in different ways, one aspect being the production of metabolites. Compared to chemicals it is likely to be more difficult to list all possible intrinsic properties for microorganisms as they are more complex.*
*The regulations for chemicals have been further improved with guidance documents and criteria. This is also necessary for microorganisms. A lot has already been done but there is still need for further improvement. Especially there is a need to develop further guidance in detail and decision criteria that concern the fact that microorganisms are living organisms that can die, survive or proliferate. There is also a need to develop different exposure scenarios. The dissemination of microorganisms may be performed with different techniques which give varying exposure to man and environment. With negligible exposure perhaps less information on intrinsic properties is needed.*

*It is recommended to take note of the following:*
- *As chemicals have been assessed for much longer and for many more active substances – take note of valuable experiences*
- *Improve the interpretation of data requirements with detailed guidance for the assessment of the biological aspects*
- *Take special consideration to the fact that microorganisms are living organisms and improve the related exposure assessments*

Specific conclusions and recommendations, presented below in text boxes with explanations following each box, are grouped so that information items follow an order commonly used in plant protection product and biocide registration/authorisation dossiers and assessment reports: Identification, including quality assurance & contaminants; potential production of secondary metabolites; technical equivalence; growth temperature; mode(s) of action; genetic transfer; analytical methods; efficacy testing; sensitization; exposure; residues requirements; (environmental) persistence; effects on bees/pollinators; natural exposure versus plant protection product application; sewage treatment; earthworms; labelling; test methods; justification for information/ rationale ("waivers"); procedural/regulatory questions.

***1. Identification, including Quality Assurance & Contaminants***

**(see also Annex 3*; Identification and biological properties including mode of action*)**

**RECOMMENDATIONS - Identification**

- Prepare issue papers on particular biological properties (e.g. growth temperature) which can have an influence on the risk assessment in a particular area.
- Continue to develop specific issue papers for individual taxonomical groups.
- Read across between closely related sub-strains should be possible if phenotype is similar – but caution / a case-by-case approach must be exercised (likely to be possible if the only difference is because of a taxonomic name change.)
- By using a marker approach, identification at strain level can be done as well as fate quantification. A marker as an identifier ensures quantifiable fate when considered necessary.
- Limited genetic identification, not full genome sequencing, is considered sufficient at species/strain level. However, this may evolve in the future.
- Regarding methods for identity of the strain, not the "best available technology" should be used but rather "the most appropriate justified" technology.

Further ideas from the workshop included: that a characteristic sequence or a few characteristic sequences for a microbial species or strain should be sufficient (e.g. to prove/disprove relationship of a microorganism to a known pathogen); that information on biological properties can be used more (for identifying critical issues, targeting data generation necessary for environmental (and human health) risk assessment and to facilitate evaluation.

It was noted that the lack of a (validated) method for microorganism identification at strain level was an issue, although this may become more important when there is an outdoor large scale application rather than a local application (with low exposure). However, it was also stated that identification should be done at strain level where possible, with the example of some strain collections having established methods for identification.

The idea of using a marker approach was suggested. In theory this would enable identification at strain level to be done as well as fate quantification, and should be possible for fungi and bacteria (it has been done for *Trichoderma* spp. at strain level). Traceability is considered to be more the challenge in *in vivo* and exposure studies. In addition with this approach, if the microorganism's name changes, one can still be sure that studies were performed with that strain. Further, loss of the marker by mutation is very unlikely, and the use of markers may benefit monitoring of drinking water (*Bacillus thuringiensis* and *Bacillus cereus*; see the test methods section). With a marker the same strains in different culture collections can be identified. However, there was less discussion on the types of marker that could be used (although the SCAR technique was mentioned), and the practicality of using this approach for commercial products.

Incorporating the production method as an identifier (if confidential business information (CBI) rules allow) may also aid in identification and enables changes in manufacturing site (if authorised) at a later stage using the same production method with respect to microorganism identification.

***2. Potential production of secondary metabolites***

**(see also Annex 3; *Potential production of secondary metabolites*)**

**RECOMMENDATIONS - Potential production of toxic secondary metabolites**

- Develop an OECD guidance document with a clear decision tree, which should address the protection goals of different regions (e.g. EU/US/etc…).
- Carry out further academic research and literature searching [leading to reviews, consensus documents].
- In terms of what to test, determine the toxicity of the TGAI (technical grade active ingredient) as default.

The workshop thought a guidance document on microorganisms' potential to produce secondary metabolites could be usefully produced. Questions and points that would need to be addressed in the document could include, for example:

- A review of literature on related species and strains, and determination of the toxicity of the technical grade active ingredient (TGAI):
    - If negative, no further information needed
    - If positive, evaluate exposure and if still a risk, further information required (further experimental data are only recommended if this initial information indicates a risk to humans, non-target organisms, or the environment.)
- Microorganisms can potentially produce a wide array of secondary metabolites under different conditions. What is the level of evidence that is required to show that no secondary metabolites of concern are formed? Which metabolites should be considered for risk assessment?
- A consideration of microorganisms' biology as it relates to secondary metabolite production.
- Does the product contain metabolites or are metabolites formed after application at levels that are biologically significant?
- Degradation in the environment - consider stability of the metabolite, and how this affects potential effects.
- Potential for effects of secondary metabolites in birds and mammals

### *3. Technical equivalence*

**(see also Annex 3; *Equivalence*)**

**RECOMMENDATIONS – Technical equivalence**

- Prepare guidance on technical equivalence (can be covered by EU technical guidance on equivalence[3] which will be sent out for comments in the near future).

- Equivalence: Minimum detection level that can be reached with a certain method to be mentioned (advantage of validation). No general arbitrary rules should be stated. The `most appropriate justified method` is a better wording than "best available technique".
- Method is more important than manufacturing place. Method could be relevant to efficacy and non-target organisms. Flexibility of manufacturing place is key for industry to meet increasing demand.

The main points coming out of the discussion were that a change of production method can change the properties of the microorganism (for example the presence of spores determines attractiveness to insects), that the production method is more important than manufacturing place, that the production method may also be relevant for efficacy, and that flexibility of manufacturing place is key for industry to meet (increasing) demand for a product. It was also noted that changes in the manufacturing process may lead to differing registration procedures, and this needs to be clarified.

It may be that equivalence can be covered by an EU draft equivalence Guidance document (which will be sent out for comments later in 2013), but that this (draft) Guidance document is applicable for production changes for the same strain only. The level of equivalence may differ between methods used; it is method specific and depends on the biology.

### *4. Growth temperature*

**(see also Annex 3; *Growth temperature*)**

**RECOMMENDATIONS – growth temperature**

- Growth temperature cannot be an absolute parameter for not conducting infectivity studies and can only be used for human and warm blooded vertebrates. Justification needed when used.
- Growth temperature can be used to bridge (infectivity) data from one strain with data to another strain with limited data (read across approach) in combination with other information (e.g.supported by phenotype similarity).
- A threshold should be fixed for human temperature. Literature review, and in addition a study on microorganism growth limit, should result in submission of a limited toxicological package (one infectivity study or no study at all).

[3] Draft template for the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 – Microorganisms

The workshop discussed the use of growth temperature as an exclusion criterion for further infectivity testing. It was thought there was scope for this to be used under certain circumstances, but that criteria for its use would need to be set and other factors would need to be taken into account. For example:

- Growth means multiplying: however, if organisms do not grow at a certain temperature (so do not multiply) theoretically they could still remain hazardous as they still can be viable and can produce toxins.
- Some parts of the body of an animal can have lower temperature, should this be taken into account?
- During torpor or hibernation, birds and mammals may have lower body temperature.

It also depends on the organisms, as some are very opportunistic.

So overall it was felt that growth temperature cannot be an absolute parameter but can be used for human and warm blooded vertebrates, but justification would always be needed when used.

***5. Mode(s) of action***

**(see also Annex 3; *Mode of action*)**

**RECOMMENDATIONS – mode(s) of action**

- Where possible a good description of modes of action would help design relevant risk assessment.
- Novel mechanisms of biopesticide action may require consideration of new or amended guidelines and information requirements.

The workshop clarified that the mode of action is one aspect that influences risk assessment. For example, with good knowledge of the mode of action the risk assessment might be designed in accordance with this and thereby be more focused. In case the mode of action is a trigger to production of secondary metabolites (see section 2, Potential production of secondary metabolites, above) this has to be taken into account in the risk assessment.

Knowledge of modes of action is necessary to differentiate e.g. from plant strengtheners. Often when there are several modes of action, major modes of action should be described.

Mode of action can also be used for resistance management as a combination of several modes of action reduce the risk of resistance.

***6. Genetic transfer***

**RECOMMENDATIONS – Genetic Transfer**

- Guidance would be needed on issues about genetic transfer.
- Consideration should be given to exposure scenarios.

Genetic transfer is a natural phenomenon. Its frequency can be higher depending on the genotype. The issue polarised the groups to a large extent, with some delegates believing this phenomenon to be of

paramount importance and others doubting its relevance for microbial products.[4] Where/if there is reason for concern, all available information on the potential for transfer of genetic material to other species (primary concern usually plasmids between bacteria species) should be provided to identify level of risk.

If Guidance is to be developed, it could address genetic transfer especially for bacteria regarding antibiotic resistance as noted in the EU Regulation (EU) No 546/2011 (EU uniform principles): "The possibility for transfer of genes that code for resistance to antimicrobial agents must be evaluated."

### *7. Analytical methods*

**(see also Annex 3; *7. Analytical* methods)**

**RECOMMENDATIONS – Analytical methods**

- For drinking water quality: Information on lack of interference (e.g. that might result in false negative or positive results) of microorganism on methods of analysis for pathogens in drinking water should be routinely provided.
- Specific microbials OECD Guidance document for validation of analytical methods is needed. Validation of analytical methods –clarification on the data requirement would be needed
- Contaminants: Use of approved analytical methods (e.g. for feed/food).

For the control of quality of drinking water, methods require pathogenic bacteria to be identified and confirmed as absent. The microorganism should not interfere with these methods.

It was thought that methods with microbials can be validated (possible for qualitative identification-quantitative validation is more difficult and more variable than for chemicals). Although the (chemical) Guidance Document for these analytical methods[5] is not directly applicable, some of the principles can also be used for microbials. Validation should include the standard inter- and intra-laboratory testing (i.e. different labs applying the same protocol having the same result, and multiple replication of the protocol in the same lab giving the same result, within the confines of the applied and appropriate analytical method). Identification depends on the comparison of specific genomic sequences to type strains (see identification section).

As far as contaminants were concerned, these were branded a problem of the production method. Testing of contaminants should be on the end product, using standardised methods (such as ISO) or other methods if detailed and/or validated.

[4] One view put forward was that: Genetic transfer between biocontrol strains and indigenous strains is only relevant if

1. the biocontrol strain harbours a plasmid containing gene encoding resistance to antibiotics used in human or veterinary medicine and;
2. if human or animal pathogenic bacteria are exposed to this biocontrol strain under conditions where plasmid transfer is possible at all (at least metabolic activity for these organisms)

If the biocontrol strain is not resistant to antibiotics/ antimycotics commonly used in human or veterinary medicine, genetic (in)stability does not affect the risk assessment.

[5] Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3030/99 rev.4; 11/07/00)

***8. Efficacy testing***

**(see also Annex 3; *Efficacy and label claim*)**

**RECOMMENDATIONS – Efficacy testing**

- Review OECD guidance on efficacy (biocide area). Is it useful for microbials?
- Label claims should be justified by efficacy evaluations [cf. OECD Working Document on the Evaluation of Microbials for Pest Control (Series on Pesticides No. 43, 2008)].

Testing depends on mode of action and the defined level of control.

Guidelines for chemicals are not entirely appropriate for microbials. It should be indicated how lower levels of efficacy or longer durations for efficacy than for chemical products can be justified, and how degradation in a formulated product can be measured/taken into account. Specific conditions of use necessary to ensure the required level of efficacy, e.g. temperature, usually longer contact times, specific time frame of treatment corresponding to the developmental stages of the pest, have to be taken into account during testing and consequently should be specified on the label or in the leaflet of the product.

There is an EPPO guideline specific to microbial pesticides (Principles of efficacy evaluation for microbial plant protection products- EPPO PP1/276) – this could be adapted for biocides.

***9. Sensitization***

**(see also Annex 3; *Risk and safety phrases*)**

**RECOMMENDATIONS - Sensitisation**

- Study with active substance not necessary, specific labelling applies.
- Study with end product might be necessary depending on chemical composition.

Although there was generally consensus on no need to test the active substance for sensitisation, a test on the product might be needed since the CLP regulation applies to product classification even if the products contain microbials, as the co-formulants may be sensitising.

Because of the lack of methods for respiratory sensitisation, this potential cannot be excluded so the label phrase would still be applied: “Microorganisms may have the potential to provoke sensitising reactions”.

***10. Exposure***

**(see also Annex 3; *Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments*)**

**RECOMMENDATION – exposure assessment**

- Develop methodology/models for an exposure assessment for operator, bystander, worker and resident that are specific for application methods for microbials differing from chemical techniques.

It was mentioned that without reference values for local and systemic effects on human health the exposure assessment is qualitative/semi-quantitative and relies mainly on options for risk reduction (Personal protective equipment, re-entry intervals).
In addition, for sensitive individuals, i.e. young, old, pregnant and immune-compromised persons (YOPI):

- There is a lack of information in this area about the potential for effects following exposure.

- The EU Directive 2000/54/EC on "the protection of workers from risks related to exposure to biological agents at work" may apply.

For environmental exposure assessment there may be the need for new metrics (e.g. "expected environmental density"; refer to the presentation of Marco Nuti in Annex VI, part I, pp 36 - 44) instead of mass per unit volume or mass-based predicted environmental concentrations, as is used for chemicals.

***11. Residues requirements***

**(see also Annex 3; *Residue requirements*)**

**RECOMMENDATION – Residue requirements**

- As default, no MRL for microbials is to be fixed. If it is shown that a toxic metabolite is produced/present in the product as applied, additional information and/or studies may be needed.

Residue requirements concern two aspects: (1) the microorganism itself and (2) non-viable residues (the latter are not relevant if no toxic metabolite is produced). For consumers, non-viable residues are only relevant if metabolites are produced in the field in contact with the crop/pest and if they have toxic properties. Quantities and potential for degradation of toxic metabolites would need to be taken into account.

It was mentioned that no models for viable residues after repeated use are available.

As for microorganisms usually no ADI and/or ARfD will be set; the consumer risk assessment will be a qualitative risk assessment.

Usually, routine analytical methods for enforcement or monitoring purposes do not distinguish between the strain used in the product and naturally-occurring strains.

***12. Persistence***

**(see also Annex 3; *Discussion/inventory of factors determining the persistence of microorganisms in the environment*)**

**RECOMMENDATIONS - Persistence**

- Especially the requirements regarding persistence could be addressed by information instead of studies/data.
- Competitiveness (unwanted *versus* desirable) between microorganisms or the study on their 'population dynamics' may be the criterion for persistence in the environment.
- If a microorganism is shown to be persistent, consideration of this for non-target effects assessments should be considered. Information on biological properties should be used.
- Re-consider this decision making criterion (in the current text of EU Uniform Principles: the microbial level has to decrease to the background level within one year).
- Some other criteria (indigenous/non-indigenous) may need to be considered?

The use of a marker as identification would ensure quantifiable fate (see section 1, Identification). Rather than using the terminology *persistence*, the focus should be on unwanted and desirable competitiveness, e.g. *Phlebiopsis* spp. is highly competitive on the tree stump but this is desirable (see the presentation of Jan Stenlid). Taking this a step further, instead of *competitiveness*, the term *population dynamics* could be used. But again, regardless of the terminology used, guidance would be needed. The

real question should be: "Has the microbial an unintended impact on the function of a specific soil or other growing media with respect to its microbial community?"

It was noted that desired environmental fitness of a microbial product may in some circumstances increase the microorganism's potential for uncontrolled growth.

In terms of assessing mobility for microbials (i.e. in groundwater), it was thought lysimeter studies were suitable (but would normally not be required).

***13. Effects on bees/pollinators***

**(see also Annex 3; *Effects on bees/pollinators and bee brood*)**

**RECOMMENDATIONS – Effects on bees/pollinators**

- OECD insect pollinators group (PEIP) working on this should not forget to include microbials in their work.
- Adaptation of test methods (e.g. duration) in line with the biology of the microbials needs to be considered.
- Non-conduct of bee tests may be justified by using information regarding the biology of the microorganism and of pollinators. Further guidance on conditions of use would be needed with input from the OECD PEIP group.
- Repellency for bees might be considered by regulators, provided it is documented/demonstrated.
- The Bumblebee as a vector for microbials: need for environmental assessment of these vectors is questioned.

In the case of baculoviruses, the workshop felt that overall the concern is low (effects of baculoviruses on bee larvae were never observed, even when baculoviruses were used to control *Galleria mellonella* larvae in bee hives, so the risk should be considered as negligible). Effects could not be excluded for bee brood if the virus attacks the larval stage of the host, but for baculoviruses this is unlikely as they are very host specific so there should be no concern. (see OECD consensus document (ENV/JM/MONO(2002)1), Consensus Document on Information used in the Assessment of Environmental Applications involving Baculoviruses. *Series on Harmonization of Regulatory Oversight in Biotechnology, No. 20*.)

Bees are affected by stress if they are tested for more than 48 hours; therefore, specific appropriate test design would be needed. It was felt that experiences at US EPA might be able to provide some pointers for test design modifications. One possible difficulty in testing mentioned was that nurse bees eject larvae when they detect microbes before the microbe can harm directly.

The issue of justifying the non-conduct of a bee test was discussed: in many cases, current regulatory practice accepts proof of absence of exposure as a justification for not conducting a particular (eco)toxicity study. This proof of absence needs to include not only the immediate and direct exposure (overspray or similar) but also other, more indirect routes of exposure (for example residues on treated plant surfaces). N.B. Such justifications (of no exposure) are already used in the case of drenching, incorporation in soil,

tree injection, stump brushing. For microbial plant protection products more information on application techniques – also in relation to the specific biology of the bee colony - would be needed; and further guidance would be needed with input from the OECD PEIP group.

Some participants thought it unlikely that an MPCA would be transported to the hive by the bees, because guard bees at the hive will kill infected bees (and infected bees often would not return to the hive). However, it is not clear if guard bees notice that spores, for example, are attached to the returning bees; it is likely that the duration of exposure is too short for the spores to penetrate the returning bee's cuticle, meaning that the returning bee is not yet itself infected.

Some participants felt that repellence should be accepted by regulators; e.g. bees did not eat in feeding studies where the microbial product was mixed with sucrose solution (other participants however thought these conditions may not reflect realistic conditions). This might be considered on the label: "Repellent to bees, may interfere with pollination".

Finally, bumblebees as a microbial vector are a contained unit with a limited life time and as such they are not sustainable. It is unlikely that they would bring the microbial back to the hive (different exit/entry). Therefore the need for the environmental assessment of these vectors was questioned (N.B. this is not the case for honeybees or other pollinators).

***14. Natural Exposure versus Plant Protection Product application***

**(see also Annex 3; *Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments*)**

**RECOMMENDATIONS – Natural exposure versus PPP application**

- If there is an indication that the microbial becomes dominant in local population, information would be required to address this.
- Feedback on the work with the "OECD Guidance to the Environmental Safety Evaluation of Microbial Biocontrol Agents" (Series on Pesticides No.67, 2012) should be provided.

Natural occurrence of the microorganism at a low level is relevant, but only makes sense in relation with other aspects and can be a positive indicator of a lack of potential for harm.

The potential for infectivity/pathogenicity may be related to the applied dose rate. While a decline in the level of the microorganism is expected, the definition of "background level" in the criterion "time needed to reach background level" is problematic because: there may be no general background level; how can the background level be defined correctly (e.g. the geometric mean of all studies? – there are many factors influencing background level). Furthermore, what time scale to reach background occurrence level is acceptable? This may in part depend on the microorganism's potential for pathogenicity/infectivity; a longer time scale to reach background occurrence level may be acceptable if the microorganism has no adverse effect.

Knowledge whether the microbial is more competitive than naturally-occurring microorganisms (and consortia) in the soil is needed. This is not a data requirement, and the population dynamics would need to be studied (for example, with the use of a marker – see Identification section). This could be a huge

burden, but could be carried out during efficacy testing and open literature could be searched for relevant information. This said, other opinions stated that most microbial plant protection products will not out-compete relevant species/strains in the community, and after 3 months would become part of the local microbial community (and therefore become naturally occurring to all intents and purposes). A related question was whether exposure should be considered at genus, species, strain or isolate level.

***15. Sewage treatment***

**(see also Annex 3; *The risk assessment for organisms involved in biological methods for sewage treatment*)**

**RECOMMENDATIONS – Sewage Treatment**

- Sewage treatment has been removed from data requirements for biocides and may be removed('waived') for PPP as well.
- This issue is not a high priority (unlikely to cause problems for microbial PPPs.)

The issue of microbial products reaching sewage treatment plants, and so having an adverse effect on the microbial communities responsible for carrying out the biological function of the treatment plant, might be an issue for products applied directly to water (a permit would need to be obtained from the waste water company). So this is likely to be only an issue for biocides, and not for PPP, and studies on potential effects might be needed if biocides are applied directly to sewage treatment. It should be noted that some microorganisms are already applied for waste water treatment in some plants, so these types are not likely to harm or replace the existing microbial communities.

***16. Earthworms***

**RECOMMENDATIONS - Earthworms**

- Earthworm study is not required unless the microbial is not naturally occurring in the soil.

It was questioned whether the duration of the acute earthworm toxicity study is long enough to address infectivity/pathogenicity, and if not, what length of time would be needed. Specific data on infectivity/pathogenicity on earthworms would be needed to get an idea on this; but would a lab study on artificial substrate be representative?

Other participants questioned the importance of this endpoint for microbial products, citing the earthworm's highly developed immune system as a reason for a lack of effects. On balance, this endpoint was not seen as a high priority for microbials.

***17. Labelling***

There was limited discussion on this topic: it was felt that labels should contain only the information that is relevant and that careful consideration is needed of what is actually relevant.

***18. Test Methods***

**RECOMMENDATIONS – General Test Methods**

- Test methods for chemicals should be evaluated and proposals for adaptation to microorganisms should be made.
- Information on alternative methods and their results should be taken into account.
- Effects studies provided for characterising environmental risk can be too short to conclude lack of pathogenicity or infectivity to non-target species. It should be ensured that information on the biology of the active organism strain / species is considered when designing tests, particularly test duration
- Design of long term daphnia toxicity study (OECD TG 211) needs to be amended for microbials in consultation with OECD and other biopesticides groups.
- Develop a priority list for development of new/amended TGs for microbials.

The OECD BioPesticide Steering Group questionnaire on issues and problems with Test Guidelines for microbials is very relevant here. This has so far resulted in a table with all OECD data requirements for microbials (MPCA and MPCP), and Member Countries and industry have indicated deficiencies/problems with test guidelines or any other problems (e.g. lack of test guideline, different interpretations of guideline or of data point). Eventually, the work should result in a priority list for the development of new/amended TGs.

Some of the problems encountered regarding test guideline availability for microbials and lack of guidance for the adaptation of test guidelines (designed for chemical testing) are, for human health:

- difficulties with testing for skin sensitization (with the supposition that the Guinea Pig Maximisation Test (GPMT) may be over-predictive for microorganisms and questions over the applicability of local lymph node assay (LLNA));
- the lack of tests for acute toxicity (including lack of pathogenicity testing), respiratory sensitization and genotoxicity (Ames test not suitable)

and for the environment:

- the appropriateness of non-target test species, lack of pathogenicity and infectivity testing for non-vertebrate organisms

Regarding ecotoxicity testing in particular problems with turbidity in the aquatic testing of microbials were identified (particularly in the OECD TG 211 on daphnia toxicity study, as this problem is more relevant for the chronic 21–day study rather than the 48h acute study, OECD TG 202). Turbidity may cause physical effects and not direct toxic effects, the former not usually being considered a “true” adverse effect in risk assessment (one suggestion at the workshop was to include a coarse filtering of fermentation residue/particulates from the test substance prior to toxicity testing). In addition, if the microbial starts degrading in water this might lead to an oxygen concentration drop and rise in ammonia concentration results, to which daphnia are sensitive. Setting test concentrations is therefore very important. The test

method might need some further theoretical analyses and considerations followed by an adaptation to microorganisms.

***19. Justification for information/ rationale ("Waivers")***

**RECOMMENDATIONS - Justification for information/ rationale ("Waivers")**

- Prepare a Guidance Document on Justification for information and argumentation describing recommended approach (e.g. first: a literature search, second: read across from other strain/species, third: ….)

This section links to others discussed above (for example identification, in terms of the use of read across, conducting an assessment of potential for effects on sewage treatment plants, earthworm toxicity, potential production of secondary metabolites and consequent testing (for example residue requirements), testing on bumblebees).

In general data requirements can be fulfilled by submitting studies, a reasoned approach and/or relevant literature. A reasoned approach/justification must be based on a scientific rationale and should include supporting documentation. As a more general point, participants felt that the term waiver should be avoided as it can be ambiguous and create confusion.

***20. Procedural/regulatory questions***

**(see also Annex 3; *Related procedural/regulatory questions*)**

**RECOMMENDATIONS – Procedural/regulatory questions**

- Establish OECD network / wide web of experts to help risk assessors:
  - Need for ground rules to guarantee objectivity
  - Stakeholder acceptance
  - Funding and planning needed
- Amendments of data requirements for microbials need to be considered AND guidance is needed. Preferably this should be an OECD consensus document.
- Risk/benefit analysis could be needed, where relevant for OECD member countries.
- Include EFSA in the pre-submission meetings (rather: records/minutes of pre-submission meetings to be part of the dossiers) to improve the registration process. EFSA involvement in developing GD should be encouraged.
- Prepare consensus document for specific plant strengtheners/biostimulants on one hand (not PPPs) and biopesticides (PPPs) on the other hand and reduce data requirements for these groups.
- Take into account risk assessment from other areas when possible (e.g. QPS - qualified presumption safety).

- An official 'communication document' – providing a list of test methods and guidance documents (as is done in the EU for chemicals[6]) how to address each item of the data requirements would be very helpful.
- Reconsider the regulatory approach to microbials at regional and international levels
- Current regulatory frameworks should not prevent the placing on the market of innovative products.
- "Regulatory Toolbox" on microbials? Collecting e.g.:

  - OECD Guidance documents

  - Involving all OECD countries + key partners + countries engaged in working relationships

  - Existing assessments

This "Regulatory Toolbox" should be available for cross-adoption on a global basis and for all stakeholders (assessors, regulators, NGOs, public, etc.)

The workshop felt there is an urgent need for more multidisciplinary microbiologists in the area of risk assessment. The question of how experts can be more involved was explored. It was recognised that in general EU Member States can only send one expert to meetings who does not necessarily have expertise on all aspects. Ideas put forward to improve regulatory/industry communication included:

- A Forum for the EU
- Face to face meetings to ensure informal knowledge transfer

Industry would like EFSA to be involved from the pre-submission state, maybe via teleconference. However, this seems unlikely to happen taking into account the high workload of EFSA, limited resources, and the fact that as EFSA performs the peer reviews there is the potential for conflicts. Involvement of EFSA in developing Guidance documents is more realistic.

It should be ensured that microbial agents are correctly categorized (and so assessed); there is an increasing "grey area" between pest control agents and plant strengtheners/stimulators (and the respective requirements depending on which regulations apply, which in turn depends on the label claim). In this respect the revision of the EU fertiliser regulation was mentioned in which biostimulants will be included with a limited data set of requirements. The fear was expressed that pesticide label claims will no longer be made for microbials. There has also been a proposal to put all biologicals together in terms of regulation, whatever intended use (although this is unlikely to go further in the EU).

Specificity and lack of invasiveness could be a criterion for a 'low risk organism', and might be linked to low stability or low persistence. These provisions could result in a reduced data package requirement.

[6] Commission Communications 2013/C 95/01 and 2013/C 95/02
http://eur-lex.europa.eu/JOHtml.do?uri=OJ:C:2013:095:SOM:EN:HTML

Prepare for the (near) future how products that are mixtures of microbials or involve microbial consortia should be assessed.

***Overall recommendations***

These recommendations should be read with reference to the specific sub-sections covered above.

**Relevant for all stakeholders:**

- Attempt to more closely align terminology used in different regions: “Harmonize and harmonise”
- More collaboration between industry and regulators
- Improve communication between regulators about product labels’ use and applicability (EU)
- Improve risk communication especially from regulators to the 'general public'
- Encourage steps towards global joint reviews

**OECD:**

- Ensure timely and consistent progress towards harmonisation (discussion at Working Group on Pesticides)
- Lead in harmonisation of guidance and (test) guidelines
- Establish OECD network / wide web of experts to help risk assessors

**Projects for OECD Biopesticides Steering Group (BPSG)**

- Guidance document addressing secondary metabolites
- Address relevance of particular biological properties e.g. growth temperature in risk assessment
- Address taxonomy, equivalence and read across
- Fill the data gaps (modelling, quality control, guidance on justification for not testing {'waivers'})
- Develop a priority list for development of new/amended TGs for microbials
- Continue the focus workshops to maintain open discussions: e.g. a workshop on spray drift and exposure modelling within the next two years
- Perform case studies/lessons learned from previous evaluations/assessments

**Projects for OECD Task Force on Biocides (TFB)**

- Achieve harmonised procedures and requirements (e.g. on efficacy)

# ANNEX 1: List of Participants

## OECD/KemI/EU WORKSHOP on Microbial Pesticides: 17-19 June 2013 Vår Gård, Saltsjöbaden, Sweden

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## ANNEX 2: Workshop Agenda

# OECD/KemI/EU WORKSHOP on Microbial Pesticides: Assessment and Management of Risks

*17-19 June 2013*

*Vår Gård, Saltsjöbaden, Sweden*

## WORKSHOP AGENDA

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

| Monday 17 June 2013 | | |
|---|---|---|
| 08.30-09.00 | | **Registration** |
| 09.00-09.05 | Plenary session | **Welcome and introductions (KemI)**<br>**Kersti Gustafsson,** Swedish Chemicals Agency |
| 09.05-09.25 | | **Setting the scene**<br>– Background to the OECD, Work of the OECD-BioPesticides Steering Group (BPSG) and Task Force on Biocides (TFB)<br>– Objectives of the workshop<br>**Sylvie Poret, OECD, Edmund Plattner, TFB Chair, and Jeroen Meeussen, BPSG Chair and workshop chair** |
| **Understanding of existing data requirements for microbial pesticides and biocides** | | |
| 09.25-10.25 | Short overviews and case studies experiences, EU and non-EU countries | • Overview on the existing EU regulatory system (biocides and pesticides): Human Health Data Requirements. **Vera Ritz, Germany**<br>• Overview on the existing EU regulatory system (biocides and pesticides) with focus on differences and similarities between environmental data requirements for microorganisms. **Christine Vergnet, France**<br>• Critical Issues about Microbials used as Biocides and Plant Protection Products. **Mario Nuti, Italy** |
| 10.25-10.45 | Coffee break | |
| 10.45-12.15 | Short overviews and case studies experiences, EU and non-EU - continued | • An overview of Australia's regulatory system for biological pest control products. **Jay Kottege, Australia**<br>• The actual regulatory frame for the use of microorganisms for pest control. **José Herrera, Mexico**<br>• Microbial Pesticides Regulation. **Chris Wozniak, US EPA**<br>• Regulation of Microbial Pesticides: The New Zealand Experience. **Warren Hughes, New Zealand** |
| 12.15-12.45 | | EFSA's role in the peer review process within the EU: experience so far. **Christopher Lythgo, EFSA** |
| 12.45-13.45 | Lunch | |
| 13.45-14.00 | | Basic strategies in risk assessment - comparison with chemicals. **Kersti Gustafsson, Sweden** |
| 14.00-14.20 | | Feedback from survey on test guidelines and data requirements. **Marloes Busschers, Netherlands** |

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| 14.20-16.00 | Industry/ consultants views | • Registration of Biopesticides: The challenges for the biocontrol industry. **Philip Kessler, Andermatt**<br>• Experience with data requirements. **Rüdiger Hauschild, GAB-consulting**<br>• Experiences with compilation of dossiers etc. where is there a need for more guidance and criteria, obstacles. **Mark Whittaker, Biosphere Biopesticide Consulting**<br>• Experiences with compilation of microbial dossiers: Relevance of current data requirements. **Roma Gwynn, Rationale - Biopesticide Strategists**<br>• The way forward – a vision from IBMA**, David Cary** |
| 16.00-16.15 | Coffee break | |
| **Possibilities for improvements in understanding data requirements, procedures and collaboration** | | |
| 16.15-17.45 | Break-out group session #1<br><br>(1h30) | topics relating to interpretation of data requirements:<br>• Identification and biological properties including mode of action<br>• Potential production of secondary metabolites<br>• Methods for counting of viable/non-viable cells and other test methods<br>• (Level of) efficacy and formulation<br>• Production and quality assurance<br>• Contaminants |
| 17.45-18.00 | Plenary session | **Presentation of KemI**<br>**By Ronny Fransson-Steen,** Director, Department for Authorisations and Guidance, Swedish Chemicals Agency |
| 19.00 | **Workshop Dinner** | Participants at the invitation of KemI<br>(informal continuation of BOG 1 discussions) |

| Tuesday 18 June 2013 | | |
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| **Understanding of existing data requirements for microbial pesticides and biocides – continued** | | |
| 8:30 – 10.10 | Plenary session<br><br>Science/academia view | • Scientific support, literature review and data collection and analysis for risk assessment of microbial organisms used as active substance in plant protection products: Lot1-Environmental Risk characterization. **Maria Arena, EFSA**<br>• The SLU Center for Biological Control. **Margareta Hökeberg, Swedish Agricultural University**<br>• Evaluation of non-viable residues and relevant metabolites. **Ingvar Sundh, Swedish Agricultural University**<br>• Experiences of biological control, risk assessment, fungi. **Jan Stenlid, Swedish Agricultural University**<br>• Test methods for metabolites. **Jacqueline Scheepmaker, Netherlands** |
| 10.10-10.30 | Coffee break | |
| **Possibilities for improvements in understanding data requirements, procedures and collaboration – continued** | | |
| 10.30-12.30 | BOG session #2<br><br>(2h) | Cont'd from previous day (see also session 3 for continued topics) |
| 12.30-13.30 | Lunch | |
| 13.30 – 17.00 (coffee break will be at 15.00) | BOG sessions #3<br><br>(3h30) | topics related to non-target organism effects, fate and regulation:<br>• Residue requirements<br>• Effects on bees/pollinators and bee brood (ENV only)<br>• Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments<br>• Discussion/inventory of factors determining the persistence of microorganisms in the environment (ENV only)<br>• The risk assessment for organisms involved in biological methods for sewage treatment (ENV only)<br>• Risk and safety phrases<br>• Related procedural/regulatory questions |
| 17.00-17.30 | Plenary session | Initial verbal feedback from BOGs |

| Wednesday 19 June 2013 | | |
|---|---|---|
| **Suggestions for improvements** | | |
| 8.30-10.00 | Plenary session<br><br>BOG suggestions | *BOG presentations in plenary*<br>*Questions and clarifications*<br>• Criteria<br>• Collaboration<br>• Procedures<br>• Other problems |
| 10.00-10.20 | | Coffee break |
| **Workshop conclusions and suggestions** | | |
| 10.20-12.15 | Plenary session | *Summary and Conclusions – written draft document*<br>Proposals for criteria and activities, and the way forward<br>Further guidance document and further OECD work BPSG & TFB |
| 12.15-12-30 | Closing remarks | The way forward, **Jeroen Meeussen, workshop chair** |

## ANNEX 3: Background Document on Discussion Topics

# OECD/KemI/EU WORKSHOP
# on Microbial Pesticides:
# Assessment and Management of Risks

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

# Background document
# on discussion topics
# including questions for the break-out groups
-
**A Thought Starter**

*Workshop participants are kindly invited to print and bring their own copy of documents as no additional copies will be available at the workshop*

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

## Background document on discussion topics with questions for the BOGs

**Table of Contents**

## INTRODUCTION

In this document information is compiled related to some technical/scientific issues that have arisen during the planning of the workshop. The document should be seen as a help and background to the discussions. In addition to references there are also six annexes; information on guidance, information on regulation, a separate xls-file with extracted information from published conclusions (mostly from EFSA, US EPA and Health Canada's Pest Management Regulatory Agency (PMRA)), a draft template on the assessment of the equivalence of technical materials of microbial substances, a draft EU scientific guidance package for active microorganisms and biocidal products, and a compilation of a questionnaire on test guidelines. In the xls-sheet with compiled information it is possible to filter in order to sort information. These compiled background documents are not exhaustive even though they cover quite a lot of information.

In this document:

PPP plant protection product or agricultural pesticides

BP biocide or non-agricultural pesticides

## IDENTIFICATION AND BIOLOGICAL PROPERTIES INCLUDING MODE OF ACTION

### Identity

Taxonomy is dealt with in two OECD documents[7,8], and also an EU document[9] . Specific modern molecular techniques that are commonly used for strain identification might need further detailed information like ITS/tef for fungi, 16sRNA for bacteria, and RFLP for virus.

### Phenotype/genotype and read across

As taxonomy changes a strain can change species which can have a lot of implications. This becomes somewhat peculiar when in a dossier species specific information is used or read across is done between two strains in a compiled dossier when in the end the two strains represent different species. With a pragmatic view due to developments in genotyping it is now possible to differentiate at the genotype level while the phenotype continues to be similar.[10]
Classical or traditional phenotypic tests constitute the basis for the formal description of taxa, from family down to subspecies level. Phenotyping can usually not be used for typing at strain level whereas some genotypic methods have the necessary discriminative power. Phenotypic characterization at every taxonomic level is still needed to delineate taxa and appreciate their phenotypic coherence and to evaluate their physiological and ecological functions.

### Growth temperature

The growth temperature has been considered to be a strain specific parameter, not extrapolatable between strains. Just knowing the growth temperature is not enough for waiving toxicological studies but could be used to read across infectivity data. Phenotype similarity together with growth temperature can be enough to extrapolate infectivity data from one strain to another.[11]

### Infectivity

Infectivity studies should be waived when all of the following requirements are met: no clinical reports; for the EU not listed in 2001/54 EC; humans and animals are already regularly exposed to the microorganism; and susceptibility against antibiotics. At an OECD workshop in Washington infectivity was discussed[12].

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[7] WORKING DOCUMENT ON THE EVALUATION OF MICROBIALS FOR PEST CONTROL
http://www.oecd.org/env/chemicalsafetyandbiosafety/agriculturalpesticidesandbiocides/41946259.pdf

[8] Series on Harmonisation of Regulatory Oversight in Biotechnology, No. 29 GUIDANCE DOCUMENT ON THE USE OF TAXONOMY IN RISK ASSESSMENT OF MICROORGANISMS: BACTERIA
http://www.oecd.org/dataoecd/17/42/46815778.pdf

[9] Guideline developed within the Standing Committee on the Food Chain and Animal Health on the taxonomic level of microorganisms to be included in Annex I to Directive 91/414/EEC
http://ec.europa.eu/food/plant/protection/resources/taxonomic_level_dir91414.pdf

[10] Discussed at EFSA PRAPeR M05 2012

[11] Discussed at EFSA PRAPeR M05 2012

[12] REPORT OF WORKSHOP ON THE REGULATION OF BIOPESTICIDES: REGISTRATION AND COMMUNICATION ISSUES
http://www.oecd.org/dataoecd/3/55/43056580.pdf

• Canada allows for waivers when infectivity is not expected, but not for all routes of exposure. At least one route is needed (usually pulmonary or injection, rather than oral) that covers infectivity (clearance) to make sure that it is not pathogenic or infective. It will consider an infectivity waiver for the other two routes depending on the results of the one toxicity/infectivity study.
• In the US, it depends on the biology of the microorganism and whether it has the potential to affect mammals. Some organisms are common and ubiquitous while others are newly discovered (novel). This depends on level of familiarity. Novel microbes may need all data requirements to be addressed. If a pattern of clearance can be established and there are no adverse effects (pathogenicity) during the study (intra-peritoneal/intra-venal or pulmonary route), then it is possible to obtain waivers for the clearance (infectivity) portion of the toxicity/pathogenicity studies for the other required actual studies. The EPA generally does not recommend the oral route as the only study to address clearance/infectivity because the acidity of the stomach can digest or inactivate the microbe.
• How is clearance defined? Is it absolute elimination from the body or establishment of a distinct pattern of clearance? The answer could have a profound impact on the duration of the study and number of animals involved. It is especially important for spore-formers which generally take longer than non-spore formers to clear the body.
• It may be sufficient to establish a pattern of clearance, not an absolute zero detection of the microorganism in tissues, fluids, organs, and observe decline in orders of magnitude over several time points to establish clearance pattern.
• The EU does not need to show 100% clearance to zero detected microorganisms. For spore formers slow clearance is expected, but one must ask the question whether this increases risk. Such a question does not necessarily automatically trigger higher tier toxicity testing or diminish the chances for waiving other test requirements.

**Mode of action**

With the mode of action it might be possible to focus risk assessment.

**Questions**

- What is necessary for identification at strain level from a regulatory point of view?
- Is the pragmatic view to consider the genotypes different at species/strain level while the phenotypes continue to be similar acceptable? Is this also relevant for read across?
- Can growth temperature be a parameter that can exclude pathogenicity for humans and animals?
- How is clearance defined? Is it absolute elimination from the body or establishment of a distinct pattern of clearance?
- How important is mode of action for designing risk assessment?

**POTENTIAL PRODUCTION OF SECONDARY METABOLITES**

EFSA conclusions on the peer review of the pesticide risk assessment shows there is a lack of guidelines to address the data requirements with regard to metabolites. Several of the EFSA conclusions raise concerns of issues that could not be finalised because the production of toxins/secondary metabolites of unknown toxicity cannot be excluded. Therefore the risk assessment cannot be finalised for humans (including operators, workers, bystanders and consumers) and the environment, including the assessment of potential groundwater contamination and residues in plants (Annex 3: "Some published conclusions on microorganisms").

Secondary metabolites are not directly involved in the growth, development or reproduction of a microorganism, unlike primary metabolites. Secondary metabolites are not vital to the cell's survival itself but are more so for that of the entire organism. Relatively few microbial types produce the majority of secondary metabolites. Secondary metabolites are produced when the cell is not operating under optimum conditions e.g. when primary nutrient source is depleted. Secondary metabolites are synthesized for a finite period by cells that are no longer undergoing balanced growth. Many microorganisms express secondary metabolites that influence competitive outcomes. The precise function of many of these compounds in the natural environment however, is unclear.

It is impossible to characterise all of the metabolites produced by a microbial control agent at the different stages of its life cycle, on all different substrates or plants. So only those present at a quantifiable level in the technical product, and known to be of concern, might be subject to risk assessment.

We must recall that the phytopathogenic microorganisms that we are aiming to control also produce secondary metabolites and toxins, which are tolerated at low levels in feed and food. We should not be more restrictive on a biological control agent than we are for the pathogenic microorganisms it controls.

Metabolites have been discussed in an OECD document[13], and also in EFSA opinions (see Annex 3) However, a strategy for control of metabolites would be useful.

Human and environmental exposure to secondary metabolites is expected to be to low concentrations, unless there are residues from the fermentation process in the product. A pragmatic approach could be that if there are no effects seen in the available toxicity tests nor any indication is available from public literature, then there are no relevant metabolites expected.

In the EU regulation on plant protection products it is indicated that metabolites need to be assessed if they are related to the mode of action or if they are present in significant amounts under practical conditions of use and not related to the mode of action of the microorganism. As laid down in the data requirements, quality assurance criteria for the production should be submitted.[14]

**Questions**

- Should only (secondary) metabolites present at a quantifiable level in the technical product, and known to be of concern, be subject to risk assessment?
- Could a pragmatic approach be used that if there are no effects seen in the available toxicity tests nor any indication is available from public literature, then there are no relevant metabolites expected?
- How could a strategy to characterize relevant metabolites be outlined?

[13] WORKING DOCUMENT ON THE EVALUATION OF MICROBIALS FOR PEST CONTROL http://www.oecd.org/env/chemicalsafetyandbiosafety/agriculturalpesticidesandbiocides/41946259.pdf

[14] Discussed at EFSA PRAPeR M02 2009

**METHODS FOR COUNTING OF VIABLE/NON VIABLE CELLS AND OTHER TEST METHODS**

**Methods**

Test methods might need further adaptation to microorganisms. There is a compilation of results from an OECD BPSG questionnaire on test methods and data requirements in Annex 6.

**Validation of methods**

For example there is a draft guidance document on validation of quantitative analytical methods for chemicals which has been circulated for comments[15] . The guidance is of course not directly applicable to quantitative methods for microorganisms, but the outline could nevertheless be useful when drafting a validation document for microorganisms.
There is also a whole series on GLP for chemicals which can be used as a basis also for microorganisms[16].

**Questions**

1. Is there a difference in validating methods for microorganisms compared to those for chemicals?
2. What kind of results need to be included in test reports, like all raw data etc.?
3. How should methods used for testing of microorganisms including quantitative methods be validated?

[15] Draft Guidance Document on single laboratory validation of quantitative analytical methods in support of pre- and post-registration data requirements for plant protection and biocidal products http://www.oecd.org/env/ehs/testing/GD%20on%20chemistry%20analytical%20method%20validation_30%20April%202013.pdf

[16] OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring http://www.oecd.org/env/ehs/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm

**(LEVEL OF) EFFICACY AND FORMULATION**

**Efficacy and label claim**

Amounts of microorganisms should be described in a relevant way, e.g. CFU and for toxins ITU, related to weight of product.
Regarding efficacy for microbial plant protection products (PPP) within the EU the principle has been agreed that even if the microbial product has a lower efficacy against the target pest than that of the reference product, its efficacy may still have value due to the following considerations:

- Use over a wider range of growth stages of the crop or the target pest;
- Greater compatibility with cultural practices or other plant protection measures;
- Lower potential of resistance development, or providing a useful alternative as part of the overall resistance management strategy for a particular target;
- Fewer undesirable effects on beneficial organisms, other crops, etc.;
- Acceptable for use in "organic" productions;
- Absence of residues.

EPPO has published a standard for efficacy testing with microorganisms[17]. Also reference is made to chapter 5 of the Working Document on the Evaluation of Microbials for Pest Control. OECD (2008), Series on Pesticides, No. 43[1].

**Questions**

- Can efficacy testing be outlined in a similar way as for chemical plant protection products?
- As there are no standard rules for efficacy testing of chemical biocidal products, how can efficacy testing be outlined for microbial biocidal products?
- Is it possible to develop standard rules for label claims related to efficacy?

[17] EPPO Bulletin (2012) 42 (3), 348–352. Principles of efficacy evaluation for microbial plant protection products. http://onlinelibrary.wiley.com/doi/10.1111/epp.2607/pdf

**PRODUCTION AND QUALITY ASSURANCE**

**Equivalence**

On the basis of the EU guidance document for the equivalence of technical materials of chemical substances[18] (explicitly indicating it does not apply to microorganisms) a specific template for microorganisms has been drafted (see Annex 4, available separately). The procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 Regulation (EC) No 1107/2009 is considered the same for chemicals as for microorganisms as regards a change of the manufacturing process and/or manufacturing location. However, the issue of a different source has to be handled in a slightly different way compared to chemicals.
In the guidance document for chemicals it is stated that as a general principle for the same active substance the level of hazard posed for health and environmental protection must be comparable for different sources of technical material. The document only addresses the hazard of technical materials. If the hazard is considered to be greater for the new source than the reference source, then an appropriate risk assessment should be conducted for the new source to determine whether plant protection products containing the new technical material will fulfil the safety requirements laid down in Article 4 of Regulation (EC) No 1107/2009.
Some points for discussion:
Is 'assessment of equivalence' an appropriate description for microorganisms or should it rather be 'comparability assessment'?
The evaluation should be intended to compare two sources of the same strain of a microorganism. In this case a determination of genetic identity does not make sense if the starter cultures for the new source are originating from the same stock culture as the original source, which needs to be the case because all production needs to originate from the same culture deposited in the culture collection. A comparison at genetic level is only necessary for two different strains, but these are (and should also in the future be) considered as different active substances. The aim of the equivalence check should be to ensure that the new technical product, originating from a new fermentation (with a different method or at a different site) complies with the evaluated and approved material for the following parameters:

- content of the active ingredient (determined in viable units e.g. CFU or by a biotest)
- content of relevant metabolites
- Content of microbial contaminants according to SANCO/12116/2012[15] (= OECD publication 65[16]).

The five batch analysis to check the above are more often conducted on the end-use product than the technical in the case of microbials.
EU practice is to approve microorganisms at strain level. The question has to be discussed if different isolates of a strain (i.e. new inoculums which do not originate from the collection strain / stock culture but from a production site or a product) can still be considered as the same strain. The current practice at US EPA is to consider each new isolate on its own merits for registration.
It might be useful to develop detailed guidance addressing identification and taxonomy before addressing technical equivalence.

- The methodology suitable for identification and for taxonomic classification depends on the group of microorganisms analysed. Furthermore, technology and criteria for similarity are evolving very fast.

[18] SANCO/10597/2003 rev. 10.1 *Guidance document on the assessment of equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009*

- Differences / similarities occurring in molecular genetic tests depend on the technology and methodology used. It should be noted that the impact of a change in the genetic material on the phenotype cannot be expressed by a percentage of differences in gene sequences.

Reference is made to chapter 1 of the Working Document on the Evaluation of Microbials for Pest Control. OECD (2008), Series on Pesticides, No. 43:

This general principle that for the same active substance the level of hazard posed for health and environmental protection must be comparable for different sources of technical material makes sense for chemicals but not necessarily for microbials. A slight change in the manufacturing controls for microbials could significantly change the safety or efficacy profile of the resulting batch. Quality control and contamination levels are more often conducted on the end-use product rather than the technical material in the case of microbials.
*"If in an equivalence check there is a high degree of similarity with the approved strain of the microorganism regarding identity by gene sequencing and in addition for the batch analyses there is a high degree of similarity regarding identity and contaminants[19] within the batches it is not necessary to perform a Tier II check."* However for microbials it is not sufficient to know that the strain of the microorganism is genetically similar, as the way that they are grown can significantly change the outcome for safety and efficacy.
Analytical methods:

- Validation of methods for identification of microorganisms is still a matter of debate. Methods presented for the approval of the microorganisms under Regulation (EC) No 1107/2009 should be accepted here. Interlaboratory validation or identification methods are in general not required.

- Methods for the determination of microbial contaminants should be those that are internationally recognized e.g. for food use.

- Metabolites of concern need to determined, not just by the fact that a gene may be present but whether it is turned on or not.
- Due to current technological limitations, almost all genotyping is partial. That is, only a small fraction of a genotype is determined. To determine strain characterization then, the amount of genome to be used should also be indicated. For microbes the whole genome may be possible but this should be indicated in the document.
- Genotyping can be done by selecting certain regions, but the question becomes how to select the regions which may be important for pathogenicity, and even then how do you know if the correct operons are present. Gene expression is the most fundamental level at which the genotype gives rise to the phenotype (any observable characteristic of a gene). Within a genome, only a fraction of these genes may be turned on – or "expressed" – and it is this subset of genes that may confer the unique properties of each strain. This biological mechanism acts as both the switch to control which genes are expressed within a cell, as well as a "volume control" that increases or decreases the level of expression of particular genes. In general genotyping is a good start, but further definition needs to be used and especially a pathogenic consideration needs to be made.

[19] SANCO/12116/2012 rev. 0 *Working document on microbial contaminants limits for microbial pest control products*

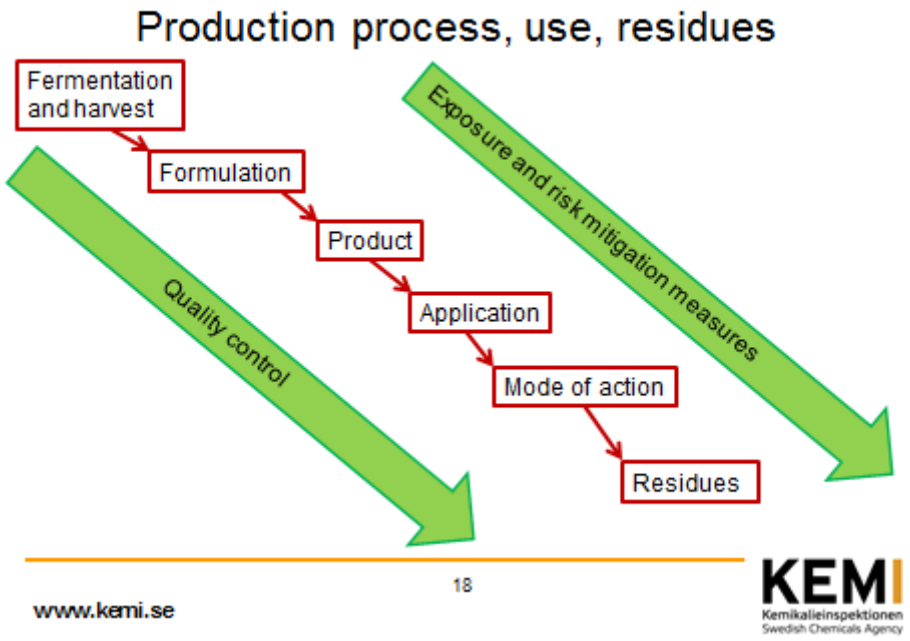
**Questions**

- Different isolation sites give different strains, however same strain deposited at different culture collections should be seen as the same strain. What can be a source for a microorganism?
- Is it possible that a specific strain of a microorganism will have the same properties with a change of the manufacturing process and/or manufacturing location?
- Is it in general possible to validate methods used with microorganisms?
- With regard to the EU Template for the Assessment of the Equivalence of Microorganisms (Annex 4) there are two issues:
  - Equivalence criteria: The identity of the sources should be established by 99 % similarity at genotyping! What is exactly "99 % of genotyping"?

    We need to show strain similarity. In other words strain similarity has to be demonstrated by a typing method or a polyphasic approach of typing methods with a power of discrimination enabling it to clearly differentiate unrelated strains and at the same time to demonstrate the relationship of the organism in question.
  - Statement of subject matter and purpose for which the report was prepared: Change in the manufacturing process, and/or manufacturing location. In some cases it may not be necessary to require an equivalence report, but rather only a declaration by the company? E.g. if only the fermentation plant location is changing and the company will continue to supply the microbial inoculums as sub-samples of the original strain and the suppliers of the starting materials for the fermentation are being maintained the same. The formulation plant remains the same, and most release parameters, inclusive of microbial contamination, are conducted on the final formulated product.

**Contaminants**

Primarily the culture should be clean so that it is not necessary to look for multiple contaminants; this should be part of the quality control process. A strategy for this would be useful.
The proposed OECD microbial contamination screening requirements (Table 1.1 and Table 1.2, in the OECD paper on contaminants cited below), which employ standard methods from the food industry, provide practical microbiological specifications for microbial pest control products, and will provide meaningful data to assess the overall acceptability of microbial pest control products without posing an unreasonable burden on applicants/notifiers. Authorities can be reasonably assured that products which meet these microbiological specifications do not contain microbial contaminants which will pose a risk to human health or to the environment.[20]
Alternatively a good quality control program might be enough. Combined with controls along the whole production line and information on application and use of the product, it would be possible to design risk mitigation measures.




**Questions**

- Is it possible to find a quality control scheme and thereby minimise the testing for pathogenic contaminants?
- Can a good quality control scheme result in relevant risk mitigation measures?
- Is it enough to determine contaminants for the technical active microorganisms? Are there reasons also to test the end product?

[20] OECD ISSUE PAPER ON MICROBIAL CONTAMINANT LIMITS FOR MICROBIAL PEST CONTROL PRODUCTS Series on Pesticides No. 65
http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/JM/MONO(2011)43&doclanguage=en

**RESIDUE REQUIREMENTS**

Different demands on residues have been identified like:

- Strain specific residue trials to address residues at harvest and at consumption
- Residues on food are expected to be minimal because of the typical method used to apply the microbial fungicide to soils. The results of the oral toxicity testing demonstrated that no toxicity or pathogenicity in treated animals occurred.
- Maximum residue levels

Regulation (EC) No 396/2005 of the European Parliament and of the Council on Maximum Residue Levels for pesticides foresees the establishment of Annex IV, containing a list of active substances for which maximum residue levels (MRLs) are not required. In practice, today no ADI or ARfD are defined for microorganisms approved under regulation (EC) 1107/2009. In the toxicological part of the DAR it is usually mentioned that:
"In the absence of any significant evidence for toxicity, pathogenicity or infectivity of "*the microorganism*" in animal studies it was neither possible nor necessary to establish an ADI or an ARfD."

In practice the main condition to approve a microorganism, is that this organism is sufficiently well defined to established that it has no toxicity, or infectivity to humans, and that it does not produce/contain any toxin that could adversely affect consumer health.
So, when proposed to be approved under Regulation (EC) 1107/2009, a microorganism is also an implicit candidate for inclusion in Annex IV of Regulation (EC) 396/2005.

**Questions**

- What kinds of residues are expected?
- How can residue trials be performed?
- How can maximum residue levels be defined?

**EFFECTS ON BEES/POLLINATORS AND BEE BROOD**

Given the current political impact of the risk of pesticides to bees this issue should also be looked at for microbial pesticides. Indeed, products are available on the market that use bees as carriers for the microbial pesticide, and so direct exposure may occur as well as indirect exposure.

**Questions**

- Can a possible risk to bees and bee brood be excluded for baculoviruses given the fact that they are not able to infect any life stage of bees?

**NATURAL EXPOSURE IN RELATION TO EXPOSURE FROM THE USE AS A PPP (OR BIOCIDE) IN DIFFERENT COMPARTMENTS**

**Application techniques related to exposure and fate**

From the understanding of application techniques/ how biopesticides are disseminated it should be possible to make exposure scenarios. This should be of importance for the exposure to operators /workers/bystanders and to the environment, e.g:

- Bti for mosquito control and dissemination by air
- Btk for control of cabbage lepidopterans and wax moth
- Trichoderma for control of fungi on golf greens, strawberries, wound painting on ornamentals
- Pythium for wall painting after flooding
- Phlebiopsis spraying of freshly cut stumps of pine and spruce
- Metarhizium tree injection
- Pseudomonas seed treatment
- Bumble bees as vectors

It might be that bacteria and fungi are enough to consider as baculoviruses are so specific to be almost considered low risk. Later from the exposure scenarios and calculations it should be possible to find possibilities for risk management, and also identify negligible risk due to lack of exposure.

**Questions**

- How relevant for risk assessment, both for man and environment, is the natural occurrence at low levels related to the use of the same microorganism at high levels for the control of a harmful organism?
- Would development of exposure scenarios be beneficial for performing risk assessment?
- Can baculoviruses in all situations be considered as to be of low risk?
- What is your opinion on exposure scenarios where the microbial pesticide is disseminated via vectors like pollinators?

**DISCUSSION/INVENTORY OF FACTORS DETERMINING THE PERSISTENCE OF MICROORGANISMS IN THE ENVIRONMENT**

**Persistence**

In the OECD guidance document *on environmental safety evaluation of microbial biocontrol agents* [21] it is identified that there is no criterion for persistence of mBCAs. From this follows that the length of the period that the applied concentration is higher than the upper background concentration is to be discussed case-by-case. In general, the persistent mBCA may be present in an inactive state, probably in a patchy distribution confined to small pockets in the soil. The mBCA may be activated under very specific conditions.
In order to harmonise risk assessment procedures among different regulatory agencies other options to improve the qualitative risk assessment of mBCAs, such as better insight into fate and behaviour of mBCAs, are necessary.

**Mobility**

There is a fear that metabolites and / or toxins could contaminate groundwater. By identification and / or quantification it might be possible to assess the risk as negligible. It might be necessary to assess the mobility of metabolites/toxins and even the microorganism to be able to do a risk assessment for groundwater.

**Questions**

- How to get better insight into fate and behavior of microbial control agents?
- How could a criterion for persistence in the environment be outlined?
- Is persistence the appropriate term to be used for mBCAs or should it rather be "competitiveness"?
- How to assess mobility for microorganisms, metabolites/toxins and the risk for contamination of groundwater?

[21] OECD GUIDANCE TO THE ENVIRONMENTAL SAFETY EVALUATION OF MICROBIAL BIOCONTROL AGENTS Series on Pesticides No. 67
http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)1&doclanguage=en

**THE RISK ASSESSMENT FOR ORGANISMS INVOLVED IN BIOLOGICAL METHODS FOR SEWAGE TREATMENT**

Problems with sewage treatment.

**Questions**

- Is it realistic that microbial pesticides could reach a sewage treatment plant in high enough concentrations such that the activated sludge would be affected?

**RISK AND SAFETY PHRASES**

While there is a lack of appropriate methods for the investigation of sensitization potential, there is a general agreement for the following phrase: “Microorganisms may have the potential to provoke sensitising reactions”.
In the EU regulation on data requirements for plant protection products [Reg. (EU) No 283/2013, part B on microorganisms, section 5 Human Health], it is required that, information provided must be sufficient to:

- specify risk and safety phrases (once introduced) for the protection of man, animals and the environment to be included on packaging (containers),

- specify the pictograms (once introduced), signal words, and relevant hazard and precautionary statements for the protection of the environment, to be mentioned on packaging containers)

Since there is no legislative action yet on the development of these phrases and pictograms, Member Countries in the EU (and other OECD countries) need guidance on the most appropriate tools that are available in order to communicate the risk associated with the use of microbials.

**Questions**

- Give examples on risks that need to be communicated?
- What issues could be relevant for safety phrases?

**RELATED PROCEDURAL/REGULATORY QUESTIONS**

In all jurisdictions we have to work within existing legislative frameworks and timelines. However it should be explored if a better and more efficient use can be made of the knowledge within the member countries.

**Questions**

- Is it considered necessary to amend the data requirements for microorganisms or should only further guidance to be developed related to the interpretation of data requirements?
- How can experts already be involved at an early stage of the process (e.g. during the drafting of the Assessment Report)?
- Would it be beneficial to already involve (in the EU) EFSA at an earlier stage of the process so that they are fully aware of discussions that have taken place?
- Would it be beneficial to create an OECD-wide web of experts?
- With the new EU-regulation on plant protection products official communications have been prepared for chemical substances and products in which for every data requirement the available testing method(s) and guidance documents are listed[22][23]. Are similar document necessary for microorganisms?

[22] Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF

[23] Commission communication in the framework of the implementation of Commission Regulation (EU) No 284/2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF

**Annex 1 of The Background Document. Information on guidance for microorganisms for use as BP. PPP, MPCA or as GMO**

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|---|---|---|---|
| 1. | Procedure | OECD | OECD Guidance for Country Data Review Reports on Microbial Pest Control Products and their Microbial Pest Control Agents (Monograph Guidance)<br>http://www.oecd.org/dataoecd/27/25/43464397.pdf (2013-05-28) |
| 2. | Procedure | OECD | OECD Guidance for Industry Data Submissions for Microbial Pest Control Products and their Microbial Pest Control Agents (Dossier Guidance)<br>http://www.oecd.org/dataoecd/22/40/43435253.pdf (2013-05-28) |
| 3. | Procedure | OECD | REPORT OF WORKSHOP ON THE REGULATION OF BIOPESTICIDES: REGISTRATION AND COMMUNICATION ISSUES<br>http://www.oecd.org/dataoecd/3/55/43056580.pdf (2013-05-28) |
| 4. | Procedure | CAN | Evaluation templates. Evaluation templates are used to review the scientific studies that are submitted to support applications to register pest control products. These templates capture specific data components and record the reviewer's conclusions and rationales that are based on each data set. Executive summaries from templates are used to create an overall science monograph (i.e., review document) on which the regulatory decision is based.<br>http://www.hc-sc.gc.ca/cps-spc/pest/registrant-titulaire/prod/templates-modeles-eng.php (2013-05-28) |
| 5. | Procedure | FAO | GUIDELINES FOR THE REGISTRATION OF BIOLOGICAL PEST CONTROL AGENTS.<br>http://www.fao.org/ag/AGP/AGPP/Pesticid/Code/Download/BIOPEST.pdf (2013-05-28) |
| 6. | Taxonomy<br>Genetic toxicity<br>Exposure<br>Metabolites<br>Efficacy | OECD | WORKING DOCUMENT ON THE EVALUATION OF MICROBIALS FOR PEST CONTROL<br>http://www.oecd.org/env/chemicalsafetyandbiosafety/agriculturalpesticidesandbiocides/41946259.pdf (2013-05-28) |
| 7. | Taxonomy | EU | Guideline developed within the Standing Committee on the Food Chain and Animal Health on the taxonomic level of microorganisms to be included in Annex I to Directive 91/414/EEC<br>http://ec.europa.eu/food/plant/protection/resources/taxonomic_level_dir91414.pdf (2013-05-28) |

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|---|---|---|---|
| 8. | Taxonomy | OECD | Series on Harmonisation of Regulatory Oversight in Biotechnology, No. 29 GUIDANCE DOCUMENT ON THE USE OF TAXONOMY IN RISK ASSESSMENT OF MICROORGANISMS: BACTERIA http://www.oecd.org/dataoecd/17/42/46815778.pdf (2013-05-28) |
| 9. | Identity | OECD | Report of the 1st OECD BioPesticides Steering Group Seminar on Identity and Characterisation of MicroOrganisms Series on Pesticides No. 53 http://www.oecd.org/dataoecd/6/60/46952150.pdf (2013-05-28) |
| 10. | Equivalence | EU | GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL MATERIALS OF SUBSTANCES REGULATED UNDER Regulation (EC) No 1107/2009 http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc23_en.pdf (2013-05-28) |
| 11. | Equivalence | OECD | REPORT OF THE 4TH OECD BIOPESTICIDES STEERING GROUP SEMINAR ON TRICHODERMA SPP. FOR USE IN PLANT PROTECTION PRODUCTS: SIMILARITIES AND DIFFERENCES, Series on Pesticides, No. 74 ENV/JM/MONO(2013)25<br>Available from http://oecd.org/env/ehs/pesticides-biocides/publicationsonbiopesticides.htm |
| 12. | Detection methods | OECD | Working Group on Harmonisation of Regulatory Oversight in Biotechnology No. 30 GUIDANCE DOCUMENT ON METHODS FOR DETECTION OF MICROORGANISMS INTRODUCED INTO THE ENVIRONMENT: BACTERIA http://www.oecd.org/dataoecd/36/12/46815788.pdf (2013-05-28) |
| 13. | Contaminants | OECD | OECD ISSUE PAPER ON MICROBIAL CONTAMINANT LIMITS FOR MICROBIAL PEST CONTROL PRODUCTS Series on Pesticides No. 65 http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/JM/MONO(2011)43&doclanguage=en (2013-05-28) |
| 14. | Endotoxins | NEG and DECOS | The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety<br>144. Endotoxins. Arbete och Hälsa nr 2011;45(4)<br>https://gupea.ub.gu.se/bitstream/2077/26596/2/gupea_2077_26596_2.pdf (2013-05-28) |
| 15. | Gene transfer | OECD | GUIDANCE DOCUMENT ON HORIZONTAL GENE TRANSFER BETWEEN BACTERIA http://www.oecd.org/dataoecd/36/44/46815958.pdf (2013-05-28) |
| 16. | Pathogenicity | OECD | GUIDANCE DOCUMENT ON THE USE OF INFORMATION ON PATHOGENICITY FACTORS IN ASSESSING THE POTENTIAL ADVERSE |

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|---|---|---|---|
| | | | HEALTH EFFECTS OF MICROORGANISMS: BACTERIA Series on Harmonisation of Regulatory Oversight in Biotechnology No. 52 http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2011)41&doclanguage=en (2013-05-28) |
| 17. | Risk assessment | KemI / EU COM | Proccedings "Microbiological Plant Protection Products - Workshop on the Scientific Basis for Risk Assessment" Stockholm, Sweden 26-28 October, 1998 http://www.kemi.se/Documents/Bekampningsmedel/Vaxtskyddsmedel/Vagledning/microbio_proc_99.pdf (2013-06-04) |
| 18. | ERA | OECD | OECD GUIDANCE TO THE ENVIRONMENTAL SAFETY EVALUATION OF MICROBIAL BIOCONTROL AGENTS Series on Pesticides No. 67 http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)1&doclanguage=en (2013-05-28) |
| 19. | ERA | OECD | REPORT OF THE SECOND OECD BIOPESTICIDES STEERING GROUP SEMINAR ON THE FATE IN THE ENVIRONMENT OF MICROBIAL CONTROL AGENTS AND THEIR EFFECTS ON NONTARGET ORGANISMS Series on Pesticides No. 64 http://www.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/JM/MONO(2011)42&doclanguage=en (2013-05-28) |
| 20. | ERA | EFSA | Scientific support, literature review and data collection and analysis for risk assessment on microbial organisms used as active substance in plant protection products –Lot 1 Environmental Risk characterisation, Shailendra Mudgal, Arianna De Toni, Clément Tostivint, Heikki Hokkanen, David Chandler, EFSA supporting publication 2013:EN-518<br>Available from http://www.efsa.europa.eu/en/supporting/pub/518e.htm |
| 21. | Test methods | CAN | Guidance Document for Testing the Pathogenicity and Toxicity of New Microbial Substances to Aquatic and Terrestrial Organisms http://www.ec.gc.ca/Publications/F9BF9993-4BAC-4215-BD3E-9B0962980915%5CGuidanceDocumentForTestingThePathogenicityAndToxicityOfNewMicrobialSubstancesToAquaticAndTerrestrialOrganisms.pdf (2013-05-28) |
| 22. | Test methods | USA | OCSPP Harmonized Test Guidelines. Series 885 - Microbial Pesticide Test Guidelines http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series885.htm (2013-05-28) |
| 23. | Efficacy | EPPO | Principles of efficacy evaluation for microbial plant protection products. Bulletin OEPP/EPPO Bulletin (2012) 42 (3), 348–352. http://onlinelibrary.wiley.com/doi/10.1111/epp.2607/pdf (2013-05-28) |
| 24. | Baculovirus | EU | Guidance Document on the assessment of new isolates of baculovirus species already included in Annex I of Council Directive 91/414/EEC http://ec.europa.eu/food/plant/protection/resources/guidance_document_baculovirus.pdf (2013-05-28) |

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|---|---|---|---|
| 25. | Baculovirus | OECD | Series on Harmonization of Regulatory Oversight in Biotechnology, No.20 CONSENSUS DOCUMENT ON INFORMATION USED IN THE ASSESSMENT OF ENVIRONMENTAL APPLICATIONS INVOLVING BACULOVIRUSES http://www.oecd.org/dataoecd/16/59/46815698.pdf (2013-05-28) |
| 26. | *Pseudomonas Acidithiobacillus Acinetobacter* | OECD | Consensus Documents for the Work on Harmonisation of Regulatory Oversight in Biotechnology. Consensus Documents on Microorganisms http://www.oecd.org/document/38/0,3746,en_2649_34385_46760166_1_1_1_1,00.html (2013-05-28) |

**Annex 2 of The Background Document. Information on regulation of microorganisms for use as BP. PPP, MPCA or as GMO**

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|---|---|---|---|
| 1. | PPP | EU | COUNCIL DIRECTIVE of 15 July 1991 concerning the placing on the market of plant protection products (91/414/EEC) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1991:230:0001:0032:EN:PDF (2013-05-28)<br><br>REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF (2013-05-28) |
| 2. | PPP | EU | COMMISSION DIRECTIVE 2001/36/EC of 16 May 2001 amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:164:0001:0038:EN:PDF (2013-05-28)<br><br>COMMISSION REGULATION (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:155:0001:0066:EN:PDF (2013-05-28)<br><br>Commission Regulation (EU) No 283/2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0001:0084:EN:PDF (2013-05-28) |

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| | | | Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF (2013-05-28)<br><br>COMMISSION REGULATION (EU) No 545/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for plant protection products http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:155:0067:0126:EN:PDF (2013-05-28)<br><br>Commission Regulation (EU) No 284/2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0085:0152:EN:PDF (2013-05-28)<br><br>Commission communication in the framework of the implementation of Commission Regulation (EU) No 284/2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF (2013-05-28) |
| 3. | PPP | EU | COUNCIL DIRECTIVE 2005/25/EC of 14 March 2005 amending Annex VI to Directive 91/414/EEC as regards plant protection products containing microorganisms http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:090:0001:0034:EN:PDF (2013-05-28)<br><br>COMMISSION REGULATION (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:155:0127:0175:EN:PDF (2013-05-28) |
| 4. | BP | EU | DIRECTIVE 98/8/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 February 1998 concerning the placing of biocidal products on the market |

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| | | | http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:123:0001:0063:EN:PDF (2013-05-28)<br><br>REGULATION (EU) No 528/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 May 2012 concerning the making available on the market and use of biocidal products<br>http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:FULL:EN:PDF (2013-05-28) |
| 5. | BP | EU | Technical Notes for Guidance on data requirements for microorganisms including viruses and fungi<br>http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/doc/TNsG/TNsG_DATA_REQUIREMENTS/Addendum-TNsG_Data_Requirements_microorganisms.pdf (2013-05-28) |
| 6. | GMO | EU | DIRECTIVE 2001/18/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC<br>http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:106:0001:0038:EN:PDF (2013-05-28) |
| 7. | MPCA | CA | Health Canada. Regulatory Directive DIR2001-02 Guidelines for the Registration of Microbial Pest Control Agents and Products.<br>http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir2001-02/index-eng.php (2013-05-28) |

The background document also included some more Annexes that are not reproduced in this report.

# ANNEX 4: Reports from the Break-Out Groups

**Human Health issues**

- **Report of Break-out Group HH 1** (Chair: Warren Hughes, New Zealand)
- **Report of Break-out Group HH 2** (Chair: Willem Ravensberg, industry/IBMA)
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**Environmental issues**

- **Report of Break-out Group ENV 1** (Chair: Christopher Lythgo, EFSA)
- **Report of Break-out Group ENV 2** (Chair: John Dale, UK)

## Report of Break-out Group HH 1

Chair: Warren Hughes, New Zealand
Rapporteurs: Vera Ritz, Germany and Denise Munday, industry

Issues discussed:
- Genotoxicity testing/Secondary metabolites
- Sensitisation studies
- Guidance document on waiving,
- Lack of appropriate methodology for the testing of microbials
- Risk for bystanders and residents, YOPI
- Risk communication
- Technical equivalence
- Read-across between strains
- Efficacy
- Awareness of new testing methods: Tox21
- Gene transfer of resistance genes

Issues listed but not discussed:
Need for earthworm repro study

**Genotoxicity/secondary metabolites**

Clear guidance should be provided for which types of micro-organisms genotox testing might be waived. From a human toxicology point of view as there are many questions from EFSA there is a need for clear guidance which could be used for dossier preparation.
There is no evidence so far that a genotoxic secondary metabolite of a BCA caused a problem. The question remains as to whether there is a need for genotox testing at all?
It is very unlikely that significant amounts of genotoxic secondary metabolites are in the product. The risk of secondary metabolite production after use in relevant quantities is even lower.
Are these studies really required for risk management reasons or just for comfort? If metabolites are known to be formed then genotox testing is required, in this case clear guidance on test protocol should be provided. There is a need to refine the guideline for genotox studies – so that it is fit for purpose.
Test methods: for the testing of secondary metabolites, information is needed as to where the secondary metabolite is to be found in the broth, in the spores...)
Appropriate test methods are lacking. In the Ames test there might be problems with histidine in the broth. Guidance on adaptation of other genotox test methods is also needed.
Conclusion on secondary metabolites: what material should be tested and what relevance does it have? Need guidance as to how, when and what to test, as well as what to test for.

Accumulation of metabolites would not usually occur outside the production due to limited medium. There may be some production of metabolites in the field as part of the mode of action. For known microbials the metabolites would typically be known. Time frame between application and harvest should be considered.
MRL is based on residue data, what does it mean no health standard is available, and what are the secondary metabolites? Are they toxicologically significant? If you can't test for compliance it is pointless to set a numbers.

**Guidance for data waiving**

Decision Tree when to perform studies and which studies are required. Regulators need to provide details of their specific requirements in case a study is required, and why this study is required.
When can read-across from other strains, sub-species be considered possible?

If specific effects or unexpected results are obtained from the acute tox, infectivity and pathogenicity tests further testing should be considered.

**Sensitisation/labelling phrases**
Sensitisation – why conduct such a study when classification criteria and test methods are not available for microbials? Need robust test method in the case that a sensitisation study is to be conducted. A product containing proteins can provoke reactions in sensitive populations.
GPMT is not a robust test for microbials. The Bühler test seems to be more relevant. Industry and consultants don't think that a testing method is really necessary if the risk is communicated via labelling.
How does this information transfer to labelling with respect to communication of the risk – is this to communicate something to the user, standard statements or to cover the precautionary principle.
Conclusion on sensitisation: Although there was generally consensus on no need to test the active substance for sensitisation, a test on the product might be needed since the CLP regulation applies to product classification even if the products contain microbials, as the co-formulants may be sensitising.
For consumer/home garden products it might be needed for authorisation to exclude skin sensitising effects since no PPE can be applied to those products. However, since the GPMT gives unreliable results can a potential really be excluded? Also because of the lack of methods for respiratory sensitisation this potential cannot be excluded so the label phrases would still be applied (EU label: contains XXXXXXXXXX (name of microbial substance), microorganisms can provoke sensitising reactions).

**Gene transfer of resistance genes**
Strain should not carry the resistance gene for antibiotics that are generally used, if this is the case then there should be no concern. This is done for bacteria strains used in feed additives: EFSA journal 2012; 10(6):2740 Guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance (FEEDAP) http://www.efsa.europa.eu/en/efsajournal/pub/2740.htm

**Technical equivalence**
Possible to bridge from strain to strain: From a practical point of view, strains are often closely linked, why should a complete data package to provide similarity between strain – how should this be decided? Definition of similarity could be very different.
Behaviour and mode of action are more informative than genetics where a similar point mutation can lead to completely different set of secondary metabolites - 99% similarity in genotyping can therefore not be used as a marker of equivalence. Strain and production method makes the product. If you use a competitor's similar strain the product can be completely different because of the different fermentation process. Therefore, no extrapolation from one strain to another should be allowed.
Other points to consider:

- pre-submission meetings: US system does not work in EU: waiver agreed upon between applicant and RMS might not be agreed upon later in peer review and EFSA conclusion
- information requirements instead of data requirements

Conclusion: the technical equivalence document can only be applicable to minor changes in the production, but not to equivalence of other strains to those already approved.

**Toxicology advances/Tox 21:**
This is just an information point, it might take another decade until methods become applicable for regulatory purposes. **Furthermore,** for testing of infectivity/pathogenicity a functioning immune system is needed therefore there might be very limited use for vitro methods for the evaluation of micro-organisms.
But for secondary metabolites/toxins this might be a chance after validation of the methods.

**Efficacy:** is it possible to adapt the methods used for chemicals to microbials?

The time-point of application and the life-stage of the micro-organism is more critical than for chemicals. Also, it can take quite a long time to see efficacy – even up to 4 weeks.
Except for bt products microbial products tends to be less curative and more preventive.
Even 40 % efficacy can be a defined level of control.
It should not be necessary to use a chemical or biological standard for comparison.
Before a field trial is conducted design of the trial should take into account the knowledge MoA, very generic, applicant should do their homework before they conduct the trial, label sufficiently informative to inform the user what he have to expect.

**Labelling information – risk communication:**
Don't put on the label what hasn't been tested (eg. CMR).
According to the EU regulations the applicants are responsible for product labelling.
In contrast, the product labelling is part of the authorisation in Italy. For zonal authorisations in the EU there should be only one label in future.
This is currently not the case.
Sensitisation: how does this translate on language to labelling? In the EU a phrase has been developed that is put on the label: micro-organisms might have the potential to provoke sensitisation reactions.

## Participants in BOG HH1

| | Country/organisation (representing) | Name |
|---|---|---|
| **CHAIR** | **New Zealand** | Mr. Warren Hughes |
| **Rapporteur** | **Germany** | Ms. Vera Ritz |
| **Rapporteur** | **Industry** | Ms. Denise Munday |
| | **Denmark** | Ms. Birte Fonnesbech Vogel |
| | **France** | Ms. Karine Angeli |
| | **Germany** | Ms. Martha Sikorski |
| | **Greece** | Ms. Paschalina Papadaki |
| | **Hungary** | Ms. Agnes Palovics |
| | **Italy** | Ms. Maristella Rubbiani |
| | **Netherlands** | Ms. Ester De Jong |
| | **Sweden** | Mr. Henrik Appelgren |
| | **US** | Ms. Jennifer Mclain |
| | **EC** | Mr. Jeroen Meeussen |
| | **ECHA** | Ms. Judit Janossy |
| | **Industry** | Mr. Nigel Cheeseright |
| | **Industry** | Mr. Mark Whittaker |
| | **Industry** | Mr. Mike Tichon |
| | **Industry** | Ms. Estefania Hinarejos |
| | **Other experts** | Mr. Rüdiger Hauschild |

## Report of Break-out Group HH 2

Chair: Willem Ravensberg, industry/IBMA
Rapporteurs: Anne Duval, France and Jay Kottege, Australia

The group was composed of 18 persons. Ten were representatives of national authorities, including six risk assessors and four risk managers, from the European Union, Australia, Japan and Norway. Two were representatives of an academic institution. The remaining six were representatives of industry covering all types of microorganisms used as pesticides, bacteria, fungi and baculoviruses. Only two persons were professional toxicologists, and representing regulatory authorities.

The group identified the following closely interlinked topics as priorities with regard to human health risk assessment and thus focused the discussion on those:

1. identification;
2. secondary metabolites;
3. residues requirements;
4. contaminants;
5. equivalence;

In addition, certain procedural/regulatory questions were also discussed.

6. Procedural/regulatory questions.

As the basis of every discussion, the group attempted to answer the question as to what is relevant for authorising microorganisms as pesticides. Details of the discussions are given below.

### 1- Identification

**Identity**
The group discussed what minimum criteria allow for the differentiation of one strain from another. It was considered that morphological characteristics alone are not enough. An appropriate method should be genetically based and must use the best available technology. However, in the short to medium term, a limited genetic characterization in contrast to complete genome sequencing is sufficient. Even though complete genome sequencing is currently becoming economically feasible for organisms like bacteria (from 4000€) or fungi (from 10000€), the information cannot be used without knowledge on how to interpret it (e.g. specific genes allowing comparison between genomes of strains or species). This may evolve in future as genome sequencing becomes more accessible and bioinformatics is able to provide readily usable information for risk assessment. For instance, if a gene for a specific toxin is known, it can be searched for provided there is sufficient knowledge about it. There is a need to establish a threshold for similarity between two genomes in order to consider two strains as being identical.

This approach, however, is not appropriate for baculoviruses, which are regulated at the *isolate* level (an isolate may contain various genotypes). For baculoviruses, enzyme tests are used to identify the species that the isolate belongs to. The emphasis to be placed on a review of literature varies depending on the species.

In EU, approval of a new isolate of a baculovirus generally only requires an information package on identity to prove that the isolate belongs to a species that has been already assessed and approved. This European approach (to regulate at species level) could perhaps be generalised. Refer to EU "Guidance Document on the assessment of new isolates of baculovirus species already included in Annex I of Council Directive 91/414/EEC".

**Phenotype/genotype and read across: how far can we read across form one strain to another**

Read across between two closely related strains should be possible. Guidance is needed to define which data can be extrapolated between strains. Currently this approach is not harmonised between countries, it is discussed on a case-by-case basis between applicants and authorities. More harmonisation is therefore needed with general requirements being defined while retaining enough flexibility to enable the use of a case-by-case approach when necessary.

As taxonomy changes, a strain once considered as belonging to one species may be found to belong to a different species. In that case, specific information in the dossier that was based on read across between those two strains can still be useful, as it is the phenotype that matters most in risk assessment. Thus, read across between strains should remain possible.

**Growth temperature – infectivity**

The discussion on growth temperature applies to bacteria and fungi, but not to baculoviruses.

A temperature threshold to be used in risk assessment must be fixed for human body temperature, with an acceptable margin of safety. Currently the temperature values used in testing are chosen somewhat arbitrarily. A review of relevant literature could help in choosing a value that is more relevant for the organism (mammal, bird) concerned.

The BOG HH 2 group agreed that a literature review combined with a study on the microorganism`s growth limit (max. temperature allowing growth or reproduction) would be generally sufficient to justify a limited human toxicity package (one infectivity study as this is also a check for the presence of toxins in the active/product, or no infectivity study at all). Medical information (clinical reports) can augment the dossier, but is not considered sufficient on its own.

For the ecotoxicity assessment: If an acceptable justification is provided for a limited mammalian infectivity package based on the growth temperature, this might also account for several other indicator species in the ecotoxicity assessment, since e.g. for birds and bees the body respectively bee hive temperatures are usually higher than human body temperatures. Guidance is needed on the most appropriate criteria for selection of temperature to conduct tests. While defining procedures and requirements, it is important to bear in mind the need to minimise animal testing.

**Mode of action**

The modes of action of microorganisms are often difficult to define. A thorough general description of the mode of action is needed to help in designing relevant risk assessment. However, comprehensive details of the exact mechanisms are not necessary. Only information that is relevant for a risk assessment is necessary. In particular, details of mechanisms are necessary when relevant metabolites (especially toxic metabolites) are produced. The level of detail at which the mode of action is described may vary on a case-by-case basis as the mode of action is specific to each microorganism.

**2- Secondary metabolites**

Assessment should only focus on relevant metabolites. Criteria to determine if a metabolite is relevant are needed as interpretation of data requirements and uniform principles leave room for too much subjectivity.

A guidance document on secondary metabolites is needed that also includes a section on lessons learnt thus far (including the projects RAFBCA, REBECA and the EU-List 4 Green Track lessons).

A literature review on related species and strains should be conducted. In parallel, the toxicity of the TGAI (technical grade active ingredient) should be determined. If both point conclusively to the absence of toxicity, no further investigation should be necessary. If only one of the two elements indicate a potential for toxicity, the exposure has to be evaluated to determine if the metabolite (especially toxins) induces risk to humans or non-target organisms. In such a case, further information has to be provided. This should be clarified via a guidance document. A decision tree on this specific topic would also be helpful.

In the EU biocide and PPP regulation have similar requirements. Both require to submit a dossier for a metabolite on its own, following chemicals data requirements, when the metabolite is responsible for the activity of the product or when it is present in significant amounts (see point (viii) of Part B introduction in regulation (UE) n° 283/2013). This situation, however, is not common. As a default approach, the group concluded that the best way to assess the risk is to test the TGAI, including metabolites.

A detailed description of the production method of the TGAI will be very helpful. For instance, when potentially present metabolites are rinsed out in the downstream process, this will affect the risk assessment significantly.

**3- Residue requirements**

In considering residue data requirements, two aspects have to be considered: presence of the microorganism itself on the crop used as foodstuff and presence of non-viable residues. If the toxicity assessment demonstrated that there is no toxic metabolite present, then no further information is needed to satisfy the latter requirement.

For microorganisms, no ADI nor ARfD are usually established. The consumer risk assessment is conducted primarily as a qualitative risk assessment. The workshop believed that, as default, no MRL needs to be set. Only if a toxin is produced or present in the product as applied, additional studies are needed. If contamination via food is possible, an extrapolation should also be made to livestock. Establishment of relevant MRLs must be considered. Clarification via a specific guideline would be beneficial.

**4- Contaminants**

It is the end product that should be tested for contaminants. In order to limit the number of tests, a guidance document should provide a list of situations (manufacturing conditions) where a given type of contaminant cannot be produced. For example, when the production facility is based in a country where the given contaminant does not occur, testing on it is obsolete. An applicant should be able to obtain a waiver from data requirements on contaminants by an argumentation explaining why the contaminant cannot be present in the particular manufacturing conditions. Notably, such guidelines already exist in some countries (USEPA).

In the assessment of pesticides, the evaluating agencies (such as EFSA) should accept testing done by the applicant according to validated methods in other areas, in particular (ISO) methods developed for the medical field, and if contracted out to accredited laboratories.

With regard to human health, the risk is acceptable if the level of each contaminant remains below the threshold set in the OECD issue paper on microbial contaminant limits (accepted by EU Member States and EFSA).

With regard to analytical methods and validation of methods, the group concluded that clarification and guidance is needed. For this purpose, it would be helpful if EFSA could explain their exact requirements: the procedure for sampling, the procedure for counting (ISO standard? GLP CFU counting?), etc. For instance, in the EU data requirements, the following text is confusing as several interpretations of it are possible:
"Methods to determine the content of the microorganism in the manufactured material used for the production of formulated products and methods to show that contaminating microorganisms are controlled to an acceptable level." (point 4.1 of Part B of RUE/283/2013)

**5- Equivalence**

For chemical substances, two manufacturing sites that are recognised as equivalent are considered to produce the same (identical) active substance. For micromicroorganisms, however, there is uncertainty as to whether two manufacturing sites can produce the same strain with regard to equivalence. There are likely to be small differences. Equivalence is assumed as long as there are no significant changes to the production process. Guidance is needed to indicate what significant changes are.

**6- Procedural/regulatory questions**

The group proposed to take into account risk assessment approaches from other areas, like EFSA QPS classification.

For European applications, the group considered the benefits of including EFSA in pre-submission meetings, with one unique reference person for microorganisms which could dispatch information and questions within EFSA as necessary. Minutes or records of the pre-submission meeting approved by the applicant and the EFSA person could help in maintaining consistency between the pre-submission meeting and the later assessment by agencies and EFSA, even if those are non-binding.

Access to a network of experts could help risk assessors during their evaluation. However, the information may be subjective, depending on the expert opinion. If such a network is set up, ground rules will have to be defined to guarantee objectivity as it is for expert discussions within the framework of Global Joint Reviews. Upfront permission from applicants might be needed.

A simple 'communication document' explaining how to address each item of the data requirements would be very helpful, as it was done by the Commission (EC) for chemicals when revised data requirements were recently adopted in the EU (for each data requirement, the Commission indicated which method or guidance should be followed).

**Priority areas for action**

The group feels that the five topics discussed related to data requirements need actions to facilitate a consistent approach to microbial risk assessment. The topics could be ranked by importance in the order they were discussed. It should be noted, however, that all five topics discussed are closely interlinked.

In the short term, to make rapid progress, new or improved guidance documents are needed. On the medium to long term, regulation should be improved to clarify requirements and ensure they are relevant to microorganisms whilst leaving enough flexibility for innovative products. For chemicals revised data requirements were recently adopted in the EU. The ones for microorganisms are not revised and the group feels that those current requirements do not fully reflect the progress of knowledge on microorganisms made over the past 15 years. Work on a draft regulatory proposal to improve data requirements should be initiated quickly to achieve a change of the regulation in the medium term.

Actions should be taken at regional and international levels for greater harmonisation. Industry needs clarity and consistency between countries with regard to data requirements. The objective should be to improve the data requirements and not to increase them.

Secondary metabolite is an area where further academic research is needed. Abundant literature would need to be examined and organised. Such research will of course need funding.

In parallel, sharper focus should be placed on ensuring compliance with the existing laws in the marketplace (clean the market from 'snake oils').

**Actions to be implemented by the OECD**

The group recommends that specific topics listed above should be addressed by the OECD, consistently between the different programmes, especially between the Pesticide and Biocides Programmes.

***1- Working Group on Pesticides:***

- Ensuring timely and consistent progress towards harmonisation

***2- Projects for OECD Biopesticide Steering Group (BPSG)***

- Prepare guidance document addressing secondary metabolites
- Address relevance of growth temperature in risk assessment
- Address equivalence and read across

***3- Projects for OECD Task Force on Biocides (TFB)***

- Achieve harmonised procedures and requirements across jurisdictions.

**Participants in BOG HH2**

| | Country/organisation (representing) | Name |
|---|---|---|
| **CHAIR** | **Industry/IBMA** | Mr. Willem Ravensberg |
| **Rapporteur** | **France** | Ms. Anne Duval |
| **Rapporteur** | **Australia** | Mr. Jay Kottege |
| | **Austria** | Mr. Edmund Plattner |
| | **Czech Republic** | Ms. Nadia Novakova |
| | **Estonia** | Mr. Elari Hain |
| | **Germany** | Mr. Eckhard Koch |
| | **Hungary** | Mr. Zoltan Repkenyi |
| | **Japan** | Mr. Makoto Irie |
| | **Netherlands** | Ms. Marloes Busschers |
| | **Norway** | Ms. Jana Johansen Hladilova |
| | **Sweden** | Ms. Pernilla Birgander |
| | **Sweden** | Ms. Anneli Widenfalk |
| | **Industry** | Mr. Andrew Scarr |
| | **Industry** | Mr. Sergio Franceschini |
| | **Industry** | Mr. Nick Wright |
| | **Other experts** | Mr. Philip Kessler |
| | **Other experts/Academia** | Ms. Margareta Hökeberg |

## Report of Break-out Group ENV 1

Chair: Christopher Lythgo, EFSA
Rapporteurs: Chris Wozniak, US and Christina Donat, industry/IBMA

*(final version 2 Sept 2013 from Chris Lythgo)*

### 1. Workshop topics the group decided not to discuss.

Methods for counting of viable/non-viable cells and other test methods.
(Level of) efficacy and formulation.
Production and quality assurance.
Contaminants.
Residue requirements.
Risk and safety phrases.

### 2. Workshop topic individuals wrote down their ideas on, that was not discussed due to lack of time.

Related procedures / regulatory questions.

### 3. Workshop topics that were discussed by the group.

Identification and biological properties including mode of action.
Potential production of secondary metabolites.
Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments.
Discussion/inventory of factors determining the persistence of microorganisms in the environment.
Effects on bees/pollinators and bee brood.
The risk assessment for organisms involved in biological methods for sewage treatment.

### 4. How the group organised the break out.

For each topic that was prioritised for discussion each group member made proposals on:

1. Which questions should be asked from an environmental risk assessment point of view?
2. Do we have the right tools to address the questions identified?

The group then discussed and concluded on each topic.

## 5. Conclusions on what the OECD Pesticide and Biocide Programmes should do to facilitate a consistent approach to microbial assessment

Identification and biological properties including mode of action

Information on biological properties is not currently used to the extent possible, for identifying critical issues, targeting data generation necessary for environmental (and human health) risk assessment and facilitate evaluation.
Issue papers on certain biological properties which can have an influence on the risk assessment in a certain area to be developed.
Issue papers on taxonomic groups continue to be developed (e.g. *Trichoderma spp.*)

Potential production of secondary metabolites

Develop an OECD guidance document with a clear decision tree, which should address the protection goals of different regions (EU/US and others, i.e. it is known that EU groundwater decision making criteria diverge compared to that of the US). Some delegates expressed the opinion that EU definitions given for metabolites in regulation (EC) 1107 are related to metabolites of chemicals rather than to secondary metabolites produced by MO, but this was not agreed by all.

Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments

No further action needed.
Feedback on the work with the OECD Environment guidance document should be provided once there is experience

Discussion/inventory of factors determining the persistence of microorganisms in the environment

EU Uniform Principles: …has to come back to the background level within one year, unless…
Remove this decision making criterion
Something else may be considered? Other criteria might be better than this one? Maybe related to an indigenous/non indigenous approach? For non-indigenous strains, we may want reassurance of lack of competitiveness of the organism. For indigenous / ubiquitous strains, evidence of lack of pathogenicity and infectiveness to soil organisms may be enough, such that competiveness is not so important. However one delegate stated that such an approach should be treated with caution as the definition of an indigenous strain is not clear (i.e. following introduction, after how long is a strain categorised as being indigenous?)
Alternatively persistence might be considered in order to choose the best representative species for non-target effect assessment and the duration of the test that is necessary. Information on biological properties is important to be used for this.

Effects on bees/pollinators and bee brood
OECD group (PEIP) working on this should not forget to include / consider microorganisms.
Adaptation of test methods (duration) in line with the biology of the microorganism is appropriate. Bee brood should be tested when the MO has activity against larval stages of arthropods (target and / or non target). There was a minority view in the group that such testing could be negated for an MO which has well demonstrated target species specific action, e.g. baculoviruses (Cydia pomonella GV etc.).

The risk assessment for organisms involved in biological methods for sewage treatment

Not a high priority. Unlikely to cause problems for PPPs or biocides due to limited potential for exposure (except when a biocide is actually used in a sewage treatment plant).

### 6. Recommendations to all stakeholders on what should be done to facilitate a consistent approach to microbial assessment

Potential production of secondary metabolites: engage in guidance development (international, short term)
Identification and biological properties including mode of action: develop issue papers (international medium term).
Natural exposure in relation to exposure from the use as a PPP (or biocide) in different compartments
Discussion regarding the persistence of microorganisms in the environment, update via guidance criteria for product decision making regarding goal in relation to competitiveness / persistence (regional, EU stakeholders, short term)
Effects on bees/pollinators and bee brood
Continue contributing to existing initiatives ensuring microorganisms are adequately covered. (International, medium term)

Records of what the working group members wrote down as their key questions and what they identified as available tools, before discussions commenced.

1. **Identification** and biological properties including mode of action

| **Questions** |
|---|
| Characteristic sequence / markers should be enough |
| Description of the phenotype |
| Mode of action, host range |
| Manufacturing process |
| Where does it come from? |
| Ecological niche? |
| Temperature growth range |
| Taxonomical/Functional group |
| Biological characteristics |
| Relationship – to what level relevant? |
| strain specific |
| Evaluation for different groups together (eg Insect, parasite,..) |
| Possibility to transfer genetic material |
| Tools |
| Molecular techniques (Whole genome sequencing[24] might become useful but in the future only) |
| Growth study techniques |

**2. Potential production of secondary metabolites**

| **Questions** |
|---|
| Does the **product** contain secondary metabolites? |
| Does the MO produce secondary metabolites in situ? |
| Concern from acute tox tests? |

[24] It should be noted that this is not the only molecular technique available for characterization of microorganisms. Other, much more simple methods like RAPD PCR could be considered.

Does the mode of action include metabolites?

Look at biology

Literature check for the species

Effects on birds and mammals

Decision on taxonomical groups

Stability? Persistence?

Relevance vs natural background

Define low/medium/high risk

Ensure applicators risk adequately assessed?

Relevant amounts?

Production Process?

Dilution prior to application?

Which metabolite to look at?

Tools

More systematic literature reviews needed
(EFSA is working on that / applicants should follow EFSA guidance on systematic peer review of literature for secondary metabolites known to be produced by the species)

Review of Scheepmaker and Butt

Compendium of EFSA for plants in food additives

RAFBCA report

Analyse product batches looking for compounds identified in systematic literature reviews

How to quantify secondary metabolites?

How to identify them?

HPLC, Bioassay

Criteria for stability

3. Natural **exposure** in relation to exposure from the use as a PPP (or biocide) in different compartments, Discussion/inventory of factors determining the persistence of microorganisms in the environment

**Questions**

Natural occurrence ≠ relevant exposure

eg soil microorganism applied on leaves = new exposure for Thyphlodromus sp

How does intended release relate to relevant compartments?

Will the microorganism decline?

At which taxonomic level should exposure be considered, at genus, species or strain level?

Will exposure result in interaction – MoA to be considered

Duration of exposure

How can the natural exposure levels be defined? What is the likelihood of adverse effects?

List of factors which could impact persistence -> GD

Influence on indigenous species?

Epizootic on target and nontarget species?

Presence/Absence of host has an influence

Indigenous or not?

Spores?

Disturbance is not greater than from other agricultural practice, effect is transient, returns to equilibrium

Microorganisms are not suspected to persist in the environment

Natural background and its definition

Persistence of what? Strain?

In relation to what?

Concern: permanent establishment of new, non indigenous strains with adverse effects

## Tools

Policy decisions on benefits

Scheepmaker and Butt review paper on fungal bio insecticides (background level and decline of the microorganism, degradation of the microorganism)

Literature search: recent scientific reviews, general knowledge from scientific text books should be accepted

Justification for non-submission of data based on biology, MoA and specificity

Approach analogous to botanicals (see EU GD currently under

commenting)

Non-target testing

OECD doc No67

Molecular tools

RT PCR

No way to demonstrate its complete disappearance

4. Effects on **bees/pollinators** and bee brood

| **Questions** |
|---|
| Are there effects on bees, biology of bees? |
| Is the BCA an entomopathogen? |
| Are bees / pollinators exposed? |
| Will the MPCA be transported to the hive by the bees? |
| Tools |
| PEIP group of OECD is working on that (Chemicals only?). |
| EFSA guidance doc exists (2013) that identify exposure routes, to be checked if suitable for microorganism. |
| Reliable test methods needed |
| Contact and oral tox study, bee brood (for entomopathogic targeting the larvea) |
| Literature reviews |

5. The risk assessment for organisms involved in biological methods for **sewage treatment plant (STP)**

| **Questions** |
|---|
| Literature data on effects and STP community |
| Theoretical exposure |
| Argumentation on biology |
| Only in case of a mass accidental release |
| Compare with effects on wastewater organisms |

On what basis MPCAs pose a risk greater than run off/effluent organisms?

Can MPAC reach STP?

Can BCA survive in STP?

Tools

Baseline data on STP microbes

6. Related procedural/regulatory questions
Ideas written down by group members (not discussed)

**Questions**

**Procedural questions**
Are studies required for earthworm toxicity?

Politics of fees/resources/expertise in regulatory organisations why do they vary so much?

Are data requirement all appropriate for microbials?

**Tools**

EFSA should be involved at earlier stage for development of amendments of data requirements

Use outcomes of this workshop to justify amendment of data requirements for MOs

Understanding of benefits – environmental, economic, political,

Develop GD for justification for not providing earthworm studies

Literature reviews, Rebeca outputs

Toxicity should be expressed in same way as for chemicals and ideally calculated by standard models

**Participants in BOG ENV 1**

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| | **Industry** | Mr. Ulf Heilig |
| | **Industry** | Ms. Flora Limache |
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| | **Other experts/Academia** | Mr. Ingvar Sundh |

## Report of Break-out Group ENV 2

Chair: John Dale, UK
Rapporteurs: Adi Cornelese, Netherlands and Sofie Hofkens, EC

*(final version received 27 August 2013 from John Dale)*

The questions that were listed on the various subjects in the background document served as thought starter for the break-out sessions. The subjects were evaluated by the group and a number of them were selected for further discussion.

During the course of the discussions within the group it quickly became clear that with each of the questions selected, other topics automatically became relevant. This seems to be the result of the interdisciplinary approaches that are clearly required when dealing with risk evaluation of microorganisms (m.o.) used in pesticides. This however does make structuring and streamlining the report of the break-out group discussion a real challenge. However, this report tries to summarise and reflect as much as possible, the discussions by the group during the two half day break-out sessions covering the various input on the different topics. Although, for reasons outlined above a clear division to the selected questions as reflected in the background document is sometimes lost in the report.

*Identification, biological properties, quality assurance and contaminants*

The ENV2 break-out group started discussion on the first question with regard to the identification at strain level. It appeared during the discussion this could be considered together with some other questions indicated in the thought starter. Therefore in summary this section of the discussion covered areas of Identification/Quality Assurance and Contaminants.

Identification at strain level was identified as necessary for regulatory purposes. During discussion it was mentioned that for some issues in regulation it seems not to be important because there is no risk. However, to be able to say so it has most probably to be addressed for some other issues. For some species biology is so specific that it is not needed (e.g. *Phlebiopsis*). For some other it is essential to identify at strain level, e.g. when related to pathogenic m.o. It was stated that identification at strain level can be done (both for fungi and bacteria), the methods are available such as SCAR markers for PCR method. However, for the overall risk assessment just identification may not be enough. The question was asked whether the description of production process is included in the requirement for identification and quality assurance, this would help. It was suggested that incorporating production method aids in identification and enables changes in manufacturing site at a later stage using the same production method. This was not conclusively discussed further. However, it was highlighted that identification is important also for marketing, production control and knowing that what you are producing has been tested. Based on the SCAR marker you can see if a strain from a different location is the same strain. Also requirements for monitoring can benefit from markers (drinking water as well as quantification of fate studies and traceability of which

species was tested in certain studies when the species name changed). It was also claimed that the loss of markers by mutation is very unlikely.

Can methods with m.o. be validated? For the identification method it is possible with current state of the art methods. It is however not possible to simply follow the chemical guidance document (GD) for validation. Therefore it was agreed that specific GD for validation of microbial methods is needed. It was suggested that validation should include results from different labs applying same protocol that should be comparable; multiple replication of a protocol in the same lab should also give comparable results. Methods according to general internationally recognised methods (like ISO) should not require further validation. The minimum detection level is relevant for the risk assessment of microorganisms and therefore a validated method helps because then you have a defined detection level.

It was highlighted that a draft guidance document on equivalence for m.o. has been prepared and it was agreed that this should l be sent out for comments. It was pointed out that a change of production method can change the properties of the microorganism (e.g. presence of metabolites). Just a change in production location does not have to do so. If the complete method stays the same (including quality control) the location should not matter. As production sites are usually small there is a need of flexibility of manufacturing place by industry to meet increasing demand. Notification of the site should be enough as is the current requirement by EPA, but sometimes a 5 batch analysis is required.

In response to the thought starter question on genotyping it was proposed that to test equivalence it is not possible to require 99% of genotyping as this cannot be used for every method. Some methods have other levels and are still acceptable. Therefore, no general arbitrary rules should be stated in the equivalence document. It is method specific, depends on the biology and developments in science will change it. The group generally felt that ‘most appropriate justified method` is a better wording to be used.

Regarding contaminants the consensus of the group was that these should be tested in the end product as this is the most relevant. In other stages it is a problem of the production line and therefore a problem for the manufacturer. It was considered that the methods used here should be international standardised ones or they should be provided in detail.

Growth means multiplying: if an organism does not grow at a certain temperature (so does not multiply) it theoretically could still remain hazardous as it is still viable and can produce toxins. It was suggested that growth temperature is a useful factor for the assessment of m.o. but only in combination with other information. Growth temperature can help to address infectivity in warm-blooded animals. However, some parts of the body of an animal can have lower temperature or animals can go in hibernation and it was raised whether this should be taken into account? It depends as well on the organism and its biology as some may be very opportunistic. So it cannot be an absolute parameter and can only be used for human and warm-blooded vertebrates. It was also agreed that justification is needed when used.
It was highlighted that growth temperature can be used, and has been used in the EU review process, to bridge from one strain with data to another strain with limited data.

It was noted that mode of action is important information for the risk assessment together with the method of application. Knowledge of the mode of action is also necessary to establish the difference with other compounds such as plant strengtheners etc. Often you may have several modes of action. Then the major modes of action should be described. This can also be used for resistance management as several modes of action reduce the risk of resistance.

It was agreed that genetic transfer is a natural phenomenon. Frequency can be higher depending on the genotype. But does it bring a risk? Theoretically yes and you can think of unwanted effects but how relevant are these in reality? It was proposed that all information should be put together to identify the level of risk.

*Effect on bees/pollinators and bee brood*

The question was raised if Baculoviruses can be excluded for bee brood studies if they attack the larval stage of their host. Given the fact that baculoviruses are very host specific they are not able to infect any life stage of bees. How can you know they are very host specific? See OECD consensus document. Overall the concern was considered to be low.

The group discussed a number of pollinator issues and it was considered that more guidance is required for proper testing of pollinators. Bees are affected by stress if tested for more than 48 hours. Therefore, a specific appropriate test design is needed which clearly addresses the risk to bees/pollinators. Can the acute bee test be waived when the product is applied if bees are not present (no exposure)? From the group discussion it seems that it is not required to test everything for bees. Waivers have already been used for specific methods of application like drenching, incorporation in soil, tree injection, stump brushing. Further guidance needed with input from the OECD pollinators group. For products containing m.o. also specific biology from bee colonies is relevant. For example, nurse bees eject larvae when they detect microbes before the microbe can harm the colony and guard bees at hive entrance will kill infected bees, infected bees will not return to hive or will not be allowed to enter the colony. Therefore standard requirements are less relevant.

Repellency should also be accepted by regulators. For example, bees did not eat in feeding study where m.o. was mixed with sucrose solution. There is a field test available showing this repellence effect. This might than be considered on the label: repellent to bees, may interfere with pollination.

The topic of Bumblebee vector use was also discussed. It was highlighted that in pollinator vectoring by commercial bumblebees the product is manufactured to be transported. Bumblebee as a vector is a contained unit with a limited life time. It is not sustainable. They will not bring it back in the hive (different exit/entry). Need for environmental assessment related to the 'hive' of these vectors is questioned. This is not the case for honeybees or other pollinators.

*Natural exposure in relation to exposure from use as a PPP (or biocide)*

Natural exposure in relation to exposure from use of biopesticides was discussed and number of questions considered. Some members of the group expressed the view that natural occurrence at low level is relevant. However such information only makes sense in relation with other aspects. It can be a positive indicator of harmlessness. If it is present and has not shown any pathogenic impact it is probably not pathogenic. To what extend is infectivity/pathogenicity related to the applied dose rate? Normally the high applied dose will decline to low levels, certainly in an environment where there is already a low level present naturally. How much time is needed to reach background level and what time line is acceptable? That depends on pathogenicity/infectivity, a longer time line can be acceptable, in case there is no effect. Furthermore, it is a fact that there is no general background level. How should this be defined correctly, the geometric mean of all studies available? Many factors are influencing background level. What is needed is to know if the m.o is more competitive in soil. This is not a data requirement. It was suggested that what was really needed is to study the population dynamics of the applied strain (with the marker). However, this is a huge burden. A proposal in the group was to do this during efficacy testing. It was also highlighted that open literature can be used.

It was commented within the group that the fear is that a newly introduced m.o. will be invasive, shows uncontrolled growth and becomes dominant in local population. Therefore this needs to be addressed. However, it was considered that, competitiveness is mostly low. Most m.o will not persist and after 3 months it is part of the local m.o. community.

*Persistence and mobility in the environment*

It was commented that marker identification ensures quantifiable fate by strain. Competitiveness should be the criterion for persistence in the environment, not persistence for a certain time period. However also competitiveness is not entirely correct as we should distinguish between unwanted and desirable competitiveness (e.g. *Phlebiopsis* is highly competitive on the tree stump, but this is desirable).
Instead of competitiveness, the word population dynamics could be used. But also for population dynamics guidance would be needed. It was questioned as to whether we should be really looking at the desired environmental fitness? Has the m.o. an unintended impact on the function of media? These should be the real questions. Like already discussed with natural exposure, what should be addressed is the absence of uncontrolled growth. However, what are the criteria that are needed?

Mobility of the m.o. to groundwater level was not considered to be an issue as most of the m.o. will be consumed by other m.o. on the way to the groundwater if they show mobility to deeper soil layers. It could be an issue for metabolites but this break-out group did not discuss metabolites. Although there was general agreement expressed to the need for further guidance on secondary metabolites.

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*The risk assessment for organisms involved in biological methods for sewage treatment*

The question of the relevance of sewage treatment plant (STP) assessments was discussed. There was a general agreement on this issue in the group and a short discussion. STP exposure might be an issue for biocidal products that are directly applied to sewage water or water systems that feed into sewage systems. In the draft proposal for the EU data requirements for biocides it has been left out. It is proposed in the group to take it out of the EU data requirements for PPP as well. For other OECD countries it is not a requirement.

*Earthworms*

Earthworm risk assessment was not covered by any question in the background document, but was raised by a member of the group for discussion, particularly with regard to the need for such earthworm studies. It was the opinion of the group that studies are not required unless the m.o. is not naturally occurring in the soil. This includes m.o. living on plants which also end up in soil when leafs fall down and are degraded. It was suggested that for a m.o. really foreign to soil a study may be required. It was highlighted that an issue with earthworm studies is often whether the duration of acute study is long enough to address infectivity/pathogenicity. But what time is needed? To get an idea on this, specific data on infectivity/ pathogenicity on earthworms would be needed. Is a lab study on artificial substrate representative, whereas the real exposure is in a multi microbial environment? In the EU peer review process it has been concluded a 14d study is long enough. It was considered that this area needed to be considered in more detail.

*Related procedural/regulatory questions*

*A number of questions related to procedural and regulatory questions were highlighted in the thought-starter document. The brief discussion on these and other related topics is recorded below:*

- It was highlighted that the study design of daphnia test needs to be reviewed for m.o. in consultation with other biopesticides groups. In a number of studies there are problems with turbidity. There must be some physical effects and not direct toxic effects. Tested concentrations are problematic. Test design as it is would not survive ring testing. If the applied m.o. starts degrading in water this might lead to a drop in oxygen level and a rise in ammonia to which daphnia are sensitive.
- There was general agreement that the EU Data requirements for m.o. need to be reviewed and amended where necessary AND guidance needs to be developed related to the interpretation. Preferably the latter should be a consensus document that could also help OECD country experts outside the EU.
- It was highlighted that the results of a review and assessment may conclude that there is a low level of acceptable risk that is limited in space and time. A risk which can be reversed depending on time and other factors (e.g. reversible effects, recovery). This is normally specified for chemicals which then require mitigation measures at MS level. It was felt that this approach should also be possible for m.o. However, it was an area where guidance would be needed.

- It was suggested that risk/benefit analysis should be introduced in regulatory for microbial pesticides.
- It was considered to be important to involve experts in the process during drafting of a review report. This can only be done if they get appropriate timelines available. For example, the Swedish University of Agricultural Sciences (Sveriges lantbruksuniversitet (SLU)) could act as such an expert group but they cannot solve problems in a few hours either. What about the grounding of an OECD wide web of experts. Yes but funding and planning is needed otherwise it will not work.
- It was highlighted that there is an urgent need for more multidisciplinary knowledge in regulation. A lot of this knowledge is available in Academia and this expertise should be better available to regulators.
- How can experts be involved better? It was highlighted that in the EU review process MSs can only send 1 expert which does not have expertise on all aspects. It was commented that face to face meetings are important to ensure informal knowledge transfer like this workshop. Therefore it was suggested that more than 1 expert and experts covering all aspects would guarantee better exchange of knowledge.
- Industry highlighted that they would like EFSA to be involved from the pre-submission stage. Maybe via teleconference. At current pre-submission meeting, industry has the impression that there is no time anymore for more studies**.** However, this is not necessarily the case. It was felt that EFSA involvement seems unrealistic for a number of practical and a remit reasons. However, the involvement of EFSA in GD development is welcomed and more realistic.
- It was highlighted by the IBMA that at the moment in EU and OECD MS there is divergence in biological products: there is overlap; there are attempts to draw lines. The numbers of products in the EU are decreasing. The revision of fertiliser regulation in the EU is currently ongoing in which bio stimulants will be included with limited data set (evaluation after approval). This may lead to this change. There is fear that no longer pesticide label claims will be made for m.o. The division in the fertiliser regulation will be abiotic or biotic function. If it influences an abiotic function it is a plant strengthener if it influences a biotic function it is a PPP. A proposal could be to put all biologicals together whatever the intended use. An evaluation could follow via a tiered approach. Active substances that come via 2003/2003 EC with a reduced dataset and see if these have a low risk for man and the environment. It was felt that these developments are important and that the Biopesticide steering group needs to be informed further of this issue.
- It was also suggested that specificity and lack of invasiveness could be a criteria for a low risk organism (low risk substance working group). This might be linked to low stability or low persistence. Other criteria proposed are long history of safe use; host specificity and narrow host range.

## Participants in BOG ENV 2

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|---|---|---|
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| | **Industry** | Mr. Guenther Eberz |
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| | **Industry** | Mr. John Fournier |
| | **Industry** | Ms. Maria Herrero |
| | **Industry** | Mr. David Cary |
| | **Industry** | Ms. Mikaela Bistrom |
| | **Other experts/Academia** | Mr. Jan Stenlid |
| | **Other experts** | Mr. Claude Alabouvette |

# ANNEX 5: Abstracts for Presentations

## I. Setting the Scene

### Background to the OECD

*Sylvie Poret, Principal Administrator for Pesticides and Biocides, OECD*

This first talk of three "setting the scene" presentations will focus on the OECD as an organisation and describe, in general terms, the OECD pesticides and biocides work programmes.

In 1961 the Organisation for Economic Co-operation and Development (OECD) was established with a trans-Atlantic and then global reach. Today the OECD, based in Paris, has 34 member countries, with more than 70 developing and transition economies engaged in working relationships with the OECD.

The OECD provides a forum in which governments can work together and with representatives from business and civil society to compare and share policy experiences (social, economic, environmental), seek answers to common problems & identify good practices, and promote decisions and recommendations.

As part of the OECD's Environment Directorate, work on pesticides and biocides falls under the remit of the Environment, Health and Safety division along with work programmes on chemical test guidelines, hazard assessment, good laboratory practice, biotechnology, food safety, nanomaterials, chemical accidents, and Pollutant Release & Transfer Registers.

The Pesticides programme at OECD, created in 1992, is administered by the Working Group on Pesticides (WGP), which has a busy agenda with work areas covering illegal trade in pesticides, bio-pesticides, risk reduction, compliance and enforcement, registrations. Work is progressed through a series of steering groups and ad hoc groups for these specific work areas.

In 1992 biocides work at the OECD was incorporated within the WGP. The Biocides programme at OECD was created in 2002 as an independent body to reflect the increasing interest of member countries in this area in its own right, with its numerous identified use patterns and exposure scenarios that are distinct from the pesticides arena and considered separately in legislation by many member countries.

The overall goals of both programmes include: reducing risks for human health and the environment; minimising duplication of effort between countries and reducing barriers to trade; and improving the efficiency of assessment and control.

### The OECD task Force on Biocides

*Edmund Plattner, Chair of the OECD Task Force on Biocides*

This second talk of three "setting the scene" presentations will focus on the work of the OECD's Task Force on Biocides (TFB), the body which steers OECD work in the area of biocides assessment.

The Task Force was set up in recognition of the fact that many of the issues around use, exposure and risk are very different for human health and the environment for biocides, and that legislation in member countries for biocides varies both in scope and administration. Another big issue that the Task Force seeks to address is the lack of harmonised approaches to assessing the efficacy of biocides placed on the market.

Work of the TFB towards the harmonisation of exposure assessment has resulted in the publication of a number of Emission Scenario Documents (ESDs), covering diverse use patterns such as wood

preservatives, antifoulants, and insecticides. Work is ongoing to produce more ESDs for important areas of use of biocides.

The TFB has overseen the publication of various test methods for biocides, in particular, with regard to efficacy, the efficacy of pool and spa disinfectants, and baits against cockroaches. Work is ongoing to produce a test guideline for antimicrobials for porous and non-porous surfaces, while the efficacy of biocides used as indoor baits for ants and quantitative methods for measuring the activity of microbiocides on hard surfaces have both recently been approved.

The TFB will meet for the 11th time directly after the workshop on antimicrobials, and will discuss a range of topics of interest to member countries and aligned with the OECD's objectives of reducing risks for human health and the environment, minimising duplication of effort between countries and reducing barriers to trade, and improving the efficiency of assessment and control.

**The work OECD-BioPesticides Steering Group (BPSG)**

*Jeroen Meeussen, BPSG and Workshop Chair*

This third talk of three "setting the scene" presentations will focus on the work of the OECD's BioPesticides Steering Group (BPSG), the body which steers OECD work in the area of biopesticides assessment.

The BioPesticides Steering Group (BPSG) was established by the WGP in 1999 to help member countries harmonise the biological pesticides assessment and improve the efficiency of control procedures. Biological pesticides involve: microbials, pheromones and other semiochemicals, plant extracts (botanicals) and invertebrates as biological control agents. The BPSG has been chaired by Canada since its inception and by The Netherlands/European Commission from mid-2005 onward. The first tasks of the BPSG consisted of:

1. reviewing regulatory data requirements for three categories of biopesticides (microbials, pheromones and invertebrates); and
2. developing formats for dossiers and monographs for microbials, and pheromones and other semio-chemicals.

This was achieved in 2004 and resulted in several OECD-publications in the Series of Pesticides (No. 12, 2001; No. 18, 2003 and No. 21, 2004).

The BPSG then decided to concentrate its efforts on science issues that remain as barriers to harmonisation and work-sharing. This resulted in the preparation of a "working document" which does not provide 'mandatory' guidance but being essentially a set of examples/case studies aimed at helping the regulatory authorities. The document is titled: *"Working Document on the Evaluation of Microbials for Pest Control"* and has been published in OECD Series on Pesticides No. 43, 2008.

The report of the Workshop on the Regulation of Biopesticides: Registration and Communication issues, 15 – 17 April 2008, EPA, Arlington, USA, in another publication in the OECD Series on Pesticides (No. 44, 2009). More recently an "Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products" (OECD Series on Pesticides No. 65, 2011) and a "Guidance to the Environmental Safety Evaluation of Microbial Biocontrol" (OECD Series on Pesticides No. 67, 2012) were published.

In 2009 the BPSG started to organise seminars on topics related to biopesticides. The first seminar was titled "*Identity and Characterisation of microorganisms"* (OECD Series on Pesticides No. 53, 2010). The 2nd seminar on "*The fate in the environment of microbial control agents and their effect on non-target*

*organisms"* was held in May 2010 (OECD Series on Pesticides No. 64, 2011). The 3rd seminar on botanicals was held in March 2011 and was titled: "*Characterisation and Analyses of Botanicals for the use in Plant Protection Products" (*OECD Series on Pesticides No. 72, 2012).

Publication of the 4rd seminar on: "*Trichoderma spp.* for the use in Plant Protection Products: similarities and differences" is in preparation.

The main workshop objectives will be to:

- provide an overview about current achievements in microbial regulations worldwide
- discuss problems that countries face with assessing microorganisms as microbial pesticides and biocides
- identify technical and scientific solutions to those common assessment problems
- suggest harmonised solutions to facilitate the approval process
- draw conclusions and recommendations for OECD, the governments of its member countries and identified stakeholders.

The objectives, scope and structure of the workshop are described in detail in the 'Workshop outline'.

## II. Understanding of existing data requirements for microbial pesticides and biocides

### Overview on the existing EU regulatory system (biocides and pesticides): Human Health Data Requirements

*Vera Ritz, Federal Institute for Risk Assessment, Germany*

In the EU, new challenges with respect to the data requirements for human health risk assessment are triggered by the new legal background for the regulation of biocides and pesticides.

For biocides, the new requirements are laid down in Regulation (EU) No. 528/2012, Annex II, Title 2 (active substances) and Annex III, Title 2 (products) applicable from 1 September 2013 but the data requirements for microorganisms remained the same as in the old Regulation 98/8/EC.

For pesticides, the data requirements according to Regulation (EC) No. 1107/2009 are laid down in Commission Regulations (EU) No. 283/2013 (active substances) and No. 283/2013 (products) applicable from 1 January 2014. For microorganisms, the data requirements are based on the old Commission Regulations (EU) No. 544/2011 (active substances) and No. 545/2011 (products).

In conclusion, the human health data requirements for microorganism were not updated in the last years, in contrast to the data requirements for chemical active substances.

For biocides, the Netherlands and Sweden started to redraft the guidance document complementing the data requirements to address some of the problems that were identified in the evaluation of microbial biocidal active substances during the last few years.

There is longer experience in the pesticides human health evaluation because the program has been running a longer time and there are much more microbials in this field than for biocides. Furthermore, in the biocides field exposure situations are different to those in the pesticides field.

Some common problems in both areas include missing guidelines for the performance of studies or inappropriate guidelines adapted from the toxicological testing of chemicals.

E. g., the following points are challenging:

- **Toxicity testing**
  - Genotoxicity testing: Should an Ames test be performed? If yes, how?
  - Toxins: no harmonised test protocols are available. How can the potential for expression of encoded toxins in exposure situations be realistically predicted?
  - Sensitisation studies: are GPMT and LLNA predictive for the sensitising potential of microorganisms? Is there a higher risk for respiratory sensitisation than for chemicals?
  - Acute toxicity testing: how should pathogenicity testing included? What is an adequate limit dose to be tested?

- **User/Bystander exposure models**
  - Without reference values for local and systemic effects on human health the assessment is qualitative/semi-quantitative and relies mainly on options for risk reduction (PPE, re-entry).
  - Development of models and harmonisation is necessary.

- **Residue studies**
  - Usually, routine methods do not distinct between the strain used in the product and environmental strains.

- No models for viable residues after repeated use are available.
- Inactivation after use: data for field/greenhouse applications are needed.

These unsolved problems are a major obstacle for the approval of microbial active substances and authorisation of microorganism-containing biocides and pesticides. Working towards a harmonised approach for both areas may facilitate and promote regulatory decisions for those products in the future.

**Overview on the existing EU regulatory system (biocides and pesticides) with focus on differences and similarities between environmental data requirements for microorganisms**

*Christine Vergnet, DPR & ANSES, France*

Since the implementation of directive 91/414 and regulations, a number of microorganisms were or are currently assessed for their risks to the environment. The data requirements are very similar. Exposure scenarios based on the intended uses lead the data requirements for non-target organisms being exposed. Literature data are questioned (species/strain identification) but also regulatory studies (test batch/specification, extrapolation active substance to product). With regard to the uniform principles for the environment and non-target species (which are similar), the principal issues for the environment extracted from the published conclusions of the pesticide peer review are presented: assessment of potential interference with analytical systems and of potential transfer of genetic material to other organisms, assessment of persistence / competitiveness, accumulation in soil and contamination of groundwater, assessment of the risk to biological methods of sewage treatment, environmental risk assessment of potentially produced secondary metabolites.

**Critical Issues about Microbials used as Biocides and Plant Protection Products**

*Maristella Rubbiani, Istituto Superiore di Sanità, Italy*
*Marco Nuti, University of Pisa, Italy*

During the last decade, several “microbials” have been authorized for commercialization as biocides and as plant protection products at both active substance level (EU) and formulated product (many European Member States). During and after the authorization (re-evaluation) process some critical issues emerged. They include the identity and biological traits of the active ingredient of the microbial, along with its toxicology/genotoxicity and workers/operators/bystanders exposure, the contaminants level, the ecotoxicology /environmental fate. In addition, some issues of general relevance were raised by different Member States, including data protection, cumulative risk assessment, harmonised approaches, “low-risk” active substances, sensitization, development of further guidance for applicants. These issues are discussed taking into consideration the recent scientific advances in the different fields, in order to identify major biosafety-oriented research needs, international harmonisation opportunities in the context of the European legislation, and the need for re-evaluation/guideline update.

**An overview of Australia’s regulatory system for biological pest control products**

*Jay Kottege, Principal Evaluator Pesticides, Australian Pesticides and Veterinary Medicines Authority*

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the authority responsible for regulating agricultural and veterinary chemicals in Australia. Australia regulates agricultural and veterinary chemicals pursuant to the Agricultural and Veterinary Chemicals Code Act (1994). The legislative

definition of an agricultural chemical product is wide in scope and encompasses biological agricultural products, including microbial pest control products.

In Australia the regulation of chemicals is a function of the States. Subject to a cooperative agreement between the States and the Commonwealth of Australia, the APVMA (which is a Commonwealth Government Authority) regulates agricultural and veterinary chemicals up to and including the point of retail sale, with States controlling their use, pursuant to State based Control-of-Use legislation. The Agricultural and Veterinary Chemicals Code Act (1994) and associated legislation provide the legislative basis for the APVMA's regulatory role. The APVMA seeks risk assessment advice on public health and safety, and environmental safety from its Commonwealth regulatory partner agencies, the Department of Health, and the Department of the Environment, respectively. Efficacy assessments are conducted by experts that are employed as external service providers to the APVMA.

As is the case in most countries, microbial pesticides in Australia are regulated similarly to the chemical pesticides as they are used for similar purposes. Given the key differences between chemical pesticides and some microbial pesticides, it can be problematic to use essentially chemical pesticide- orientated data requirements to regulate microbials. The data requirements need to be matched to the specific risks posed by biologicals or chemicals-orientated requirements need to be adapted in ways that are relevant and justifiable. In essence, the regulator needs to be able to strike the right balance by retaining the ability to examine product risks thoroughly when it is necessary to do so while also finding ways to provide flexibility to introduce innovative lower risk products quickly. Striking this balance has proven difficult at times.

Several brief examples are cited from the APVMA's recent experience in regulating biologicals to illustrate the type of issues that have arisen. Determining the appropriate level of efficacy and data support for safety aspects have remained an enduring challenge. Against this backdrop, the value of greater interactions with, and learning from the experience of fellow regulators at international level who have encountered similar issues, could not be overstated.

## The actual regulatory frame for the use of microorganisms for pest control

*Jose Herrera, Federal Commission for the Protection from Sanitary Risk, Ministry of Health, Mexico*

The Federal Commission for the Protection against Sanitary Risk (COFEPRIS) is a decentralized organ of the Department of Health of Mexico, with technical, administrative and operational autonomy, whose mission is to protect the population against sanitary risks, through sanitary regulation, control and promotion under a single command, which provides unity and homogeneity to the policies which are determined.

At the COFEPRIS, the scope previously attributed to sanitary regulation, control and promotion was enlarged and transformed from an instrumental policy into a public policy by objective; that is, it went from being a medium to becoming the social purpose of the latter, including other non-regulative instruments, with the intention of preserving more efficiently the population's health.

The scope of competence of COFEPRIS is the sanitary regulation and promotion of the production, commercialization, import, export, publicity of, or involuntary exposure to: Health-related drugs and technologies (drugs, medical equipment and devices, blood and hemo derivatives, organ transplant, health services), Products and Services (food, beverages, tobacco, perfumery and beauty products, biotechnologicals), Health at Work (work exposure), Basic Maintenance (water, markets, residues, trails

sanitary emergencies), Risks derived from Environmental Factors (water, air, soil), and Toxic and Dangerous Substances (pesticides, fertilizers, chemical precursors, essential chemicals).

In Mexico, pesticides and plant nutrients requires sanitary registration, that is a shared process between the agricultural (SAGARPA), environmental (SEMARNAT) and health (SALUD) Mexican authorities under the established on the General Health Act (Article 376) and in the Regulation for Registration, Export and Import Permits and Certificates for Export of Pesticides, Fertilizers and Toxic and Hazardous Substances.

On the Mexican pesticide regulation, the biopesticides category is not defined, and the pesticides are grouped on: Chemicals, Biochemicals, Botanicals, Miscellaneous (e.g. soaps) and Microbials (including Microbial Basis of Genetically Modified Organisms). In comparison with chemical pesticides that requires around 62 requirements to be authorized, the microbial pesticides needs around 41 requirements and 30 the GMO microbial pesticides, and actually COFEPRIS/Mexico have authorized about 100 of microbial pesticides (including bacteria, fungi, virus and nematodes).

However, the data requirements need to be actualized to the specific risk of biological pesticides considering the scientific knowledge and the state of the art on microbial pesticides and thus, for COFEPRIS/MEXICO is so important to learning and sharing from experiences with another sanitary regulators and international organisms.

**Regulation of Microbial Pesticides in the United States**

*Chris A. Wozniak, U.S. Environmental Protection Agency*

Several statutes influence the regulatory process for microbial biopesticides in the US, however, this presentation will focus on the two principal statutes, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). FIFRA defines what organisms are considered as microbial biopesticides for regulatory purposes and defines what constitutes a pest as well. Bacteria, viruses, fungi, protozoa and algae are included in the realm of biopesticides whereas entomopathogenic nematodes and arthropods used as biological control agents are not considered for registration under FIFRA except in cases of paratrangenesis wherein the microbial symbiont has been somehow modified (e.g., *Wolbachia* in mosquitoes).

Residue levels of pesticides are assessed through toxicity studies to determine if a numerical, quantified tolerance or if the level of the pesticidal substance is safe for consumption by man and animals or if an exemption from the requirement for a tolerance is justified with no numerical residue level determined. To date, all of the microbial pesticides registered under FIFRA have received an exemption from the requirement for a tolerance under FFDCA.

The EPA's Office of Pesticide Programs considers toxicity and pathogenicity in its assessment of microbial biopesticides as well as potential effects on non-target organisms. Guidelines exist for testing on mammals, birds, fish, beneficial insects and plants; these documents are not legally binding, however, they do represent agreed upon methods for satisfying data requirements as detailed in Title 40 of the Code of Federal Regulations which governs pesticide regulation. Guideline documents are periodically updated as new information is available or as novel biopesticides are noted to present challenges to approved testing methodology.

The US EPA registers strains of microorganisms for pesticidal purposes, however, previous knowledge regarding the natural history of the microbial species can influence the course of the risk assessment. This aspect will be discussed with Bacillus pumilus used as an example of significant strain variation within a species and the impact of this variation on pesticide label restrictions relative to use sites.

**Regulation of Microbial Pesticides – The New Zealand Experience**

*Warren Hughes, Ministry for Primary Industries, New Zealand*

The New Zealand regulatory regime for microbial pesticides is covered by two principle pieces of legislation. These are the Agricultural Compounds and Veterinary Medicines Act (ACVM) 1997 administered by the Ministry for Primary Industries (MPI) and the Hazardous Substances and New Organisms (HSNO) Act 1996 administered by the NZ Environmental Protection Authority (NZ EPA).

The ACVM Act registers trade name products and considers their risks in relation to trade, agricultural security, animal welfare, public health and ensures their compliance with domestic residue standards. The HSNO Act approves hazardous substances and new organisms and considers their hazards for health and safety and environmental purposes.

Registration of microbial pesticides under the ACVM Act requires the applicant to submit information on its chemistry and manufacturing properties, residues (if application) and efficacy. The regulatory information requirements are focussed on chemical based pesticides with applicants of microbial pesticides being required to adapt them for their products.

In the case of the HSNO Act, the NZ EPA seeks applicants of microbial pesticides to submit information generally in line with the US EPA requirements for microbial pesticides.

Maximum Residue Limits for pesticides are set as standard under the Food Act 1981. There is an exemption in this standard for Microbial pesticide organisms provided certain criteria are complied with.

The main regulatory issue for regulatory oversight of microbial pesticides is lack of specific information requirements for such products and the applicability of chemical based pesticide information requirements to microbial pesticides. In particular, determining the information requirements in the chemistry and manufacturing, efficacy and toxicology areas.

**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.**

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

The European Food Safety Authority (EFSA) has been ascribed roles in the European Union (EU) regulatory procedure for the approval of microbial active substances and authorisation plant protection products containing these organisms. These are set out in: Regulation (EC) No 1107/2009, Commission Regulation (EU) 188/2011 (applicable to organisms where requests for EU approval are more recent) and Commission Regulations (EC) No 2229/2004 / 1095/2007 (for organisms that have been on the European market before July 1993).

Dossiers to support applications for approval under these regulations are submitted to a nominated competent authority in an EU member state, who provides their evaluation of the information provided and consequent risk assessment in a 'Draft Assessment Report' (DAR). The DAR is then submitted to EFSA who makes it available to all member state competent authorities and the public. EFSA requests comments on the DAR and its own experts also provide comments. Based on the comments received (to which the applicant and evaluating member state get an opportunity to respond) further information may be requested from the applicant and/or discussions can be arranged by experts working for the member state competent authorities. At the end of this process EFSA staff write and EFSA publishes its conclusion on the risk

assessment carried out for representative uses, for each organism. The conclusion is made in the context of the EU data requirements and considering the uniform principles for evaluation and authorisation of plant protection products (part II of Commission Regulation (EU) 546/2011).

The European Commission and Member States then use the EFSA conclusion and DAR to inform their decision making on the approval of the organism. In these assessments the information / guidance contained in OECD series on pesticides No. 65 (ENV/JM/MONO(2011)43; 12-Oct-2011) and Submission of scientific peer-reviewed open literature for the approval of pesticide active substances, EFSA Journal 2011;9(2):2092 is important. Aspects of OECD series on pesticides No. 67 (ENV/JM/MONO(2012)1; 17-Feb-2012) have also proved useful in the assessments.

The following aspects required by the EU regulatory framework are often not completely addressed in the available assessments: Appropriateness of methods for strain identity; Lacking evidence on relationships / lack of relationships to known pathogens; metabolite presence / absence in the product; potential for metabolite formation in environmental compartments following application; transfer of genetic material to other species; lack of information on absence of interference on EU 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. There is a need for guidance, on practice for risk assessment for microorganisms when used in plant protection products, against the EU regulatory framework (data requirements and uniform principles for product decision making).

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

*Kersti Gustafsson, Swedish Chemicals Agency*

Pesticides including biocides are used to control harmful organisms. Chemicals are the most common pesticides; however the use of microorganisms is increasing. At least in the EU these microorganisms are regulated with the same regulations as chemicals and outside the EU often in a similar way as chemical pesticides. Microorganisms differ from chemicals especially as they are living organisms with biological properties, in that way it is quite strange that microorganisms and chemicals can be regulated in the same way. However, taking into account the purpose of controlling harmful organisms a similar regulation is instead logical.

For the risk assessment of chemicals the basis is knowledge of the intrinsic properties and knowledge of the exposure to humans and to the environment. The same is valid for microorganisms.

The difference between chemicals and microorganisms is the biology including the property to proliferate. As living organisms microorganisms respond to the environment in different ways, one aspect is producing metabolites. Compared to chemicals it might be more difficult to list all possible intrinsic properties for microorganisms as they are more complex. With microorganisms it could therefore be that the exposure part of the risk assessment should be paid more attention to than with chemicals.

The regulations for chemicals have been further improved with guidance documents and criteria. This is also necessary for microorganisms, a lot has been done but there is still need for further improvement. Especially there is a need to develop further guidance in detail and decision criteria that concern the fact that microorganisms are living organisms and can either die or proliferate. There is also a need to develop different exposure scenarios. The dissemination of microorganisms is performed with different techniques

which give varying exposure to man and environment. With negligible exposure maybe a little less information on intrinsic properties is needed.

It is recommended to take note of improvements for chemicals and improve the regulations with regard to the biology of and the exposure to man and environment for microorganisms.

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

*Marloes Busschers, Ctgb, the Netherlands*

During the OECD BioPesticides Steering Group (BPSG) meeting of 12 June 2012 at OECD in Paris, it was decided, that in order to promote harmonisation of data requirements, hazard assessment and risk assessment, a simple questionnaire was to be circulated to regulators of OECD member countries and via IBMA to their members. In the questionnaire the respondents were asked to indicate what issues and/or problems they encounter with Test Guidelines using these for microbial testing.

The table contained all OECD data requirements for the Microbial Pest Control Agent (Part A) and the Microbial Pest Control Product (Part B).

Input came from 11 regulatory bodies (7 EU countries, Canada, USA, Japan and Australia), and 10 biocontrol companies/consultants via IBMA.

From the replies it appeared that there was a large variety of issues and problems, rather evenly distributed over the different chapters and aspects of the data requirements.

There was some consensus, e.g. on the scientific name and on repeated dose toxicity testing, it appeared that despite the lack of relevant test protocols or guidelines, further guidance seemed not necessary.

However, one of the main discussion issues was on toxins/metabolites. Other fields where problems are indicated or where there was divergence between countries, are e.g. in the field of characterisation of the microbe, analytical methods, impurities including pathogens, mammalian toxicity, fate and behaviour, and ecotoxicity. Data requirements give rise to different interpretations, there is insufficient guidance, the proof for a non-existence is rather difficult, or the test protocols are not applicable (either chemically orientated or not tailored to the microbial and the country specific circumstances).

## III. Industry/consultants views

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

*Philip Kessler, Andermatt Biocontrol AG*

One characteristic of many biopesticides is their narrow host range. This represents a lot of advantages, e.g. protecting the beneficial fauna, its harmlessness towards human health etc., but it significantly reduces the potential market size for such products. The procedures for the registration of a biopesticide are mostly the same as for a chemical plant protection product, even if the characteristics of the active substance and the exigencies for the risk assessment differ in many aspects. The difficulties of registering biopesticides are (1) unknown or inappropriate data requirements for the registration of biopesticides, often leading to (2) high or unpredictable costs for registration data packages; (3) lack of experience within authorities to assess biopesticides, often resulting in (4) unreasonable delays of the evaluation procedures; and last but not least (5) high registration fees. These high investments and uncertainties represent a major constraint when registering a biopesticide for a small niche market.

The OECD provides already suitable consensus documents and guidelines that should facilitate the registration of microbial pesticides, and build also a fundament for the risk assessment of certain groups of microorganisms to be used for plant protection (e.g. baculoviruses). Whereas such guidelines and documents has been appreciated and accepted by many OECD countries, single OECD countries still do not accept or fully implement them. Harmonisation would help to increase predictability and reduce costs for unnecessary studies.

The new EU regulation 1107/2009 provides new criteria for the approval of plant protection products, but difficulties to predict exact data requirements and timelines still remain. Although big agrochemical companies are playing recently a major role within the biocontrol industry, the high investments still keep these companies from registering products for small sized markets. Such niche markets often represent an attractive potential for the small and medium enterprises (SMEs). However, the high investments and uncertainties to register their products within the EU are financially too risky or just not affordable for SMEs. It can already be observed that companies are forced to market their products outside of the EU, where the registration of biopesticides is easier, as for example in the US or Canada. As a consequence, European growers will lack new innovative, environmental friendly biopesticides in the near future, especially in niche markets.

Conclusively, biopesticides need to be regulated, but the requirements should stay reasonable, so that companies are still able to further invest not only in the marketing, but also in R&D for new products. Data requirements and timelines need to be more predictable and transparent, the fees adapted, and the evaluation conducted by authorities specialised on biopesticides.

### Experiences with data requirements

*Rüdiger Hauschild, GAB Consulting*

Data requirements for microbial plant protection products and biocides and their active ingredients are quite similar in different regulatory systems. These data are needed to exclude negative effects on humans, non-target organisms or the environment during use of the products. Although formal requirements are well harmonised, differences exist in the interpretation of these requirements.

In all regulatory systems, microorganisms are evaluated at strain level. It is commonly agreed that published literature may be used to address different data requirements. Discussions may arise on the question to which extent studies with the respective strain are needed or if published data are sufficient.

Most of the microorganisms currently used as biocontrol agents are scientifically well characterized and some of them are used since decades, for example species of the genera *Bacillus*, *Pseudomonas*, *Trichoderma*, *Verticillium*, *Beauveria* or Baculoviruses. For these organisms, many publications which can be used for the risk assessment are available. In spite of the long use of microorganisms in biocontrol, very few reports on negative effects of microorganisms used for biocontrol are available in published literature.

One point where data requirements can be interpreted very differently is the assessment of microbial metabolites. Microorganisms can produce and secrete metabolites in the environment, but chemical properties of these metabolites differ considerably. Microbial metabolites may be inhibitory to fungi or bacteria, toxic to insects, or induce resistance in plants. Other metabolites may be toxic to non-target organisms. They can be – alone or in combination with other mechanisms - involved in the mode of action.

The assessment should be based on literature information on the biology and systematics of the microbial species and data of the plant protection product. Further experimental data are only recommended if this initial information indicates a risk to humans, non-target organisms, or the environment.

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

**Experiences with compilation of microbial dossiers: relevance of current data requirements**
*Roma L Gwynn, Rationale*

The occurrence of microorganisms as insect and plant pathogens has been documented for over 100 years and there is a good body of literature detailing this. That said, research is constantly finding out more about the biology and ecology of these microorganisms. For use as plant protection agents we are harnessing a small part of the potential of microorganisms to cause short terms effects that will reduce the presence of the economically damaging pests weeds or diseases to below the economic damage threshold long enough to get the crop to harvest or market.

However, we need to be able to use these products with the confidence that we are not going to cause harm to humans or the environment so we need to assess their safety. The current systems of active substance approval and product authorisation, designed for chemicals, have been adapted, mainly through guidance documents, to accommodate microorganism based products. However, there still remain questions/data requirements for which the study or test results are always negative. This raises the question whether these studies are relevant and if not what studies are required.

The presentation provides more details on experiences with registration of microbial PPP and indicates some areas where there is need for further changes to the data requirements.

## The Way Forward – A Vision from IBMA

*David Cary, Executive Director, IBMA*

The Biocontrol industry is working under regulations designed to assess and regulate the risk that conventional pesticide products pose to human health and the environment. These are in many instances inappropriate for the types of substances produced by our industry.

Reviews of regulatory frameworks and events including the work done by Grant & Chandler in the Biopesticides: The Way Forward RELU Project and the EU REBECA Project have highlighted the need for change but only when we have reached political maturity.

With the increased forecast use of alternative control products in the future and an increasing level of political maturity and interest the time may be right to set a harmonised system sponsored by and overseen by Intergovernmental Organisations led by OECD and strongly involving FAO. Such a harmonised scheme would then utilise the limited existing expertise and focus on developing co-operation and expansion of expertise where needed with minimal duplication and inconsistency between competent authorities across the globe.

There is a unique opportunity to focus on areas of appropriate concern for substances from the biocontrol industry that are feasible and of value and add to the assessment of risk of these substances. The guidance can be established by OECD to ensure that the regulation of biocontrol products is proportionate to the risk they pose to human health and the environment.

FAO can act as a conduit to ensure access to biocontrol products is not limited to OECD countries but outreach is designed and inbuilt into any new or modified system.

## IV. Science/academia view

### Scientific support, literature review and data collection and analysis for risk assessment of microbial organisms used as active substance in plant protection products
### Lot1-Environmental Risk characterization

*Maria Arena, Pesticides Unit, European Food Safety Authority*

The Pesticides Unit of EFSA launched a procurement call to collect and evaluate all the relevant information supporting the preparation of a guidance on how to conduct risk assessments for microbial pesticides within the frame of EU peer review of active substances in pesticides also with a view to gauge the extent of uncertainties associated with the use of such pesticides which will be important in regard to potential precautionary elements to be introduced in a future guidance.

The procurement call was split in 2 lots covering both the environmental risk characterization and the toxicology of microbial active substances.

The lot on environmental risk characterization was awarded to Bio Intelligence Service, a French consultancy company, which is supported by two subcontractors, while the lot on toxicology could not be awarded.

For the lot on environmental risk characterization, the systematic review of all the available literature will support the evaluation of whether the extrapolation or read across among species/strains/isolates with regard to infectivity, pathogenicity and the different ecotoxicological endpoints/adverse effects (as described in Regulation 544/2011) is scientific valid and whether and which conditions could be set for waiving experimental data on non-target organisms

The preliminary results of the project highlighted the importance of a systematic literature review for a complete Risk Assessment of the microbial a.s., as required by the Article 8.5 of the Regulation 1107/2009 and the need for a guidance document on the Risk Assessment methodologies for microbial active substances. (Note: the published report for Lot 1 is available from http://www.efsa.europa.eu/en/supporting/pub/518e.htm)

### The SLU Center for Biological Control

*Margareta Hökeberg, Swedish Agricultural University*

The Swedish University of Agricultural Sciences, SLU, has started a Centre for Biological Control (CBC), on a mandate and funding from the Swedish Ministry for Rural Affairs. At CBC, we conduct fundamental and applied research on biological control (i.e. the use of living organisms to control or restrict damages caused by harmful organisms), which aims to strengthen the knowledge base and facilitate the development and implementation of new biocontrol products and approaches. The centre considers augmentation, conservation and classical approaches, with utilization of both microorganisms and invertebrate animals. Close cooperation with stakeholders, such as growers, industry, authorities and organisations is an integral part of CBC activities.

Biological control has a great potential to restrict damages caused by pests and diseases within e.g. agriculture, horticulture and forestry. It is expected to gain in importance as a significant part of Integrated Pest Management (IPM), which should be implemented in all EU countries by 2014. There is still a lack of biological control products and methods against important pests and diseases and new product concepts are being developed. While still ensuring human and environmental safety, rules and regulations concerning

plant beneficial microorganisms should ideally not cause unintended restrictions to new evolving concepts in the area.

**Evaluation of non-viable residues and relevant metabolites**

*Ingvar Sundh, Swedish University of Agricultural Sciences*

The common EU data requirements and uniform principles as regards plant protection products containing microorganisms as active agents have strong emphasis on evaluation of potential risks from relevant metabolites and non-viable residues of the microbes. This emphasis on chemical risks and the concept of 'relevant metabolites' has its foundation in the risk assessments for xenobiotic chemicals. However, the concepts and requirements connected with relevant metabolites and non-viable residues has been very problematic to apply to the naturally occurring, living microorganisms of microbial plant protection products. Examples of data requirements which have resulted in particularly problematic evaluations will be presented and discussed.

In EFSA:s (European Food Safety Authority) 'Conclusion on Pesticide Peer Review' for microorganisms several data gaps are usually identified, in the area of metabolites and residues, where the provided information was deemed insufficient for evaluation according to pertaining requirements. In this presentation, these data gaps will be discussed in light of the data requirements' comparatively weak coverage of current knowledge regarding general safety assessment of microorganisms. One critical point is poor recognition of aspects of the natural turn-over of microbial biomass (i.e. 'relevant metabolites' and 'non-viable residues') in the detrital food chain of soil and other ecosystems. It will be argued that the requirements' exaggerated emphasis on chemical risks has strongly contributed to the difficulties of fulfilling the requirements and finalising assessments.

One conclusion of this presentation is that evaluations that are both less complicated and more relevant could be achieved if the strong emphasis on chemical risks of data requirements and guidance was replaced with more consideration to advances in general microbial ecology and microbial safety assessment. Another conclusion is that today the principle 'guilty until proven innocent' is very strictly followed in the assessments of potential toxicity of non-viable residues and metabolites of microbial plant protection agents. However, the *absence* of toxicity can never be 100% proven and there is a need to critically discuss how far this principle actually has to be drawn, to achieve appropriate protection for humans and the environment in applications with microorganisms.

In conclusion, updated data requirements and guidance regarding evaluations of metabolites and non-viable residues of microbial control agents are urgently needed, both for industry when preparing dossiers and for regulatory authorities performing the assessments.

**Experiences of biological control, risk assessment, fungi.**

*Jan Stenlid, Swedish University of Agricultural Sciences*

Fungi are eukaryote organisms with wide occurrence throughout the terrestrial ecosystems. They play active roles as saprotrophs, parasites and symbionts with other organisms. When evaluating risks with using fungi as biological control agents against pests or pathogens there are several aspects that needs to be taken into account. In addition to health and environmental risks that might potentially be associated with chemical pesticides, fungi also have an inherited ability to spread away from the site where they are applied and interact with the microbial community. These aspects are all part of the activities that can be

used for biological control. Using *Phlebiopsis gigantea* used to control *Heterobasidion* root rot of conifers, I will discuss the potential of applied biological control fungi to interact with the resident fungal flora and the potential of a biological control agent to introgress into a local population of the biological control species. In field studies, neither of these two aspects where shown to have a significant importance.

**Secondary metabolites: a literature study - Key stones for risk assessment methodology**

*Jacqueline Scheepmaker, the Netherlands*

**Incentives for registration:**

Fears:

- Secondary metabolites can be mycotoxins (aflatoxin by *Aspergillus*)
- Stability metabolites in product after application
- Uncontrolled production of metabolites
- Secondary poisoning (birds, mammals, amphibians, earthworms)

Data requirements and the corresponding risk assessment needs to be fulfilled if ***all*** the following conditions are met:

The relevant metabolite is stable outside the microorganism

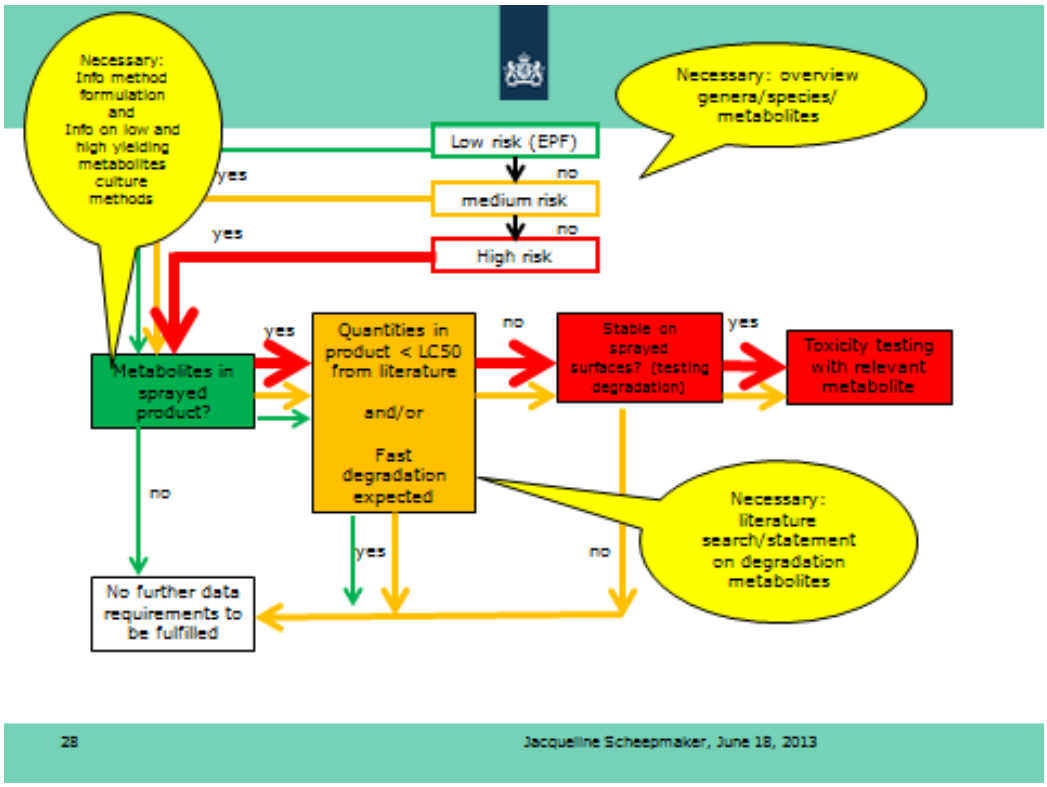
3. A toxic effect of the relevant metabolite is independent of the presence of the microorganism
4. The relevant metabolite is expected to occur in the environment in concentrations considerably higher than under natural conditions

Relevance of a metabolite depends on quantities produced and toxicity

**Conclusions of literature search:**

- Large range of metabolites produced by one species in liquid media
- Only few metabolites of *Metarhizium* in insects
- Range and quantities depend on contents of medium
- Time dependent optima of production
- Quantities produced vary among the strains
- Quantities of Beauvericin are 100x higher in non-EPF strains
- Data from literature are incoherent and incomplete:
  - Studies differ in all parameters : difficult to create coherent subsets
  - Incomplete descriptions of culture methods

**Scheme for discussion**




| **Statement** | **Necessary to justify statement** | **In what way simplifying data requirements** |
|---|---|---|
| Makes sense to differentiate into low, medium and high risk microorganisms (EPF = low risk) | Prepare general overview genera/species/metabolites | No further data requirements for low risk microorganisms |
| Many commercial microbial products only contain spores or biomass | General overview on formulation process. Contribution Industry? | Tool to differentiate into low, medium and high risk |
| Culture methods can be made either low or high yielding in metabolites | Determine what is low yielding. Comparison with LC50 values if present in literature? | If low yielding no further data requirements on metabolites |
| Secondary metabolites are degraded rapidly outside the microorganism, therefore the condition<br>“The relevant metabolite is stable outside the microorganism” is never met | Literature search necessary | No further data requirements (for fate and behaviour, domino effect for other data points) |

# ANNEX 6: Slides for Presentations

***Please refer to separate publication for full Annex 6***
**ENV/JM/MONO(2014)2/ADD**

Slides for the presentations given at the workshop can be found as separate files, published as addenda to the report.