

**Minutes: Risk Assessment of Microbials, Participants and Results  
Workshop on 12. – 13. April, Innsbruck, Austria**

Participants:

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**Plenum session:**

**Current data requirements and suggestions for reduced data requirements  
(Comments given by participants)**

Risks related with the use of the alternatives to BCAs should be considered (chemicals, doing nothing) in the registration process.

Direct communication between regulators and applicants can accelerate the registration process (for example see the new [‘Biopesticide Scheme’](#) of the UK Pesticides Safety Directorate).

Dossiers should be well prepared. E.g., data from literature should be summarised in an appropriate way by the applicant. If requirements are not relevant or applicable, it should be explained/demonstrated in detail by the applicant.

More mutual recognition and trust in the expertise of other countries is needed.

Scientific approaches instead of the precautionary principle should be the basis on a decision about a monograph. Focus on facts and not on perceived risks.

Fees for registration low risks plant protection products should be reduced and harmonised in the EU.

Member states and the Commission should give higher priority to the EU evaluation of the BCAs with the intention of quicker Annex I inclusion of these substances.

REBECA should define waivers and improved guidelines based on existing schemes rather than propose a new directive, which would take years to be accepted by member states.

EFSA should establish a „micro-organism group“ to evaluate microbial dossiers.

Farmer organisations should be used as a lobby promoting the better availability of low risk plant protection products on the market.

## Results of the group work

**(Evaluation and categorisation of risks, ranking/priority list of risks, suggested assessment strategies for relevant risks)**

*Common suggestions for microbial plant protection products (MBCAs):*

Species/strains must be identified by molecular characterisation (RFLP, ITS1-5.8S-ITS2, SSU, LSU,  $\beta$ -Tubulin, mtDNA, elongation factor, rpb, fingerprinting, IGS). In case of bacteria and fungi it is important to distinguish the strains used in the product from clinical isolates of the same species. In case of viruses identification of strains is not possible since no strain concept exists for these organisms. Consequently a regulation on the strain level is not applicable for viruses.

The species/strains must be deposited in a culture collection

The host range and the targets must be indicated

Efficacy data:

- Needed are data on intended use, application rate and method for the formulated product (also needed for an appropriate risk assessment).
- The beneficial effects should be described. No obligatory comparison with chemicals.
- Efficacy should not be required for each crop/application.
- GEP-assays should not be obligatory.

*Remarks for viruses:*

For baculoviruses it comes to the agreement that the published data are sufficient to cover the risk assessment data requirements. There is no need to submit new data under Annex IIB. Currently, three baculoviruses are being evaluated for Inclusion in Annex I: *Spodoptera exigua* NPV, *Adoxophyes orana* GV, *Cydia pomonella* GV. It was suggested that after evaluation of these dossiers, (and the expected inclusion into Annex I) all species of insect-specific Nucleopolyhedroviruses and Granuloviruses should be included into Annex I of Directive 91/414. However, basing on the available data and the OECD consensus document it can be questioned why baculoviruses can not be included into Annex I already.

For a new baculovirus product, only the following data are required at Member State level: In case of changed production methods or formulation, the applicant would need to submit data on the production method, medium components (preferable food grade) and occurrence of insect hairs (see as well table 2). In case of new baculovirus species only data on molecular identification and the host range has to be submitted and the species has to be deposited in a culture collection.

**Table 1: Risk associated with viruses (excluding product formulation)**

Risk	Impact	Suggested waiver	Comments
<b>Adverse effects on human health</b>			
Pathogenicity	Low	For Baculoviruses all data requirements are covered by the OECD consensus document.  In case of novel species, different from baculoviruses, cell culture studies can show that no interaction with mammalian cells exists and no activation of retroviruses occurs.	Baculoviruses are not pathogenic to vertebrates or non target invertebrates. OECD document: <a href="#">ENV/JM/MONO(2002)1</a>
Toxins Non-viable residues	Low	For Baculoviruses all data requirements are covered by the OECD consensus document.	
Sensitisation	Low		Available methods are not suitable for micro-organisms. New methods need to be developed.
Allergenic effects	Low	For Baculoviruses all data requirements are covered by the OECD consensus document.	It was suggested to waive the requirements for the investigation of allergenic effects since all living organisms can cause such effects and allergic people can protect themselves.
<b>Adverse effects on the environment</b>			
Adverse effects on non-targets	Low	No impact by baculoviruses	
Persistence	Low	For Baculoviruses all data requirements are covered by the OECD consensus document.	

<b>Genetic instability</b>	Low		It was suggested that the risks of reduced effectivity and altered specificity due to a genetic instability should not be a part of regulation since it will be controlled by quality control measures. On the other hand it was demanded that the producer demonstrates the ability to secure the genetic stability.
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**Table 2: Risk associated with the production and application of virus products**

Risk	Impact	Suggested waiver	Comments
<b>Adverse effects on Human health</b>			
Sensitisation	Low		Since viruses are produced <i>in vivo</i> , sensitisation (due to skin and inhalation exposure) might be caused by insect residues (hairs).
Microbial contamination	Low		Human pathogens must be excluded. Food safety standards would be sufficient to exclude risks. So far no defined thresholds are given for microbial contaminations in plant protection products. The occurrence of contaminations must be controlled for each product batch (quality control issue) and not only for the registration process. Therefore, it was suggested that it should only be verified that the quality control methods are sufficient to secure the food safety standards. It would be possible to demand standard quality control methods. On the other hand it was demanded that it should be demonstrated on the basis of product samples that the producer of the MBCAs is able to keep the threshold levels for contaminations.
<b>Adverse effects on the environment</b>	Low		Risks due to additives are low because of low amounts in the environment/application side.

*Remarks for fungi and bacteria:*

The presented tables (3, 4) for fungi and bacteria should be used as a basis for further discussions. There are not final recommendations. The rationale for all suggested waivers still needs to be justified in subsequent workshops.

It was questioned if there is any scientific evidence for environmental risks of MBCAs, especially for persistence. Data should be collected to prove if environmental effects can be excluded from regulation. Jaqueline Scheepmakers (RIVM, The Netherlands) is gathering information on the environmental impact of MBCAs.

The current mandatory test systems for the risk assessment of MBCAs need to be evaluated and justified regarding the applicability. It should be evaluated to which extent animal experiments with vertebrates can be substituted by other methods. For example test systems basing on the nematode *Caenorhabditis elegans* were already used for toxicity and pathogenicity investigations.

Clear pass/fail criteria for all risk assessments assays are needed in the guidelines for applicants and regulators.

**Table 3: Risks associated with bacteria or fungi (excluding product formulation)**

Risk	Impact	Suggested waiver	Comments
<b>Adverse effects on Human health</b>			
Pathogenicity Viable residues	High	No impact if the strain is not growing at a certain temperature (e.g., 37°C).	Animal ethics should be taken into consideration. Unnecessary assays or replicates of already performed risk assessment studies should be avoided. E.g., it can be questioned if clearance after intratracheal injection gives additional safety information compared to acute infection studies. It should be evaluated if alternatives to animal experiments can be applied.
Toxins Metabolites Non-viable residues	High	No impact if no toxic effects reported for the formulated product.	Animal ethics should be taken into consideration. It should be evaluated if alternatives to animal experiments can be applied.
Genotoxicity	High	No impact if Ames-test with the culture supernatant is negative.	



Sensitisation	Low		<p>Available methods are not suitable for micro-organisms. New methods need to be developed.</p> <p>It was suggested to waive the requirements for the investigation of sensitising properties since all living organisms may cause sensitisation.</p>
Resistance to antibiotics	Medium		<p>Due to the risk for infection of immune suppressive patients, data on susceptibility to antibiotics must be provided.</p>
<b>Adverse effects on the environment</b>			
Adverse effects on non-targets	Medium		<p>Only organisms relevant for the intended use should be tested.</p> <p>The origin and mode of action of the MBCA must be considered.</p> <p>Fungal MBCAs produce toxins in interaction with the target. Therefore, the toxin content in the product can be kept low. Consequently, exposure of humans resp. non-targets to toxins are usually negligible.</p>
Persistence	Low	<p>No impact if the MBCA is autochthonous in the application area.</p> <p>No impact if there are negligible non-target effects.</p>	<p>The mode of action of MBCAs is in many cases slower than for chemical pesticides. Therefore, persistence for at least several weeks might be needed for the efficacy of the products. E. g. in many soil applications of MBCAs the microbials need to build up a biofilm on the roots to be effective or they propagate in the target insects which keeps up their persistence.</p>

Persistence			<p>Knowledge on general occurrence of the MBCAs and background levels should be submitted.</p> <p>MBCAs disappear in the soil usually over time. Abundance of MBCAs is negligible compared to the natural microflora.</p>
<b>Genetic instability</b>	Low		<p>It was suggested that the risks of reduced effectivity and altered specificity due to a genetic instability should not be a part of regulation since it will be controlled by quality control measures. On the other hand it was demanded that the producer demonstrates the ability to secure the genetic stability.</p>

**Table 4: Risks associated with the production and application of bacteria or fungi based products**

Risk	Impact	Suggested waiver	Comments
<b>Adverse effects on Human health</b>			
Sensitisation	Low		Assessment only necessary for unknown (so far not tested) additives or residues of media compounds.
Microbial contamination	Low		See comments for viruses.
<b>Adverse effects on the environment</b>	Low		Assessment only necessary for unknown (so far not tested) additives or residues of media compounds.

**Final discussion:**

**Consequences for the availability of save plant protection products**

**Conclusions and future activities**

**Action plan** (to be initiated/carried out by REBECA)

The relevance of fungal metabolites in the risk assessment process will be summarized and recommendations for waivers will be developed. Therefore, REBECA will use the knowledge already acquired in EU projects like [BIPESCO](#), [RAFBCA](#) and by other experts.

REBECA should manage the establishment of a database containing the results of ecotoxicological investigations on MBCAs. This should be implemented into the REBECA web page ([www.rebeca-net.de](http://www.rebeca-net.de)).

A major problem is the lack of methods for the evaluation of pathogenic, toxicological and allergenic risks and models to assess different exposure scenarios. Sometimes 'standard' methods must be developed during the registration process at the expenses of the applicant. Risk assessment methods better adapted for the use with MBCAs should be evaluated by REBECA (Working Group 3). If no methods are available, REBECA can support the production of guidelines or propose research efforts for the development of novel methods.

It was discussed whether the current test systems to assess toxicological/clinical risks are appropriate for MBCAs. Many risk assessment requirements may not be relevant for MBCAs, e. g. no activation of the immune system ([Directive 2005/25/EC](#)). It was recommended to carry out a special workshop about this topic within the REBECA project to improve test systems which can better assess the specific risks related with MBCAs.

Regarding the consideration of animal ethics and costs related to animal experiments the REBECA project (Working Group 3) should evaluate the availability of alternative test systems for risk assessment. The applicability of such systems should be discussed with experts and research project might be initiated.

REBECA can bring together experts, in order to develop improved guidelines for the risk assessment of MBCAs and to prepare documents which qualify the presumption of safe use for certain MBCAs.