Miljøministeriet
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Evaluation Manual for the Authorisation of Microbial pesticides according to Regulation (EC) No 1107/2009

version 1; April 2021

Microbial Plant Protection Products

Changes in the Evaluation Manual Microbial Plant Protection Products

Evaluation Manual Microbial Plant Protection Products			
Version	**Date**	**Paragraph**	**Changes**
1.0	April 2021		Initial Microbial Plant Protection Products E.M.

General introduction

In this Manual we consider plant protection products that contain microorganisms (including viruses), as active ingredient. This groups of ingredients have different data requirements and guidances, which justifies a separate Evaluation Manual (E.M.).

This E.M. describes the Danish evaluation of Microbial Plant Protection Products in the EU framework under Regulation (EC) No 1107/2009. This Evaluation Manual addresses the evaluation of Microbial Plant Protection Products based on the data requirements and uniform principles. Mainly those issues that need further explanation are addressed. Where needed, important information from the Regulations or additional explanations and interpretations are provided.

The risk assessment described in this E.M. can be used both for the approval procedure for microorganisms as active substance, as well as for zonal and interzonal applications for the authorization of Microbial Plant Protection Products (i.e. core registration reports).

If the active substance used in the plant protection product has been registered under the plant protection framework in other non-EU countries, or under a different regulatory framework, the dossier and evaluation should preferably be made available.

Article 51 authorisations are authorised on a national level and may also be relevant for low risk products. For Denmark more information about article 51 authorisations can be found on the minor use section of the DEPA website.

1. Microbial Plant Protection Products

1.1 Introduction

Under Regulation (EC) No 1107/2009 a microorganism is defined as any microbiological entity, including lower fungi and viruses, cellular or non-cellular, capable of replication or of transferring genetic material.

Due to the ability of microorganisms to proliferate, there is a clear difference between chemical active substance and microbial active substance. Hazards arising from microbial active substances are not necessarily of the same nature as chemicals and these differences should be taken into account in the assessment.

The approval of microbial active substances is done on strain/isolate level. The exception to this is the group of **Baculoviruses** which have been approved on species level. A separate Guidance Document is available on how new isolates of Baculovirus species can be evaluated and added to the already approved isolates (SANCO/0253/2008 rev. 2).

For all microorganisms that are subject to application all available relevant knowledge and information in literature should be provided. The literature search should be carried out in accordance with the EFSA Guidance on the submission of scientific peer-reviewed open literature (EFSA Journal 2011; 9(2): 2092). Literature retrieved from this search should be reported in the relevant sections of the dossier. When a literature search is conducted it is important to also take into account previous taxonomic names which may have been used in past publications.

The data requirements are laid down in Part B of Commission Regulation (EU) No 283/2013 for active substances and in Part B of Commission Regulation (EU) No 284/2013 for plant protection products (PPP) based on microorganisms. The uniform principles for the evaluation and authorisation of plant protection products are described in Commission Regulation (EU) No 546/2011.

The Guidance Document on dossier preparation describes how the applicant should submit a dossier for the approval or the renewal of approval of an active substance which is a microorganism to comply with the Table of Contents described in Part B of the Annex to Regulation (EU) No 283/2013 and Part B of the Annex to Regulation (EU) No 284/2013.

For the submission of dossiers for zonal approval of plant protection products containing microorganisms, the microbial dRR formats should be used.

A guidance for applicants on preparing dossiers for the approval of a microbial active substance (SANCE/12545/2014 rev 2) is available on the EU website.

1.2 Identity of the microorganism

1.2.1 Name and species description, strain characterisation (283/2013; 1.3)

Each microbial active substance should be identified and named at the strain level.

Strain level identification should be carried out using the best available technology. The appropriate test procedures and criteria used for identification must be provided; nowadays DNA/RNA sequencing is considered the most appropriate procedure.

Taxonomy can change in time due to the transition to DNA sequence analysis for use in systematics, the names of microorganisms may change as well as the species affiliation. When a literature search is conducted it is important to also take into account previous taxonomic names which may have been used in past publications.

1.2.2 Specification of the material used for manufacturing of formulated products (283/2013; 1.4)

A Guidance on the Assessment of the equivalence of technical grade active ingredient for identical microbial strain or isolates (SANCO/12823/2012 rev 4) is available.

Content of the microorganism (283/2013;1.4.1)

The minimum content of the microorganism should be reported. Appropriate terms that are relevant to microorganism, e.g. colony forming units (CFU) per volume or weight, should be applied. Information of a maximum content should also be reported if concern for human health or the environment exists due to exposure to the microorganism or if relevant metabolites are produced.

Identity and content of impurities, additives, contaminating microorganisms (283/2013;1.4.2)

It should be shown that the level and nature of contaminating microorganisms are within the acceptable limits as stated in the OECD issue paper on microbial contaminant limits for microbial pest control products. Batch analysis should be provided to show that the TGAI complies with the OECD issue paper. This should be done under GLP.

If relevant metabolites are formed by the microorganism they shall be identified and characterised at different states or growth stage of the microorganism.

If present, additives (eg. organic solvents) contaminating the microorganisms have to be identified and quantified.

Analytical profile of batches

In principle five representative batches from recent and current industrial scale production of the microorganism shall be analysed for content of pure microorganism, impurities, additives and relevant metabolites, as appropriate. Submission of less than 5 batches should be justified.

The requirements in part A 1.11 regarding determination of all components in quantities of 1 g/kg or more and at least 980 g/kg of the material to be analysed is considered not appropriate for microorganisms. Relevant impurities and relevant metabolites need to be addressed.

Where the information provided relates to a pilot plant production system, the information required shall again be provided once industrial scale production methods and procedures have stabilised. Where available, industrial scale data shall be provided before approval under Regulation (EC) No 1107/2009. Where data on industrial scale production are not available, a justification shall be provided.

1.3 Biological properties of the microorganism

1.3.1 Origin and natural occurrence (283/2013; 2.1.2)

This section should be a summary of the information on the origin and natural occurence of the microorganism given in the section Fate and behaviour in the environment. It should include the following information:

- The geographical region and the place in the ecosystem (e.g. host plant, host animal, or soil from which the microorganism was isolated).
- Information on the geographical range and habitat of the strain and species.
- Information on the natural abundance (prior to application) of the species/strain in natural systems, if available.

1.3.2 Infectiveness, dispersal and colonisation ability (283/2013; 2.5)

This section should be a summary of the information on the infectiveness, dispersal and colonisation ability of the microorganism given in the section Fate and behaviour in the environment. It should

include the following information:

- Information on possible dispersal routes of the microorganism (via air as dust particle or aerosols, with host vectors etc.) under typical environmental condition.

- The persistence of the microorganism and information on its life cycle under the typical environmental conditions of use must be indicated. In addition, any particular sensitivity of the microorganism to certain environmental conditions (UV light, temperature, pH, humidity, nutrition requirements etc.) should be provided.

- Information on the growth of the specific strain at different temperatures.

1.3.3 Relationship to known plant or animal or human pathogens (283/2013; 2.6)
The possible existence of one or more species of the genus of the active and/or, where relevant, contaminating microorganisms known to be pathogenic to humans, animals, plants or other non-target species and the type of disease caused by them must be indicated. It must be stated whether it is possible, and if so, by which means to clearly distinguish the active microorganism from the pathogenic species. When appropriate, particularly with regard to detection techniques, reference can be made to sections on identification and quality control. Appropriate scientific literature on related pathogens should be cited.

1.3.4 Genetic stability and factors affecting it (283/2013; 2.7)
This section should be a summary of the information on the genetic stability of the microorganism and factors affecting it given in the section Fate and behaviour in the environment.

1.3.5 Information on the production of metabolites (especially toxins) (283/2013; 2.8)
Microbial metabolites are the intermediates or products of the metabolism of a microorganism and are not to be confused with the metabolites that are the result of degradation of a chemical active substance. Microorganisms produce a wide range of metabolites, mostly as a result of growth or as a response to environmental conditions in order to regulate their own growth, control competitors or to foster other organisms beneficial to them. In this process microorganisms can also produce toxins.

The interpretation of the data requirements for metabolites/toxins has been an issue of considerable debate in the EU for years. The new "Guidance on the Risk Assessment of Metabolites Produced by Microorganisms Used as Plant Protection active substances", has recently been noted by the PAFF and published.

This guidance document addresses metabolites present in the active substance1 and the plant protection product and also those produced by the microorganism after application (in situ production). In contrast to metabolites of chemicals, which are breakdown products metabolites addressed in this guidance document are components produced by the microorganism. Thus, chemical and microbial metabolites are equivalent in name only. Therefore, data requirements concerning metabolites of chemical plant protection products would not be applicable to microbial plant protection products.

The approach described in the guidance document is based on the consensus reached by the EU Working Group on Biopesticides and endorsed by the Standing Committee on Plants, Animals, Food and Feed. The approach implies that the assessment of all metabolites produced by a microorganism through an evaluation as performed for chemical active substances is not required, not feasible and unnecessary from a risk perspective, however parts of such assessment are needed under certain circumstances described in this document. The approach ensures that applicants provide all available data on metabolites including any indication of hazardous effects of any of these metabolites. For those metabolites for which a hazard is identified, this identified hazard is followed-up on by generating

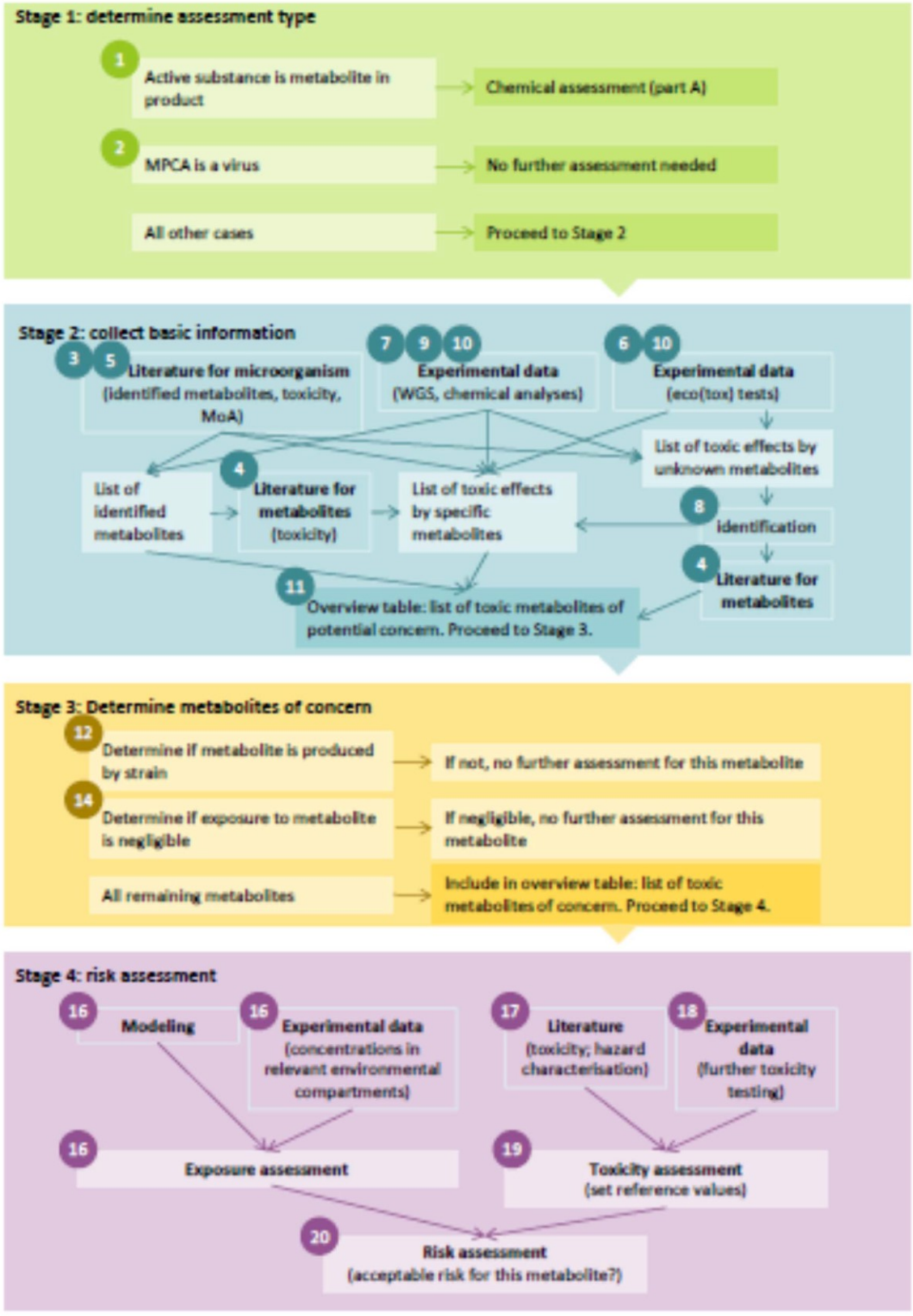
additional data where needed for a focused risk assessment for those particular metabolites.

To determine whether the microorganism is producing a metabolite of concern, the guidance document is organised according to a “step-by-step” procedure.

The structure of the guidance consists of 4 stages (see the figure below):

- Stage 1: Determining the assessment type
- Stage 2: Collecting a basic set of information on metabolites, resulting in a list of metabolites of potential concern
- Stage 3: Determining which of the identified metabolites are of concern, resulting in a list of metabolites of concern
- Stage 4: The risk assessment for metabolites of concern.

Each stage consists of several steps. These steps contain questions for the applicant and the risk assessor to guide them through the process of each stage.


Stage 1: determine assessment type
1
Active substance is metabolite in product
Chemical assessment (part A)
2
MPCA is a virus
No further assessment needed
All other cases
Proceed to Stage 2
Stage 2: collect basic information
3 5
Literature for microorganism (identified metabolites, toxicity, MoA)
7 9 10
Experimental data (WGS, chemical analyses)
6 10
Experimental data (eco(tox) tests)
List of toxic effects by unknown metabolites
List of identified metabolites
4
Literature for metabolites (toxicity)
List of toxic effects by specific metabolites
8
Identification
4
Literature for metabolites
11
Overview table: list of toxic metabolites of potential concern. Proceed to Stage 3.
Stage 3: Determine metabolites of concern
12
Determine if metabolite is produced by strain
If not, no further assessment for this metabolite
14
Determine if exposure to metabolite is negligible
If negligible, no further assessment for this metabolite
All remaining metabolites
Include in overview table: list of toxic metabolites of concern. Proceed to Stage 4.
Stage 4: risk assessment
16
Modeling
16
Experimental data (concentrations in relevant environmental compartments)
17
Literature (toxicity; hazard characterisation)
18
Experimental data (further toxicity testing)
16
Exposure assessment
19
Toxicity assessment (set reference values)
20
Risk assessment (acceptable risk for this metabolite?)

1.3.6 Antibiotics and other anti-microbial agents (283/2013; 2.9)

Applying micro-organisms in the environment by spreading them as plant protection products may potentially contribute to the antimicrobial resistance concern, through the spread of resistance genes which can be horizontally transmitted from the microbial pest control agent to pathogenic bacteria. The main objective of any policy to contain AMR is to reduce the above-mentioned risks related to spread of resistance genes and their impact on human and animal health.

Active substances must be approved under Regulation (EC) No 1107/2009 before they can be used in plant protection products. Uniform principles apply as regards the resistance to antimicrobial agents of importance for human and veterinary medicine. In addition to the approval criteria, the Regulation allows for the approval of an active substance as "low-risk substance" when it meets certain low-risk criteria, as specified in Annex II, point 5 of Regulation (EC) 1107/2009.

The Commission recently amended these low-risk criteria[1] to facilitate the identification of low-risk substances while ensuring a high level of protection of human health, animal health and the environment. They now provide distinct criteria for chemicals and micro-organisms.

Currently the only low-risk criterion for micro-organisms considers "multiple antimicrobial resistance". The text reads as follows:
“An active substance which is a microorganism may be considered as being of low-risk unless at strain level it has demonstrated multiple resistance to antimicrobials used in human or animal medicine”

This guidance document explains how to assess antimicrobial resistance of microorganism, as well as the risk of increasing the spread of antimicrobial resistance of human and veterinary concern, in relation to the approval criteria and the low risk criteria set under Regulation (EC) 1107/2009. The new “Guidance on the Approval and low-Risk Criteria linked to “Antimicrobial resistance”, has recently been noted by the PAFF and published.

1.4 Further information on the microorganism (283/2013; 3)

1.4.1 Information on the occurrence or possible occurrence of the development of resistance of target organism(s) (283/2013; 3.5)

Low risk plant protection products often have novel modes of action that do not show cross-resistance with existing products, as such they can offer advantages to resistance management. It is however possible for pests or pathogens to develop resistance to certain low risk products. Resistance management therefore needs to be addressed.

Resistance risk depends for a large part on the mode of action. As stated in EPPO PP1(276(1) microorganisms with an indirect mode of action (e.g. host plant defence induction or competition for nutrients) are often not at risk of resistance development in target organisms. In such cases this data point can be addressed with a statement. Microorganisms with a direct mode of action (for example infection of the target organism, or production of a toxin) can be at risk of resistance development, and several such cases are known from practice. In these cases the EPPO standard for resistance risk analysis should be followed. Please refer to EPPO standard PP1/213(4) (Resistance risk analysis)

It should be noted that most microorganisms and other low risk products are not listed in the FRAC, IRAC or HRAC mode of action classifications. Therefore, it is important to clearly describe the mode of action and the current resistance situation, preferably with references to scientific literature.

In some cases target organisms may develop resistance to some strains of a microorganism, but not to other strains of the same species. This differs from conventional plant protection products where often

[1] Commission Regulation (EU) 2017/1432, OJ L 205, 8.8.2017, p. 59

cross resistance exists between many active substances.

1.5 Properties plant protection product

1.5.1 Content of the microorganism and co-formulants in the plant protection product (284/2013; 1.4)

The content of the microorganism in the plant protection product should be reported in % w/w and in the appropriate units (eg. CFU/kg, spores/kg, IU/g). For liquid preparations, the content should also be reported in g/L.

For co-formulants in the plant protection product, referral is made to the regular evaluation manual (Chapter 2).

When the production process is a continuous process of an end-use product the five batch analysis can be provided for the product instead of the MPCA. The investigation should include the content of the microorganisms as well as to show that the product complies with OECD issue paper on microbial contaminants. This should be done under GLP.

1.5.2 Phys-Chem and technical properties of plant protection products containing microorganisms (284/2013; 2)

For the determination of the phys-chem properties referral is made to the regular Evaluation Manual EU part (chapter 2).

The accelerated storage stability study does not have to be performed if the microorganisms are not compatible with higher temperatures. The shelf life study may be performed at lower temperatures. In this case, the label should include the correct storage temperature.
The contaminating microorganisms should be determined before and after storage unless a reasoned case can be made that these contaminants cannot be formed during storage. The correct, commercial packaging type should be used in the storage stability study and should be indicated.

All properties required for CLP labelling should be addressed; for products containing an active microorganisms, these points can often be covered by a waiver. For the technical properties a waiver is not allowed.

1.6 Analytical methods (283/2013; 4)

1.6.1 Methods for the analysis of the microorganism as manufactured (283/2013; 4.1)

The following analytical methods should be provided:

- Method for the identification of the microorganism
- Method for providing information on possible variability of seed stock/active microorganism
- Methods to differentiate a mutant of the microorganism from the parent wild strain
- Methods for the establishment of purity of seed stock from which batches are produced and methods to control that purity
- 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
- Methods for the determination of relevant impurities in the manufactured material
- Methods to control the absences and to quantify (with appropriate limits of determination) the possible presence of any human and mammalian pathogens
- Methods to determine storage stability, shelf-life of the microorganism, if appropriate

The method to identify the microorganism should be capable of identifying the microorganism at strain

level.

The method to quantify the content of the microorganism in the manufactured material should be a validated method. In addition, the method to show that contaminating microorganisms are controlled to an acceptable level should be validated.

If the microorganism has the potential to produce a relevant metabolite with harmful effects to human health and/or the environment a validated method should be provided which can detect and quantify this relevant metabolite.

1.7 Effects on human health (283/2013; 5)

Hazards arising from microorganisms should be assessed differently from chemicals. Microorganisms are unlikely to be toxic in themselves but they may produce toxic metabolites. Microorganisms also have the potential to replicate and therefore their ability to cause infection or pathogenicity must be carefully assessed. They may also have the potential to cause sensitising reactions and non-specific effects such as an inflammatory response after exposure via inhalation.

The typical OECD test guidelines are not tailored towards microorganisms. Pending the acceptance of specific guidelines at international level, the information required shall be generated using available test guidelines accepted by the competent authority (e.g. US EPA Series 885 Microbial Pesticide Test Guidelines). Where appropriate if no US EPA test guideline is available, test guidelines as described in Part A of Commission Regulation (EU) No 283/2013 could be adapted in such a way that they are appropriate for microorganisms.

For all studies actual achieved dose in colony forming units per kg body weight (cfu/kg bw), as well as in other appropriate units, must be reported.

Evaluation of microorganisms is carried out in a tier-wise manner with the first tier consisting of basic information and basic studies and the second tier consisting of additional studies if the first tier tests have shown adverse health effects.

1.7.1 Active substance: Tier 1: Basic information and basic studies

Basic information (283/2013 ; 5.1)

Information related to symptoms of infection or pathogenicity caused by the microbial active substance that may be available from medical reports or from case reports should be reported. Information on the effectiveness of first aid and therapeutic measures should be submitted as well.

Reports on occupational health surveillance programmes should include detailed information on the design of the programme as well as on frequency, level and duration of exposure to the microorganism. Preferably, these reports must include data from persons exposed in manufacturing plants or after application of the microorganism (e.g. in efficacy trials). Available information on the sensitisation and allergenic response from workers, e.g. in the manufacturing plants, agricultural and research workers, must be provided as well. These records provide useful information, particularly as there are no validated methods for testing of sensitisation in animals.

Clinical case reports and epidemiological studies of the active microorganism or of any taxonomically related strains and species should be considered to assess whether the active microorganism is known to cause infection and pathogenicity in humans. If the microorganism in the study is a different species than the microorganism being assessed, it is important to clarify what distinguishes the two and whether it is likely that the active microorganism could exhibit the same properties. For such an analysis, information on the biological properties of the microorganism such as growth requirements and the presence of genes encoding known toxins may be useful. If the pathogenic species requires significantly different growth conditions or is taxonomically not closely related, that could be indications of a lower

risk of pathogenicity associated with the active microorganism.

Basic studies (283/2013 ; 5.2)

Sensitisation (283/2013; 5.2.1)

Although the data requirements do request a sensitisation study, there are currently no validated methods to evaluate sensitisation potential of microorganisms. Consequently, no study is required. If a study is carried out the results of this study, either positive or negative, should be interpreted with caution since the current dermal sensitisation studies are not validated for microorganisms. At the moment all microorganisms are regarded as potential sensitisers and the following precautionary phrase should be included on the label: Microorganisms may have the potential to provoke sensitising reactions'. In case there is clear evidence in literature that the microorganism is a respiratory sensitiser, classification applies instead of the warning phrase.

Acute toxicity, pathogenicity and infectiveness (283/2013; 5.2.2)

Studies on acute oral and inhalation toxicity, pathogenicity and infectiveness must be reported.

The inhalation toxcity can be tested either through inhalation or intratracheal exposure. Intratracheal exposure would ensure adequate exposure of the test animal to the microorganisms. For the inhalation exposure, generally the concentration of microorganisms in the atmosphere becomes too low and the particle size distribution is too high when administered via inhalation. Further, the viability can be affected due to shear forces from nebulisation. Most vegetative microbes, particularly Gram-negatives, suffer considerable damage (about 95% are killed) while gram positives are less sensitive and most spores survive. Fungi are difficult to get into respirable aerosols without significant loss in viability because of their size. Due to these considerations inhalation exposure is normally not recommended for microorganisms and an intratracheal study is preferred.

In addition to the oral and inhalation study, an intraperitoneal injection study is required. However, expert judgement may be exercised to evaluate whether subcutaneous injection is preferred instead of intraperitoneal injection if the maximum growth temperature and multiplication is lower than 37 degrees. This is because in those cases the microorganism would be more likely to cause infections in the skin rather than deep tissue infections.

All acute toxicity, pathogenicity and infectiveness studies should be carried out in accordance with GLP and the US EPA guidelines (OPPTS, series 885).

Genotoxicity (283/2013; 5.2.3)

It is considered unlikely that the microorganisms themselves can cause a genotoxic effect. Genotoxicity testing however may be relevant for metabolites. The specific metabolite could be tested in purified form using the same test methods as for chemical biocides. However, since microorganisms may produce a large array of metabolites, testing of a crude extract (i.e. the chemical constituents of the TGAI with cell walls etc., removed) could be considered. In such a test, the study design needs to be carefully considered as the concentrations of each component can be expected to be low and a component with a low genotoxic potential would thus not be detected in the test.

When performing genotoxicity studies with a crude extract it is important to avoid interference by constituents in the test samples such as provision of nutrients by lysates (e.g. histidine), growth factors that may produce abnormal growth, growth inhibition of DNA synthesis, enzymatic activity that could mimic endogenous activity in the test organism (e.g. kinase or phosphokinase activity in the $TK^{+/-}$ or HPRT assays), the occurrence of potentially active constituents as bound or complexed forms, or intracellular molecules with nuclease or proteolytic activity from *in vitro* lysates that would not normally have access to mammalian cell *in vivo* (J.T. MacGregor, 2005[2]).

[2] James T. MacGregor. Genetic Toxicity Assessment of Microbial Pesticides: Needs and Recommended

In the case of a virus the risk of insertion mutagenesis in mammal cells and the risk of carcinogenicity has to be discussed.

Cell culture study (283/2013; 5.2.4)
A cell culture study gives information on the ability of a microorganism to infect, replicate in, transform or cause toxicity in the cell system. The data requirements state that for intracellular replicating microorganisms, such as viruses, viroids of specific bacteria and protozoa, a cell culture study should be carried out.

The study shall be performed in human cell or tissue cultures of different organs. Selection can be based on expected target organs after infection. If human cell or tissue cultures of specific organs are not available, other mammal cell and tissue cultures can be used.

OPPTS guideline 885.3500 states that if the data show that the viral pest control agent preparation is toxic to any of the test cell cultures, but does not infect, replicate in or
transform any of the cell cultures, further information may be required to identify the toxic components of the preparation. Moreover, an acute toxicity study may be required with the toxic components.

Information on short-term toxicity and pathogenicity (283/2013; 5.2.5)
If adverse effects have been observed in the acute toxicity, pathogenicity and infectivity studies than further testing may be necessary to clarify the nature and severity of effects that may result from repeated administration of the microbial active substance.

1.7.2 Active substance: Tier 2 studies

Specific toxicity, pathogenicity and infectiveness studies (283/2013; 5.3)
In certain cases, it may be necessary to carry out additional studies to further clarify the adverse human effects. In particular, if results from earlier studies indicate that the microorganism may cause long-term health effects, studies on chronic toxicity, pathogenicity and infectiveness, carcinogenicity and reproductive toxicity must be carried out. Microorganisms infective to human cell lines may also need further investigations.

Before performing such studies it is recommended that the applicant shall seek the agreement of the competent authorities on the type of study to be performed.

Genotoxicity - In vivo studies in somatic cells (283/2013; 5.4)
If a positive result has been obtained with an *in vitro* study an *in vivo* genotoxicity study is required. The recommended methods are the same as for chemicals.

Genotoxicity – In vivo studies in germ cells (283/2013; 5.5)
When any results of an *in vivo* in somatic cells is positive, *in vivo* testing for germ cell effect may be justified. The recommended methods are the same as for chemicals.

1.7.3 Product

Basic acute toxicity studies (284/2013; 7.1)
Instead of carrying out the basic acute toxicity studies it would also be possible to address the need for classification and labelling of the product by using the calculation rules in accordance with Regulation (EC) No 1272/2008.

Additional acute toxicity studies (284/2013; 7.2)
A skin irritation and eye irritation study is required in accordance with the OECD test guidelines.

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approaches. Report to OECD. December 2005

Instead of carrying out these studies it would also be possible to address the need for classification and labelling of the product by using the calculation rules in accordance with Regulation (EC) No 1272/2008.

As there are currently no validated methods to evaluate sensitisation potential of microorganisms no study for skin sensitisation is required. To address the potential sensitising properties of co-formulants the calculation rules in accordance Regulation (EC) No 1272/2008 can be used.

If based on the co-formulants no classification for sensitisation is needed the following precautionary phrase should be included on the label: Microorganisms may have the potential to provoke sensitising reactions'. In case there is clear evidence in literature that the microorganism is a respiratory sensitiser, classification applies instead of the warning phrase.

Data on exposure (284/2013; 7.3)
Exposure to the microorganism:
In most cases no reference values are set for microorganism and therefore no quantitative exposure assessment is required.

In the absence of appropriate test methods all microorganisms are currently assumed to have the potential to cause sensitisation reactions in humans. Therefore, the user may be assumed to wear protective clothing (PPE). However, it should be noted that with regard to PPE there is no harmonized approach possible due to national requirements. Some Member States require respiratory protective equipment (RPE) for certain types of products (e.g. mixing and loading of powders) or type of application (indoor) while other Member States always prescribe RPE for all microorganisms. For low risk products in Denmark RPE is required for powder formulations but not for liquid formulations (without H332, H334 or H335 classification) or granule formulation which are nearly dust-free. Guidance on the use of personal protective equipment for use of pesticides in Denmark can be found: http://www.barjordtilbord.dk/Files/Billeder/BARjobo/pdf/saerlige_NET_2015.pdf

Exposure to relevant metabolites:
The exposure assessment should include any relevant metabolites/toxins present in the product. If quantitative data is available for a relevant metabolite, the exposure may be assessed in the same way as for chemical plant protection products. The level of the metabolite in the product can be used as input parameter in the model. This would address the risk to the operator, bystander and resident. Since in general no specific dermal absorption values will be available default values should be used.
For worker exposure some additional argumentation may be needed to show that the relevant metabolite is not expected to increase on the crops after application. Generally the information that is provided in the residue section can be useful to address this concern.

Supplementary information for combination of plant protection products (284/2013; 7.5)
In certain cases it may be necessary to carry out additional studies for combination of plant protection products where the product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix. However, this is not often the case for microbial plant protection products.

1.8 Residues in or on treated products

Information should be provided that allow an evaluation to be made regarding the risk arising from exposure to the microorganism and its residual traces and relevant metabolites (toxins) remaining in or on plant or plant products.

To evaluate the risk arising from residues, exposure data on levels of exposure to the residue may not be required where it can be justified that the microorganism and its metabolites are not hazardous to humans in the concentrations that could occur as a result of authorised use.

1.8.1 Persistence and likelihood of multiplication in or on crops, feedingstuff or foodstuffs (283/2013; 6.1)

The persistence of toxic metabolites, where relevant, and the likelihood of persistence and multiplication of the microorganism in or on treated articles, food or feedingstuffs must be addressed.

1.8.2 Further information required (283/2013; 6.2)

Non-viable residues (283/2013; 6.2.1)

Non-viable residues could be non-viable microorganisms or metabolites/toxins produced by the active microorganism either during fermentation or during growth of the active microorganism after application. Information on levels of non-viable residues in or on the crop is required when the following applies:

- relevant metabolites or other chemical substances of concern are present in the product; and/or
- relevant metabolites are expected to be produced by the microorganism in or on the crop

If a relevant has been identified this should be addressed in the consumer risk assessment taking into account the two points above.

If the relevant metabolites is present in the MPCA than a consumer risk assessment should be provided for the maximum level that the metabolite may be present in the product.

In addition, potential in situ production of the relevant metabolite needs to be addressed. Relevant information that can address this concern includes:

a) Translocation of the microorganism to the edible part of crop, e.g. for seed treatment
b) Persistence and multiplication of the microorganism on crops
c) Degradation of the relevant metabolite on crops
d) Residue data on the potentially relevant metabolite

Full residue data as required for chemicals is rarely needed as usually sufficient information is available to address the concern. However, if significant quantities of the relevant metabolite are expected and a risk to humans cannot be excluded residue studies may be required.

Viable residues (283/2013; 6.2.2)

If the information on persistence and multiplication indicate that persistence of relevant amounts of the microorganism may occur than possible risk to humans and/or animals must be investigated, unless it can be justified that the microorganism are not hazardous to humans in the concentrations that could occur as a results of the authorized use.

1.9 Fate and behaviour in the environment (283/2013; 7)

The basis for the assessment of the environmental fate and behaviour of a microorganism is information regarding its origin and the properties, and regarding the survival of both the microorganism and its potential residual metabolites after application.

The assessment of the environmental fate and behaviour therefore partly relies on information that is also required in Section 2 of the assessment dossier, reflecting the data requirements on the biological properties (2.1-2.9). To avoid duplication within the dossier, it is preferred to provide the full description of the paragraphs from Section 2 listed below related to the biological properties of the microorganism as part of the current section (using the same headers). A summary of this information should be provided in Section 2, along with a reference to the current section. The paragraphs from Section 2 that should be described here, are (first number between brackets refers to the numbering used in this document):

- **Origin and natural occurrence (1.3.1; 283/2013; 2.1.2)**
  The geographical region and the place in the ecosystem (e.g. host plant, host animal, or soil from which the microorganism was isolated) must be stated. Information must be provided on the geographical range and habitat of the strain and species. Moreover, if information is available on the natural abundance (prior to application) of the species/strain in natural systems, this information should be provided to support the environmental evaluation.

- **Infectiveness, dispersal and colonisation ability (1.3.2; 283/2013; 2.5)**
  Information on possible dispersal routes of the microorganism (via air as dust particle or aerosols, with host vectors etc.) under typical environmental condition should be reported.

  The persistence of the microorganism and information on its life cycle under the typical environmental conditions of use must be indicated. In addition, any particular sensitivity of the microorganism to certain environmental conditions (UV light, temperature, pH, humidity, nutrition requirements etc.) should be provided.

  Growth temperature:
  The growth temperature provides information which is relevant to human health risk and some other non-target animals such as mammals and birds. If the growth temperature is comparable to human body temperature, this may indicate a potential for infection. In contrast, a growth temperature incompatible with human body temperature could indicate a low concern for infectivity in humans. Therefore, a study on the growth of the specific strain of microorganism should be provided. If the growth temperature data is used to waive infectivity/pathogenicity studies than the growth temperature study should be carried out under GLP. Please note that the growth temperature data is not sufficient for waiving all toxicological infectivity/pathogenicity studies.

- **Genetic stability and factors affecting it (1.3.4; 283/2013; 2.7)**
  Information on genetic stability (e.g. mutation rate of traits related to the mode of action or uptake of exogenous genetic material) under the environmental conditions of proposed use must be provided.
  In addition, if the microorganism contains plasmids or other mobile genetic elements known to be involved in pesticidal activity, pathogenicity, toxicity, resistance etc., the stability of the encoded traits shall be indicated.

Relevant metabolites
All relevant metabolites of the MPCA that are identified in the section ‘information on the production of metabolites’ (283/2013; 2.8; see section 1.3.5 of this evaluation manual) need to be addressed in the assessment of the environmental fate and behaviour. Information on these relevant metabolites includes:

- Exposure of environmental compartments to the relevant metabolite. The exposure depends on the intended use (e.g., protected crop vs. field use, application method), the concentration of the relevant metabolite in the MPCP, and the *in situ* production of the relevant metabolite. As an example, the latter can be addressed for entomopathogenic fungi by information on quantities of the relevant metabolite in insects.
- Information on the environmental fate and behaviour of the relevant metabolite if exposure of environmental compartments to the relevant metabolite cannot be excluded. In the section ‘persistence and multiplication’ (1.9.1), information on the degradation rate of the relevant metabolite can be addressed. The adsorption potential of the relevant metabolite can be included in the section ‘mobility’ (1.9.2).

In contrast to chemical pesticides, no standard OECD test guidances are currently available for

microorganisms to provide data for the assessment of environmental fate and behaviour. As an alternative, OPPTS guidelines from the US Environmental Protection Agency can be used for the assessment dossier. In addition, all relevant scientific, peer-reviewed, open literature should be provided in the application.

1.9.1 Persistence and multiplication (283/2013; 7.1)

The persistence and multiplication of the microorganism is assessed in three environmental compartments (soil, water and air) as described below, unless it can be justified that exposure of a specific environmental compartment is unlikely to occur. During the assessment, special attention is paid to the competitiveness of the microorganism in question and to its population dynamics upon application of the biopesticide. The persistence and multiplication of the microorganism is evaluated within the context of the ecology of the microorganism based on information provided in section 2 on biological properties.

For each of the three compartments (soil, water and air) information is required to determine if it is expected that the microorganism and relevant metabolites/toxins persist in the environment in concentrations considerably higher than the natural background levels, taking into account repeated applications over the years. A methodology to determine the natural background levels is suggested in Scheepmaker and Butt (2010)[3]. If the microorganism is expected to be persistent, then a robust risk assessment should be provided to show that the risks from accumulated plateau concentrations are acceptable (Uniform Principles; point 2.7.7 of Commission Regulation (EU) 546/2011).

A full assessment of the environmental fate and behaviour according to 283/2016 Part A.7 may be required for any relevant metabolites that have been identified in section 2.8 which meet all of the following criteria:

- the relevant metabolite is stable outside the microorganism
- the toxic effect of the relevant metabolite is independent of the presence of the microorganism
- the relevant metabolite is expected to occur in the environment in concentrations higher than under natural conditions

Soil (283/2013; 7.1.1)

If there is no expected exposure of soil to the microorganism due to the use of the representative formulation according to the proposed use, a clear statement should be provided on why exposure to soil does not occur. In all other cases, the information as described below should be provided.

To assess the environmental fate and behaviour of microorganisms in soil, the test guidelines for chemical pesticides (described in Part A of EU Regulation 283/2013) should be adapted in such a way that they are appropriate for microorganisms. This means that the viability and population dynamics of the microorganism upon application must be reported in several cultivated and uncultivated soils that are typical of the various EU regions where use exists or is anticipated, or in other media (e.g. rockwool) in which use is intended. The data should include population numbers of the microorganism before application and during a time period of sufficient length after applications (including just after application). The method of quantification (e.g. counting of CFUs, or copy numbers) should be specific enough to draw conclusions about the dynamics of the applied test organism. Note that data from both laboratory and field tests can be used.

In addition, the initial predicted environmental density in soil (PEDsoil,initial) upon application of the representative formulation should be determined. This value can be calculated with the method described below.

[3] Natural and released inoculum levels of entomopathogenic fungal biocontrol agents in soil in relation with risk assessment and in accordance with EU regulations. Biocontrol Science and Technology 20, 503-552.

PEDsoil

The method to calculate the Predicted Environmental Density (PED) in soil is based on a worst-case scenario. The application rate in CFU/ha and the total amount of applications per year is used to determine the initial PEDsoil. All applications are dosed at once, no degradation and growth is taken into account and no crop interception is taken into account.

PEDsoil (CFU/ kg dry soil) = AR x n per Y/ 10.000 x d x ρ

- AR is application rate (CFU/ha; assuming the highest concentration of the microorganism according to the product specifications)
- n per Y is number of applications per year
- 10.0000 is the conversion factor from ha to m^2
- d is the thickness of the soil layer (default of 0.05 m)
- ρ is the density of soil (default of 1500 kg/m^3)

Water (283/2013; 7.1.2)

If there is no expected exposure of surface water to the microorganism due to the use of the representative formulation according to the proposed use, a clear statement should be provided on why exposure to surface water does not occur. In all other cases, the information as described below should be provided.

The viability and proliferation of the microorganism in natural water/sediment systems has to be addressed under both dark and illuminated conditions. The data should include population numbers of the microorganism before application and during a time period of sufficient length after application (including just after application). The method of quantification (e.g. counting of CFUs, or copy numbers) should be specific enough to draw conclusions about the dynamics of the applied test organism. Note that data from both laboratory and field tests can be used. When data is missing for either dark or illuminated conditions, a statement should be included as to if and why the results for the one condition can be used for the both conditions.

The Initial Predicted Environmental Density in surface water (PEDsw,initial) upon application of the representative formulation should be provided. This value can be calculated with the method described below.

PEDsw

The method to calculate the PEDsw is a worst-case application scenario. The application rate in CFU/ha and the total amount of applications per year is required to estimate the PEDsw. All applications are dosed at once, no degradation and growth is taken into account.

PEDsw (CFU/L) = AR x n per Y x (D/100) / (10.000 x Vd)

- AR is application rate (CFU/ha)
- n per Y is number of applications per year
- D drift percentage
- 100 conversion of percentage
- 10.0000 is the conversion from ha to m^2
- Vd is volume of the standard ditch per m^2

DEPA uses the BBA drift values[4] in combination with the TOXSWA standard ditch (30 cm deep with a

[4] Ganzelmeier and Rautmann drift values according to the BBA (Federal Biological Agency of Agriculture and Forestry, Germany) 2000: Bekanntmachung des Verzeichnisses risikomindernder Anwendungsbedingungen für Nichtzielorganismen. Bundesanzeiger 100: 9878-9880.

slope of 45 degrees and volume of 210 L/m^2) to determine the PEDsw values for microorganisms. For greenhouse uses of microorganisms, DEPA uses an emission percentage of 0.1%.

Air (283/2013; 7.1.3)
In case of particular concerns for operator, worker or bystander exposure, information on the concentrations in air should be provided.

1.9.2 Mobility (283/2013; 7.2)

The possible dispersal of the microorganism and its degradation products in relevant environmental compartments has to be evaluated, unless it can be justified that exposure of the particular environmental compartments to the microorganism is unlikely to occur. For each of the compartments which are exposed to the microorganism upon application, information should be provided on the mobility of the microorganism (e.g., dispersal of dormant stages, rain-splash dispersal).

In addition, information should be provided to demonstrate that the use of the microorganism, under the proposed conditions of use, does not have any harmful effects on groundwater.

If the microorganism poses a possible hazard to humans, animals or the environment, the applicant and the competent authority should first come to an agreement on which studies should be performed to provide sufficient information on the mobility of the microorganism.

1.9.3 Additional information required regarding the uniform principles for evaluation and authorisation of plant protection products

1) No authorisation shall be granted if contamination of ground water, surface water or drinking water expected as a result of the use of a plant protection product under the proposed conditions of use, may cause interference with the analytical systems for the control of the quality of drinking water provided for in Directive 98/83/EC (point 2.7.2 of 546/2011).

If a route of exposure of ground water, surface water or drinking water upon application exists, information should be provided to demonstrate that there is no interference of the microorganism or its residues with the analytical systems for the control of the quality of drinking water.

2) No authorisation shall be granted if it is known that transfer of genetic material from the microorganism to other organisms, may lead to unacceptable effects on the environment (point 2.7.5 of 546/2011).

This information should be provided under point 2.7 of 283/2013 and does not need to be addressed in the environmental fate and behaviour section.

Additional information on the environmental risk assessment is for example available in the OECD Guidance to the environmental safety evaluation of microbial biocontrol agents (OECD Series on Pesticides No. 67) and EFSA literature review on microbial organisms used in plant protection products[5].

1.10 Effects on non-target organisms

1.10.1 Data requirements

Pending the acceptance of specific guidelines at international level, the information required for the risk assessment on non-target organisms shall be generated using available test guidelines accepted by the

[5] Mudgal et al. Scientific support, literature review and data collection on microbial organisms used as active substance in plant protection products – Lot 1 Environmental risk characterisation. EFSA supporting publications 2013: EN-518

competent authority, i.e. US EPA microbial pesticide test guidelines: https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-885-microbial-pesticide-test-guidelines. The US EPA test guidelines do not require dose-response testing in the first Tier level, but instead a maximum hazard dose is tested, which is based on a safety factor times the maximum predicted environmental exposure. Where appropriate or if no US EPA test guideline is available, test guidelines as described for the data requirements in Part A of Commission Regulation (EU) No 283/2013 could be adapted in such a way that they are appropriate for microorganisms (the relevant test guidelines are included in in Commission Communication 2013/C 95/01 and Commission Communication 2013/C 95/02). Adaptation is for example relevant with respect to the test duration, which in the acute OECD guidelines usually is too short for investigating infectivity.

Testing shall include viable and, if appropriate, non-viable microorganisms, and a blank control. In general, GLP studies are preferred, but peer reviewed, scientifically sound studies can also be accepted. In section 3 of Commission Regulation (EU) No 283/2013, it is stated that by way of derogation from point 3.1 (conducting tests under GLP) for the a.s consisting of microorganisms and viruses, tests done to obtain data on safety with respect to other aspects than human health, may be conducted by official or officially recognised testing facilities or organisations which satisfy at least the requirements under points 3.2 and 3.3 of 284/2013, meaning organisations with qualified personnel and suitable testing equipment.

Tests must be performed unless it can be justified that non-target organisms will not be exposed. When according to the applicant a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

The data requirements for microorganisms in Commission Regulations (EU) No 283/2013 and 284/2013 ask for information on toxicity, infectiveness and pathogenicity (except when stated otherwise) on the following non-target organisms:

- Birds
- Aquatic organisms:
    - Fish
    - freshwater invertebrates
    - algae (effects on algal growth, growth rate and capacity to recover)
    - plants other than algae (any effects)
- Bees
- Arthropods other than bees
- Earthworms
- Non-target soil microorganisms (impact on relevant non-target microorganisms and on their predators)

The choice of the appropriate test organism shall be based on the identity of the microorganism (including the host-specificity, mode of action and ecology of the organism).

1.10.2 Risk assessment

An active microorganism may give rise to risks because of its potential to infect and multiply in host systems, or due to its ability to produce relevant toxic metabolites during the production of the MCPA and/or in contact with the (non-)target organism. Therefore, the risk for non-target organisms should be assessed, unless it can be demonstrated that non-target organisms will not be exposed.

For the environmental risk assessment, information obtained by the characterisation and identification of a microorganism forms the starting point. This information is obtained in the sections on “Identity, Biological properties and Further information on the microorganism” (section 1-3 in the data

requirements). Additional useful information may be found in the section on environmental fate and behaviour (section 7) and residues in plants (section 6). The proposed manner of use defines the nature and extent of potential exposure.

In short, the risk evaluation should take into consideration the following information:

- Mode of action and other biological properties
- Survival and dispersal of the active microorganism in the environment
- Its ecological niche
- The natural background level of the active microorganism, where it is indigenous
- Where relevant, other authorised uses of the plant protection product in the area of envisaged use containing the same active substance or which give rise to the same residues
- Studies on toxicity, pathogenicity and infectivity

No Guidance Document for the environmental risk assessment has been established in EU-context. During expert meetings on general issues on the risk assessment for microorganisms in 2007 and 2009 (the 'List 4 meeting' and PRAPeR M2 resp.) it was agreed that initial off-crop exposure densities in soil and water could be determined using the 'chemical' approach, but using a crop interception value of 0% for predicted densities in soil and using BBA (Ganzelmeier and Rautmann) drift values in combination with an 'all at once' worst-case loading approach for predicted densities in water (see section 1.9 for further considerations).

The use of the chemical guidance for the risk assessment for birds and mammals (EFSA 2009) is considered less relevant, since exposure parameters in this guidance (e.g. DT50, RUD) are based on chemical databases.

For any given environmental compartment, the risk characterisation should, when possible, contain a comparison of the predicted exposure with the available effect values from effect studies with the microorganism. However, when such a comparison is made no assessment factors are available to decide whether the risk is acceptable or not. The assessment factors used for chemical substances are not validated for microorganisms, and are only used for relevant metabolites/toxins, according to the decision criteria in Regulation (EU) No 546/2011.
Therefore, in most cases the risk assessment for the microorganism will consist of a qualitative or semi-quantitative evaluation of the likelihood that an adverse effect will occur under the expected conditions of exposure. Based on this evaluation it is decided whether the risk is acceptable or not.

For further guidance it can be referred to the OECD Guidance to the environmental safety evaluation of microbial biocontrol agents (OECD Series on Pesticides No. 67).

Relevant information from the open literature can be found in an EFSA literature review on microbial organisms used in plant protection products [6].

For a general discussion and working approach on metabolites/toxins it is referred to section 1.3.5 in this Evaluation Manual.

Specifically for the ecotoxicology section, information that can be used to determine the expected exposure of different non-target species to the relevant metabolites includes:

a) The concentration of the potentially relevant metabolite in the MPCA and/or MPCP.

[6] Mudgal et al. Scientific support, literature review and data collection on microbial organisms used as active substance in plant protection products – Lot 1 Environmental risk characterisation. EFSA supporting publications 2013: EN-518

b) The *in situ* production of the potentially relevant metabolite (e.g. by determining quantities of metabolites in insect in the case of entomopathogenic fungi).
c) For exposure of the environment, relevant information includes:
    - Degradation of the relevant metabolite in the relevant environmental compartments.
    - Adsorption potential of the relevant metabolite
    - In the case of non-target species, the information on the type of application (e.g. F, G and/or I) and MoA can helps to determine which non-target species will be exposed to the relevant metabolites.

1.11 Efficacy

The Guidance document for evaluation of efficacy in the Northern zone describes the requirements for registration of PPPs containing new active ingredients, new uses of existing PPPs registered for other purposes and new formulations of PPPs.

The data requirements for efficacy for a low risk product can differ markedly from those for a conventional product. At the start of the efficacy evaluation the status of the product (low-risk or not) is however not known with certainty. In some cases a product based on a low risk substance may not receive low risk status as mitigation measures need to be prescribed due to the risk assessment.

Description of the product.
Microbial products may require specific environmental conditions to reach optimal effectiveness, or may have other characteristics that need to be understood when evaluating their effectiveness. In addition the evaluation of these products depends for a large part on the mode of action of the active substance. To facilitate evaluation of the dossier by the ZRMS and concerned memberstates it is very important to clearly describe the microorganism and its mode of action.

Evaluation of the efficacy dossier

General EPPO standards

Because of the lower associated risk, there is more room for flexibility regarding the level of effectiveness and variability for low risk microbial products but if this is case, it should be clearly reflected in the label claims and recommendations. In addition there are other characteristics that differ from conventional products. To address these issues EPPO has drafted a specific standard on the principles of efficacy evaluation for low risk plant protection products, EPPO PP1/(296). This standard contains essential information on reduced data and efficacy requirements for these types of products and should be taken into account when writing a dossier for a low risk product. This evaluation manual does not repeat the content of this EPPO standard, but provides some further context.

The low risk standard EPPO PP1/(296) is also used for non-microbial low risk products, and therefore does not go into much detail on specific characteristics of microorganisms. For biopesticide products based on microorganisms another standard is available (*Principles of efficacy evaluation for microbial plant protection products* EPPO PP1(276)), this standard is also relevant for microbial products that are not low risk.

Specific EPPO standards

The EPPO standards database includes many standards on specific plant-pest combinations. It should be noted that these have mostly been written with conventional products in mind. As low risk products often have novel application methods, label claims or modes of action, existing standards may not be fully relevant.

In principle, EPPO standards should be followed, and trials should be performed according to GEP. When deviating from GEP and/or EPPO standards, the applicant should give a clear justification for the use of alternative (trial) data. Valid data from other sources, e.g. published papers and laboratory studies, may be used as supplemental data.

Extrapolations
The aforementioned EPPO standard PP1/(296) provides guidance on data requirements for low risk products such as the number of fully supportive results. It should be noted that when this standard is followed a robust dataset and number of trials is still required even if requirements are reduced (refer to the standard for details). Low-risk products have a major advantage however, in the extent of extrapolations that are possible depending on the mode of action (direct or indirect). As a result, a low risk product may end up with a much wider label claim compared to a conventional product with a similar initial claim supported by trials.

For a more detailed description please refer to chapter 9 (extrapolation possibilities for effectiveness of PP1/296, in addition some further context is provided below, consisting of an explanation of extrapolations in general, followed by a section specifically for low risk products.

Principles of extrapolation
The regular extrapolation principles (non low-risk) are described in EPPO Standard PP 1/257 "Efficacy and crop safety extrapolations for minor uses". Extrapolations are either based on extrapolation tables, or on expert judgement. Extrapolation tables that can be used are available from the EPPO website.

It should also be noted that Denmark take a flexible approach to the requirement in PP 1/257 that extrapolations are from major to minor crops only. For Danish labels, extrapolations may also be possible to major crops (see Guidance document for evaluation of efficacy in the Northern zone Annex 1)

Extrapolation for low-risk products
The above-mentioned extrapolation tables have mostly been written for conventional crop protection products. For low-risk products different extrapolations may be possible using expert judgement. The possibility for extra extrapolations depends for a large part on the mode of action of the microorganism, the biology of the target pest or disease, and the microorganism itself.

It is therefore important that the applicant clearly describes the mode of action of the active substance and the reasoning behind the extrapolations, and if possible provides literature studies that support these extrapolations. Where multiple modes of action are claimed, the relative importance of the different modes of action should be described.

Resistance management
For information on the evaluation of the occurrence or possible occurrence of the development of resistance of target organisms please refer to paragraph 1.4.1 in this document