Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

24-Jan-2017

English - Or. English

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

REPORT OF A SURVEY ON THE NEED FOR FURTHER GUIDANCE ON DATA REQUIREMENTS AND UPDATED TEST GUIDELINES TO SUPPORT THE ASSESSMENT OF MICROBIAL PESTICIDES

Series on Pesticides
No. 87

JT03408122

ENV/JM/MONO(2016)71
Unclassified
English - Or. English

OECD Environment, Health and Safety Publications
Series on Pesticides
No. 87

REPORT OF A SURVEY ON THE NEED FOR FURTHER GUIDANCE ON DATA REQUIREMENTS AND UPDATED TEST GUIDELINES TO SUPPORT THE ASSESSMENT OF MICROBIAL PESTICIDES

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2016

About the OECD

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.

The Environment, Health and Safety Division publishes free-of-charge documents in eleven different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides**; **Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents;** and **Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

Also published in the Series on Pesticides link

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/chemicalsafety/)

or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

FOREWORD

This document is a report of an OECD questionnaire submitted to member countries to identify where existing test methods or guidance are not sufficient to generate data needed to assess *microbial pesticides* (e.g., bacteria, algae, protozoa viruses, fungi) before they are marketed. The ultimate goal of this survey is to develop a list of priorities for the development of new and/or amended test guidelines or guidance documents that are applicable to microbials.

This report includes all of the responses to the questionnaire and a summary of those responses including an indication of where additional guidelines or guidance is either *necessary*, or could be *supportive*.

The questionnaire was submitted to members of the OECD Biopesticide Steering Group (BPSG) - a sub-group of the OECD Working Group on Pesticides - in December, 2012. The OECD Working on Pesticides (WGP) approved the report, and 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 26 November 2016.

Table of Contents

Introduction

1. Micro-organisms used as pesticides (i.e., microbial pesticides) are regulated in ways that are similar to chemical pesticides as they are used for the same purpose. However, the biological properties of living micro-organisms differ from the properties of chemical pesticides, and, hence, the same test methods used to determine, for example, the toxicological and environmental properties of a microbial pesticide, may not be the same as used for a chemical pesticide. While chemical pesticides have been available, and assessed, for decades, the assessment of microbial pesticides is relatively new, and hence regulators of microbial pesticides do not yet have the broad spectrum of assessment methods that are available to regulators of chemical pesticides. This report has been developed to identify where differences exist, and where new or modified guidance is needed for the assessment of microbial pesticides.

2. In 2012, an OECD questionnaire was distributed to members of the OECD Bio-Pesticides Steering Group (BPSG) to collect the relevant information for this report. This questionnaire consisted of a table which listed all of the data elements in the *OECD Dossier Guidance for Industry Data Submissions for Microbial Pest Control Products and their Microbial Pest Control Agents* (2004) and, for each element, respondents were invited to indicate where existing test methods for generating relevant data were not sufficient to meet their needs (e.g. lack of test guidelines, different interpretations of guidelines or of data points). The *OECD Dossier Guidance* is a common format and structure for applicants wishing to have a particular active substance approved or plant protection product registered in OECD countries.

3. A first compilation of responses was presented as a background document for an OECD/Swedish Chemicals Agency (KemI)/EU workshop held in Saltsjöbaden, Sweden in June 2013, entitled *Microbial Pesticides: Assessment and management of Risks* (OECD, 2014).

4. The objective of this initiative is to prepare a priority list for the development of new or amended Test Guidelines.

5. The following document includes the responses to the questionnaire and a summary of those areas where, based on these responses, it appears that better guidance on data requirements or (updated) guidelines are considered necessary to improve the risk assessment of Microbial Pest Control Agents (MPCA) and Microbial Pest Control Products (MPCP).

6. The document is divided into three sections: Part A (OECD data requirements for Microbial Pest Control Agents); Part B (OECD data requirements for Microbial Pest Control Products); and Appendix 1 (responses to the survey).

PART A: MICROBIAL PEST CONTROL AGENT – ACTIVE SUBSTANCE

7. For microbial pest control agents (active substances), sufficient guidance is available to adequately address several data requirements, and, based on the replies from the questionnaire it appears that no additional guidance is needed.

8. For some data requirements, guidance can be found in the test guidelines Series 885 of the US Environmental Protection Agency (US EPA, 1996), or in OECD issue papers or guidance documents:

- OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing (OECD, 2011)

- OECD (ENV/JM/MONO(2012)1) is available for the environmental safety evaluation of microbial biocontrol agents (OECD, 2012)

9. For other data requirements, the results of the survey suggest that in the following areas further guidance on data requirements or (updated) guidelines is considered necessary. An overview is presented hereafter and more details can be found in Appendix 1.

Identity of the Microbial Pest Control Agent

10. Regarding the identity of MPCAs, in December 2012 the EU commented that guidance on how to assess the equivalence for a microbial product would be useful. Meanwhile this guidance has been prepared in the EU and an OECD document on this issue is in preparation and it will be made publically available as part of the OECD Biopesticides publications.

11. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirements:

- characterisation of the strain or serotype;

- identification of metabolic by-products/impurities;

- presence and level of secondary metabolites and toxins. An OECD document on this issue is in preparation and it will be made publically available as part of the OECD Biopesticides publications;

- acceptable quality control data or analytical profile data.

12. For the following data requirement, further guidance or (updated) guidelines would be useful:

- the acceptable range for content of the MPCA.

Biological Properties of the Microbial Pest Control Agent

13. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirements:

- natural occurrence of the micro-organism including geographic distribution, hosts, habitat, ecological niche, level of natural occurrence; guidance is especially needed on bridging data;

- information on Mode of Action (MoA);

- genetic stability; guidance is especially needed on how to assess genetic stability and the relevance of the data point for many micro-organisms.

14. For the following data requirements, further guidance or (updated) guidelines is considered useful:

- physiological properties; guidance is needed regarding data points for which non-GLP data would be acceptable;

- information on resistance/sensitivity to antibiotics/anti-microbial agents used in human or veterinary medicine.

15. For data point 2.8 (Information on physiological properties, especially effect of environmental parameters on growth, infectivity, dispersal and colonisation ability: temperature, pH, redox potential, humidity, light, nutritional requirements) non-GLP data have been accepted for a long time, however this is not a common practice. Guidance on which non-GLP data are still acceptable would be helpful.

Analytical methods

16. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirement:

- methods to detect, isolate, and enumerate the micro-organism; especially criteria for validated methods are needed.

17. For the following data requirement, further guidance or (updated) guidelines is considered useful:

- storage stability. An OECD document on this issue has been published recently and it has been made publically available as part of the OECD Biopesticides publications.

Toxicological and Exposure Data and Information on the Microbial Pest Control Agent

18. The OECD Test Guidelines are specific for chemicals and are not always suitable for micro-organisms. As indicated in the EU data requirements, the US EPA Series 885 test guidelines (US EPA, 1996) can be more applicable for toxicological testing of MPCA.

19. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirements:

- sensitisation potential;

- intratracheal/inhalation infectivity, toxicity and pathogenicity; guidance is especially needed on interpretation of effects often seen after intratracheal instillation (unspecific effects, mortality) and clearance;

- genotoxicity; guidance is needed for when and how to test micro-organisms and/or metabolites for genotoxicity.

20. For the following data requirements, further guidance or (updated) guidelines is considered useful:

- oral infectivity/toxicity; more detailed guidance regarding OPPTS 885.3050: (positive controls, in which cases pathogenicity cannot be assessed by animal studies, limit dose...).

21. In general, more guidance on waiving of studies for certain micro-organisms would be useful.

Metabolism and Residues Studies on the Microbial Pest Control Agent

22. For the following data requirement, further guidance or (updated) guidelines is considered useful:

- Rationale for waiver of residue data.

Fate and Behaviour Studies on the Microbial Pest Control Agent in the Environment

23. For the following data requirements, further guidance or (updated) guidelines is considered useful:

- exposure scenarios related to way of application;

- rationale for the non-submission of data.

24. Application of microbial species to any particular environment usually results in a temporary increase of its population followed by a gradual decrease to background levels. However, background levels are not easy to define. Further guidance on how to address it, in relation to exposure, is considered useful.

Ecotoxicological Studies on the Microbial Pest Control Agent (Effects on non-target organisms)

25. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirements:

- effects on bees, including brood testing.

26. In general more guidance is needed on the applicability of OECD Test Guidelines for ecotoxicological effects.

27. For the following data requirements, further guidance or (updated) guidelines is considered useful:

- ecotoxicological effects; updating of several of the US EPA Series 885 test guidelines for ecotoxicological studies (US EPA, 1996), e.g. the honeybee Tier I test has a duration of 30 days which is too long for a Tier I test set-up; additional information on exposure route and test duration of non-target insect testing.

28. For individual studies, US EPA Series 885 test guidelines are available for a number of organisms but the study design may need to be reconsidered and updated where necessary for some of the studies.

29. To address effects on bees, sometimes it seems useful to ask for brood testing. However, no guidelines are available for testing such effects.

PART B: MICROBIAL PEST CONTROL PRODUCT – PLANT PROTECTION PRODUCT

Identity of the Microbial Pest Control Product

30. Several data requirements for which further guidance or (updated) guidelines is considered necessary are relevant to both the MPCA and the MPCP.

31. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirements:

- identification of metabolic by-products/impurities;
- presence and level of secondary metabolites and toxins;
- acceptable quality control data or analytical profile data.

32. For the following data requirement, further guidance or (updated) guidelines is considered useful:

- the acceptable range for content of the MPCA.

Physical, Chemical and Technical Properties of the Microbial Pest Control Product

33. For data point 2.6 ‘Adherence and distribution to seeds, for seed treatment products’, there are methods available for chemicals. Technical guidance for microbial formulations is not available but it is unclear if there is a real need for this.

Further information on the Microbial Pest Control Product

34. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirement:

- sensitisation potential.

35. Addressing this will assist to address the requirement for label instructions.

Methods of Analysis, Manufacturing, Quality Control and Post-Registration Monitoring of the Microbial Pest Control Product

36. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirement:

- Methods to define content of micro-organism in appropriate terms; especially criteria for validated methods are needed.

37. For the following data requirement, further guidance or (updated) guidelines is considered useful:

- storage stability. An OECD document on this issue has been published recently and it has been made publically available as part of the OECD Biopesticides publications.

Toxicological Studies and Exposure Data and Information for the Microbial Pest Control Product

38. Based on the responses received, it can be concluded that further guidance or (updated) guidelines is considered necessary for the following data requirement:

- sensitisation potential.

39. For the following issue, further guidance would be helpful:

- acceptability of qualitative risk assessment.

References:

OECD (2011) OECD Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products. Series on Pesticides No 65. ENV/JM/MONO(2011)43

OECD (2012) OECD Guidance to the Environmental Safety Evaluation of Microbial Biocontrol Agents. Series on Pesticides No 67. ENV/JM/MONO(2012)1

OECD (2014) Report of the OECD/KEMI/EU Workshop on Microbial Pesticides: Assessment and Management of Risks. ENV/JM/MONO(2014)2

US EPA (1996) Series 885 - Microbial Pesticide Test Guidelines

Appendix 1

Part A: Microbial Pest Control Agent – Active Substance

Text in colour indicates responses were provided by different individuals within the same organisation/association

Multiple entries for the EU reflect the position of different EU Member States

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
1	**Identity of the Microbial Pest Control Agent**	EU: Guidance on how to do an equivalence check for a microbial product would be useful. USA: Dossiers with inadequate data or rationale to support a bridging argument In dossier, identity or other characteristics (e.g., viability) of test material is unclear, or several forms exist and no data are provided to show its relevance to what is applied in the field	Not applicable
1.1	Applicant (name, address, contact, telephone and telefax numbers)	-	Not applicable
1.2	Producer (name, address, contact, telephone and telefax numbers)	-	Not applicable
1.3	Scientific information	-	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
1.3.1	Scientific name of micro-organism to species level or a level sufficient to show taxonomic relation to known micro-organisms, especially pathogens;	EU: N CA: PMRA DIR2001-02 Part 2.7.1 (see list of Canadian Guidelines at end of document): No. Problems are rarely encountered for this requirement. However, there were cases where the microbial pest control agent was only identified to the genus level and this genus included pathogens or opportunistic pathogens. In such situations, it should be imperative that applicants attempt to properly identify the proposed microbial pest control agent. The attempts ought to be demonstrated with data/study reports. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100/1400: No. But as discussed above for PMRA guidelines, it should be imperative that the applicant attempt to properly identify the proposed microbial pest control agent in situations where the identified genus includes pathogens or opportunistic pathogens. The attempts ought to be demonstrated with data/study reports. EU: N, However the identification and characterisation depend on point 1.3.3. We have to accept that names will change since the taxonomy is still in development and should always represent "the state of the art". IBMA: Microbial Taxonomy is always subject to changes. Taxonomic relation: to which level?	The description in the data requirements is considered sufficient. No further guidance needed.
1.3.2	- accession no. of sample in a recognised culture	EU: N CA:	The description in the data requirements is considered sufficient. No further

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	collection	PMRA DIR2001-02 Part 2.7.1: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1250: No. EU: Y: Until now I have not had any problems because only well-known culture collections have been used. However I am not able to answer the question: Which culture collections are recognised? I do not know where to find a list of recognised culture collections or criteria to be met for a recognised culture collection IBMA: N	Guidance needed.
1.3.3	- test procedures and criteria, using best available technology, to characterise the strain or serotype;	EU: In some cases, the open literature mentions techniques that are much more sophisticated than what is proposed by the company. What should be reported at this point: the best available method described in open literature or the method proposed by the company which is sometimes not very specific? CA: PMRA DIR2001-02 Part 2.7.1: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100/1400: Yes. Although these guidelines require extensive data to support the taxonomic designation, these guidelines do not require the use of the best available technology criteria. The guidelines only require applicants to submit the results of tests irrespective of the method used.	Some data requirements (EU and PMRA) require the use of the best available technology criteria. Further guidance on acceptable methods needed.

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification Suitable method available with modifications No suitable method available
		PMRA has encountered problems with applicants using outdated methods for identifying microbial pest control agents (especially with older databases). EU: Y: guidance is available on the methods and the degree of differentiation from other strains, what is meaning of "best", the method needs to be robust, reliable and unambiguous. Depending on the type of MPCA (bacteria, fungi, virus), this is likely to differ. EU: Y: Correct identification of the strain is a prerequisite for the correct attribution of published scientific data. The identification of micro-organism is not trivial, since the taxonomy is still in development and should always represent "the state of the art". In Denmark we suggest a polyphasic approach. Polyphasic taxonomy aims at the integration of different kinds of data and information (phenotypic, genotypic, and phylogenetic) on microorganisms and essentially indicates a consensus type of taxonomy. I don't think it is possible to make a guidance document on this issue. It will always need an expert evaluation. EU: Y No guidance available on methods and degree of differentiation from other species. No criteria available. EU: Y There is neither guideline nor criteria for this. IBMA:	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y, guidance is available on the method and the degree of differentiation from other strains. Lack of a required specific method can lead to difficulties when different regulatory authorities don't accept the same data. In addition over time the methods for distinguishing strains become more specific and may result in a "misidentification of the MPCA". - No standard method recognised. Genetic techniques for microbial identification are constantly advancing. This data point is likely to remain a challenge for MPCA. Data provided should at least include phylogenetic tree with species type strain and other commercially available similar organisms to provide a reference point. No. No TGs available to demonstrate which molecular identification methods are accepted. How to proceed if the microbe can't be identified and named according to species level – guidance is called for. This is the situation for e.g. *Streptomyces* strain K61: the active ingredient is identified as an unknown species – no species name available. Molecular tools are available to identify the specific strain. Still this is considered as data gap as the strain can't be named to species level. *Y. Lack of TG* *No clear rules for strain specificity* Y not clear which (molecular) methods are sufficient/ insufficient for identification at strain level.	
1.3.4	- for mutant or genetically-modified strains,	<u>EU:</u> This point is not clear because the Regulation is related to not genetically modified strains	<u>Sufficient guidance available to meet data requirements.</u> <u>No further guidance needed.</u>

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	indicate all known differences between the modified micro-organism and the parent wild strain(s)	CA: PMRA DIR2001-02 Part 2.7.3: No. However, PMRA has not yet registered any genetically modified microorganisms. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. EU: see 1.3.3. EU: N EU: See 1.3.3 IBMA: N	
1.3.5	- include any trade names, common names, developmental code names	EU: N IBMA: N	Not applicable
1.3.6	- indigenous or non-indigenous at the species level to the intended area of application.	EU: Y: A clear definition, whether or not a microorganism is indigenous or non-indigenous with respect to the area in which the MPCP is used, is missing. This is discussed in: WORKING DOCUMENT ON THE EVALUATION OF MICROBIALS FOR PEST CONTROL http://www.oecd.org/findDocument/0,3770,en_2649_34383_1_119666_1_3_1,00.html IBMA: What means indigenous? On species or strain level? Region vs. climatic zone?	Mixed answers, however it seems not to be a critical issue in the dossier evaluation. No further guidance needed.
1.4	Composition of Technical Grade of	EU: Y: Composition of Technical Grade is a chemical concept. This is a general problem for	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	MPCA/Active Substance	several the points below point 1.4… Characteristics of chemicals are required for microorganism and not relevant.	
1.4.1	Concentration of micro-organism (and metabolite, if appropriate) in terms of g/kg or g/L (for US and Canada, also in % w/w) and cfu's/mL or appropriate potency units; include acceptable range for each term. Potency should be expressed in recognised units of potency or an appropriate expression of biological activity per unit weight/volume	EU: What is the meaning of Potency should be expressed in recognised units of potency or an appropriate expression of biological activity per unit weight/volume? CA: PMRA DIR2001-02 Part 2.9.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. EU: Y: It is not defined for which metabolites concentrations are required. EU: Y Like for Bti there should be information on the toxin as well. IBMA: Y, No guidance is available on the range for the content of the MPCA in the technical or the product. It is not clear which units can or need to be chosen, e.g. mass units like g/kg or g/L, or biological units like CFU or biotest units. Due to the method of production the concentration of the MPCA in regard to CFU/g as well as in regard to w/w might change in a wide range (usually exponentially). Metabolite(s) in general or relevant (toxic) metabolite(s)? For integrated production of MPCP by % w/w may not be enforceable (cannot be analysed in	Mixed answers, however it seems not to be a critical issue in the dossier evaluation. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		the end-use product) but is still required. Only the enforceable concentration of the MPCA, CFU/ g or ml or appropriate potency unit, should be required. *Y* *Lack of TG for metabolites* **In this context, as for other data requirements specific for micro-organisms in general, metabolites should mean "relevant metabolites" only.**	
1.4.2	Composition of microbial material used for manufacture of end use products in terms of g/kg or g/L (for US and Canada also in % w/w) for each active ingredient including:	EU: N EU: Y, For risk assessment it is necessary to give relevant microbial/toxin amount information.	
1.4.2.1	- the MPCA. This information is not required if Technical Grade of MPCA is a hypothetical stage in a continuous production process	EU: N CA: PMRA DIR2001-02 Part 2.9.1: No. This information is required for the technical grade of the active ingredient even if it is a hypothetical stage. The percent weight of the active ingredient in such a technical product is 100% culture unless formulation ingredients are intentionally added.	Further guidance needed on the acceptable range for the content of the MPCA?

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	of an end-use product.	OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. <u>EU:</u> Y, No guidance is available on the range for the content of the MPCA in the technical or the product. <u>IBMA:</u> Y, No guidance is available on the range for the content of the MPCA in the technical or the product.	
1.4.2.2	- additives (preservatives, stabilisers, diluents). This information is not required if Technical Grade of MPCA is a hypothetical stage in a continuous production process of an end-use product.	EU: What is the meaning of "hypothetical stage"? CA: PMRA DIR2001-02 Part 2.9.1: No. As noted above, this information is required for the technical grade of the active ingredient even if it is a hypothetical stage. The percent weight of the active ingredient in such a technical product is 100% culture unless formulation ingredients are intentionally added. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. IBMA: No	Not applicable
1.4.2.3	- microbial impurities, classified/identified	<u>EU:</u> See 1.4.2.2. <u>CA:</u>	OECD (ENV/JM/MONO(2011)43) is available for guidance on

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	to a taxonomic level required by quality criteria to support the hygienic state of the production process. This information is not required if Technical Grade of MPCA is a hypothetical stage in a continuous production process of an end-use product.	PMRA DIR2001-02 Part 2.8C/2.9.3: Yes. Insufficient guidance is provided therefore microbial screens are highly variable between dossiers. More often than not, applicants devise their own quality control testing based on their own experiences. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. <u>EU:</u> Y OECD issue paper on contaminants is useful. However, it does not address the following: Should the tests be performed under GLP? <u>IBMA:</u> N, OECD guidance and methods for determination available in "OECD Issue Paper on Microbial Contaminant Limits for Microbial Pest Control Products", Series on Pesticides, No. 65. Document adopted by EU as well. ENV/JM/MONO(2011)43 Table 1.1: Proposed OECD microbial contamination screening requirements for microbial pest control products. Some indicators, such as Vibrio and Shigella, might be unnecessary, depending on the MPCA and the co-formulants of the MPCP.	microbial contaminant testing.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		This should be limited to the detection / identification of common human pathogenic micro-organisms present in the final product.	
1.4.2.4	- non-microbial impurities (e.g. metabolic products, impurities in starting materials, fermentation residues, extraneous host residues). This information is not required if Technical Grade of MPCA is a hypothetical stage in a continuous production process of an end-use product.	EU: See 1.4.2.2. CA: PMRA DIR2001-02 Part 2.7.2/2.9.3: No. These guidelines clearly articulate the requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines clearly articulate the requirement. *Note:* Despite these guidelines, this is an area that is frequently ignored by applicants, particularly with respect to metabolic by-products. Little or no information/discussion is provided for metabolic by-products or toxins. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. IBMA: Y No guidance available. It is not clear which information is required here The composition and structure of potential metabolites present in the product is extremely difficult to elucidate taking into account the complex nature of the growth media. It would make sense to ask only for measurement of levels of *toxic* metabolites which are known from scientific literature. If technical grade is not a hypothetical stage in a continuous process, but is the biomass recovery from a fermentation process, why describing the % of any fermentation residue?	Further guidance needed, especially on the information required for metabolic by-products.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Shouldn't be enough to describe the fermentation process? Y: what is a relevant metabolite: definition analogue to EU definition for relevant impurities i.e. undesirable because of their toxicological, ecotoxicological or environmental properties **Y. The technical grade is typically a complex mixture, and in practice it is not possible to identify the numerous ingredients such as residues from starting materials and fermentation residues.** **When a metabolite, known to be directly responsible for the activity of the micro-organism possesses a toxic effect on non-target organisms, detection methods should be developed/described/validated** **Toxicology tests with the technical material and the formulated products can reveal if impurities of toxicological concern are present**.	
1.4.2.5	Composition in terms of g/kg or g/L, (for US and Canada also in % w/w), for each ingredient: The identity and maximum content of all microbial impurities must be reported, if possible and appropriate, as outlined in point 1.3, and expressed	EU: N CA: PMRA DIR2001-02 Part 2.9.1/2.9.3: Yes. As previously noted, microbial screening is highly variable between dossiers. The identity and maximum content (limit on microbial contaminants) are often variable or missing altogether. Better guidance is required on the expectations of maximum contents of microbial impurities. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing and establishing limits. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	in appropriate units (in terms of cfu's/mL or appropriate expression of biological activity/viability).	do not specify any standard indicator species. Again, better guidance is required on the screening procedures and maximum content of microbial impurities. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing and establishing limits. IBMA: Y See above	
1.4.3	Methods of production and quality criteria for the production and storage of the active micro-organism, including:	CA: PMRA DIR2001-02 Part 2.8: No. These guidelines provide adequate details. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines provide adequate details.	Not applicable
1.4.3.1	- criteria for consistency and integrity of the master and working seed stock, typically, measures of biological activity and phenotypic or genotypic properties:	EU: N CA: PMRA DIR2001-02 Part 2.8/2.10.1: No. These guidelines provide adequate details. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines provide adequate details. EU: Y No guidance available. IBMA:	Mixed answers, however it seems not to be a critical issue in the dossier evaluation. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y, No guidance available. It is not clear which information is required here	
1.4.3.2	- acceptable range for content of MPCA, in appropriate terms;	EU: N CA: PMRA DIR2001-02 Part 2.8/2.10.1: No. These guidelines provide adequate details. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No These guidelines provide adequate details. IBMA: Y, No guidance is available on the range for the content of the MPCA in the technical or the product. It is not clear which units can or need to be chosen, e.g. mass units like g/kg or g/L, or biological units like CFU or biotest units.	Mixed answers. Further guidance needed on the acceptable range for the content of the MPCA?
1.4.3.3	- presence of human/mammalian pathogens;	EU: N CA: PMRA DIR2001-02 Part 2.8C/2.10.3: Yes. As previously noted, insufficient guidance is provided therefore microbial screens are highly variable between dossiers. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. These guidelines provide guidance for primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), but they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing.	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Y No harmonised standard list of human/mammalian pathogens available IBMA: N, Guidance available in OECD issue paper, Series on Pesticides, No. 65, which refers to the product. *No, ISO methods for list of contaminants included in OECD Issue Paper Document 5*	
1.4.3.4	- presence or maximum accepted level of known mammalian toxins, if their presence is suspected at any stage in process, or if MPCA is closely related to a toxigenic human pathogen;	EU: This should be clarified because the presence of mammalian toxins is not acceptable. CA: PMRA DIR2001-02 Part 2.8C/2.10.3: No. These guidelines clearly articulate the requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200/885.1300: No. These guidelines clearly articulate the requirement. *Note:* As previously noted, this is an area that is frequently ignored by applicants. Little or no information/discussion is provided for metabolic by-products or toxins. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. EU: Y No guidance available. The term "known mammalian toxin" is not clear and gives a lot of room for interpretation.	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Y No guidance available. No good definition nor a harmonised list of "known mammalian toxins" available. EU: Guidance on how to test for and handle the issue of secondary metabolites and toxins not just in relation to human health but also the environment. IBMA: Y No guidance available, the term "known mammalian toxin" gives too much room for interpretation. What does means suspected?	
1.4.3.5	- maximum accepted level for microbial impurities, using suitable indicators of an unhygienic process.	EU: N CA: PMRA DIR2001-02 Part 2.9.3/2.10.2: Yes. As previously noted, microbial screening is highly variable between dossiers. The identity and maximum content (limit on microbial contaminants) are often variable or missing altogether. Better guidance is required on the expectations of maximum contents of microbial impurities. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing and establishing limits. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they do not specify any standard indicator species. Again, better guidance is required on the screening procedures and maximum content of microbial impurities. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing and establishing limits. EU: The OECD issues paper can be used as reference (OECD ISSUE PAPER ON MICROBIAL CONTAMINANT LIMITS FOR MICROBIAL PEST CONTROL PRODUCTS Series on Pesticides No. 65 EU: Y OECD issue paper on contaminants is useful. However, it does not address the following: Should the tests be performed under GLP? IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65, which refers to the product. Definition by 5 batch analysis	
1.4.4	Quality control data (measures of quality criteria) from 3 - 5 production batches, including storage stability data. If the	EU: What should be exactly being reported under this point? Should it be possible to define the requirements? CA: PMRA DIR2001-02 Part 2.8C/2.11. No.	Further guidance would be helpful

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	Technical Grade of MPCA is a stage in a continuous production process of an end-use product, this information should be provided for the entire production process.	OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200/885.1500: Yes. These guidelines state that quality control measures are needed during manufacturing but no representative data are required. *Note:* The submission of representative quality control data is rarely a problem. Guidance should state that data be collected from the proposed site of manufacturing. In some dossiers, data were provided for past production facilities and their usefulness are limited since each site can, in theory, harbour different kinds of contaminating microorganisms. EU: Y Should the tests be performed under GLP? IBMA: Y Guidance only available for chemicals. Quantification of the microorganism is not defined. 1.4.4 does not exist in COMMISSION REGULATION (EU) No 283/2013 Part B Storage stability data for 3-5 batches are not required within EU. - No guideline and for many metabolites no recognised acceptable limit (e.g. Beauvericin from *B. bassiana*) is an exception. - Just because a metabolite has been identified in academic literature as existing for some strains, it does not mean that it is commercially available for comparative testing (e.g. Paecylotoxin from *P. linacinus*). *Lack of TG for storage stability of microbial formulations*	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
1.4.5	The formation, presence and/or impact of unintentional ingredients	IBMA: - What means unintentional impurities? Definition by recipe!	
1.4.5.1	A theoretical discussion regarding the formation and/or presence of unintentional ingredients, including impurities of toxicological concern, likely to occur in the Technical Grade of the MPCA.	EU: What is the meaning of theoretical discussion? CA: PMRA DIR2001-02 Part 2.9.3: No. These guidelines have adequate information. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines have adequate information. Despite adequate guidelines, many theoretical discussions focus on the source of ingredients and the unlikeliness of impurities but very few dossiers discuss the formation of unintentional ingredients such as metabolic products. Metabolic products, if they do occur, are often not properly discussed in dossiers and no maximum levels are established. Obviously, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. IBMA: N On what would one base this discussion? If the testing supporting the MPCA and MPCP has no significant end-points what is the relevance of this requirement? Only rule out production	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		of known toxins?	
1.4.5.2	A theoretical discussion regarding the impact of these ingredients on product quality.	EU: see 1.4.5.1 CA: see 1.4.5.1 IBMA: N Same comment as for 1.4.5.1	See 1.4.5.1
1.4.5.3	A theoretical discussion regarding appropriate quality criteria.	EU: see 1.4.5.1 CA: PMRA DIR2001-02 Part 2.9.3: No. These guidelines have adequate information. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines have adequate information. IBMA: N Same comment as for 1.4.5.1	No further guidance needed
1.4.6	Physical and chemical properties, if MPCA is produced as a manufacturing	EU: N CA: PMRA DIR2001-02 Part 2.12: No. However, no specific methods are described. Applicants are free to choose any valid method. A reference to a standard procedure or protocol is	Guidelines for chemical products are appropriate

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	product that is stored prior to formulation of end-use products: physical state; density; viscosity or surface tension; explosivity, corrosive character, oxidising properties; technical characteristics as appropriate	required for each parameter. OECD Section 1 guidelines: No. Appropriate guidelines may be found under this section. U.S. EPA: No. Appropriate guidelines are available. EU: It is highly unlikely that a MPCA can be explosive or have a corrosive character IBMA: N Guidelines for chemical products are appropriate *Lack of guidelines specific for microbials*	
1.4.7	International regulatory status of micro-organism	IBMA: N	
1.4.8	Sample of MPCA and analytical standard of metabolite	IBMA: Sample of MPCA means deposit in a culture collection?	
1.4.8.1	Sample of MPCA: if requested	-	
1.4.8.2	Analytical standard of metabolite: if requested	-	
1.4.8.3	Reference substances for the	IBMA: Define “relevant impurities” for a MPCA.	In general: guidance needed on how to test for and handle

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	relevant impurities: if requested		the issue of secondary metabolites and toxins
1.5	Patent status	IBMA: Is this really of interest for the regulatory authority?	
2	**Biological Properties of the Microbial Pest Control Agent**	EU: Y: For this chapter the quality will depend on the general studies and available literature of the microorganism in question and closely related strains and species. It is not clear how much information is required EU: Y Important information, however detailed guidance would facilitate	
2.1	Origin of the isolate; method of isolation; preservation and maintenance of strain during development; historical information on testing and use of the strain; history of use of closely related strains or species; Description of any unusual	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. EU: Guidance on methodology for population decline studies in soil for soil microbials. Sometimes these have been included by applicants and can be very useful across specialisms – e.g. efficacy (giving an idea of how long product effective/intervals for repeat applications) and fate/ecotox aspects to understand longer term viability/persistence of population. (and support/replace the sometimes weak arguments that e.g. populations decline to natural levels).	Mixed answers, however, in general it seems that no further guidance is needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	morphological, physiological, pesticidal or resistance characteristics of the MPCA which differ from classical description of the species	IBMA: N What means classical description of species for newly isolated strains? Does this mean a given type strain?	
2.2	Natural occurrence of the micro-organism including geographic distribution, hosts, habitat, ecological niche, level of natural occurrence	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. EU: This point should refer to the species, not (only) to the strain. EU: Y No guidance available. This point should (also) refer to species level. EU: Further details on what is meant by natural occurrence and its relevance would be useful IBMA:	Mixed answers. General guidance on bridging data is needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		This point should refer to the species, not to the strain. What happens if there only little known from the literature? Will information on a closely related species be accepted to support the MPCA? Different regulatory authorities allow bridging with reasoned cases for the genus or closely related species. *Y. Natural background levels are hard to establish.*	
2.3	Information on target organism(s)	-	
2.3.1	Description of the target organism(s)	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. IBMA: N	No further guidance needed
2.3.2	Information on mode of action, kind of antagonism to target host, infective/toxic dose, transmissibility	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. Information on mode of action is often lacking even though the requirements are clearly articulated in both PMRA and U.S. EPA test guidelines. Information is often missing when the mode of action is toxic. Applicants ought to be urged to provide additional information.	Guidance on information on MoA is needed

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Additional guidance/strategies may be required to help applicants to properly address these omissions. EU:\Y No guidance available. As micro-organisms have many MoA under different environmental circumstances, guidance would be helpful. IBMA: N	
2.4	Available information on host specificity; possible effects on species closely related to the target pest. Any experience of toxic effect of the active substance or its metabolic products on human or animals, of whether the organism is capable of colonising or invading humans or animals and whether it is pathogenic shall be stated. Any	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. As previously noted, dossiers are often lacking on details with respect to the production of potentially toxic metabolites. Additional guidance/strategies may be required to help applicants to properly address these omissions. IBMA: N Toxic effect of the active substance or its metabolic products on human or animals: Only relevant if MCPA is based on metabolites Metabolites should be only addressed if they are known toxins. Many MPCA produce metabolites that are not toxins or toxic to mammals and non-target organisms.	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	experience of whether the active substance or its products may irritate skin, eyes or respiratory organs of humans or animals and whether it is allergenic in contact with skin or when inhaled.		
2.5	Life cycle of the micro-organism including various forms that may occur, differences in pathogenic/ toxigenic character of various forms, virulence and survival time of resting stages, interactions with other species (vector, parasitism, competition)	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
2.6	Potential of the micro-organism to produce metabolites that are of concern for human health and/or the environment.	EU: This point should be clarified because: to be considered as a m.o suitable for use as pesticide it should not be able to produce metabolites that are of concern for human and/or environment. CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. As previously noted, dossiers are often lacking on details with respect to the production of potentially toxic metabolites. Additional guidance/strategies may be required to help applicants to properly address these omissions. EU: Y No guidance how to assess this. EU: Y No guidance how to assess this. IBMA: N The composition and structure of potential metabolites present in the product is extremely difficult to elucidate taking into account the complex nature of the growth media. It would make sense to ask only for measurement of levels of toxic metabolites which are known from scientific literature. The existence of respective genes does not mean at all that toxins will be formed during production or after application!	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		No Guidance to indicate theoretical vs practical relevance. If it's stated in literature that eg. Actinomycetes in general might have potential to produce metabolites and if demonstrated that no metabolites are produced by specific strain (*Streptomyces* K61) – how much of concern is this then? How much data needed to assure this fact?	
2.7	Information regarding closely related species	IBMA: Definition of "closely" is required. The dossier is provided on strain level - evaluation should be done on strain level.	Sufficient guidance available to meet data requirements. No further guidance needed.
2.7.1	Among closely related species, provide information on pathogenicity to plants, animals or humans	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. IBMA: N What happens if no information is available? *Y. Different interpretations about degree of similarity- No clear rules*	Sufficient guidance available to meet data requirements. No further guidance needed.
2.7.2	Among closely related species, provide information on formation of toxic metabolites: structure, stability,	EU: N CA: See 2.7.1. IBMA:	Sufficient guidance available to meet data requirements. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	conditions under which they are formed, mode of action	N Only possible for known metabolites *Y. Different interpretations about degree of similarity- No clear rules*	
2.8	Physiological properties, especially effect of environmental parameters on growth, infectivity, dispersal and colonisation ability: temperature, pH, redox potential, humidity, light, nutritional requirements	EU: N CA: See 2.7.1. IBMA: Y No guidance available. Although non-GLP data have been accepted for a long time, this was recently questioned.	Guidance for which data point non-GLP data are acceptable could be helpful.
2.9	Description of any plasmids or other extra chromosomal genetic elements involved in pesticidal activity, pathogenicity, toxicity, *etc*.	EU: If I am not wrong, when plasmids or extra chromosomal elements are involved, the mo should be considered as genetically modified. The regulation does not apply to genetically modified mo. CA: See 2.7.1. IBMA:	Sufficient guidance available to meet data requirements. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		N Is a genetic analysis necessary? This should only be provided if the literature suggests for the species that plasmids confer pesticidial activity, pathogenicity or toxicity	
2.10	Genetic stability (mutation rate of traits related to the mode of action), factors affecting genetic stability; micro-organism's capacity to transfer genetic information to another population	EU: The mo must be stable from a genetic point of view: if not, the dossier could not be relevant. CA: PMRA DIR2001-02 Part 2.7.1/2.7.2: Yes. PMRA requires a description of any plasmids or other extrachromosomal genetic elements involved in pesticidal activity. Such information is useful for assessing genetic stability. PMRA, however, does not require data concerning mutation rates etc. unless the microbial pest control is genetically modified. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100/1500: No. IBMA: Y No guidance available. This point only seems relevant for GMOs. Not possible to do Ames test with microbials. Only with the fermentation broth without microbials. *Different interpretations about risk. Horizontal gene transfer is a common motif in the microbial world*	Guidance needed on how to assess this, and the relevance of the data point for many m.o.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU:Y No guidance how to assess this, and the relevance of the data point for many m.o.	
2.11	Detailed discussion of relationship of micro-organism to any known human dermatophyte (see point 5.2)	EU: Should be clarified. CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: No microbial-specific guidelines. U.S. EPA 885.1100: No. These guidelines dot not specifically require a discussion on the relationship of dermatophytes, however, they do require a discussion on the potential for this organism to harm mammals (i.e., pathogenicity). IBMA: N See 2.7.	Sufficient guidance available to meet data requirements. No further guidance needed.
2.12	Information on resistance/sensitivity to antibiotics/anti-microbial agents used in human or veterinary medicine	EU: N CA: PMRA DIR2001-02 Part 2.7.2: No. OECD: No microbial-specific guidelines. U.S. EPA 885.1100: Yes. These guidelines do not require information on resistance/sensitivity to antibiotics or antimicrobial agents used in human or veterinary medicine. These guidelines, however, do require information on any unusual biochemical,	Mixed answers. Guidance how to address antibiotic resistance and production could be helpful

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		physiological or resistance characteristics (which should include antibiotics). <u>EU:</u> Y In EU also the production of antibiotics by the m.o. is an issue, discussed under this data point. However, no guidance is available on the relevance of it, compared to the amount of antibiotics that will be produced in the field and hence the human/environmental exposure <u>IBMA:</u> Y No guidance available. Although non-GLP data have been accepted for a long time, this was recently questioned. Method used for yeasts: The National Committee for Clinical Laboratory Standards (NCCLS) M27A. Developed for testing of Candida sp. Adaption necessary concerning growth media and temperature. Which antibiotics to be tested? EFSA and CLSI guidelines can be used for breakpoints to determine resistance classification. However, the two sets of guidelines do not always give the same breakpoint values (e.g. Gentamycin) - Understanding needed from the authorities that interpretation of "resistant" according to these guidelines for medical pathogens needs to be different for non-pathogenic microbial PPPs.	
3	**Further information on the Microbial Pest**		

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	Control Agent (Function, Mode of Action, Handling)		
3.1	Function, e.g. fungicide	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.
3.2	Placeholder	-	
3.3	Field of use, e.g. forestry	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.
3.4	Information on target crop and target organism(s)	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.
3.4.1	Details of existing and intended uses (crops, groups of crops, plants or plant products treated or protected)	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.
3.4.2	Details of harmful organisms against which protection is afforded	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No.	Sufficient guidance available to meet data requirements. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
3.4.3	Effects achieved e.g. sprout suppression	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. PMRA: The "effects achieved" is determined by PMRA during the review of efficacy/value data. IBMA: N	Sufficient guidance available to meet data requirements. No further guidance needed.
3.5	Information on mode of action and metabolites	EU: N CA: PMRA DIR2001-02 Part 2.7.2; DIR2003-04; DIR96-01; DIR2012-01: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: No. As noted previously, information on mode of action is often lacking even though the requirements are clearly articulated in both PMRA and U.S. EPA test guidelines. Information is often missing when the mode of action is toxic. Applicants ought to be urged to provide additional information. Additional guidance/strategies may be required to help applicants to properly address these omissions. EU: Y: Microorganism may produce a huge variety of different metabolites. Determination of all metabolites produced during fermentation and after application is impossible. Therefore we need guidance of which metabolites need to be assessed. A pragmatic reasoning on	Further guidance needed, especially on the information required for metabolic by-products. Guidance on information on MoA is needed

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		metabolites should be preferred. IBMA: N Metabolites only if they are involved into MoA! Many strains produce natural products that are not involved in the MoA, which are known to not be toxins yet some regulatory authorities demand their identity which is not warranted if they are not relevant toxic compounds. Regulators need to understand the difference from the small molecule term "metabolite" versus natural products, substances produced naturally by MPCAs. This applies to the entire 3.5 Annex point.	
3.5.1	Statement of the mode of action of the Microbial Pest Control Agent in terms of biochemical and physiological mechanism(s) and biochemical pathway(s) involved. (see IIM 2.3.2)	EU: N CA: See 3.5 EU: Y A guidance would facilitate IBMA: N *Y. Different interpretations. For some microbials is difficult to determine the mode of action at strain level*	Guidance on information on MoA is needed
3.5.2	Details of active metabolites (especially toxins)	EU: N CA:	Further guidance needed, especially on the information required for metabolic by-

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	and degradation products, cross referenced to the toxicological and residues data provided, to include:	See 3.5 EU: Y A guidance would facilitate IBMA: N - No guidelines exist. - Development of full metabolite profile is expensive ~€100k. The profile also has the potential to vary depending on the condition of the organism. Lead metabolites only should need to be identified and then linked to academic literature review. Y. *Lack of TG* *In many cases metabolites are not fully characterized or standards are not available*	products.
3.5.2.1	- IUPAC and CA names	IBMA: N to be deleted; instead Accession number of internationally recognized culture collection	Not applicable
3.5.2.2	- ISO common name proposed or accepted	IBMA: N	Not applicable
3.5.2.3	- CAS, CIPAC, EINECS and ELINCS numbers	IBMA: N	Not applicable
3.5.2.4	- molecular and structural formula	IBMA: N	Not applicable

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
3.5.2.5	- molecular mass	IBMA: N	Not applicable
3.5.3	Information relative to the formation of active metabolites (especially toxins) and degradation products, to include:	EU: In case of fungi, a high number of metabolites could be produced depending of the environmental conditions. Should we discuss only mammalian pathogenic metabolites or metabolites involved in the MOA or both? CA: PMRA DIR2001-02 Part 2.7.2: Yes. These guidelines, however, do not require this level of information on the formation of active metabolites. IBMA: N	Further guidance needed, especially on the information required for metabolic by-products.
3.5.3.1	- the processes, mechanisms and reactions involved	CA: See 3.5.3 IBMA: N	See 3.5.3
3.5.3.2	- kinetic and other data concerning the rate of conversion and if known the rate limiting step	EU: Rate of conversion of what? CA: See 3.5.3 IBMA:	See 3.5.3

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		N	
3.5.3.3	- environmental and other factors effecting the rate and extent of conversion	EU: What do you mean by this point? CA: OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100: Yes. These guidelines, however, do not require this level of information on the formation of active metabolites. As noted previously, information on mode of action is often lacking in this area. Information is often missing when the mode of action is toxic. Applicants ought to be urged to provide additional information. Additional guidance/strategies may be required to help applicants to properly address these omissions. IBMA: N	See 3.5.3
3.6	Information on the possible occurrence of the development of resistance or cross-resistance	EU: N CA: PMRA DIR2001-02 Part 10.4.4: No. Applicants must submit information on the potential development of pest resistance to the microbial pest control agent and provide strategies to mitigate resistance management. OECD: Yes. No microbial-specific guidelines.	The description in the data requirements is considered sufficient. No further guidance needed.

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N	
3.7	A material safety data sheet for the Microbial Active Substance	IBMA: N Yes for integrated products regulators still ask for this although a true technical is not produced to make the MPCP.	
3.8	Detailed instructions for safe disposal	EU: N CA: PMRA DIR2001-02: Yes. There are no such requirements in these guidelines. PMRA provides information on the proper disposal of products containing microbial pest control agents using information available in the dossier. Specific procedures, however, are rarely required for microbial pest control agents. The decontamination procedures (e.g., bleach) are often more damaging to health and/or environment than the microbial pest control agent itself. OECD: Yes. No microbial-specific guidelines. IBMA: N	The description in the data requirements is considered sufficient. No further guidance needed.
3.9	Procedures for the decontamination of water in case of an accident	EU: Clear requirements should be defined for this point because survival in water is frequently subject of important and hopeless discussions… CA: See 3.8 IBMA: N	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
3.10	Other/special studies	EU: N IBMA: N	Not applicable
3.11	Crops or products to be protected or treated (see IIM 3.4.1)	IBMA:N	Not applicable
3.12	Measures to render micro-organism harmless, in case of an accident	EU: N CA: PMRA DIR2001-02: Yes. There are no such requirements in these guidelines. PMRA provides information on the proper disposal of products containing microbial pest control agents using information available in the dossier. Specific procedures, however, are rarely required for microbial pest control agents. The decontamination procedures (e.g., bleach) are often more damaging to health and/or environment than the microbial pest control agent itself. OECD: Yes. No microbial-specific guidelines. IBMA: N	Not applicable
4	**Analytical methods**	EU: Y A guidance on validation of methods would facilitate EU: Guidance on methods and method validation would be really useful i.e. what criteria should be looked at to validate plating techniques, how to address linearity, accuracy and in particular specificity. This point would be relevant to any of the methods below that rely on plating or other microbilogical techniques.	
4.1	Method to preserve	CA:	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	and maintain the master seed stock; criteria for an acceptable level of consistency and integrity of seed stock	PMRA DIR2001-02 Part2.8A/2.10.1: No. The requirement is clearly articulated. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: Yes. Applicants must describe all methods aimed at maintaining the integrity of the microbial pest control agent. This information could include method(s) to preserve and maintain the master seed stocks but it isn't very specific. Additional guidance is recommended to ensure that the dossiers will contain sufficient information. <u>EU:</u> Y No guidance available <u>IBMA:</u> Y No guidance available	
4.2	Production process for Technical Grade of MPCA, describing techniques used to ensure a uniform product and procedures when hazardous contamination is detected in a batch. List starting and intermediate	<u>EU:</u> For microbials, this point is not easy because a clear separation between confidential and not confidential methods/ processes cannot always be set. <u>CA:</u> PMRA DIR2001-02 Part 2.8B/2.8C/2.9.3: No. These guidelines clearly articulate this requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines clearly articulate this requirement. <u>IBMA:</u> N	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	materials, with source and purity of each.		
4.3	Quality control and post-registration monitoring methods	EU: N CA: **Quality Control** PMRA DIR2001-02 Part 2.8B/2.8C/2.10.2/2.10.3: No. These guidelines clearly articulate this requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines clearly articulate this requirement. **Post-Registration Methods** PMRA DIR2001-02: *For viable microorganisms*; Yes. PMRA does not have this requirement. However, PMRA does recommend that the applicant possess a method to differentiate their strain or isolate of the microbial pest control agent from other isolates of the species in case of any post-registration effects or violations. Without such data, PMRA will assume that effects or violations were due to the registered microbial pest control agent. *For non-viable products, i.e., toxins* Part 7: No. If the presence of a mammalian toxin has been identified and the applicant wishes to pursue registration, the product will be subject to the same data requirements as a chemical pesticide, and appropriate data will be required to establish a maximum residue limit. OECD: Yes. No microbial-specific guidelines. U.S. EPA: No. Applicants must apply for an exemption from establishing a tolerance. If this	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		application for an exemption is rejected, the applicant will have to submit all the necessary data under 885.2000 series. IBMA: Difficult to develop a SCAR marker this approach is extremely labour-intensive (different primers, many strains, many amplicons to be screened, etc.) and the generated amplicons often originate from unknown DNA regions, meaning that success of developing a specific marker depends on the screening of a huge (!) strain collection (to ensure marker specificity), Technologies are now based on whole genome sequencing or genotyping by sequencing (GBS), followed by bioinformatic analysis and selection of strain specific regions for developing the specific markers, but that is very expensive and it takes a long time to develop.	
4.3.1	Methods to detect, isolate, and enumerate the micro-organism	EU: N CA: PMRA DIR2001-02 Part 2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review. OECD: Yes. No microbial-specific Guidelines. U.S. EPA 885.1200. No. These guidelines require all methods aimed at maintaining the purity and the identity of the microbial pest control agent. EU: Y No guidance available. Guidance for chemicals is not appropriate as variation is far higher for microbials. Criteria for validation need to be defined, as validated methods are required e.g., in the EU.	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		EU: Y: No guidance is available for validation criteria for the quantification of microbials. Methods used for the detection and quantification of microbial contaminants are the same as those used for food. These methods are validated and internationally accepted. However usually EFSA will not accept this as an answer EU: Y No guidance available. Chemical guidance is not appropriate. Criteria for validation are needed. IBMA: Y No guidance available. Guidance for chemicals is not appropriate as variation is far higher for microbials. Criteria for validation need to be defined. GLP Validation of the methodology used is not always possible.	
4.3.2	Methods to differentiate a mutant or genetically-modified micro-organism from the parent strain.	EU: see earlier comments related to genetically modified mo. CA: PMRA DIR2001-02 Part 2.7.3/2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review (including methods to distinguish revertants). OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. Applicants must submit sensitive methods to determine the MPCA	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		in the presence of revertants/mutants and contaminants that may have formed or been introduced during the replication/manufacturing process. IBMA: Y No guidance available. It is not clear which information is required.	
4.3.3	Methods to detect spontaneous change in major characteristics of micro-organism.	EU: see earlier comments related to genetically modified mo. CA: PMRA DIR2001-02 Part 2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. Applicants must submit sensitive methods to determine the MPCA in the presence of revertants/mutants and contaminants that may have formed or been introduced during the replication/manufacturing process. EU: Y No guidance available. Which information is required. EU: Y No guidance available. Seems not to be part of EU DAR? IBMA: Y	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		No guidance available. It is not clear which information is required. Only if MoA is touched (modified)? Checking for spontaneous change in MPCA is an integral part of manufacturing quality control and involves numerous parameters and is integrated in to the entire production process, it is burdensome for registrants to provide method. Should only be required if the MPCA is mutant of a wild type strain. In addition what would characterize a "major" change?	
4.3.4	Methods to define content of micro-organism in appropriate terms (same as IIM 1.4.1), incl. standardisation, sensitivity, reproducibility, statistical validity, and representative data to validate the bioassay.	EU: N CA: PMRA DIR2001-02 Part 2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. Applicants must submit methods to verify the certified limits of the MPCAs and any microbial impurities. Please note that these methods are often simple plating procedures. Standardisation and statistical validity data are rarely required. Representative data, however, are required. EU: Y No guidance available. Chemical guidance is not appropriate. Criteria for validation are needed. IBMA: Y	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		No guidance available. Guidance for chemicals is not appropriate as variation is far higher for microbials. Criteria for validation need to be defined. GLP Validation of the methodology used is not always possible. *Y. Validation principles of Doc SANCO 3030/99 are difficult to apply on some bioassays.* Y If methods used are classical microbiological methods then validation should not be necessary	
4.3.5	Methods to show control to a specified and acceptable level, of microbial impurities and of any other impurities of toxicological concern, including toxic metabolites, which are known or suspected to be present at any stage of the manufacturing process.	EU: Acceptable level should be clearly defined. CA: **Microbial Impurities/Pathogens** PMRA DIR2001-02 Part 2.10.2: Yes. As previously noted, insufficient guidance is provided therefore microbial screens are highly variable between dossiers. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. These guidelines provide guidance for primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), but they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing.	

OECD Annex IIM point (OECD data point number)	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		Other Impurities of Toxicological Concern PMRA DIR2001-02 Part 2.10.3: No. These guidelines clearly articulate the requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines clearly articulate the requirement. *Note:* Despite these guidelines, this is an area that is frequently ignored by applicants, particularly with respect to metabolic by-products. Little or no information/discussion is provided for metabolic by-products or toxins. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. <u>EU:</u> N. OECD issue paper on contaminants can be used. <u>IBMA:</u> N Guidance available for microbial contaminants in OECD issue paper, Series on Pesticides, No. 65. Y No guidance available for "impurities of toxicological concern, including toxic metabolites"	
4.3.6	Methods to show presence of any human and mammalian pathogens.	<u>EU:</u> N <u>EU:</u> Y No microbial specific guideline available. Guidelines on analytical methods for pesticide residues such as SANCO/825/00 are not applicable to biological agents.	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Y No guidance available. Which methods are acceptable? IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65. *N. ISO methods for list of contaminants included in OECD Issue Paper Document 5*	
4.4	Storage stability test, data and determination of shelf life, if MPCA is stored	EU: N CA: PMRA DIR2001-02 Part 2.11: No. Applicants are required to submit storage stability data (and methods of analysis) to ensure product performance and safety (if stored). These guidelines also provide a list of suggested environmental parameters to study. Additional guidance on the storage stability study, however, may be helpful (e.g., include several temperatures and many data time points in case of poor product stability). OECD: Yes. No storage stability test guidelines. U.S. EPA 885.2400: Yes. These guidelines are confusing since they do not seem to pertain to shelf-life but rather stability of the microbial pest control product on treated commodities for magnitude of residue testing. IBMA: N	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y. Lack of TG specific for microbial formulations	
4.5	Post-registration monitoring methods to determine and quantify residues of viable or non-viable micro-organism and metabolites (especially toxins)	EU: N CA: PMRA DIR2001-02: *For viable microorganisms*; Yes. PMRA does not have this requirement. However, PMRA does recommend that the applicant possess a method to differentiate their strain or isolate of the microbial pest control agent from other isolates of the species in case of any post-registration effects or violations. EU: No microbial specific guideline available. Guidelines on analytical methods for pesticide residues such as SANCO/825/00 are not applicable to biological agents. IBMA: Y No guidance available for microbials. Guidance for chemicals does not fit well. Non-viable MOs and metabolites: Yes - Only if metabolites are relevant known toxins. If the MPCA is ubiquitous in the environment how can you be absolutely sure that low concentrations of the same strain are the MPCA? If the MPCA is ubiquitous in the environment what is the purpose of post-registration monitoring? What means residue of non-viable MO (genetic markers or others)?	
4.5.1	Food (where relevant)	EU: N CA: See 4.5 IBMA: See 4.5	
4.5.2	Feed (where relevant)	EU: N CA: See 4.5 IBMA: See 4.5	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
4.5.3	Animal tissue (where relevant)	EU: N CA: See 4.5 IBMA: See 4.5	
4.5.4	Soil (where relevant)	EU: What is relevant in the case of mo? CA: See 4.5 IBMA: See 4.5 *Y. Lack of TG- different interpretations* *Recovery of strain specific metabolites from soil samples are in some cases impossible*	
4.5.5	Water (where relevant)	EU: What is relevant in the case of mo? CA: See 4.5 IBMA: See 4.5 *Y. Lack of TG specific for microbials*	
4.5.6	Air (where relevant)	EU: What is relevant in the case of mo? CA: See 4.5 IBMA: See 4.5	

OECD Annex IIM point (OECD data point number)	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y. Lack of TG- different interpretations	
4.5.7	Analytical methods for amount or activity of proteinaceous products (where relevant)	EU: proteinaceous products? CA: Without such data, PMRA will assume that effects or violations were due to the registered microbial pest control agent. *For non-viable products, i.e., toxins* Part 7: No. If the presence of a mammalian toxin has been identified and the applicant wishes to pursue registration, the product will be subject to the same data requirements as a chemical pesticide, and appropriate data will be required to establish a maximum residue limit. OECD: Yes. No microbial-specific guidelines. U.S. EPA: No. Applicants must apply for an exemption from establishing a tolerance. If this application for an exemption is rejected, the applicant will have to submit all the necessary data under 885.2000 series. IBMA: See 4.5	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
5	**Toxicological and**	EU:	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	Exposure Data and Information on the Microbial Pest Control Agent	Y: the present OECD guidelines are designed to study the toxicity of chemicals and are not validated for testing microorganism. One of the drawbacks is that no microorganisms that fulfil the function of positive controls are available. There is a urgent need of setting up methods better adapted to the study of microbials and decide which methods are applicable and necessary. <u>USA:</u> Dossier with inadequate data or rationale to support a bridging argument In data package identity or other characteristics (e.g., viability) of test material is unclear, or several forms exist and no data are provided to show its relevance to what is applied in the field Missing studies – in general. Also with non-target organism studies, conditional data requirements are often just dismissed without rationale, assuming that they meet the conditions (marine/estuarine testing is typically one that is not addressed) Toxicity/Pathogenicity studies are of too short duration to assess pathogenicity Rationale(s) are not presented as well-thought-out arguments in some cases. Instead, data and other information are provided with little explanation as to their relevance or how they meet / fulfil the data requirement. <u>IBMA:</u>	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		General for Point IIM5: OPPTS guidance is suitable.	
5.1	Summary: potential of microbial pest control agent to be hazardous to humans with consideration of its pathogenic potential, its ability to infect and pattern of clearance, and its toxicological effects	EU: N CA: PMRA DIR2001-02 Part 4.1: No. OECD: Not applicable. There are no data summary guidelines. EU: N IBMA: N	Not applicable
5.2	Occupational health surveillance report on workers during production and testing of MPCA, including information on: see IIM 5.2.1 to 5.2.4. Published reports of adverse effects, especially reports of clinical cases and follow-up studies. Proposed first aid measures and medical treatment.	EU: N CA: PMRA DIR2011-02 Part 2.7.2/4.6: No. Applicant must submit literature search results and submit all incidents of sensitization during production, testing and manufacturing. Proposed first aid measures and medical treatment can be made on draft label (part 1.1). OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1100/885.3400: No. Applicants must submit a description of any potential hazard (presumably including reports of adverse effects) as well as submit all incidents of hypersensitivity. EU: Data submitted is usually very limited. No good guidance IBMA: N	Not applicable, guidance necessary
5.2.1	The sensitisation and	EU: N	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	allergenic response of workers	CA: See 5.2 EU: **Y: OPPTS 885.3400:** too less detailed EU: Y – no good guidance or test guideline IBMA: N	Not applicable, guidance necessary
5.2.2	Details on any occurrence of hypersensitivity and chronic sensitisation	EU: N CA: See 5.2 EU: **Y: OPPTS 885.3400:** too less detailed EU: Y – no good guidance or test guideline IBMA: N	Not applicable, guidance necessary
5.2.3	Any significant clinical findings related to exposure, with special attention to those whose susceptibility may be affected.	EU: N CA: See 5.2 EU: Data submitted is usually very limited. No good guidance IBMA: N	Not applicable, guidance necessary
5.2.4	Published reports of adverse effects, especially reports of clinical cases and follow-up studies; list databases and key words used in a	EU: N CA: See 5.2 EU:	Not applicable, guidance necessary

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	literature search.	Data submitted is usually very limited. No good guidance IBMA: N *Y* *Different interpretations*	
5.2.5	Proposed first aid measures and medical treatment	EU: N CA: PMRA DIR2001-02 Part 1.1: No. The proposed first aid and medical treatment procedures should be included on the proposed label. PMRA will review the proposal and make any required changes based on data in the dossier. OECD: Not Applicable. U.S. EPA: There are no guidelines. Applicants must submit draft labels as per 40CFR 152.50 40CFR 156. U.S. EPA will review the proposal and make any required changes based on data in the dossier. EU: N – generally symptomatic, no specific antidotes or treatment available. IBMA: N	Not applicable, guidance necessary
5.3	Basic studies	EU: N EU:	Not applicable. Guidance needed for which MOs which endpoints needs to be addressed

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y: The first Tier requires all basic studies have to be performed. Microorganisms are very diverse and therefore need to be assessed case by case and usually not all studies are needed.	
5.3.1	Sensitisation properties	EU: N CA: PMRA DIR2001-02 Part 4.6: No. PMRA requires reports on all incidents of hypersensitivity during production, testing and manufacturing. No sensitization studies are required since all microbial pest control agents are considered to contain substances that could elicit sensitization reactions. OECD 406/442: Yes. These guidelines only address exposure via the dermal route. All microorganisms contain complex molecules that could elicit sensitization reactions in individuals. U.S. EPA 885.3400/870.2600:No. U.S. EPA requires reports of all hypersensitivity incidents as well as a skin sensitization study. As noted for OECD above, this study only addresses exposure via the dermal route. EU: **Y:** **OECD406:** - Bühler method: not suitable, because MOs usually don't overcome the intact skin barrier - GPMT: seems to work but no validation data **OECD 429:** LLNA: no experience, no validation data **Missing test method for respiratory sensitisation** (same as for chemicals)	Diverse answers: follow up by questionnaire upon acceptance of test methods OECD406: GPMT might be suitable without modification Bühler: Not suitable LLNA: No data Further guidance needed, when to use which method.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		OPPTS 885.3400: too less detailed <u>EU:</u> Y: The available methodology is based on assays developed for pure chemicals and is producing inconsistent results with microbials. In principle the regulation for classification is applicable to chemicals and not to microbials. The regulation (EC 1272/2008) and the directive (EC 67/548) for classification and labelling are not applicable to microorganisms. There exist no guidelines for testing if microorganisms may cause an allergic reaction by inhalation. However, since some warning concerning the sensitising properties by inhalation should be indicated on the label. It was agreed in a EFSA meeting and consequently the Danish Environmental Protection Agency use the sentence on all microbial pest control agents "Contains "*name of the microorganism*"; may have the potential to provoke sensitising reactions". Hence it is important to avoid exposure by inhalation. <u>EU:</u> Y Clear guidance on which test protocol is suitable, if any, in missing. <u>EU:</u> Y How should this be tested? <u>EU:</u> Y – no good guidance or test guideline. Default assumption is of sensitising potential	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N Label all products as potential sensitizers, no Xi box, with the agreed upon Praper M3 meeting statement until an agreed upon study guideline is agreed upon. Study is no longer required for European registration following the PRAPeR M2 meeting on 16-18th February 2009 in Parma Italy. Buehler test – Skin sensitization: OECD Guideline for testing chemicals No. 406 (1981). This has not been considered as an adequate test method for microbials and thus not accepted by some authorities. Proper Test Guidance for testing sensitisation properties of microbials is required. *Y. Lack of TG specific for microbials* Y: no TG for microbials	
5.3.2	Acute oral infectivity, toxicity and pathogenicity	EU: N CA: PMRA DIR2001-02 Part 4.2.2/4.2.3/4.3: No. However, PMRA does not provide specific methods. Instead, we require studies conducted in accordance with U.S. EPA test guidelines (see below). OECD Section 4 Guidelines: Yes. No microbial-specific guidelines. None of these studies are suitable to properly assess infectivity (e.g., duration is too short, no interim sacrifices to detect clearance).	OÉCD guidelines not suitable. OPPTS: more detailed guidance needed or further guidance document (positive controls, in which cases pathogenicity cannot be assessed by animal studies, limit dose...)

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		U.S. EPA 885.3000/885.3050/885.3150/885.3200: No. <u>EU:</u> **Y:** **OECD401/420/423/425:** suitable only for acute toxicity, pathogenicity and persistence cannot be tested, no guidance for range finding or limit dose for micro-organisms **OPPTS 885.3550** (tier II, toxin test): too less detailed **N** **OPPTS 885.3050** (tier, might need to be updated) EU: Y: The oral toxicity test enables to test both the direct pathogenicity/ infectivity and also indirect toxicity linked to presence of potentially toxic secondary metabolites. However one of the weaknesses of the existing methods, are that no positive controls (pathogenic isolates) are used, giving the uncertainty whether a pathogenic isolate would give a response in the animal models used. In a former research project for the Danish Environmental Protection Agency, it was demonstrated that using a known human pathogenic *Bacillus cereus* strain in an oral rat study, did not give rise to illness or diarrhea in the animals (Wilcks et al., 2006). So there is a strong need to develop new models and methods to assess the potential human pathogenicity of microbial organisms used in plant protection products. <u>JP:</u> Y TG number : 420, 423, 425	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Infectivity and pathogenicity are not covered. EU: N. OPPTS guideline available. EU: Y Can the tox data requirements for infectivity studies be waived if the microorganism does not grow at temperatures above 30ºC? How to include immunocompromised individuals? EU: N IBMA: N Acute oral toxicity testing of MCPA according to OPPTS 885.3050.	
5.3.3	Acute intratracheal/inhalation infectivity, toxicity and pathogenicity	EU: N. CA: See 5.3.2 EU: **Y** **OECD403:** acute toxicity only, - not suitable for pathogenicity or persistence testing, - no guidance for range-finding or limit dose for micro-organisms **OPPTS 885.3550** (tier II, toxin test): too less detailed **OPPTS 885.3150** (tier I)	OECD guidelines not suitable OPPTS guidelines: intratracheal instillation can cause mortality or unspecific effects. Further guidance on interpretation of clearance needed.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		- intratracheal instillation: very often effects are observed, which might often be unspecific. EU: Intratracheal instillation can cause high control mortalities for several reasons. Reasons can be high stress for the laboratory animals, and anesthetization and intoxication or irritation/sensitization of the lungs by the control substances. Sometimes slow clearance process from the lung and other organs can be observed, although no infections and no clinical manifestations were recorded. <u>JP:</u> Y TG number : 403 Infectivity and pathogenicity are not covered. <u>EU:</u> Y. OPPTS guideline available, however, interpretation of cause of mortality (toxicity/toxin, immune system overload due to test set-up) is sometimes unclear. <u>EU:</u> Y Can the tox data requirements for infectivity studies be waived if the microorganism does not grow at temperatures above 30ºC? How to include immunocompromised individuals? <u>EU:</u> Y – can be problems with physical effects of overdosing with viscous solutions.	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N Acute intratracheal toxicity testing of MCPA according to OPPTS 885.3150	
5.3.4	Acute intravenous/intraperitoneal infectivity	EU: N EU: **Y:** **OECD:** Guideline missing **OPPTS 885.3550 (tier II):** too less detailed **N:** **OPPTS 885.3200** (tier I, might need to be updated) EU: Y: In our opinion there is no need to perform the intraperitoneal test since this represent the "worst case", which is not realistic according to the use of the MPCP JP: Y There is no OECD TG applicable for this study. EU: Y Can the tox data requirements for infectivity studies be waived if the microorganism does not grow at temperatures above 30ºC? How to include immunocompromised individuals? EU: N. OPPTS guideline available. IBMA: N	OECD: no suitable test guideline OPPTS: Open questions when to perform and how to address immunocompromised status

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Acute intraperitoneal toxicity testing of MPCA according to OPPTS 885.3200.	
5.3.5	Genotoxic potential, especially for fungi and actinomycetes: a discussion of the potential for genotoxin production based on the relationship of the micro-organism to a genus/species known to produce genotoxins. If a related fungus/ actinomycete produces a genotoxin, either an appropriate and sensitive analytical test (e.g. HPLC) must be done to detect its presence in the MPCA (for Canada), or genotoxicity testing is required (for EC).	EU: At this point it is important that the company demonstrates that the microbial preparation used for testing genotoxicity is relevant: this means that intracellular as well as extra cellular metabolites should be evaluated. CA: PMRA DIR2001-02 Part 4.8: No. If characterization data indicate a potential for the production of known genotoxic compounds, an appropriate and sensitive analytical test must be performed to detect the presence of such compounds. OECD: Yes. There are numerous guidelines on evaluating the genotoxic potential of compounds but there are no guidelines to detect such compounds from microbial pest control agents. U.S. EPA: Yes. There is no requirement for such information. EU: **Y:** **Problem with all genotox tests:** Testing for non-secreted genotoxins is only possible with extracts. This will usually dilute the possible genotoxins and thus, the sensitivity of the tests might not be high enough. **OECD 471:** unsuitable for most viable micro-organisms (use of histidine-deficient medium might decrease viability of the tested micro-organisms.	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Development and validation of sensitive standard bioassays for the cyto- and genotoxicity assessment are needed to test culture supernatants and crude extracts JP: Y There is no OECD TG applicable for this study. EU: N EU: Y During what conditions should the presence of genotoxins be analysed (considering that genotoxins may be produced in response to external factors)? EU: Y – No guidance on which stage of the organism to test – metabolites produced in one stage might not be produced in another. No specific test guideline or guidance. IBMA: Y No appropriate guidance for micro-organisms and their metabolites is available. No decision scheme is available when testing is required and which material needs to be tested. -Based on the relationship? Related to what extend? -Method used: Dir 2000/32/EC B12, OECD 474 -Still no appropriate guideline available. All cell culture tests are	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		difficult to perform with microbials since the microorganism may grow on the agar plates and using nutrients foresee for the cells to be tested. Testing in vivo can be regarded as a waste of animals Not always easy to demonstrate the non production of metabolites or toxins *Y. Available methods for in vitro test (Ames) are not applicable to microbials* *Lack of available standards for some metabolites*	
5.3.6	Cell culture study, for viruses and viroids or specific bacteria and protozoa with intracellular replication	EU: N CA: PMRA DIR2001-02 Part 4.7: No. These studies, however, would be performed on viral agents only. Most viable microorganisms would overwhelm eukaryotic cells in tissue culture studies due to much faster growth rates. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.3000/885.3500: No. EU: **Y: No specific guidelines available** JP: Y There is no OECD TG applicable for this study.	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Y – no TG or guidance IBMA: N See 5.3.5 Only if relevant!	
5.3.7	Short-term toxicity (including inhalatory short-term toxicity), pathogenicity, infectivity	EU: N CA: PMRA DIR2001-02: PMRA does not have these requirements. PMRA, however, may require such studies, if adverse effects are noted in other studies (i.e., a higher tier requirement). OECD: Yes. No microbial-specific guidelines to assess infectivity. There are however, appropriate guidelines to assess toxicity only. U.S. EPA 885.3000/885.3550: No. These studies may be required at Tier 2. EU: Y. No clear guidance. Usually a waiver is acceptable. EU: N – TG OK, but test rarely performed IBMA: N	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		OPPTS Guideline No. 885.3600	
5.3.7.1	Short-term toxicity, pathogenicity, infectivity (28-day minimum)	EU: N CA: See 5.3.7 EU: **Y:** **OECD 407/408/409:** Pathogenicity/infectivity not addressed. No guidance on range-finding/limit dose for micro-organisms. **N:** **OPPTS 885.3600** (might need to be updated) JP: Y TG number : 407 Infectivity/viability and pathogenicity are not covered. EU: See 5.3.7 EU: Y Can the tox data requirements for infectivity studies be waived if the microorganism does not grow at temperatures above 30ºC? EU: N – TG OK, but test rarely performed IBMA: N	
5.3.7.2	Inhalatory short-term toxicity	EU: N CA: See 5.3.7	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: **Y:** **OECD 412/413:** Pathogenicity/infectivity not addressed. No guidance on range-finding/limit dose for micro-organisms. **N:** **OPPTS 885.3600** (might need to be updated) JP: TG number : 412 Viability is not covered. EU: See 5.3.7 EU: N – TG OK, but test rarely performed IBMA: Y. Inhalatory short term toxicity study not possible to perform as the administration is done by intratracheal route which needs anesthesia; so not possible to repeat it each morning	
5.4	Toxicity studies on metabolites (especially toxins)	EU: N CA: PMRA DIR2001-02: Yes. These guidelines do not address this requirement. Although it is not explicitly stated in the guidelines, if analytical data show that the microbial pest control products contains a known toxin then PMRA might require additional toxicological data. Studies performed according to U.S. EPA 870 series or OECD	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		section 4 would be accepted. OECD Section 4: No. There are appropriate guidelines to perform such studies. U.S. EPA 870 Series: No. There are appropriate guidelines to conduct such studies. EU: **Y: No specific guidelines available,** **very important issue!** EU: Y: Microorganism may produce a huge variety of different metabolites. Determination of all metabolites produced during fermentation and after application is impossible. Therefore we need guidance of which metabolites need to be assessed. A pragmatic reasoning on metabolites should be preferred. JP: N EU: Y No guidance on which metabolites and tests EU: Y How should this be addressed? Metabolites could be produced during different conditions in response to different environmental factors. Only tests with isolated and identified metabolites? Testing with plant extracts?	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N	
5.5	Other/special studies	EU: N CA: PMRA DIR2001-02: PMRA does not have these requirements. PMRA, however, may require such studies, if adverse effects are noted in other studies (i.e., a higher tier requirement). Studies performed according to OECD and/or U.S. EPA 885 series guidelines would be accepted. Note: *In vivo* studies would presumably be performed on metabolites or other cellular extracts since most living microorganisms would overwhelm eukaryotic cells in tissue cultures. OECD: There are various appropriate guidelines to conduct toxicity studies but no appropriate guidelines to conduct infectivity studies on microbial pest control agents. U.S. EPA 885.3000/885.3550: No. These studies may be required at Tier 2. EU: Y: no guidance available EU: Y: What criteria would trigger long-term studies?	
5.5.1	Specific toxicity, pathogenicity and	EU: N	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	infectiveness studies	CA: See 5.5 EU: **Y: No specific guidelines available** EU: Y: no guidance available EU: Y: What studies are required? Growth curve at different temperatures? EU: N- Case-by-Case so guidelines probably of limited use.	
5.5.2	*In vivo* studies in somatic cells	EU: N CA: See 5.5 EU: **Y: No specific guidelines available** EU: Y: no guidance available JP: Y There is no OECD TG applicable for this study. EU: Y: What types of studies are recommended? Comet assay? Only testing of known genotoxins?	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: N – no such studies have been submitted IBMA: See 5.3.5, testing of microorganisms in cell culture not recommended Not required if Acute tests are negative	
5.5.3	Genotoxicity - *In vivo* studies in germ cells	EU: N CA: See 5.5 EU: Y: cf. to 5.3.5 EU: Y: no guidance available JP: Y There is no OECD TG applicable for this study. EU: N – no such studies have been submitted IBMA: See 5.3.5 Not required if Acute tests are negative	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
5.6	Summary of mammalian toxicity and overall evaluation		
6	**Metabolism and Residues Studies on the Microbial Pest Control Agent**	CA: PMRA DIR2001-02 Part 7. Yes. PMRA does not require any information or data on metabolism or residues of the microbial pest control agents on treated commodities. PMRA conducts its own assessment based on data and information that are available in the dossier. If such data are required for microbial pest control agents, PMRA would accept data generated as per U.S. EPA 885.2000 series. If the microbial pest control agent does contain a toxin or other toxic metabolites and the applicant wishes to pursue registration, residue and metabolism data may be required as per conventional chemical pesticides. Studies performed according to U.S. EPA 860 series would be accepted. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.2000: No. The use of a microbial pest control agent on food, feed or raw agricultural commodity requires that a tolerance or an exemption from the tolerance be established. Applicants must request an exemption from a tolerance by submitting a sound scientific rationale. In absence of such an exemption, the applicant must submit acceptable residue data following 885.2000 series (microbial) and/or 860 series (chemical) test guidelines.	
6.1	Rationale for waiver of residue data based on information showing that MPCA is not hazardous to mammals, i.e. lack of	EU: N CA: See 6. EU:	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	potential for a known mammalian toxin and negative result from the acute oral toxicity test.	**Y:** In case of potential toxin expression no clear guidance on the significance, magnitude or other aspects related to the toxin or the circumstances of its formation is given. Often the qualitative information on the potential to form toxins is waived by assumptions on the quantitative non-relevance. Clear scenarios or trigger values are required for the generation of studies and a definition should be provided, which data is required to fulfil the data requirement. Currently in case of a potential toxin, the study information/waiver justification is case by case decisions with a flexible outcome. EU: N IBMA: N	
6.2	Rationale for waiver based on a substantiated estimation that MPCA is unlikely to occur on treated food/feed stuffs in concentrations considerably higher than under natural conditions.	EU: N CA: See 6. EU: **Y:** - Often the assumed rate of decline (or growth) is not supported by data. - Inactivation by UV differs between field and glasshouse. - Potential for the formation of toxins is described in public literature on selective growth media without relation to field conditions. Questionable extrapolation in rationale. - If the MPCA is host dependent, the occurrence of the host and its fate after the infection is often not taken into account. Impurities (e.g. mycotoxins, pathogens) are not taken into account.	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: N IBMA: N	
6.3	Persistence and likelihood of multiplication in or on crops, feedingstuffs or foodstuffs	EU: N CA: See 6. EU: **Y: see 6.2.** In addition: - Conditions for transformation of spores to viable cells. - If CFU were analysed, the methods often lack strain specificity compared to background. Behaviour of microorganisms after food processing is unclear. EU: N IBMA: Y No guidance available. It is not clear when strain specific data are required, and when species specific data are sufficient.	
6.4	Further information required	EU: N CA: See 6. EU: **Y:** Assessment often based on expert judgement. Quantitative methodology to assess non-viable residues would be helpful (e.g. TTC approach on metabolites/toxins of concern).	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: N	
6.4.1	Non-viable residues	EU: N CA: See 6. EU: **Y** see 6.2 Mainly the growth and decline under field conditions (with or without host presence) is poorly described. EU: N IBMA: i.e. metabolites? Or? Method to be used? Non-viable residues = metabolites ?	
6.4.2	Viable residues	EU: N CA: See 6. EU: N	
6.5	Summary of residue behaviour and overall evaluation	EU: N	
7	**Fate and Behaviour Studies on the Microbial Pest Control Agent in the Environment**	CA: PMRA DIR2001-02 Part 8: No. Environmental fate data are Tier 2 data requirements. Few details, however, are made in the test guidelines. If these studies are required, PMRA would make specific recommendations on test protocols (e.g., U.S. EPA 885.5000 series guidelines).	Persistence is not a criterion in risk assessment. The available guidelines (PMRA DIR2001-02 Part 8 and US EPA885.5000) are sufficient.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.5000 series: No. EU: General problems: -interpretation of the data in relation to the naturally occurring background concentration of the respective micro-organisms - reliable data on background levels and persistence are often scarce and poor, strain-specific data are usually lacking [Remark: For some mBCAs (e.g. entomopathogenic fungi) it is recommended to evaluate persistence in soil at the species level since densities of individual strains often follow a very similar decline (see Scheepmaker and Butt, 2010, Biocontrol Science and Technology 20, 503-552)] EU: In contrast to the criterion for chemicals there is no criterion for persistence of MPCA and the risk assessment can only be evaluated on a case-by-case approach.	
7.1	Sufficient information on the origin, properties, survival and residual metabolites of the micro-organism to assess its fate and behaviour in the environment. Information provided in parts 2 - 6 may suffice.	EU: N CA: See 7. EU: see 7. EU: Information from public data should be accepted. Most MBCA can	Mixed answers. Guidance on exposure for secondary metabolites required. Guidance on exposure scenarios would be useful

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	Viability/population dynamics, persistence, multiplication and mobility	be considered to be part of the background population. Application of microbial species to any particular environment usually results in a temporary increase of its population followed by a gradual decrease to background levels. EU: Y: A guidance on exposure scenarios related to way of application would facilitate EU: Guidance on how to address the issue of secondary metabolites would be welcome IBMA: Y No guidance available. It is not clear when strain specific data are required, and when species specific data are sufficient. Good if information provided in parts 2 – 6 can suffice.	
7.1.1	Persistence and mobility in soil	EU: N CA: See 7. EU: see 7. EU: See 7.1 EU: Y OPPTS 885.5000 and 5200 guideline available but EU perception of requirements is sometimes different. OPPTS not often used IBMA: see 7.1	Available US guidelines should be sufficient. Persistence is not a criterion in risk assessment

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EPA OPPTS 885.5200. Recommends a Greenhouse study with soil and vegetation representative for the proposed use. This is impossible for proposed application in orchards. No clear advise which soil should be used and how and in which range the parameters humidity, temperature, precipitation, sunlight, pH and nutrients should be modified. It can be stated that persistence will be influenced mostly by the autochthone microbial community, and the microbial community is mostly correlated with the availability of organic substance. Hence it can be recommended to use soils differing mainly in availability of organic contend. A clear advice about the trial set up should be given. *Y. Lack of TG specific for microbials* *Background levels are not easy to define*	
7.1.2	Water	EU: N CA: See 7. EU: see 7. EU: Should be waived EU: Y OPPTS 885.5000 and 5300 guideline available but EU perception of requirements is sometimes different. OPPTS not often used IBMA: see 7.1	Available US guidelines should be sufficient.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		OPPTS 885.4000 See 7.1.1. It can be stated that persistence will be influenced mostly by the autochthone microbial community. What kind of water should be used? How should the parameters be modified? A clear advice about the trial set up should be given. *Y. Lack of TG specific for microbials* *Different interpretations*	
7.1.3	Air	CA: See 7. EU: see 7. EU: Should be waived EU: Y No guidance available. Which methods are acceptable? IBMA: see 7.1 *Y. Lack of TG specific for microbials* *Different interpretations*	Mixed answers, however it seems not to be a critical issue in the dossier evaluation. No further guidance needed.
7.2	Other/special studies	EU: see 7.	
8	**Ecotoxicological Studies on the Microbial Pest Control Agent (Effects on non-target organisms)**	AU: The following general comments relate to environmental toxicity testing for MPCAs (OECD Annex IIM point 8). It has been our experience that for microbial products, the traditional chemical test protocols are not directly suitable for the evaluation of toxicity to non-target organisms.	OECD 67 (ENV/JM/MONO(2012)1) is available OECD test guidelines for chemicals look at toxicity only and are too short For individual studies OPPTS guidelines are

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Australia has previously suggested the approach of radial taxonomy for the selection of appropriate test species for environmental toxicity testing, as described in paragraphs 29-31 of the *OECD Guidance to the Environmental Safety Evaluation of Microbial Biological Control Agents*. This approach is termed the "centrifugal taxonomic approach" by Environment Canada. Many MPCAs have quite specific host ranges, and radial taxonomy provides a mechanism for tailoring data requirements to provide information on target species specificity. In Australia, discussions on appropriate environmental toxicity testing protocols may occur when applicants arrange pre-submission meetings. These protocols often take into account a number of factors including the biology of the agent (e.g. bacteria, fungus, virus), the target (e.g. insect, weed, fungus), the mode of action (e.g. pathogenicity, production of toxins, competition for ecological niche), and the nature of the receiving environment (e.g. soil type, availability of moisture and oxygen). A useful reference document for environmental toxicity study design is the Environment Canada Guidance *Document for Testing the Pathogenicity and Toxicity of New Microbial Substances to Aquatic and Terrestrial Organisms.* <u>EU:</u> General problems: - studies are often submitted being developed for chemical substances (e.g. OECD 201-203, OECD 211) - the relevance of the exposure conditions in the test system might be reduced compared to the conditions in the respective environmental compartment	<u>available for a number of organisms but need to be reviewed.</u>

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Y - OECD guidance to the environmental safety evaluation of microbial biocontrol agents was published in 2012 and provides an additional tool for risk assessors. However the present OECD guidelines are designed to study the toxicity of chemicals and are not validated for testing microorganism. One of the drawbacks is that no microorganisms that fulfil the function of positive controls are available. There is a urgent need of setting up methods better adapted to the study of microbials and decide which methods are applicable and necessary. EU: The current EPA Microbial pesticide test guidelines' are quite brief. The inclusion of more detailed study protocol advice and of study validity criteria would be useful. Consideration could be given to the methodology required to confirm (or otherwise) microbial exposure concentrations and where relevant to identify the exposure profile over the study duration. Also, more detail could usefully be included in relation to the assessment of any adverse effects arising from potential infectiveness and pathogenicity. USA: Dossier with inadequate data or rationale to support a bridging argument In data package identity or other characteristics (e.g., viability) of test material is unclear, or several forms exist and no data are provided to show its relevance to what is applied in the field	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Missing studies – in general. Also with non-target organism studies, conditional data requirements are often just dismissed without rationale, assuming that they meet the conditions (marine/estuarine testing is typically one that is not addressed) Toxicity/Pathogenicity studies are of too short duration to assess pathogenicity Rationale(s) are not presented as well-thought-out arguments in some cases. Instead, data and other information are provided with little explanation as to their relevance or how they meet / fulfil the data requirement. One area where we typically differ from OECD guidance is that they do test for toxicity but not pathogenicity in non-target tests. Typically these studies are too short to assess pathogenicity; however, applicants who have done the studies first for European registrations are sometimes not willing to do another study to meet EPA guidelines. <u>IBMA:</u> Y Guidance for chemicals is useful for screening tests. Due to relatively short exposure and observation times pathogenicity and infectivity can eventually not be assessed. OPPTS guidance for Microbial Pesticide Testing for some non-target organisms is available, but not suitable for first screening. It is useful in case effects are expected.	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		General comment for studies on aquatic non-target organisms: no guidance is available for determination and maintenance of MPCA in the test medium throughout the study period, limit values for chemical pesticides are not applicable to MPCA/MPCP, as standard deviation of bioassays is usually higher compared to chemical substances. Current guidance does not take into account that some microorganisms are inactive in water and hardly reactivated during analysis. Risk assessment approaches for chemical pesticides are considered not appropriate for microorganisms, relevant units for microorganisms (CFU or IU) cannot be used in many cases In general:-Test Guidance is not relevant in all cases. It would be appropriate to have the possibility to waive some data requirements based on intended uses and the true nature of the MPCA.	
8.1	Effects on birds	CA: PMRA DIR2001-02 Part 9: No. Requirements are clearly articulated. PMRA accepts studies that were conducted in accordance to U.S. EPA 885.4000 series test guidelines or Environment Canada EPS 1/RM/44 guidelines. Environment Canada EPS 1/RM/44: No. These guidelines provide detailed information on testing. Recommended hosts, however, may be more specific to Canada. Also, recommended hosts may not be closely related to target hosts, i.e., not a centrifugal taxonomic approach to host selection. OECD: Yes. No microbial-specific guidelines. Current guidelines	Mixed answers: chemical test guidelines with adaption are mentioned. Chemical guidelines are not suitable for micro organisms OPPTS guidelines are available for micro organisms

OECD Annex IIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)	Problems with TGs (Y / N)? If Y, please specify the TG number and describe the problem	Overall Conclusion: Suitable method available without modification Suitable method available with modifications No suitable method available
		under section 2 are not appropriate for microbial pest control agents as they do not consider the unique qualities of living organisms (e.g., infectivity, clearance). U.S. EPA 885.4000 Series: No. Adequate details are available for testing microbial pest control JP: Y TG number : 223 The test period for microorganisms should be extended because it takes time between infection and the appearance of symptoms. The investigation of the infectivity/pathogenicity of MPCA should be conducted to clarify the cause of adverse effects. EU: N. However sometimes OECD 223 is used which is not suitable. IBMA: N Acute toxicity: OECD 223 Avian acute oral toxicity test, single dosing, 2000 mg/kg bw, 14 days observation (guidance for chemical pesticides), suitable for MPCA assessment due to relatively long observation period, no guidance for determination of MPCA in test item Short-term toxicity: Microbial Pesticide Test Guideline OPPTS 885.4050 Avian Oral,	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Tier I Observation period: 30 days, clearance can be included	
8.2	Effects on fish	CA: See 8.1 EU: high microbial densities in aquatic test systems may cause turbidity which may influence the test organisms and, in consequence, complicate the evaluation of the study. For instance high solids concentration may interfere with the daphnids' filtering system, thereby affecting growth, reproduction and survival (e.g. see Draft Assessment Reports for Bt kurstaki) - algal growth: Turbid media associated with high solids concentrations may affect photosynthetic activity JP: Y TG number : 203,204 The test period for microorganisms should be extended because it takes time between infection and the appearance of symptoms. The investigation of the infectivity/pathogenicity of MPCA should be conducted to clarify the cause of adverse effects. EU: N. However sometimes OECD 203 is used which is not suitable. IBMA:	OPPTS 885.4200 is available as is OPPTS 885.4700 for long term OECD test guidelines for chemicals not suitable

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y Acute toxicity: OECD 203, 96 hours, 100 mg/L (guidance for chemical pesticides) No guidance for determination of the active ingredient in the test medium, short exposure period but comparable to survival time of most MPCA in aquatic systems. Short-term: OECD 230/229 21-day Fish assay, Fish Short Term reproduction assay is available (guidance for chemical pesticides). No guidance for determination of the content of the active ingredient in the test media and maintenance of MPCA in test medium, no assessment of infection in case of mortalities Microbial Pesticide Test Guideline OPPTS 885.4200 Freshwater fish testing, Tier I. with prolonged exposure (30 days) Assessment can be adapted to reflect activity of MPCA (toxic, pathogenic), mortality or overt symptomatology Only if applied to aqueous environment? Limit data set for soil and foliar applied products? - Pre and post-testing enumeration of MPCA. Settling of the particulate MPCA may result in lower counts at end of study compared to start. Reasoned cases should be acceptable for data interpretation.	
8.3	Effects on aquatic invertebrates	CA: See 8.1 EU: See 8.2	OPPTS 885.4240 is available as well as OPPTS 885.4650.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		JP: Y TG number : 202,211 The test period for microorganisms should be extended because it takes time between infection and the appearance of symptoms. EU: N. However sometimes OECD 202 and/or 211 is used which is not suitable. EU: Y As in many cases Daphnia reproduction (OECD test guideline 211) is a sensitive parameter a deeper understanding of the reasons for effect would facilitate. USA: Aquatic testing –suggest some improvements regarding sterile filtrate and particulate matter - these should be incorporated IBMA: Y Acute test: OECD 202 *Daphnia* acute immobilisation test, 48 hours, 100 mg/L (guidance for chemical pesticides) Generally, no guidance for determination of the active ingredient in the test medium, short exposure period. Short-term tests: OECD 211 *Daphnia magna* reproduction test (21 days) (guidance for chemical pesticides)	Some problems encountered in test systems OECD test guidelines for chemicals not suitable

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Microbial Pesticide Test Guideline OPPTS 885.4240 Freshwater aquatic invertebrate testing, Tier I. with prolonged exposure (21 days) General problem during prolonged exposure to e.g. bacterial or fungal spores: if effects are observed they are usually not related to pathogenicity of the microorganism but to mechanical interference of the spores with the feeding apparatus resulting in a decreased energy uptake Only if applied to aqueous environment? Problems have arisen from MPCA in these test systems due to the physical nature of spores rather than true toxicity. MPCA need a specific guideline method Problems can sometimes occur with high levels of MPCA in the water of *Daphnia magna* tests resulting from *Daphnia* dying from suffocation or smothering rather than toxicity. Therefore reasoned cases should be acceptable for data interpretation and lower rates of MPCA used in acute studies.	
8.4	Effects on algal growth and growth rate	CA: See 8.1 EU: See 8.2 JP: N TG number : 201 EU: Y No guidance available for m.o. OECD 201 guideline used is not suitable	OECD test guidelines for chemicals not suitable. No specific guidance for micro organisms available, guidance required.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: Y Only guidance for chemical pesticides available OECD 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test, 72 hours, 100 mg/L No guidance for determination of the active ingredient in the test medium, short exposure period. Pre and post-testing enumeration of MPCA. Settling of the particulate MPCA may result in lower counts at end of study compared to start. Reasoned cases should be acceptable for data interpretation.	
8.5	Effects on aquatic plants	CA: See 8.1 EU: See 8.2 EU: Y No guidance available for m.o. OECD 221 guideline used is not suitable IBMA: Y Only guidance for chemical pesticides available OECD 221 *Lemna* sp. growth inhibition test, 7 days, 100 mg/L No guidance for determination of the active ingredient in the test medium	OECD test guidelines for chemicals not suitable. No specific guidance for micro organisms available, guidance required.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
8.6	Effects on terrestrial plants	CA: See 8.1 JP: Y TG number : .227, 208 If a MPCA relates to a plant pathogenic strain, the concurrent study using the pathogenic strain is necessary to investigate whether the MPCA has pathogenicity. The investigation of the infectivity/pathogenicity of MPCA should be conducted to clarify the cause of adverse effects. EU: N. However sometimes OECD 227 and/or 208 is used which is not suitable. IBMA: Y No EU data requirement, usually phytotoxicity assessment during efficacy trials and available knowledge from literature is sufficient OECD 227 Terrestrial plant test: vegetative vigour OECD 208 Terrestrial plant test: seedling emergence and seedling growth test Microbial Pesticide Test Guideline OPPTS 885.4300 Nontarget Plant Studies, Tier I	Mixed answers. Guideline OPPTS 885.4300 available Conditional data requirement if MPCA relates to a plant pathogenic strain? No EU data requirement? OECD test guidelines for chemicals not suitable.
8.7	Effects on bees	CA: See 8.1	Mixed answers

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		EU: Testing of acute effects may be done according to OECD 213/214 for oral and contact exposure for active substances and plant protection products. For pesticide testing, these guidelines are slightly modified from the short term exposure to chronic exposure, e.g. for oral exposure, but there are currently no specific guidelines for chronic exposure available. For testing pesticides it is currently discussed that also a guideline for testing chronic toxicity would be desirable. This is important also with respect to microbials; especially as chronic testing seems be highly desirable, as potentially these microbials may have a low acute toxicity but there may be concern e.g. of a microbial colony growth. Thus it seems necessary to create a guideline for chronic toxicity testing, which can be used for pesticides but also microbials. JP: Y TG number : 213,214 The test period for microorganisms should be extended because it takes time between infection and the appearance of symptoms. The investigation of the infectivity/pathogenicity of MPCA should be conducted to clarify the cause of adverse effects. EU: N. However sometimes OECD 213 and/or 214 is used which is less suitable.	OPPTS 885.4380 guideline available. Problems with study design encountered. OECD test guidelines for chemicals with adaptation. Less suitable? Specific guidance for microbials required. Brood testing sometimes required. No guidance for micro organisms. Guidance required

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		<u>EU:</u> Y: In some cases there might be a risk to bee broods. With products intended to be used on flowering crops foraging bees might be exposed and bring *the* microorganism back to the bee hive. In case of favourable conditions the bacterium might be able to grow in the bee hive. If it produces chitin it might affect bee broods. This needs some further guidance. <u>USA:</u> More on potential EPA-OPPT guideline modifications: Honey bee guideline – it is very difficult to meet the 30 day study duration requirement <u>IBMA:</u> Y Acute test: OECD 213 Honeybee acute oral toxicity test OECD 214 Honeybee acute contact toxicity test (guidance for chemical pesticides) 48 hours, exposure (oral test)/observation time can be extended to a level at which mortality in the non-dosed control group does not exceed 10% (usually up to 96 hours). Short-term test: OPPTS 885.4380 Honey Bee Testing, Tier I Prolonged exposure/observation time of 30 days	

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Test period needs to be adapted if tests are conducted with bees outside the hive OECD guidelines are best. - OECD (213) and EPA (OPPTS 885.4380) guidelines state different temperatures that the bees should be held at during the test. - Unlike OECD, the EPA guidelines do not include the use of a positive control (e.g. dimethoate). Positive control should be included in the study to demonstrate protocol is working. - EPA guidelines require test to be run for 30 days compared to 4 for OECD. Y. Bumblebee – toxicity test (48 hr oral and contact LD50): EPPO Guideline No. 170 + OECD Guideline for testing of chemicals. Honeybees, acute oral and contact toxicity tests 213 and 214. TG has not been considered applicable for MPCPs by some Authorities. A specific microbials TG is needed here.	
8.8	Effects on terrestrial arthropods other than bees	CA: See 8.1 EU: NTA test methods according to IOBC do not take into account biological properties of the mBCA, mode of action and relevant routes of exposure (e.g. dietary uptake in the case of Bt). Thus, IOBC test methods do not seem applicable for testing (for more information, see OECD, 2012: Guidance to the Environmental Safety Evaluation, Series on Pesticides No. 67) JP: Y TG number : 226	Mixed answers. Reference to IOBC guidelines but as mentioned IOBC guidelines do not take into account biological properties of the mBCA, mode of action and relevant routes of exposure. OECD guidelines for chemicals are not suitable for the same reason. OPPTS Microbial Pesticide Testing 885.4340 Non-target insect testing however adaption required with regard to exposure time The Canadian guidance document (Environment

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		The investigation of the infectivity/pathogenicity of MPCA should be conducted to clarify the cause of adverse effects. EU: N. However sometimes OECD is used which is in principle less suitable. Nevertheless the test can be used but RA is unclear USA: More on potential EPA-OPPT guideline modifications: Nontarget insect testing – the advice in the guideline that says the study is to be run for a prescribed number of days or until 20% mortality is observed in the control groups is sometimes abused or misinterpreted. Studies seen lately have been conducted for a few days (insufficient duration), and yet considered "valid" because control morality reached 20% on the last day of the study (i.e., the study was terminated early, but considered valid solely because 20 % or less mortality was observed in the control group). IBMA: Y Acute test: Leaf dwelling NTA: *Aphidius rhopalosiphi* *Typhlodromus pyri* ESCORT I Guidance Document (Barrett et al., 1994), ESCORT II Guidance Document (Candolfi et al., 2001) and IOBC (Mead-Briggs et al., 2000)/(Blümel et al., 2000) Laboratory glass plate tests for chemicals, 48 h/7 d, mortality and repellent effects, exposure comparable to field exposure,	Canada, 2004) also gives useful advice on designing tests.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Soil dwelling NTA *Hypoaspis aculeifer* OECD 226 *Folsomia candida* OECD 232 Acute and sublethal toxicity in artificial soil (chemicals), exposure comparable to field exposure, 14/28 days, mortality and reproduction, suitable for MPCA and MPCP assessment Short-term test: OPPTS Microbial Pesticide Testing 885.4340 Non-target insect testing. With prolonged exposure time (adaptation to mortality in the non-dosed control groups, trigger: 20%) Choice of exposure route depends on MPCA, assessment of infection when mortality occurs *Y. Different interpretations of results, test duration, conditions* *IOBC / OILB guidelines to evaluate side effects of PPP to non-target insects, OPPTS 885.4530, OPPTS 885.001*	
8.9	Effects on other terrestrial invertebrates	CA: See 8.1	
8.9.1	Effects on earthworms	CA: See 8.1 EU: 14-day acute earthworm studies (OECD 207) are commonly submitted. However, 56-day chronic earthworm studies (OECD 222) are generally considered more relevant than acute studies for the following reasons: juveniles might be more sensitive than adults, behavioural symptoms and signs of impairment might occur after 14 days. EU:	EU refers to OECD guidelines for chemicals. Short-term 14-day earthworm studies focusing on detecting lethal or sublethal effects (weight loss) are not suitable to prove the absence of infectivity or pathogenicity (OECD 67) CA registration procedure recommended test methodology Test methodology required.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		should be waived. Earthworms are well adapted to the broad spectrum of soil born pathogens. Earthworms will be more affected by agriculture measures than by the application of MBCAs. EU: Y no guideline for m.o. available OECD 207 is often used USA: More on potential EPA-OPPT guideline modifications: Non-target organisms – in general, the guidelines are so vague as to provide little in the way of guidance. IBMA: Y Only guidance for chemical pesticides available Earthworm, acute toxicity test (in artificial soil), OECD 207 14 days, mortality Usually no effects observed, as no microorganism is known as earthworm pathogen at all, testing makes no sense, data point can usually be covered by statement/published literature Only if applied to soils? As far as known, there are no reports that microorganisms jeopardize earth worms => to be deleted for MPCA	
8.9.2	Effects on other terrestrial invertebrates	CA: See 8.1 EU: Y No guidance available. Which methods are acceptable?	Seems not to be a critical issue in the dossier evaluation. No further guidance needed.
8.10	Effects on soil micro-	CA: See 8.1	OECD guidance for chemicals not relevant.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	organisms	EU: The relevance of carbon mineralization and nitrogen transformation tests according to OECD 216/217 appears to be low as stated in the OECD Guidance to the Environmental Safety Evaluation (OECD, 2012). Until now, studies with mBCAs did not indicate any effects >25% compared to control at field doses. It should be noted that effects on the microbial community may be of greater importance in some cases. EU: should be waived. Soil micro-organisms will be more affected by agriculture measures than by the application of MBCAs. EU: Y No suitable guidance available for m.o. Which methods are acceptable? IBMA: Y Only guidance for chemical pesticides available Soil microorganisms: Nitrogen transformation test and Carbon transformation test OECD 216/217 Comparison to untreated soil, trigger: 25% difference in activity; 28 days exposure Testing is not appropriate as addition of an MPCA will hardly affect C or N transformation. Moreover, these effects will not reflect interactions between indigenous soil microorganisms and MPCAs.	There may be effects from almost anything added to the soil, but there is no valid way to interpret any results one might obtain from testing (OECD 67) Data requirement obsolete.

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Only if applied to soils? As far as known, there are no reports that introduced MPCA microorganisms have long term effects on the naturally occurring soil community => to be deleted for MPCA Y OECD 216 and 217: do not address ecological impact. Open literature can provide some methods.	
8.11	Other/special studies		
9	**Summary and evaluation of environmental impact: summarise all data relevant to environmental impact and assess environmental risk by:**	EU: - interpretation of the data in relation to the naturally occurring background concentration of the respective micro-organisms - interpretation of the data compared to the conditions in environment.	
9.1	- addressing distribution and fate of MPCA	CA: PMRA DIR2001-02 Part 8.1/9.1: No. Applicants must summarize the environmental database. EU: N no specific guideline, not required	
9.2	- identifying non-target species at risk and the extent of their exposure	CA: See 9.1 EU: N no specific guideline, not required	
9.3	- identifying precautions necessary to minimise environmental contamination and to protect	CA: See 9.1 EU: N no specific guideline, not required	-

OECD Annex IIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 4)**	**Problems with TGs (Y / N)?** **If Y, please specify the TG number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	non-target species.		

Appendix 1

Part B: Microbial Pest Control Product – Plant Protection Product

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
1	**Identity of the Microbial Pest Control Product**		
1.1	Applicant (name, address, contact, telephone and telefax numbers)	IBMA: N	Not applicable
1.2	Manufacturer(s) of the preparation and producer of the microbial pest control agent	IBMA: N	Not applicable
1.2.1	Manufacturer(s) of the preparation (name, address, contact, telephone and telefax numbers)	IBMA: N	Not applicable
1.2.2	Producer of the microbial pest control agent (name, address, contact, telephone and telefax numbers)	IBMA: N	Not applicable
1.3	Trade name or proposed trade name and manufacturers code number(s), for the preparation and similar preparations (differences to	IBMA: N	Not applicable

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
	be specified)		
1.4	Placeholder	-	Not applicable
1.5	Physical state of MPCP (Crop Life formulation type)	IBMA: N *Catalogue of Pesticide Formulation Types and International Coding System" GIFAP Technical Monograph N°2, 5th Edition(1989)*	Catalogue of Pesticide Formulation Types and International Coding System" GIFAP Technical Monograph N°2, 5th Edition(1989)
1.6	Function (herbicide, insecticide, *etc*.)	IBMA: N	Not applicable
1.6.1	Biological function category and field of use category, using terms defined by each country, e.g. "control of weeds" for "forestry"	IBMA: N	Not applicable
1.7	Other/special studies	EU: N	Not applicable
1.7.1	Concentration of MPCA in MPCP, measured in terms of g/kg or g/L of the MPCP (for US and Canada, also provide figures in % w/w) and in cfu's or other appropriate potency units; provide content of MPCA in Technical Grade of MPCA, in the same terms.	EU: N CA: PMRA DIR2001-02 Part 2.9.1: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. IBMA: Y No guidance is available on the range for the content of the MPCA in the technical or the product. It is not clear which units can or need to be chosen, e.g. mass units like g/kg or g/L, or biological units like CFU or biotest units. For integrated production of MPCP by % w/w may not be enforceable	Further guidance needed on the acceptable range for the content of the MPCA.

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		(cannot be analysed in the end-use product) but is still required. Only the enforceable concentration of the MPCA, CFU/ g or ml or appropriate potency unit, should be required.	
1.7.1.1	Also indicate: scientific name and strain/serotype of MPCA, its accession number in a recognised culture collection	EU: N CA: PMRA DIR2001-02 Part 2.7.1: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1250: No. IBMA: N	The description in the data requirements is considered sufficient. No further guidance needed.
1.7.1.2	Also indicate: development phase (e.g. spore) of MPCA in MPCP	EU: N CA: PMRA DIR2001-02 Part 2.9.2. No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. IBMA: N	The description in the data requirements is considered sufficient. No further guidance needed.
1.7.2	Composition in terms of g/kg or g/L and % w/w of each ingredient in MPCP, including:	EU: N CA: PMRA DIR2001-02 Part 2.9.1. No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No.	The description in the data requirements is considered sufficient. No further guidance needed.
1.7.2.1	- technical Grade of MPCA	EU: N CA: See 1.7.2 IBMA:	Further guidance needed on the acceptable range for the content of the MPCA?

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		Y No guidance is available on the range for the content of the MPCA in the technical or the product. It is not clear which units can or need to be chosen, e.g. mass units like g/kg or g/L, or biological units like CFU or biotest units.	
1.7.2.2	- each additive: include chemical name and structure; CAS and EEC numbers of components of additive if they exist or an appropriate specification; trade name; function in the MPCP	EU: N CA: See 1.7.2 IBMA: N	No further guidance needed
1.7.2.3	- microbial impurities: taxonomic identification as required by quality criteria to support the hygienic state of the production process; express content of microbial impurities in appropriate units, e.g. cfu's/ml.	EU: It should be important to clarify or define what you understand by microbial impurity: is it acceptable to have impurities from microbial origin; are they pathogenic or not… CA: PMRA DIR2001-02 Part 2.8C/2.9.3: Yes. Insufficient guidance is provided therefore microbial screens are highly variable between dossiers. More often than not, applicants devise their own quality control testing based on their own experiences. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines.	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65. *N. ISO methods for list of contaminants included in OECD Issue Paper Document*	
1.7.2.4	- non-microbial impurities (e.g. metabolic products, impurities in starting materials, fermentation residues, extraneous host residues)	EU: N CA: PMRA DIR2001-02 Part 2.7.2/2.9.3: No. These guidelines clearly articulate the requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines clearly articulate the requirement. *Note:* Despite these guidelines, this is an area that is frequently ignored by applicants, particularly with respect to metabolic by-products. Little or no information/discussion is provided for metabolic by-products or toxins. Obviously, more guidance is required. Perhaps more information/strategies on how to address such concerns may be	Further guidance needed, especially on the information required for metabolic by-products

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		required in future guidelines. IBMA: Y No guidance available. See comments on active substances	
1.7.3	Quality criteria for the production and storage of the MPCP, including:	-	
1.7.3.1	- acceptable range for content of MPCA, in appropriate terms;	EU: What is the meaning of acceptable range for content? CA: PMRA DIR2001-02 Part 2.9.2: No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. IBMA: Y No guidance on "Acceptable range" available *Y. Lack of TG specific for microbial formulations* *Principles of validation from document SANCO 3030/99 are hardly applicable to microbial counts*	Further guidance on this data requirement would be helpful
1.7.3.2	- presence of human or non-target animal pathogens;	EU: N CA:	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		PMRA DIR2001-02 Part 2.8C/2.9.3: Yes. Insufficient guidance is provided therefore microbial screens are highly variable between dossiers. More often than not, applicants devise their own quality control testing based on their own experiences. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. <u>IBMA:</u> N Guidance available in OECD issue paper, Series on Pesticides, No. 65.	
1.7.3.3	- presence or maximum accepted level of known mammalian toxins, if their presence is suspected at any stage in process, or if MPCA is closely related to a toxigenic human pathogen	<u>EU:</u> This point is not clear because the regulation does not tolerate a MPCA that could be a toxigenic human pathogen <u>CA:</u> PMRA DIR2001-02 Part 2.7.2/2.9.3: No. These guidelines clearly articulate the requirement.	<u>Further guidance needed, especially on the information required for metabolic by-products</u>

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines clearly articulate the requirement. *Note:* Despite these guidelines, this is an area that is frequently ignored by applicants, particularly with respect to metabolic by-products. Little or no information/discussion is provided for metabolic by-products or toxins. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. IBMA: Y No guidance available, the term "known mammalian toxin" gives too much room for interpretation. *Y. Lack of commercial standards for some metabolites considered toxins*	
1.7.3.4	- maximum accepted level for microbial impurities, using suitable indicators of contamination	EU: Could you define" maximum accepted level for microbial impurities"? CA: PMRA DIR2001-02 Part 2.8C/2.9.3: Yes. Insufficient guidance is provided therefore microbial screens are highly variable between dossiers. More often than not, applicants devise their own quality control testing based on their own experiences. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant	OECD (ENV/JM/MONO(2011)43) is available for guidance on microbial contaminant testing.

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. Although these guidelines provide more guidance than PMRA's guidelines in terms of primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65t. N. *ISO methods for list of contaminants included in OECD Issue Paper Document 5*	
1.7.4	Quality control data (measures of quality criteria) from 3 - 5 production batches, including product stored for duration of shelf life if it is metabolically active. If the Technical Grade of MPCA is a stage in a continuous production process of an end use product, this information	CA: PMRA DIR2001-02 Part 2.8C/2.11. No. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200/885.1500: Yes. These guidelines state that quality control measures are needed during manufacturing but no representative data are required. *Note:* The submission of representative quality control data is rarely a problem. Guidance should state that data be collected from the	Further guidance would be helpful

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	should be provided for the entire production process.	proposed site of manufacturing. In some dossiers, data were provided for past production facilities and their usefulness are limited since each site can, in theory, harbour different kinds of contaminating microorganisms. IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65. Yes, requirement states 3 – 5 but regulatory authorities will demand 5, change to 5 for clarity. *Y. Lack of TG specific for microbial formulations*	
1.7.5	The formation, presence and/or impact of unintentional ingredients	EU: Difficult to provide a discussion here because probably related to hard to foresee ingredients. CA: PMRA DIR2001-02 Part 2.9.3: No. These guidelines have adequate information. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines have adequate information. Despite adequate guidelines, many theoretical discussions focus on the source of ingredients and the unlikeliness of impurities but very few dossiers discuss the formation of unintentional ingredients such as metabolic products. Metabolic products, if they do occur, are often not	-

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		properly discussed in dossiers and no maximum levels are established. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. IBMA: N	
1.7.5.1	A theoretical discussion regarding the formation and/or presence of unintentional ingredients, including impurities of toxicological concern, likely to occur in the MPCP	EU: Difficult to provide a discussion here because probably related to hard to foresee ingredients. CA: See 1.7.5. IBMA: N	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins
1.7.5.2	A theoretical discussion regarding the impact of these ingredients on product quality	EU: Difficult to provide a discussion here because probably related to hard to foresee ingredients. CA: See 1.7.5. IBMA: N	See 1.4.5.1
1.7.5.3	A theoretical discussion regarding appropriate quality criteria.	EU: Why a theoretical discussion regarding quality criteria? CA: See 1.7.5. IBMA: N	No further guidance needed
1.7.5.4	For metabolically-active MPCP, consider degradation or metabolic production during storage in the	EU: Not clear CA: See 1.7.5.	Guidance needed on how to test for and handle the issue of secondary metabolites and toxins

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	theoretical discussion.	IBMA: N	
2	**Physical, Chemical and Technical Properties of the Microbial Pest Control Product**	IBMA: IIIM 2, Generally: Guidance is available for PPP in general, which is acceptable for MPCP in most cases. Determination of the content of the active ingredient is the critical issue. ??? Non-homogeneity and variability may be reasonable due to the variation in the concentration of the MPCA due to fermentation and consequently in the formulation due to the variation in diluent formulation additives.	
2.1	Appearance (colour, odour, physical state)	EU: N CA: PMRA DIR2001-02 Part 2.12: No. However, no specific methods are described. Applicants are free to choose any valid method. A reference to a standard procedure or protocol is required for each parameter. OECD Section 1 guidelines: No. Appropriate guidelines may be found under this section. U.S. EPA: No. Appropriate guidelines are available. IBMA: N *N. Pantone cards, Olfactory assessment, Crop Life Technical Monograph Nº 2 Nº 2, 1989*	The description in the data requirements is considered sufficient. No further guidance needed.
2.2	Storage stability and shelf-life for MPCP which must	EU: N	Further guidance on storage stability testing is needed.

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	contain metabolically active MPCA, include QC data for hazardous contaminants originating from degradation or metabolic production during storage.	CA: PMRA DIR2001-02 Part 2.11: No. Applicants are required to submit storage stability to ensure product performance and safety. These guidelines also provide a list of suggested environmental parameters to study. Additional guidance on the storage stability study, however, may be helpful (e.g., include several temperatures and many data time points in case of poor product stability). OECD: Yes. No storage stability test guidelines. U.S. EPA 885.2400: Yes. These guidelines are confusing since they do not seem to pertain to shelf-life but rather stability of the microbial pest control product on treated commodities for magnitude of residue testing. EU: Problems concerning appropriate time/temperature regimes for "accelerated storage" (if considered necessary). Example: can a storage test at 20 °C for 4 weeks be accepted as accelerated storage, in case the recommended storage temperature is 4 °C? IBMA: N CIPAC MT17 MT171 Dustiness Acceptable loss in content of cfu/g during storage – how to set acceptable limit? Guidance document is still not officially approved. Y TGs developed for chemicals, not applicable for micro-organisms.	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Microbes are usually not metabolically active (e.g. in WP formulations) and other substances are inert co-formulants. No phys/chem. changes will or do occur during storage time. A MPCP specific Guidance would be needed. *Y. Lack of TG specific for microbial formulations*	
2.3	Explosivity, oxidising properties, flash point, flammability, spontaneous ignition, acidity, alkalinity, pH, viscosity, surface tension	EU: N CA: PMRA DIR2001-02 Part 2.12: No. However, no specific methods are described. Applicants are free to choose any valid method. A reference to a standard procedure or protocol is required for each parameter. OECD Section 1 guidelines: No. Appropriate guidelines may be found under this section. U.S. EPA: No. Appropriate guidelines are available.	Guidelines for chemical products are appropriate
2.3.1	Explosivity, oxidising properties: as appropriate	EU: N CA: See 2.3 IBMA: N No appropriate for most MPCA	No further guidance needed
2.3.2	Flash point, flammability, spontaneous ignition: as appropriate	EU: N CA: See 2.3	Guidelines for chemical products are appropriate

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N 92/69/EEC A10, A16	
2.3.3	Acidity, alkalinity, pH: as appropriate	EU: N CA: See 2.3 IBMA: N N. CIPAC MT75	Guidelines for chemical products are appropriate
2.3.4	Viscosity, surface tension: as appropriate	EU: N CA: See 2.3 IBMA: N	Guidelines for chemical products are appropriate
2.4	Technical characteristics as appropriate:	EU: N CA: See 2.3	-
2.4.1	Wettability	EU: N CA: See 2.3 IBMA: N CIPAC MT53.3	Guidelines for chemical products are appropriate
2.4.2	Persistent foaming	EU: N CA: See 2.3 IBMA:	Guidelines for chemical products are appropriate

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		N CIPAC MT 47.2	
2.4.3	Suspensibility, suspension stability	EU: N CA: See 2.3 IBMA: N CIPAC MT15, MT 161 and 168, MT174 *N. CIPAC MT 15.1*	Guidelines for chemical products are appropriate
2.4.4	Dry sieve test and wet sieve test	EU: N CA: See 2.3 IBMA: N MT167 *N. CIPAC MT 59.3*	Guidelines for chemical products are appropriate
2.4.5	Particle size distribution (dustable and wettable powders, granules), content of dust/fines (granules), attrition and friability (granules)	EU: N CA: See 2.3 IBMA: N MT170, MT171 *N. CIPAC MT 58.2*	Guidelines for chemical products are appropriate

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
2.4.6	Emulsifiability, re-emulsifiability, emulsion stability	EU: N CA: See 2.3 IBMA: N *N. CIPAC methods*	Guidelines for chemical products are appropriate
2.4.7	Flowability, pourability (rinsability), dustability	EU: N CA: See 2.3 IBMA: N *N. CIPAC methods*	Guidelines for chemical products are appropriate
2.5	Density	EU: N CA: See 2.3 IBMA: N *N. CIPAC methods*	Guidelines for chemical products are appropriate
2.6	Adherence and distribution to seeds, for seed treatment products	EU: N CA: See 2.3 IBMA: N CIPAC method (MT175) for chemical PPPs uses a dye, this is not suitable for microbials MPCP as a dye in solution does not accurately demonstrate adherence of particulate microbials. Bacteria loading on	Mixed answers. Guidance needed?

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		individual seeds can be carried out but is very labour intensive. CIPAC method states 100 seeds should be individually analysed, however for microbial analysis this is an unrealistic workload and should be limited to MPCA on 25 individual seeds. Y. TGs prepared for chemicals and not suitable for microbials. Micro-organisms do not require 100% distribution or adherence to bring in 'full efficacy' – the MOs have the potential to grow on the surface of seeds and so cover them completely at some stage, resulting in full coverage. Hence the adherence and distribution equity of MPCP to seeds are not comparable to those parameters of chemicals. *Y. Lack of TG specific for microbial formulation* *Different interpretations*	
2.7	Summary and evaluation of data on properties of the MPCP	EU: N IBMA: N	-
3	**Data on application**		
3.1	Pest to be controlled, crop to be protected, available information on mode of action (site of uptake, toxic/competitive effect, is micro-organism transmitted or translocated to another part of plant?)	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.2	Available information on the development of resistance in target pest and appropriate mitigation strategy.	EU: N CA: PMRA DIR2003-04; PRO2012-02; PRO2010-07; DIR2001-02: No.	No further guidance needed

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		IBMA: N	
3.3	Application rate in terms of mass/vol of MPCP per unit area/volume (e.g. kg/ha). Content of micro-organism in material used (diluted spray, bait, treated seed).	EU: N CA: PMRA DIR2003-04; PRO2010-07; DIR2001-02: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.4	Application rate in terms of units of micro-organism per unit area/volume	EU: N CA: PMRA DIR2003-04; PRO2010-07; DIR2001-02: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.5	Method of application (incl. type of equipment and volume of diluent)	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.6	Number, timing and conditions of applications, related to: host/pest phenology, duration of protection, application of other pesticides, pre-harvest	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use.	No further guidance needed

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	interval	EU: Guidelines addressing in more detail compatibility in fungicide programmes might be useful. However, this is related to design of efficacy trials which may be helped by recent EPPO guidance. IBMA: N	
3.6.1	Number, timing and conditions of applications, related to: host/pest phenology, duration of protection, application of other pesticides.	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.6.2	Pre-harvest interval.	EU: N IBMA: N	No further guidance needed
3.7	Precautions to avoid phytotoxic/ phytopathogenic effects on protected crop or on succeeding crops, if appropriate	EU: N CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	No further guidance needed
3.8	Proposed instructions for use as printed, or to be printed, on labels	EU: N CA:	No further guidance needed

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		PMRA DIR2001-02; DIR2012-01; LPS2011-01, DIR93-06: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use. IBMA: N	
4	**Further information on the Microbial Pest Control Product**		
4.1	Packaging: description	EU: N CA: PMRA: This information is required on the application form. There are no guidelines. IBMA: N *(FAO Guidelines)*	No further guidance needed
4.2	Specifications of packaging and measures of its suitability	EU: N CA: PMRA DIR2001-02 Part 1.1: No. PMRA will review the proposed label and make any required changes based on data in the dossier. OECD: Not Applicable. U.S. EPA: There are no guidelines. Applicants must submit draft labels as per 40CFR 152.50 40CFR 156. U.S. EPA will review the proposal and make any required changes based on data in the dossier. IBMA: N	No further guidance needed

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
4.3	Label instructions regarding cleaning equipment and protective clothing	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.4	Procedures to clean equipment and protective clothing; measures of their effectiveness	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.5	Necessary waiting periods for re-entry; recommended protective measures to reduce occupational exposure	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.6	Label instructions regarding: safe handling and storage	EU: N CA: See 4.2 IBMA: N *Y. Hazardous and precautionary statements are not always adequate for microbials* *Default sensitisation statements is not included in H phrases list of CLP*	Guidance on labelling for sensitisation would be helpful
4.7	Recommendations regarding: handling, storage, transport, fire: specify risks, specify procedures to minimise hazards and the generation of waste.	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.8	Label instructions regarding: clean-up of spills	EU: N CA: See 4.2	No further guidance needed

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		IBMA: N	
4.9	Detailed procedures in case of accident to: contain a spill, decontaminate an area or vehicle, dispose of adsorbents and packaging, protect workers and bystanders, first aid.	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.10	Procedures for destruction/disposal of MPCP and its packaging	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.10.1	Controlled incineration	EU: N CA: See 4.2 IBMA: N	No further guidance needed
4.10.2	Methods other than controlled incineration	EU: N CA: See 4.2 IBMA: N	No further guidance needed
5	**Methods of Analysis, Manufacturing, Quality Control and Post-Registration Monitoring of the Microbial Pest Control Product**	EU: See MPCA	
5.1	Quality control and post-registration monitoring methods	EU: N CA: **Quality Control** PMRA DIR2001-02 Part 2.8B/2.8C/2.10: No. These guidelines clearly articulate this requirement.	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines clearly articulate this requirement. **Post-Registration Methods** PMRA DIR2001-02: *For viable microorganisms*; Yes. PMRA does not have this requirement. However, PMRA does recommend that the applicant possess a method to differentiate their strain or isolate of the microbial pest control agent from other isolates of the species in case of any post-registration effects or violations. Without such data, PMRA will assume that effects or violations were due to the registered microbial pest control agent. *For non-viable products, i.e., toxins* Part 7: No. If the presence of a mammalian toxin has been identified and the applicant wishes to pursue registration, the product will be subject to the same data requirements as a chemical pesticide, and appropriate data will be required to establish a maximum residue limit. OECD: Yes. No microbial-specific guidelines. U.S. EPA: No. Applicants must apply for an exemption from establishing a tolerance. If this application for an exemption is rejected, the applicant will have to submit all the necessary data under 885.2000 series.	
5.1.1	Methods to differentiate a	EU: N	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	mutant or genetically-modified micro-organism from the parent strain.	CA: PMRA DIR2001-02 Part 2.7.3/2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review (including methods to distinguish revertants). OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. Applicants must submit sensitive methods to determine the MPCA in the presence of revertants/mutants and contaminants that may have formed or been introduced during the replication/manufacturing process. IBMA: Y No guidance available. It is not clear which information is required here Why is this necessary? Only require if a mutant or modified strain is going to be registered. *N. Molecular techniques*	
5.1.2	Methods to detect spontaneous change in major characteristics of micro-organism.	EU: N CA: PMRA DIR2001-02 Part 2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review. OECD: Yes. No microbial-specific guidelines.	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		U.S. EPA 885.1500: No. Applicants must submit sensitive methods to determine the MPCA in the presence of revertants/mutants and contaminants that may have formed or been introduced during the replication/manufacturing process. IBMA: Y No guidance available. It is not clear which information is required here *N. Molecular and classical microbiological techniques*	
5.1.3	Methods to define content of micro-organism in appropriate terms (same as IIM 1.4.1), incl. standardisation, sensitivity, reproducibility, statistical validity, and representative data to validate the bioassay.	EU: N CA: PMRA DIR2001-02 Part 2.10.1: No. All methods aimed at ensuring the integrity and potency of the microbial pest control agent must be submitted for review. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1500: No. Applicants must submit methods to verify the certified limits of the MPCAs and any microbial impurities. Please note that these methods are often simple plating procedures. Standardisation and statistical validity data are rarely required. Representative data, however, are required. EU: No guidance available. Guidance for chemicals is not appropriate as variation is far higher for microbials. Criteria for validation need to be	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		defined, as validated methods are required e.g., in the EU. IBMA: Y No guidance available. Guidance for chemicals is not appropriate as variation is far higher for microbials. Criteria for validation need to be defined. *Y. Lack of TG* *Principles of validation from document SANCO 3030/99 are hardly applicable to microbial counts Classical microbiological methods* Y If methods used are classical microbiological methods then validation should not be necessary	
5.1.4	Methods to identify contaminant micro-organisms in MPCP	EU: N CA: PMRA DIR2001-02 Part 2.8C/2.9.3/2.10.3: Yes. As previously noted, insufficient guidance is provided therefore microbial screens are highly variable between dossiers. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. These guidelines provide guidance for primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), but they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		contaminant testing. IBMA: N Guidance available in OECD issue paper, Series on Pesticides, No. 65. *ISO methods*	
5.1.5	Methods to show control to a specified and acceptable level, of microbial impurities and of any other impurities of toxicological concern, including toxic metabolites, which are known or suspected to be present at any stage of the manufacturing process.	EU: Acceptable level should be defined. CA: **Microbial Impurities** PMRA DIR2001-02 Part 2.10.2: Yes. As previously noted, insufficient guidance is provided therefore microbial screens are highly variable between dossiers. Better guidance is required on the screening procedures for microbial pest control products. Guidelines should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: Yes. These guidelines provide guidance for primary human pathogens (e.g., *Salmonella*, *Shigella* and *Vibrio*), but they do not specify any standard indicator species. Again, better guidance is required on the screening procedures. The guidance should refer to OECD (ENV/JM/MONO(2011)43) for guidance on microbial contaminant testing. **Other Impurities of Toxicological Concern**	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification Suitable method available with modifications No suitable method available
		PMRA DIR2001-02 Part 2.10.3: No. These guidelines clearly articulate the requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1300: No. These guidelines clearly articulate the requirement. *Note*: Despite these guidelines, this is an area that is frequently ignored by applicants, particularly with respect to metabolic by-products. Little or no information/discussion is provided for metabolic by-products or toxins. Consequently, more guidance is required. Perhaps more information/strategies on how to address such concerns may be required in future guidelines. IBMA: N Guidance available microbial impurities (identical to IIIM 5.1.4) in OECD issue paper, Series on Pesticides, No. 65. **Y** No guidance available for "impurities of toxicological concern, including toxic metabolites" Only apply to metabolites that are toxic, see discussion under MPCA. *Y. Lack of TG and standards for some metabolites*	
5.1.6	Methods to show presence of any human and mammalian pathogens.	EU: Could you suggest which method should be used? CA: See 5.1.5 IBMA:	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		N Guidance available in OECD issue paper, Series on Pesticides, No. 65. *ISO methods*	
5.2	Storage stability test and determination of shelf life (methods of analysis)	EU: N CA: PMRA DIR2001-02 Part 2.11: No. Applicants are required to submit storage stability data (and test methods) to ensure product performance and safety. These guidelines also provide a list of suggested environmental parameters to study. Additional guidance on the storage stability study, however, may be helpful (e.g., include several temperatures and many data time points in case of poor product stability). OECD: Yes. No storage stability test guidelines. U.S. EPA 885.2400: Yes. These guidelines are confusing since they do not seem to pertain to shelf-life but rather stability of the microbial pest control product on treated commodities for magnitude of residue testing. IBMA: N guidance for chemical PPP is appropriate. *Y. Lack of TG*	
5.3	Production process for MPCP, describing techniques used to ensure a uniform product and	EU: Production process is usually reported under confidential part 4. What should be reported here?	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	procedures when hazardous contamination is detected in a batch. List starting and intermediate materials, with source and purity of each.	CA: PMRA DIR2001-02 Part 2.8B/2.8C: No. These guidelines clearly articulate this requirement. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.1200: No. These guidelines clearly articulate this requirement. IBMA: N	
5.4	Method for determination of residues: required if information provided for MPCA in Annex II Part 4 is insufficient, for MPCP.	EU: N CA: PMRA DIR2001-02: *For viable microorganisms*; Yes. PMRA does not have this requirement. However, PMRA does recommend that the applicant possess a method to differentiate their strain or isolate of the microbial pest control agent from other isolates of the species in case of any post-registration effects or violations. Without such data, PMRA will assume that effects or violations were due to the registered microbial pest control agent. *For non-viable products, i.e., toxins* Part 7: No. If the presence of a mammalian toxin has been identified and the applicant wishes to pursue registration, the product will be subject to the same data requirements as a chemical pesticide, and appropriate data will be required to establish a maximum residue limit as per conventional chemical pesticides. OECD: Yes. No microbial-specific guidelines. U.S. EPA: No. Applicants must apply for an exemption from	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		establishing a tolerance. If this application for an exemption is rejected, the applicant will have to submit all the necessary data under 885.2000 series.	
6	**Efficacy Data and Information (including Value Data) for the Microbial Pest Control Product**	EU: In general, efficacy evaluators do not differentiate between the evaluations of chem.-synth. ppps and of MO-based ppps, since predominantly the effect on the target and any negative effect on the crop is assessed. Reduction of data demands is possible only for products to be applied in minor uses EC Regul.1107/09). IBMA: In general effects of micro-organisms to the pest may occur later compared to chemical pesticides, therefore assessment dates need to be adapted in most cases.	
6.1	Preliminary range finding tests	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use; biological control of aquatic pests.	
6.2	Performance assessment: field studies	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. IBMA: EPPO test guidance related to efficacy and trial protocols designed for chemicals (with curative mode of action). These are not applicable for MPCPs which are preventive in their mode of action. The preventive efficacy can't be demonstrated the way curative efficacy is. This relates to e.g. trial designs, number of needed trials and relevance of statistical significance of results.	
6.2.1	Efficacy tests	CA:	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01 : No. IBMA : Many MPCAs act by competition for nutrients and space, by colonisation of the infection sites. Therefore, application should be done before the occurrence of the pest organism, ensuring that there is enough time for growth of the MPCA. Protocols need to be adapted to microorganisms. *Y. Different interpretations* *Lack of TG specific for microbial formulations to verify efficacy*	
6.2.2	Minimum effective dose tests	EU: EPPO PP1/225 dose response/minimum effective dose in some cases difficult to assess and to follow EPPO (dose-effect- relation not so clear like for chemicals, due to the fact that MOs are able to grow. Establishment of the MO may be the more relevant factor affecting efficacy, than the dose).However, this problem is known and reflected in EPPO PP 1/276. CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No. Not required for non-conventional pesticides, including biopesticides. EU: No guidance available for MPCP. Determination of effective dose is more difficult than for chemicals as most MPCAs have a low slope of dose response. IBMA:	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		No guidance available for MPCP. Determination of effective dose is difficult as most MPCAs do not have a clear dose response. Dose response curve form MPCP is hard to establish. Within a certain orders of magnitudes no differences can be visible. Since microorganisms are able to proliferate exponentially if the conditions are favourable (or not, if not favourable), environmental factors may influence the test system much more than to double or divide the application dose.	
6.3	Toxic or pathogenic effects on the crop or host which is to be protected.	CA: PMRA DIR2003-04: No. IBMA: As the mode of action and host range of the MPCA is well described phytotoxic effects can usually be excluded. Possible effects may be caused only by the co-formulants, which are normally inert and non-hazardous. There should be a waiver option for MPCPs.	
6.4	Compatibility with products in authorised tank mixes and with other products that are applied under expected conditions of use. Recommended interval between application of MPCP and any other products, to avoid loss of efficacy.	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Information on compatibility of the microbial pesticide with other pesticides, particularly conventional pesticides is not typically provided to PMRA resulting in challenges in determining how the microbial pesticide fits in an IPM system; currently, no published guidance for non-agricultural uses, e.g. antisapstain use; biological control of aquatic pests.	
6.4.1	Physical compatibility	CA: PMRA DIR2003-04; Memorandum to Registrants – Use of Unlabelled Tank Mixes of Commercial Pest Control Products Used	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		for Crop Production or Vegetation Management, 27 October 2009: No. IBMA: *Y. Lack of TG specific for microbials*	
6.4.2	Chemical compatibility	CA: PMRA DIR2003-04; Memorandum to Registrants – Use of Unlabelled Tank Mixes of Commercial Pest Control Products Used for Crop Production or Vegetation Management, 27 October 2009: No. IBMA: *Y. Lack of TG specific for microbials*	
6.4.3	Biological compatibility	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Please see comments under OECD Annex IIIM 6.4. IBMA: *Y. Lack of TG specific for microbials*	
6.5	Contribution to risk reduction and integrated pest management strategies, for the targeted crop or resource.	CA: PMRA DIR2003-04; DIR2012-01; DIR2001-02; PRO2010-07; DIR93-17: Yes. Information not always provided to PMRA. IBMA: *Y. Lack of TG specific for microbials*	
6.6	Effects on yield and quality	CA: PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: Yes. Currently, no published guidance for non-agricultural uses, e.g. antisapstain use; biological control of aquatic pests.	
6.6.1	Impact on the quality of	CA :	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	plants and plant products	PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01: No.	
6.6.2	Effects on the processing procedure	CA: There is no specific guidance on this but PMRA may request additional information if warranted. Guidance to stakeholders is provided according to the specifics of the case.	
6.6.3	Effects on the yield of treated plants and plant products	CA : PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01 : No.	
6.7	Adverse effects	CA : PMRA DIR2003-04; DIR96-01; DIR2001-02; DIR2012-01 : No.	
6.7.1	Impact on succeeding crops	CA: PMRA DIR2003-04: No.	
6.7.2	Impact on other plants including adjacent crops	CA: PMRA DIR2003-04: No.	
6.7.3	Adverse effects on parts of plants used for propagating purposes (e.g. seeds, cuttings, runners)	CA: PMRA DIR2003-04: No.	
6.7.4	Adverse effects on beneficial and other organisms apart from target organisms	EU: There is no guidance available. Establishment of alien species (= active substance) may affect indigenous ones. CA: There is no formal guidance on this but VRD has collaborated with EAD in the past to identify appropriate label statements reflective of the pesticide's impact on non-target beneficial organisms. IBMA: It is referred to IIIM 10 and IIIM 11	
6.8	Summary and assessment of	CA:	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	data according to points 6.1 to 6.7.4	PMRA DIR2003-04; DIR96-01; DIR2001-02 DIR2003-04; DIR96-01; DIR2001-02; PRO2010-07 : No.	
6.9	List of test facilities including the corresponding certificates	CA: Agricultural uses: DIR2003-04; antimicrobial uses: No specific guidance document but applicants include this information in the section on trial protocols	
7	**Toxicological Studies and Exposure Data and Information for the Microbial Pest Control Product**	IBMA: All Exposure models available (operator, worker, bystander, resident's) are designed for chemicals and these are not very easily or well applicable for the calculations of MPCAs/ MPCPs. Some adequate Guidance for microbials is necessary.	
7.1	Acute toxicity studies	EU: N CA: PMRA DIR2001-02 Part 4: Not a requirement for end-use formulations. OECD Section 2: Appropriate OECD guidelines are available for determining toxicity. U.S. EPA 870.1000 series: No. Appropriate guidelines are available. IBMA: Appropriate OPPTS guidance is available See point 7.	
7.1.1	Acute oral toxicity	EU: N JP: TG number: 420, 423, 425	
7.1.2	Acute percutaneous	EU: N	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
	(dermal) toxicity	CA: PMRA DIR2001-02 Part 4.4: No. The requirement is clearly articulated. PMRA will accept studies using OECD and U.S. EPA 870.1200. OECD Section 2: No. Appropriate guidelines are available for dermal toxicity. U.S. EPA 870.1200: No. Appropriate guidelines are available, JP: N TG number : 402	
7.1.3	Acute inhalation toxicity to rats	EU: N CA: PMRA DIR2001-02 Part 4: Not a requirement for end-use formulations. OECD Section 2: Appropriate OECD guidelines are available for determining toxicity. U.S. EPA 870.1000 series: No. Appropriate guidelines are available. JP: N TG number : 403	
7.1.4	Skin irritation	EU: N CA: PMRA DIR2001-02 Part 4.5.2: No. The requirement is clearly	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		articulated. PMRA will accept studies using OECD and U.S. EPA 870.2500. OECD Section 2: Appropriate OECD guidelines are available for determining irritation. U.S. EPA 870.2500: No. JP: N TG number : 404 IBMA: *N. Method B4 Regulation 440/2008*	
7.1.5	Eye irritation	EU: N CA: PMRA DIR2001-02 Part 4: Not a requirement for end-use formulations. If available, PMRA will accept studies conducted in accordance with OECD guidelines and U.S. EPA 870.2400. OECD Section 2: Appropriate OECD guidelines are available for determining toxicity. U.S. EPA 870.2400: No. JP: N TG number : 405 IBMA: *N. Method B5 Regulation 440/2008*	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
7.1.6	Skin sensitisation	EU: N CA: PMRA DIR2001-02 Part 4.6: No. PMRA requires reports on all incidents of hypersensitivity during production, testing and manufacturing. No sensitization studies are required since all microbial pest control agents are considered to contain substances that could elicit sensitization reactions. OECD 406/442: Yes. These guidelines only address exposure via the dermal route. All microorganisms contain complex molecules that could elicit sensitization reactions in individuals. U.S. EPA 885.3400/870.2600:No. U.S. EPA requires reports of all hypersensitivity incidents as well as a skin sensitization study. As noted for OECD above, this study only addresses exposure via the dermal route. EU: **Y:** OECD406: - Buehler method: not suitable, because MOs usually don't overcome the intact skin barrier - GPMT: seems to work but no validation data OECD 429: LLNA: no experience, no validation data Missing test method for respiratory sensitisation (same as for chemicals) OPPTS 885.3400: too less detailed JP:	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		N TG number : 406 IBMA: See comments on requirement for microbial active substances *Y. Lack of TG for microbial formulations* Y: no TG for microbials	
7.2	Operator, bystander and worker exposure: monitoring data	EU: If necessary! CA: PMRA DIR2001-02 Part 5: There are no occupational safety data requirements at Tier 1. PMRA typically conducts its review based on available toxicity/infectivity data and the proposed use pattern. Also, the Canadian *Pest Control Products Act* requires applicants to submit all reports of adverse effects. OECD: Yes. No microbial-specific guidelines. EU: **Y:** - Missing models for exposure estimation towards micro-organisms (esp. growth and decline, respectively) or relevant toxins. EU: Y Risk assessment: No suitable models available for operator, worker, bystander. No clear guidance on acceptability of qualitative risk assessment. EU:	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		Y: How should worker exposure be assessed? Even if the exposure during application is below the AEL, the concentration may increase if the microorganism grows on the plant. EU: No specific requirement or guidance for monitoring data. See comment below. IBMA: *Y. Lack of TG for microbial formulations* *Available models for chemicals are not always suitable*	
7.3	Operator and bystander exposure: reporting of hypersensitivity incidents before and after registration	EU: N CA: See 7.2 EU: No guidance available but this is an area that could inform the evaluation. Development of standardised reporting procedures would be useful particularly in determining relevance of exposure (e.g. during manufacturing) to PPP exposure scenarios IBMA: *Y. Lack of TG for microbial formulations* *Available models for chemicals are not always suitable*	
7.4	Safety data sheet for each additive	EU: N CA: PMRA DIR2001-02 Part 2.9.1: No. Applicants must submit MSDS for all formulation ingredients.	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
7.5	Supplementary information on all data points in part 7: Effects on Human Health, if it is recommended that MPCP be tank-mixed with an adjuvant or another pest control product.	EU: N CA: The proposed use of the microbial pest control agent is to be evaluated by the PMRA. There is no equivalent data requirement.	
7.6	Summary and evaluation of health effects	CA: PMRA DIR2001-02 Part 4.1: No.	
8	**Residues in/on Food and Feed products for the Microbial Pest Control Product (Rationale to waive residue studies on MPCP)**	CA: PMRA DIR2001-02 Part 7. Yes. PMRA does not require any information or data on metabolism or residues of the microbial pest control agents on treated commodities. PMRA conducts its own assessment based on data and information that are available in the dossier. If such data are required for microbial pest control agents, PMRA would accept data generated as per U.S. EPA 885.2000 series. If the microbial pest control agent does contain a toxin or other toxic metabolites and the applicant wishes to pursue registration, residue and metabolism data may be required as per conventional chemical pesticides. Studies performed according to U.S. EPA 860 series would be accepted. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.2000: No. The use of a microbial pest control agent on food, feed or raw agricultural commodity requires that a tolerance or an exemption from the tolerance be established. Applicants must request an exemption from a tolerance by submitting a sound scientific rationale. In absence of such an exemption, the applicant must submit acceptable residue data following 885.2000 series (microbial) and/or	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		860 series (chemical) test guidelines. IBMA: Please refer to Annex II, Point 6.	
9	**Fate and Behaviour in the environment for the Microbial Pest Control Product (Rationale to waive testing, based on adequacy of information provided for MPCA, to permit an assessment of the fate and behaviour of MPCP in the environment)**	CA: PMRA DIR2001-02 Part 8: No. Environmental fate data are only required at Tier 2. If required, PMRA would accept studies that were conducted in accordance with U.S. EPA 885.5000 series. OECD: Yes. No microbial-specific guidelines. U.S. EPA 885.5000 series: No. However, environmental fate data are only required at tier 2 and are not specific to EPs (testing may be performed on TGAIs or EPs. IBMA: Please refer to Annex II, Point 7. **Positive: Rationale to waive testing, based on adequacy of information provided for MPCA**	No specific methods required for the MPCP
10	**Rationale to waive additional testing, based on adequacy of information provided for MPCA, to permit an assessment of the impact of the MPCP on non-target organisms.**	CA: PMRA DIR2001-02 Part 9: There are not separate data requirements for end use formulations. Environmental toxicology testing can be performed on technical grade of the active ingredients (TGAIs) or end use formulations (EPs). If testing is performed on TGAI then PMRA will evaluate all the available information on the formulation ingredients and provide additional mitigative measures, as required. OECD: Yes. No microbial-specific guidelines.	Mixed answers No specific methods required for the MPCP. However, depending on the additional substances (apart from the MPCA) specific testing is required.

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		U.S. EPA 885.4000 series: There are no separate data requirements for EPs. Testing should be performed on TGAIs. EU: Further guidance on this would be useful. IBMA: Please refer to Annex II, Point 8. **Positive: Rationale to waive additional testing, based on adequacy of information provided for MPCA** In general: Test Guidance's not relevant in all cases. It would be appropriate to have the possibility to waive some data requirements and to disregard some tests due to the intended uses (e.g. outdoor / greenhouse uses) and the true nature of the MPCA/MPCP in question.	
10.1	Effects on birds	CA: See 10. EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA. IBMA: *N. OPPTS 885.4050*	See 10
10.2	Effects on aquatic organisms	CA: See 10. EU: Testing of acute effects may be done according to OECD 213/214 for	See 10

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification Suitable method available with modifications No suitable method available
		oral and contact exposure for active substances and plant protection products. For pesticide testing, these guidelines are slightly modified from the short term exposure to chronic exposure, e.g. for oral exposure, but there are currently no specific guidelines for chronic exposure available. For testing pesticides it is currently discussed that also a guideline for testing chronic toxicity would be desirable. This is important also with respect to microbials; especially as chronic testing seems be highly desirable, as potentially these microbials may have a low acute toxicity but there may be concern e.g. of a microbial colony growth. Thus it seems necessary to create a guideline for chronic toxicity testing, which can be used for pesticides but also microbials. EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA. IBMA: No specific test guideline recommended. Fish: OECD 203: 96h may be sufficient if the test microorganism is not persistent in the test system. Due to the present microbial community the MPCA may disappear faster compared to a test system without fish. Daphnia: DIN 38412 L30, OECD 211, EPA OPPTS 850.1300	

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification Suitable method available with modifications No suitable method available
		Artificial media, the MPCA may use it as source for nutrients. Daphnia my feed on microbial cells. Algae: DIN 38412L33 Artificial media, the MPCA may use it as source for nutrients. Measuring algae with the help of optical density may be influenced by the growth of the microorganism in the suspension. Extinction should be measured instead of fluorescence in order to determine the amount of algae in the test media. Duckweed: ISO/DIS 20079 *N. OPPTS 885.4200* In OECD test guidelines n° 203 (fish), n° 202 (invertebrates), n° 201 (algal growth) and n°xxx (aquatic plants), the development of the tested microorganism in water have sometimes an effect on the alga, fish or invertebrate. But the case of a terrestrial microorganism, its development in pure water is totally artificial. In the environment, with a natural flora in water, it won't be competitive enough to develop. We need a test to measure the development capacity of the tested microorganism in natural water, that means in presence of an aquatic flora. If there is no real development of the tested microorganism, it won't be necessary to control its toxicity on aquatic organisms.	
10.3	Effects on bees	CA: See 10. JP: Same as 8.7 in Part A EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the	See 10

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		MPCA. IBMA: No specific test guideline recommended. OECD 213 (1998), US EPA OPPTS 885.4380: EPA guideline recommends an observation period of 30 days, the termination after mortality in the control reaches 20 % is recommended for interpretation of the results. *Y. Lack of TG for field assessment*	
10.4	Effects on terrestrial arthropods other than bees	CA: See 10. JP: Same as 8.8 in Part A EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA. IBMA: No specific test guideline recommended. Barret et al.: Guidance document on regulatory testing procedures for pesticides with Non-Target Arthropods. Escort 1994. Blümel et al.: Laboratory residual contact test with the predatory mite Typhlodromus pyri Scheuten (Acari: Phytoseiidae) for regulatory testing of plant protection products. IOBC/OILB 2000. Candolfi et al.: Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. ESCORT 2, EUTAC Europe publisher, 2001. *Y. Different interpretations of results, test duration, conditions*	See 10

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		IOBC / OILB guidelines to evaluate side effects of PPP to non-target insects, OPPTS 885.4530, OPPTS 885.001	
10.5	Effects on earthworms	CA: See 10. EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA. IBMA: ISO 11268-1 ISO/DIS 17512-1 No specific test guideline recommended. Instead of *Eisenia foetida Dendrobaena hortensis* should be used, it is of comparable or even higher sensitivity. The test substance should be mixed in the soil and sprayed on to the soil. Natural soil should be used instead of artificial soil, lower mortality rates were observed in many cases. The avoidance test should be used instead of the chronic test, the test system is regarded to be at least as sensitive as the chronic test. *N. OECD 207*	See 10
10.6	Effects on soil micro-organisms	CA: See 10. EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA.	
10.7	Additional studies	CA: See 10.	See 10

OECD Annex IIIM point	Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)	Problems with Test Guidelines (Y / N)? If Y, please specify the Test Guideline number and describe the problem	Overall Conclusion: Suitable method available without modification / Suitable method available with modifications / No suitable method available
		EU: See MPCA EU: Please refer to comments made above under Section 8 in relation to the MPCA. IBMA: No guideline available for testing of microbial organism. Y OECD 216 and 217: do not address ecological impact. Open literature can provide some methods.	
11	**Summary and evaluation of environmental impact: summarise all data relevant to environmental impact and assess environmental risk by:**	EU: Evaluation of environmental impact is difficult to be relevant because growth, multiplication survival, dormancy etc…usually related to climate conditions and therefore variable. IBMA: Guidance for evaluation of environmental risks at EU level very scarce and unspecified! This relates to e.g. distribution & drifting in water systems, soil and air; risks to STPs and waste water/sludge treatment; emissions from greenhouses (in relation to intended uses) and so on. Many Member States are considering these as requirements in the risk evaluation – at national level. These are not identical with each other, thus causing us to generate huge amount of national specific data, calculations and evaluations. No microbial specific TGs available, the ones existing are prepared for chemicals.	-
11.1	- addressing distribution and fate of MPCP	EU: See above.	

OECD Annex IIIM point	**Information, test or study (according to OECD Dossier Guidance Document, Appendix 6, Part 5)**	**Problems with Test Guidelines (Y / N)?** **If Y, please specify the Test Guideline number and describe the problem**	**Overall Conclusion:** Suitable method available without modification Suitable method available with modifications No suitable method available
		CA: PMRA DIR2001-02 Part 8.1/9.1: No. Applicants must summarize the environmental database. EU: N no specific guideline, not required IBMA: N	
11.2	- identifying non-target species at risk and the extent of their exposure	EU: N CA: See 11.1 EU: N no specific guideline, not required IBMA: N	
11.3	- identifying precautions necessary to minimise environmental contamination and to protect non-target species	EU: N CA: See 11.1 EU: N no specific guideline, not required IBMA: N	

Appendix 2: List of Canadian Guidelines

Microbial Guidelines:

· DIR2012-02, *Guidelines for the Registration of Non-Conventional Pest Control Products*

Non-Conventional Guidelines:

· DIR2012-02, *Guidelines for the Registration of Non-Conventional Pest Control Products*

Value Approach:

· PRO2010-07, Value Guidance –Benefit Information and Use History
· DIR93-17, Assessment of Economic Benefits of Pesticides

Efficacy:

· DIR2003-04, *Efficacy Guidelines for Plant Protection Products*
· DIR96-01, *Guidelines for Efficacy Assessment of Fungicides, Bactericides, and Nematicides Resistance Management*
· PRO2012-02, *Voluntary Pesticide Resistance Management Labelling Based on Target Site/Mode of Action Tank Mixes*
· Memorandum to Registrants – *Use of Unlabelled Tank Mixes of Commercial Pest Control Products Used for Crop Production or Vegetation Management*, 27 October 2009

Environment Canada Guidelines:

· EPS 1/RM/44, *Guidance Document for Testing the Pathogenicity and toxicity of New Microbial Substances to Aquatic and Terrestrial Organisms*