Organisation for Economic Co-operation and Development

ENV/JM/MONO(2019)8

Unclassified

English - Or. English

26 March 2019

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

Report of the 9th Biopesticides Expert Group Seminar on Test Methods for Micro-organisms

Series on Pesticides
No. 100

JT03445361

Foreword

This report summarises the discussion and outcomes of an OECD Expert Group on BioPesticides (EGBP) seminar on test methods for micro-organisms. This one-day seminar was held on 18 June, 2018 at OECD headquarters in Paris, France, one day before the annual meeting of the EGBP, a sub-group of the OECD Working Group on Pesticides (WGP). The seminar was the ninth in a series of EGBP (formerly the BioPesticides Steering Group, BPSG) seminars that focus on bio-pesticide related issues of interest to OECD governments and other stakeholders.

The seminar was chaired by Jeroen Meeussen (European Union Minor Uses Coordination Facility), chair of the EGBP. Fifty six experts from ten OECD member countries, the European Commission, the People's Republic of China, the Business and Industry Advisory Committee to the OECD (BIAC), the International Biocontrol Manufacturers Association (IBMA) and research institutes/universities participated in the Seminar. The list of participants can be found at Annex 2.

The seminar was organised to present and discuss the applicability of existing test methods for micro-organisms and to illustrate the hurdles and issues which biopesticide registrants and regulators face, as well as to initiate a process to make recommendations for improvements to test methods for micro-organisms.

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Introduction

This report presents the results and recommendations of an OECD Seminar on "Test methods for Micro-organisms". Its aim is to provide an overview of the issues associated with this topic from the perspective of research, industry and regulatory experts, and to provide input to the potential future development of recommendations for possible further OECD work.

The seminar focused on promoting a dialogue on "Test methods for Micro-organisms" and initiating a process to make recommendations for improvements by exchanging information on:

- governments' or organisations' experiences, challenges and problems encountered in the areas of test methods for micro-organisms; and
- regulatory guidelines for the generation and assessment of data related to test methods for micro-organisms.

Participants

People attending the OECD Seminar included:

- members of the OECD Working Group on Pesticides (WGP) and Expert Group on BioPesticides (EGBP);
- invited experts from key stakeholder groups such as the pesticide industry and manufacturers of biopesticides (BIAC and IBMA);
- invited experts from research institutes (academia), and
- regulators and evaluators from governmental or intergovernmental bodies.

Purpose and Scope of the Seminar

The main objectives of the EGBP Seminar were:

- to identify key issues and challenges in the area of test methods for micro-organisms;
- to provide updates of national and international activities and initiatives in the area of test methods for micro-organisms;
- to exchange information on OECD countries' current activities in the area of test methods for micro-organisms;
- to exchange information (and identify needs) between regulators, scientists and other stakeholders;

- to suggest and discuss further steps for OECD countries and key stakeholders in OECD and non-OECD countries to address the identified issues;
- to recommend possible further improvements to address regulatory and related issues in the area of test methodology for micro-organisms; and
- to prepare a priority list for the development of new or amended test guidelines for micro-organisms.

In particular, the following questions were raised, and statements discussed, during the Seminar:

- Is the current regulatory framework appropriate to register micro-organisms?
- What is the applicability of existing test methods for micro-organisms?
- How should the results of tests performed on micro-organisms be interpreted?
- Information on alternative methods, and the results from using such alternative methods, should be taken into account when registering micro-organisms.
- Effects studies used to characterise environmental risk can be too short to conclude lack of pathogenicity or infectivity to non-target species. Information on the biology of the active organism strain/species should be considered when designing tests, particularly test duration.
- Novel mechanisms of biopesticide action may require consideration of new or amended guidelines and test methods.
- Data requirements regarding sewage treatment are no longer required for biocide registration approval, and should be removed ('waived') for PPP as well.
- The earthworm study is not required unless the microbial is not naturally occurring in the soil.
- OECD Test Guideline 211 (Daphnia magna Reproduction Test) needs to be amended for microbials.
- Current test methods for chemicals should be evaluated and proposals for adaptation to micro-organisms should be made where necessary.

Structure of the Seminar

The Seminar programme is provided in Annex 1. Invited speakers included:

- International experts in this field;
- Government representatives; and
- Representatives from industry and research institutes.

Presentations were grouped into the following three sections:

- Introduction
- Stakeholders' Experience and Perspectives

- Government Experience and Perspectives

There was a short discussion after each set of presentations and a more general discussion at the end of the seminar.

Summary of Presentations and Discussions

All abstracts and slides of presentations are presented in Annexes 3 and 4.

Introduction to the Seminar

Presentation on the OECD and the work of OECD-EGBP and general introduction to the seminar on 'Test Methods for Micro-organisms'

by the EGBP and Seminar Chair, Jeroen Meeussen, European Union Minor Uses Coordination Facility [PPT 1]

At the beginning of the seminar, the Chair invited the participants of the seminar to introduce themselves. The Chair continued by giving a presentation on the history of OECD and the work of the OECD Expert Group on BioPesticides (EGBP), as well as a general introduction to the seminar. He explained that the topic "Test Methods for Micro-organisms" was selected based on the outcome of an OECD survey conducted in 2012 (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 ENV/JM/MONO(2016)71). An OECD questionnaire was sent to member countries to identify the suitability of the existing test methods or guidance to assess the safety of microbial pesticides (e.g., bacteria, algae, protozoa viruses, fungi).

He mentioned that micro-organisms used as pesticides are regulated following similar approaches to chemical pesticides. However, he explained that the biological properties of living micro-organisms are not similar with those of chemical pesticides, and, consequently the test methods used to determine their safety may not be appropriate.

The Chair also explained that the scope of the seminar was to discuss: (1) the applicability of existing test methods for micro-organisms, (2) the challenges in interpreting results performed in tests for micro-organisms, (3) information on available alternative methods for micro-organisms, (4) the necessity of taking into account information on the biology of the active organism strain/species when designing new tests, (5) the novel mechanisms of biopesticide action and how to capture them in new or amended guidelines and test methods, (6) the waiving of some data requirements based on scientific evidence/knowledge, and, lastly (7) if the current regulatory framework is appropriate to register micro-organisms. He emphasised that the goal of the one-day seminar is to promote a dialogue among participants and to initiate a process for drawing recommendations that could improve existing test methods for micro-organisms or could lead to the development of new methods.

Stakeholders' Experience and Perspectives

Background and feedback from the OECD Survey on Data Requirements and Test Guidelines for Micro-organisms, and challenges for human toxicology

by Marloes Busschers, Charles River's-Hertogenbosch, The Netherlands [PPT 2]

The presenter started by providing the background and summary of the OECD survey results on data requirements and test guidelines for micro-organisms that was conducted in 2012. The presentation aimed to illustrate the progress made since then in addressing some areas, for which further guidance was identified as necessary or useful based on the outcome of the survey. For example, the issue of the 'technical equivalence for microbial strains' has been addressed in an OECD guidance document. The issue on secondary metabolites was partly addressed during an OECD seminar on this topic took place in 2015 [*see* ENV/JM/MONO(2017)5], an OECD working document will be published soon and an EU guidance document is under preparation. However, for other areas such as the characterisation of strain/serotype, identification of metabolic by-products/impurities, genetic stability and acceptable quality control/analytical profile, little or no progress has been made. Similarly, in the area of analytical methods the issue of storage and stability has been addressed by an OECD guidance document [*see* ENV/JM/MONO(2016)54], whereas no criteria have been identified so far for validating analytical methods. She emphasised that the issues identified that were relevant to mammalian toxicity testing have received limited attention.

The presenter focused the rest of her talk on challenges from her experience in running toxicity tests using rodents and interpreting test results for micro-organisms by providing specific examples. The presenter stated that some test methods for micro-organisms need to be adapted or replaced as they are technically challenging (e.g., pulmonary toxicity/infectivity/pathogenicity), the administration route is not relevant (e.g., dermal sensitisation), the animal model used is not appropriate (e.g., oral toxicity/infectivity/pathogenicity and testing of Bacillus) and the obtained results are not informative as their interpretation is not simple (e.g., genotoxicity test). The possible solutions suggested from the presenter that are mainly applicable to the acute toxicity/infectivity/pathogenicity test are: (1) waiving infectivity/pathogenicity testing if the micro-organism does not grow at temperatures above 30ºC, and (2) start the tissue enumeration in the organ of entry depending on the route of administration and the draining lymph nodes. However, she expressed her concerns about the risk posed by microbial biopesticides for immunocompromised individuals and informed the audience that no test methods are available for this purpose. Lastly, the presenter stated that there are a number of critical performance factors and issues as well as critical interpretation factors that should be taken into account and described in new or amended test methods for micro-organisms.

Test methods and the evaluation of micro-organisms: The EU experience

by José Tarazona, European Food Safety Authority (EFSA), Parma, Italy [PPT 3]

The presenter started by introducing the EU regulatory framework for assessing the safety of micro-organisms and explained the three steps that need to be followed (approval criteria, principles for evaluation and data requirements). After that, the presenter introduced the EU data requirements and continued explaining the key elements that the dossiers presented by the applicants to EFSA should at least cover. The key elements suggested by the presenter, which are considered reasonable expectations that need be addressed in the dossiers, include: (1) the assumed pesticidal mode of action and concerns associated with it, (2) the potential concerns identified in the scientific literature, (3) the confirmation of efficacy for the assumed pesticidal mode of action, (4) the direct concerns for humans and environment such as production of metabolites and competition, and (5) the complete literature search at species level. He provided an example about how lack of relevance for the (active agent) strain can be demonstrated in cases where a literature search indicates production of toxins/metabolites by strains of the same species. After that, the presenter described a few experiences gained through the reviewing of dossiers in EFSA and indicated areas in which applicants can make improvements when preparing the dossiers and areas where guidance and test methods are missing or are not adequate. In conclusion, the presenter stated that in absence of relevant prescriptive guidance documents and test guidelines for assessing the safety of micro-organisms in the EU, the regulation allows justified deviations from standard data requirement or use of alternative information or data but it requires applicants to fulfil the reasonable expectations mentioned above and to present a coherent dossier.

Ecological Risk Assessment for Microbial Pesticides

by Mark Whittaker, Applied Insect Science (APIS), Ripon, North Yorkshire, United Kingdom [PPT 4]

At the beginning, the presenter indicated that registering microbials is not an easy task as there are three main problems to overcome, namely: (1) the inappropriate regulatory framework, (2) the inadequate test guidelines, and, (3) the inconsistent interpretation of the test results. Overall, the challenges derive from the fact that the microbial data requirements are similar to those for chemical pesticides and that the test species that have historically been used for chemical ecotoxicology testing are not always suitable for micro-organisms and in cases that the test species are suitable, the study guidelines often need to be adapted to take into account the microbial modes of action. After that, the presenter also stated that there is no need for dose-response studies like in chemicals as a micro-organism will either be infective to a particular organism or it won't, and that establishing the minimum effective dose is sufficient. He explained how the typical survival curve for testing organisms (e.g., bees) is different depending on the pathogenic or non-pathogenic nature of micro-organisms as well as their potential to produce toxic metabolites. In this case, he indicated that a possible solution would be to take into consideration existing biological knowledge and adapt existing test methods and he gave the example of Tier I studies on bees that are too short to detect potential mortality induced by micro-organisms that produce toxic metabolites. The presenter stated that in Europe there are no specific microbial study guidelines and when the US OCSPP 885 series guidelines are used that are specific to micro-organisms, these are lacking in detail

compared to ESCORT/OECD guidance. Then, he presented six examples from standard test species used in ecological risk assessment and he highlighted the main challenges when testing micro-organisms and why some test guidelines need to be adapted (e.g., extension of observation period up to 2-4 days for OECD TGs 213/214), whereas, certain data requirements for micro-organisms should be waived (e.g., earthworms and springtail/collembolan testing). Lastly, the presenter stated that there is an opportunity to re-think the ecological risk assessment for microbial pesticides and he closed by presenting the ongoing projects for improving the testing guidelines for microbial pesticides.

Test methods for micro-organisms and non-target organisms: aquatic and terrestrial

by Bilgin Karaoglan, German Federal Environment Agency (UBA), Dessau-Roßlau, Germany [PPT 5]

In this presentation, the speaker began by describing the EU regulatory framework (composed by the EU Regulations 1107/2009, 283/2013, 284/2013 and 546/2011) by focusing particularly on data requirements related to non-target organisms (NTOs). Then, the presenter talked about the type of data that can be used to address them, which can be derived by: (1) US EPA Microbial Pesticide test guidelines (OPPTS/OCSPP Series 885), (2) Test guidelines as described in Part A of EU Regulations 283/2013 (e.g. OECD, IOBC-WPRS, ISO), (3) Scientific peer reviewed literature, and, (4) Microbial Pest Control Products (MPCP) data used for risk assessments. Nevertheless, the presenter stressed that each of these approaches comes with its own limitations as, for example, the US EPA Microbial Pesticide test guidelines lack international acceptance, the OECD Test Guidelines require adaptation for microbials, the scientific literature is often not strain-specific and the availability of data where it appears that the plant protection product shows a stronger effect than the micro-organism is often scarce and, additionally, there is difficulty in predicting the impact of co-formulants. After that, the presenter summarised the OECD survey results on data requirements and test guidelines for micro-organisms that was conducted in 2012, focusing on NTOs. He pointed out that in most cases for both aquatic and terrestrial NTOs the test guidelines are not suitable for micro-organisms or in other cases specific guidance for microbials is required. The presenter also mentioned some issues that can be tackled now that some experience has been gained by testing micro-organisms related to: (1) test item difficulties (e.g., extreme hydrophobicity of conidial spores), and, (2) effect of some inert carrier substances (e.g., kaolin, oil and diatomaceous earth in formulations). In conclusion, the speaker suggested that it is time to re-think if we are testing the right species to assess the effect of micro-organisms to NTOs and, if yes, then to assess if the methods used are adequate. Lastly, the presenter explained that the test guidelines that originally were developed for testing chemicals are not suitable for micro-organisms. However, they might be suitable with the following adaptations: (1) extending study duration (under consideration of control mortality), (2) adding further control groups (inactivated/sterile filtrate), (3) selecting species depending on the type of micro-organism, biological properties, and use pattern, and, (4) selecting exposure routes depending on the mode of action (dietary exposure: feeding on infected host/treated food, contact exposure: topical/dipping).

Pollinators and test methods for micro-organisms

by Emily McVey, Board for the Authorisation of Plant Protection products and Biocides (Ctgb), Ede, The Netherlands [PPT 6]

In the beginning, the presenter provided some general information related to the risk assessment for pollinators in the EU and explained that no authorisation for a microbial biopesticide can be granted if the product is pathogenic to bees. Typically, the risk is calculated by adding the toxicity and exposure data. However, for microbials, the concept of maximum hazard dose or concentration applies, which means that the test result is the actual risk assessment on its own, as long as the dosing used is high enough (i.e., 100x the initial concentration applied). Furthermore, she explained that based on the EU data requirements, experimental data is required to assess potential effects (i.e., toxicity, infectivity and pathogenicity) of micro-organisms on bees unless there is publicly available peer reviewed literature or proof of no exposure to bees. After indicating the available test guidelines to assess the effect of micro-organisms on bees, the presenter explained that these tests are not optimal in terms of observation length (i.e., long enough to exclude infectivity, but too long even for controls), and experimental conditions (e.g., humidity and temperature optimal for bees but not for micro-organisms). Therefore, further combinations or adjustments of test methods are needed that ideally should be discussed with applicants. Lastly, she described the working group on microbials under the International Commission for Plant-Pollinator Relationships (ICPPR) and their work on drafting a white paper. She concluded that the current test guidelines are not fully adequate and there is urgent need for new/alternative tests or modification of existing test guidelines to assess the effects of microbials on bees as well as guidance on how to do risk assessment, including new risk assessment paradigms.

Experience with long-term Daphnia toxicity studies (OECD TG 211) for microbials and proposals for the amendment of the study design

by Maria Pilar Herrero, Valent BioSciences LLC, United States [PPT 7]

The presenter started by describing the diet of Daphnia, which consists partly of bacteria as they are not selective filter feeders but there are studies indicating that a pure bacterial diet does not support survival, growth or reproduction of Daphnia. She also emphasised that Daphnids, due to their small size and short generation times, respond rapidly to changes in their food density and composition. Before going further into the problems faced and the potential solutions by using the long-term Daphnia toxicity studies (OECD TG 211), the presenter gave some examples from tested micro-organisms assessed by US EPA and EFSA. She stated that many of the results observed can be explained by a decrease in feeding efficiency due to water turbidity. Nevertheless, the presenter stressed that there are some bacteria and fungi species that have been described parasitizing Daphnia but this can be assessed differently. In conclusion, the presenter summarised the limitations of the current test method and suggested possible solutions that would lead to the redesigning the microbial Daphnia study, which include: (1) limit to a 10-day study, which will show both mortality and reproductive effects, (2) introduce filtration to remove larger particles, (3) increase algae feeding levels, (4) start with older Daphnia, who already have some food reserves, and, (5) permit settling during the test.

by Shannon Borges, US Environmental Protection Agency US EPA, Washington DC, United States [PPT 8]

In this presentation, the speaker began by referring to common issues identified when data is submitted using long-term Daphnia toxicity studies (OECD TG 211) for microbials (i.e., high turbidity, keeping test material suspended in water column, clumping of test material, not following guideline and/or using poor technique). She, then, presented a retrospective sketch of 15 studies submitted to the US EPA and pointed out that the majority of the examined results were acceptable or supplemental, occasionally both 48-hour and 21-day studies were submitted, in most cases there were no dose-responses and varied types of controls were included. Nevertheless, the presenter indicated there were some common variations in renewal rates (e.g., every 1-3 days or 3 times per week) and the endpoints measured (e.g., mostly mortality and reproduction, whereas others included length and weight) when the test was used. The presenter also mentioned some additional problems identified with these studies related to contamination, and incomplete reporting and not following up on cause of adverse effects. Furthermore, she explained that the water turbidity, clumping of micro-organisms and use of surfactants were not commonly reported. Hence, it was suggested that in order to progress it is recommended to expand and make a more thorough retrospective analysis and, based on the findings, explore alterations in the existing test method or identify and validate new/alternative methods.

by Bilgin Karaoglan, German Federal Environment Agency, UBA, Germany [PPT 9]

In the beginning, the presenter described an analysis made to illustrate that there is no relationship between the pesticidal mode of action of *Bacillus* spp. and the *Daphnia magna* sensitivity. Also, he stated that *Daphnia magna* is usually the most sensitive test organism driving the aquatic risk assessment, compared to fish. In addition, he presented a study that was conducted in order to determine which components of the technical material are responsible for the effects seen in previous studies on daphnids, which revealed the heat labile components from the fermentation broth that are carried over into the technical material as the main reason. The possible solutions suggested from the presenter are: (1) for short time exposure of Daphnia to high concentrations of micro-organisms, the transfer to clean water and feeding with algae, and, (2) for OPPTS 885.4240 freshwater aquatic invertebrate testing, the filtration of the test material or medium to remove sediment and particulates prior to commencement of the test. Lastly, the presenter stated that there is a need to better understand some effects on Daphnia caused by micro-organisms that are commonly reported such as immobility.

How to develop and adapt OECD Test Guidelines for micro-organisms

by Magdalini Sachana, OECD, Paris, France [PPT 10]

The presenter started by explaining that the OECD Test Guidelines were originally developed for assessing the potential adverse effects of chemicals (i.e., industrial chemicals, pesticides and personal care products) on human health and the environment. She then highlighted the recent experience on developing Test Guidelines for manufactured nanoparticles and explained that most Test Guidelines are applicable once

adapted and described in guidance documents. Only a few specific test guidelines needed to be developed as some of their hazardous properties are linked to nanomaterials' specific characteristics. The presenter also stated that the micro-organisms, similarly, have specific characteristics (i.e., living organisms unlike chemicals) and different modes of pesticidal action that need to be taken into account when developing new test methods. She emphasised that first the scientific basis needs to be established as it is important to develop a sound testing methodology. After that, the presenter indicated that for new areas or issues, it is recommended to start with a detailed scoping paper capturing what is currently known, consider the different types of micro-organisms up front, review the Test Guidelines and identify what adaptations are needed in the existed test guidelines or if new tests need to be developed. Only then can a proposal be accepted and work can start under the Test Guidelines programme. Lastly, she closed her presentation by explaining the OECD process for updating and developing Test Guidelines.

Government Experience and Perspectives

The Australian experience with test methods for micro-organisms

by Alan Norden, Australian Pesticides and Veterinary Medicines Authority (APVMA), Kingston ACT, Australia [PPT 11]

In this presentation, the speaker began by describing the Australian Pesticides and Veterinary Medicines Authority (APVMA) approach for registering a wide range of Microbial Pest Control Agents (MPCAs), which acknowledges available OECD and other organisations' guidance (e.g., US EPA). Then, he indicated areas on which more guidance is needed, as follows: (1) secondary metabolites and the presence of potential genotoxic compounds, (2) sensitisation potential as the traditional protocols don't provide meaningful results, (3) interpretation and clearance of the MPCA in pulmonary exposure studies, and (4) oral infectivity/toxicity. Furthermore, he mentioned that the rationale for waiver of residue data might apply in most cases for MPCAs. However, estimation of dietary exposure may be necessary if metabolites of concern are identified and potentially guidance on this in consultation with Residue Chemistry Expert Group (RCEG) would be helpful. As regards the fate and behaviour studies for MPCAs, he pointed out the difficulty in establishing background concentrations, which could be used as rationale for the non-submission of data and informed that they use in part the US EPA requirements to obtain data and define which fate aspects need further consideration. The presenter also mentioned the need for a guideline on higher tier testing on bees as now expert judgement and scientific rationale is applied to address this need. In conclusion, the speaker suggested that there are outstanding challenges in risk/impact assessment, especially with MPCAs with potential wide host range and in estimating likelihood of risk/impact, consequences and spread/infectivity beyond treatment area/target and that more guidance on this issue would be helpful.

The Japanese experience with test methods for micro-organisms

by Hidetaka Kobayashi, Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan [PPT 12]

The presenter started by describing the Japanese registration system for microbial pesticides and informing the audience that the data requirements for microbials were established in 1997. He pointed out that only 45 micro-organisms have been registered in Japan to date, their production is estimated to be around 200 tonnes and their production represents less than 0.1% of all pesticides produced in Japan. The presenter then talked about the evaluation of data submitted for microbials that includes: (1) biological properties, (2) manufacturing process, (3) analytical methods/quality assurance methods, (4) efficacy studies, (5) toxicity studies (human), and, (6) eco-toxicity studies. After that, the presenter introduced the tiered approach used to evaluate human risk. Tier I is based

on acute toxicity studies and Tier II is needed in case of infectivity or toxicity and involves multiple administration repeatedly (1/day) for 90 days. Evaluation of the sensitisation potential after repeated exposure to microbials is also required that is based on a deleted US EPA test guideline. Hence, it was suggested that the used test guidelines need updating so harmonisation can be achieved with international standards and data requirements should be revised as they were established 20 years ago. Lastly, he closed his presentation by stating that Japan should contribute to the OECD work on this area so progress can be made.

The US experience with test methods for micro-organisms

by Shannon Borges (US Environmental Protection Agency US EPA, Washington DC, United States) [PPT 13]

At the beginning, the presenter described the US data requirements for microbial pesticides and the tiered system that is followed. She explained that for microbials there is a separate set of test guidelines (885 Series) but still some test guidelines for chemicals (870 Series) are used (i.e., acute toxicity and irritation testing). She pointed out that the 885 Series were developed in the 1970s and 1980s and they were last updated in the 1990s. The presenter also emphasised that the toxicology test guidelines are more detailed than the NTO guidelines, and that allowed testing of a wide range of test organisms but also led to a range of interpretations. The presenter also mentioned that there are relatively few issues in relation to the test guidelines used for product analysis and toxicology. As regards the product chemistry, the US EPA increasingly makes use of information derived from whole genome sequencing but there is lack of relevant libraries. For toxicology test guidelines, the issues commonly raised are related to the test material, the pattern of clearance from tissues and the length of study. She informed the group that it is still under the agenda of the US EPA cooperative programme to develop a new method for assessing the sensitisation potential of micro-organisms but it has low priority at the moment. Then, she presented all the available test guidelines for NTOs and highlighted the challenges raised from their use and interpretation of results. Also, she indicated that there is a need for some of these test guidelines to undergo validation so they can provide better information and clearer guidance. In this respect, she pointed to possible solutions related to the test guidelines for aquatic testing (freshwater), non-target insects, and honey bees. Lastly, she emphasised that currently it is advisable for registrants to consult the US EPA prior to conducting studies, whereas, in the long term there is need to incorporate certain improvements in the test guidelines and in some cases potentially develop alternative methods.

The Canadian experience with test methods for micro-organisms

by Brian Belliveau, Pest Management Regulatory Agency (PMRA), Ottawa, Canada [PPT 14]

The presenter started by listing the existing test guidelines/protocols for microbials, including some Canadian guidance documents. He informed the audience that the Pest Management Regulatory Agency (PMRA) finalised the OECD harmonised microbial data evaluation templates in January 2010, where protocol details and testing criteria are embedded and he indicated that there is value using them, especially, to facilitate joint reviews. The presenter also indicated that due to complexity and diversity of micro-organisms, tailoring of certain test methods seems necessary, but always in consultation

with the regulatory authorities. Furthermore, he described a few problems identified while assessing data from test guidelines on NTOs, which involve: (1) identification of test material and viability check of the MPCA, (2) achieving maximum challenge dose/concentration vs. test system quality, (3) determining infectivity not always possible/practical (e.g., inhalation studies for fungal spore preparations), (4) the study duration is too short, (5) suspension of MPCA in honey for dietary route exposure (i.e., honey has antimicrobial properties), and, (6) establishing non-target terrestrial insect testing guidance on dose levels especially for dietary routes of exposure. At the end, he emphasised the importance of offering timely pre-submission consultations to industry and that focus should be given on updating/revising existing microbial test guidelines (e.g., U.S. EPA Series 885) or developing new guidance documents for specific studies where there is currently little or inadequate guidance/guidelines.

Summary of Discussions, Ideas and Recommendations for Possible Future Work

Summary

The topic "Test methods for micro-organisms" was selected as the topic of this Seminar based on the results of an OECD survey conducted in 2012. To support that survey, an OECD questionnaire was submitted to members of the OECD Bio-Pesticides Steering Group (BPSG) 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.

Micro-organisms used as 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 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, evaluators of microbial pesticides do not yet have the broad spectrum of assessment methods that are available to evaluators of chemical pesticides.

The 2012 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 report on the survey was developed to identify where differences exist, and where new or modified guidance is needed for the assessment of microbial pesticides. Speakers referred many times to these findings.

Different test methods that are used for human health and environmental risk assessment were presented along with the challenges and issues arising during their implementation and interpretation. Throughout the seminar, the aim was to work towards the development of recommendations for improving test methods for micro-organisms.

The following data requirements for micro-organisms - for which it was suggested that further guidance or adaptation of the test guidelines is needed - were more extensively discussed but not limited throughout the seminar:

- sensitisation potential,
- intratracheal/inhalation infectivity,
- genotoxicity,
- presence and level of secondary metabolites and toxins, and

- non-target effects (i.e., freshwater aquatic testing, non-target insects, and honey bees).

Regulatory authorities and stakeholders do recognise the value of existing test methods for micro-organisms, but, at the same time they acknowledge some inherent limitations to these tests that could be addressed now that experience has been gained and science has advanced. Because of the importance of having reliable tests for assessing the safety of microbial biopesticides, regulatory authorities and stakeholders should work together towards improving these methods.

Conclusions/Recommendations

A general observation made during the seminar is that in the majority of OECD member countries, the data requirements for the registration of microbial biopesticides are mostly the same as for chemical plant protection products. To address part of these data requirements, test methods that have been developed to assess chemicals are routinely used to assess microbial biopesticides. In some cases, a separate set of test guidelines (885 Series), which have been developed by the US EPA to support the registration of microbial pest control agents, is applied. However, it was noted that some of these methods for testing micro-organisms: (1) present some technical limitations, (2) provide results that cannot be easily interpreted, and (3) are considered outdated as science has advanced since they were first developed. It was also acknowledged that enough experience has been gained over the last 20 years to adapt certain test guidelines and make them more suitable for testing microbials or to develop new alternative methods that better suit their needs.

It was also highlighted that the value of existing test methods to address the data requirements for micro-organisms should be reviewed. It was suggested that work should first focus on improving current test methods and then gradually toward revising the data requirements for micro-organisms using scientific arguments.

Participants developed a number of recommendations to pave the way for improving the testing of microbial biopesticides:

- Review all test methods and identify their limitations when they are used for testing micro-organisms.
- Prepare a scoping paper capturing the limitations and potential solutions for improving microbial testing which covers all types of micro-organisms. Then, consider adaptation and improvements of existing test methods or development of new alternative methods taking into account the biology of the active organism strain/species. Ongoing efforts of the working group on microbials under the International Commission for Plant-Pollinator Relationships (ICPPR) will be considered.
- Prepare documents with scientific arguments for waiving certain data requirements (e.g., earthworms and springtail/collembolan testing).

Annex 1 – Seminar Programme

The 9th Expert Group on BioPesticides

Seminar on "Test Methods for Micro-organisms"

Monday 18 June 2018

OECD, Paris, France, 2 rue André Pascal, 75016 Paris

Chair: Jeroen Meeussen, EU Minor Uses Coordination Facility

9.30 – 10.00	**Introduction** • Purpose and structure of the seminar • Tour de table to introduce participants • Presentation on the OECD and the work of OECD-EGBP and general introduction to the seminar on 'Test Methods for Micro-organisms' *by Jeroen Meeussen* (EU Minor Uses Coordination Facility, Paris, France).
10.00 – 10.30	**Stakeholders' Experience and Perspectives** - Background and feedback from the OECD Survey on Data Requirements and Test Guidelines for Micro-organisms, and challenges for human toxicology *Marloes Busschers* (Charles River, 's-Hertogenbosch, The Netherlands)
10.30 – 10.55	- Test methods and the evaluation of micro-organisms: The EU experience *Jose Tarazona* (European Food Safety Authority (EFSA), Parma, Italy)
10.55 – 11.20	**Coffee break**
11.20 – 11.45	- Ecological Risk Assessment for Microbial Pesticides *Mark Whittaker* (Applied Insect Science (APIS), Ripon, North Yorkshire, United Kingdom)
11.45 – 12.10	- Test methods for micro-organisms and non-target organisms: aquatic and terrestrial *Bilgin Karaoglan* (German Federal Environment Agency (UBA), Dessau Roßlau, Germany
12.10 – 12.35	- Pollinators and test methods for micro-organisms *Emily McVey* (Board for the Authorisation of Plant Protection products and Biocides (Ctgb), Ede, The Netherlands)

12.35 – 14.00	**Lunch break**
14.00 – 14.40	- Experience with long-term Daphnia toxicity studies (OECD TG 211) for microbials and proposals for the amendment of the study design *Maria Pilar Herrero* (Valent BioSciences LLC) *Shannon Borges* (US Environmental Protection Agency US EPA, Washington DC, United States) *Bilgin Karaoglan* (German Federal Environment Agency, UBA) - How to develop and adapt OECD Test Guidelines for micro-organisms *Magdalini Sachana* (OECD, Paris, France)
14.40 – 15.05	**Government Experience and Perspectives** - The Australian experience with test methods for micro-organisms *Alan Norden* (Australian Pesticides and Veterinary Medicines Authority (APVMA), Kingston ACT, Australia)
15.05 – 15.20	**Coffee break**
15.20 – 15.45	- The Japanese experience with test methods for micro-organisms *Dr. Hidetaka Kobayashi* (Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)
15.45 – 16.00	- The US experience with test methods for micro-organisms *Shannon Borges* (US Environmental Protection Agency US EPA, Washington DC, United States)
16.00 – 16.30	- The Canadian experience with test methods for micro-organisms *Brian Belliveau* (Pest Management Regulatory Agency (PMRA), Ottawa, Canada) – remote presentation
16.30 – 16.45	
16.45 – 17.00	**Summary of the Discussion, Ideas for Follow-up, Recommendations for possible further OECD work (with reference to the seminar outline)**
17.00	End of the seminar

Annex 2 – List of Participants

Participants list for the 9th Expert Group on BioPesticides Seminar on Test Methods for Micro-organisms

18/6/2018

Allemagne/Germany	Mr. Herbert KOEPP Department 2: Plant Protection Products Federal Office of Consumer Protection and Food Safety (BVL) Germany
	Dr. Ann-Kristin DIEDERICH Federal Office of Consumer Protection and Food Safety (BVL) Germany
	Dr. Johannes JEHLE Institute for Biological Control Julius Kühn-Institute Germany
	Mr. Bilgin KARAOGLAN Section IV 1.3 - Plant Protection Products German Federal Environment Agency (UBA) Germany
	Ms. Anne SCHAEFER Federal Institute for Risk Assessment (BfR) Germany
Australie/Australia	Mr. Alan NORDEN Registration Management and Evaluation Australian Pesticides and Veterinary Medicines Authority (APVMA) Australia
Canada	Ms. Shirley ARCHAMBAULT Canada-US IR-4 Pest Management Centre Agriculture and Agri-Food Canada Canada

via WebEx	Dr. Brian H. BELLIVEAU Pest Management Regulatory Agency Health Canada Health Effects Division Canada
Chili/Chile	Mr. Eduardo AYLWIN Chilean Food Safety Agency Ministry of Agriculture Chile
	Mr. Roberto TAPIA Plant Protection The Agricultural and Livestock Service (SAG) - CHILE Chile
Corée/Korea	Ms. Mihye JEONG Division of Agro-Materials Evaluation Rural Development Administration National Academy of Agricultural Sciences Korea
	Jimin KIM Division of Agro-Materials Industry Rural Development Administration Korea
Danemark/Denmark	Dr. Birte Fonnesbech VOGEL Danish Ministry of the Environment Danish Environmental Protection Agency, Pesticides and Genetechnology Denmark
Espagne/Spain	M. Sebastian FRAILE AREVALO Délégation Permanente de l'Espagne auprès de l'OCDE France
États-Unis/United States	Ms. Shannon BORGES Biopesticides and Pollution Prevention Division U.S. Environmental Protection Agency United States
	Dr. Michael BRAVERMAN IR-4 Project Rutgers University United States

	Dr. Daniel KUNKEL IR-4 Project Rutgers University United States
France	Dr. Chantal ARAR ANSES, DEPR France
Japon/Japan	Dr. Yukiko YAMADA Ministry of Agriculture, Forestry and Fisheries Japan
	Dr. Hidetaka KOBAYASHI Plant Products Safety Division, Food Safety and Consumer Affairs Bureau Ministry of Agriculture Forestry and Fisheries Agricultural Chemicals Office Japan
Nouvelle-Zélande/New Zealand	Mr. Warren HUGHES Assurance Directorate Ministry for Primary Industries Regulation & Assurance Branch New Zealand
Pays-Bas/Netherlands	Dr. Emily MCVEY Board for the Authorisation of Plant Protection Products and Biocides Ctgb Netherlands
	Mr. Rob VAN DRENT Board for the Authorisation of Plant Protection Products and Biocides Ctgb Netherlands
	Ms. Jacoba WASSENBERG Board for the Authorisation of Plant Protection Products and Biocides Ctgb Netherlands
Royaume-Uni/United Kingdom	Mr. John DALE Chemicals Regulation Division Health and Safety Executive Pesticides Delivery United Kingdom

Suède/Sweden	Ms. Camilla WANG Swedish Chemicals Agency (KEMI) Sweden
Suisse/Switzerland	Mr. Lucius TAMM Research Institute of Organic Agriculture FiBL Switzerland
UE/EU	Mr. Jeroen MEEUSSEN European Union Minor Uses Coordination Facility France
	Mr. Jérémy PINTE Directorate-General for Health and Food Safety European Commission Belgium
	Dr. José TARAZONA Pesticides Unit European Food Safety Authority - EFSA Italy
République populaire de Chine/People's Republic of China	Ms. Mengmeng QU International Cooperation Division Institute for the Control of Agrochemicals, Ministry of Agriculture (ICAMA) People's Republic of China
Comité consultatif économique et industriel (BIAC)/Business and Industry Advisory Committee (BIAC)	Ms. Maria Pilar HERRERO Valent USA Corporation United States
	Dr. Peter HORNE FMC Agricultural Solutions Stine-Haskell Research Center United States
	Ms. Denise MUNDAY EMEA SCAE - Valent BioSciences Switzerland
	Mr. Greg WATSON Monsanto United States

	Dr. Leah ZORRILLA Bayer CropScience United States
International Biocontrol Manufacturers Association	Ms. Marloes BUSSCHERS Charles River Netherlands
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	Ms. Adi CORNELESE GAB Consulting GmbH Germany
	Ms. Catherine DICKBURT BIOBEST GROUP NV Belgium
	Dr. Christina DONAT International Biocontrol Manufacturers Association Austria
	Dr. Thierry GROLLIER De Sangosse France
	Dr. Roma GWYNN Biocontrol Consultant Rationale United Kingdom
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Mr. Mark WHITTAKER
Applied Insect Science
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Ms. Christiana OLADINI-JAMES
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Ms. Magdalini SACHANA
ENV/EHS
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Mr. Richard SIGMAN
ENV/EHS
OECD
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Annex 3 – Abstracts for Presentations

Presentation on the OECD and the work of OECD-EGBP and general introduction to the seminar on 'Test Methods for Micro-organisms'

by the EGBP and Seminar Chair, Jeroen Meeussen, European Union Minor Uses Coordination Facility [PPT 1]

In 1961 the Organisation for Economic Co-operation and Development (OECD) was established with a trans-Atlantic and then global reach. Today the OECD has 35-member countries. More than 70 developing and transition economies are engaged in working relationships with the OECD.

OECD is a forum in which governments work together to address the economic, social and environmental challenges of interdependence and globalisation. OECD is also a provider of comparative data, analysis and forecasts to underpin multilateral co-operation.

The OECD work on agricultural pesticides (i.e. chemical and biological pesticides) aims to help member countries improve the efficiency of pesticide control, share the work of pesticide registration and re-registration, minimise non-tariff trade barriers and reduce risks to human health and the environment resulting from their use.

The Expert Group on BioPesticides (EGBP), previously called the BioPesticides Steering Group (BPSG), was established by the WGP in 1999 to help member countries harmonise the biological pesticides assessment and improve the efficiency of control procedures. Biological pesticides involve: microbials, pheromones and other semiochemicals, plant extracts (botanicals) and invertebrates as biological control agents. The first tasks of the EGBP consisted of:

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

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

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

The report of the *Workshop on the Regulation of Biopesticides: Registration and Communication issues, 15 – 17 April 2008, EPA, Arlington, USA*, is another publication in the OECD Series on Pesticides (No. 44, 2009). This was followed by publications of an "*Issue Paper on Microbial Contaminant Limits for*

Microbial Pest Control Products" (OECD Series on Pesticides No. 65, 2011) and a "*Guidance to the Environmental Safety Evaluation of Microbial Biocontrol*" (OECD Series on Pesticides No. 67, 2012).

More recently the following documents were published:

- *Guidance Document: Outline on Pre-Submission Consultations for Microbial Pest Control Products* (OECD Series on Pesticides No.81, 2016);
- *Report of a Survey on Regulatory and Testing Issues for the Sensitisation Potential of Micro-Organisms: Survey Results (2014)* (OECD Series on Pesticides No. 84, 2016);
- *Guidance Document on Storage Stability of Microbial Pest Control Products* (OECD Series on Pesticides No. 85, 2016);
- *Report of a Survey on the Need for Further Guidance on Data Requirements and Updated Test Guidelines to Support the Assessment of Microbial Pesticides* (OECD Series on Pesticides No. 87, 2017);
- *Guidance Document on Botanical Active Substances Used in Plant Protection Products* (OECD Series on Pesticides No. 90, 2017);
- *Guidance Document on Semiochemical Active Substances and Plant Protection Products* (OECD Series on Pesticides No. 93, 2017);
- *Guidance Document for the Assessment of the Equivalence of Technical Grade Active Ingredients for Identical Microbial Strains* (OECD Series on Pesticides No. 96).

From 2009 onwards the EGBP started to organise seminars which focus on key issues on biopesticides of interest to OECD governments. Until now the following seminars have been held:

- Seminar on *Identity and Characterisation of micro-organisms*, OECD Series on Pesticides No. 53, 2010;
- Seminar on *The fate in the environment of microbial control agents and their effect on non-target organisms*, OECD Series on Pesticides No. 64, 2011;
- Seminar on *Characterisation and Analyses of Botanicals for the use in Plant protection Products*, OECD Series on Pesticides No. 72, 2012;
- Seminar on: *Trichoderma spp. for the use in Plant Protection Products: similarities and differences*, OECD Series on Pesticides No. 74, 2013;
- Seminar on: *Application Techniques for Microbial Pest Control Products and Semiochemicals: Use Scenarios and Associated Risks*, OECD Series on Pesticides No. 80, 2015;
- Seminar on: *Hazard and Risk Assessment of Secondary Metabolites produced by Microbial Pesticides*, OECD Series on Pesticides No. 89, 2017;
- Seminar on: *Sensitisation Potential of Micro-organisms*, OECD Series on Pesticides No. 91, 2017;
- Seminar on: *Niche Uses of Highly Specific Biocontrol Products*, OECD Series on Pesticides No. 95, 2018.

A joint OECD/KemI/EU Workshop on "Microbial Pesticides: Assessment and Management of Risks" took place between the 17th and 19th of June 2013 in Saltsjöbaden, Sweden. The workshop aimed at addressing issues around both agricultural and non-agricultural microbial pesticides and their assessment from a scientific, technical and regulatory perspective. The report of this workshop is published in the OECD Series on Pesticides No 76, 2014.

Background and feedback from the OECD Survey on Data Requirements and Test Guidelines for Micro-organisms, and challenges for human toxicology

by Marloes Busschers, Charles River's-Hertogenbosch, The Netherlands [PPT 2]

{abstract not available}

Test methods and the evaluation of micro-organisms: The EU experience

by Jose Tarazona, European Food Safety Authority (EFSA), Parma, Italy [PPT 3]

This presentation describes the fundamental regulatory principles for the risk assessment of microbial pesticide active substances in the EU and their scientific implementation. It is based in the experience generated through the EFSA peer-review process of the risk assessment conducted by the EU (co-)Rapporteur Member States.

The expectation is that the dossier presented by the applicant should at least cover the following key elements:

- A detailed and evidence based justification of the postulated pesticidal mode(s) of action
- A robust assessment of the possible direct and indirect consequences of the postulated pesticidal mode(s) of action on humans and non-target organisms
- A complete literature search covering at least all relevant studies conducted with the species (including studies reported at genus level) and covering also the production of toxins and metabolites and its hazards. In the EU, this is mandatory, must cover the previous 10 years, and should be conducting according to the EFSA guidance (EFSA, 2011)
- An evaluation of all concerns identified from the literature search, including other postulated mode(s) of action than the one(s) proposed by the applicant, and the production of toxins/metabolites by the strain or other strains of the same species

Unfortunately, not all dossiers fulfil those expectations, and in some cases severe inconsistences between the assumptions and evidence presented within the same section or in different parts of the dossier are identified by the EU (co-)Rapporteur Member State and EFSA. Some issues frequently observed during the EFSA assessment are highlighted.

Acknowledgements: This work is based and has been compiled by the scientific officers conducting the peer-review process at the Pesticides Unit of the European Food Safety Authority.

Ecological Risk Assessment for Microbial Pesticides

by Mark Whittaker, Applied Insect Science (APIS), Ripon, North Yorkshire, United Kingdom [PPT 4]

The data requirements and corresponding study guidelines used for the environmental risk assessment of microbial pesticides in Europe were taken directly from the pre-existing agrochemical regulatory framework. As a consequence, important distinctions between the assessment of xenobiotic compounds to which non-target organisms will have had no prior exposure and microbial pest control agents that are natural and ubiquitous components of the receiving environment are inadequately addressed. These shortcomings relate not only to the design of the studies, but also to the selection of appropriate test species. In this presentation some of these issues will be highlighted, and some proposals for re-thinking the approach to the environmental risk assessment of microbial pesticides will be discussed.

Test methods for micro-organisms and non-target organisms: aquatic and terrestrial

by Bilgin Karaoglan, German Federal Environment Agency (UBA), Dessau-Roßlau, Germany [PPT 5]

EU Data Requirements 283/2013 (for micro-organisms) and 284/2013 (for plant protection products) grant some degree of flexibility for data submissions in the EU registration process for microbial pesticides. It is noted that US EPA Microbial Pesticide Test Guidelines (OPPTS/OCSPP Series 885) can be used, pending the acceptance of specific guidelines at international level. Also Test Guidelines developed for testing chemicals can be used provided that they are adapted in such a way that they are appropriate for micro-organisms. However, guidance on method adaptations are lacking. Once justifications are provided, also scientific peer reviewed literature can be used for the risk assessments. One of the problems in literature data could be the deviation from standardised test methods or uncertainties in the extrapolation when tested strains differ from the Microbial Pest Control Agent strain. In the EU Data Requirements 284/2013, it is stated that data of the formulated product have to be used for risk assessments where it appears from available data that the plant protection product has a stronger effect than the micro-organism. However, data on co-formulants is often scarce which adds some further uncertainties. In the next section of the presentation, typical test methods for both aquatic and terrestrial non-target organisms are compared and discussed together with the findings from the OECD Survey on test-methods (Series on Pesticides No. 87). In the last section some further testing issues are highlighted and questions are raised.

Pollinators and test methods for micro-organisms

by Emily McVey, Board for the Authorisation of Plant Protection products and Biocides (Ctgb), Ede, The Netherlands [PPT 6]

Currently, there is no specific risk assessment paradigm, nor devoted test guidelines for assessing the potential risk to bees from exposures to microbial plant protection products in the EU. The standard risk assessment schemes do not fully address the protection goals according to the regulation, and the current testing guidelines are not fit-for-purpose where microbials are

concerned, as both were developed mainly for use with chemicals. To that end, a working group of the bee protection group of the ICPPR has been formed to outline the problems and shortcomings of the current situation and try to address these, both in the short and long-term. As an initial "product" of the working group, a white paper is envisioned as a way of providing advice to applicants, risk assessors, and risk managers working in the field of microbial plant protection products.

Experience with long-term Daphnia toxicity studies (OECD TG 211) for microbials and proposals for the amendment of the study design

by Maria Pilar Herrero, Valent BioSciences LLC, US [PPT 7]

{abstract not available}

by Shannon Borges, US Environmental Protection Agency US EPA, Washington DC, United States [PPT 8]

Chronic testing of microbial pesticides using Daphnia magna can present challenges related to methods and interpretation of results. Unique properties of microbes introduce complexities such as turbidity and settling of test material from the water column. Other issues stem from guideline interpretation and/or poor technique. Through a rough retrospective sketch of studies submitted to EPA, common variations and problems with these studies were identified, including varying renewal rates and endpoints, contamination, and incomplete reporting. Turbidity and other issues resulting from physical properties of microbes were noted, but were not as frequent as others. Clarifications on methods may be warranted, but a more thorough retrospective would be instructive in focusing needs.

by Bilgin Karaoglan, German Federal Environment Agency, UBA, Germany [PPT 9]

{abstract not available}

How to develop and adapt OECD Test Guidelines for micro-organisms

by Magdalini Sachana, OECD, Paris, France [PPT 10]

{abstract not available}

The Australian experience with test methods for micro-organisms

by Alan Norden, Australian Pesticides and Veterinary Medicines Authority (APVMA), Kingston ACT, Australia [PPT 11]

{abstract not available}

The Japanese experience with test methods for micro-organisms

by Hidetaka Kobayashi, Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan [PPT 12]

Pesticides including biological pesticides can be registered in Japan according to the Agricultural Chemicals Control Act (Act No 82 of 1948).

For one type of biological pesticides, microbial pesticides, data on biological properties, manufacturing process, analytical methods, efficacy studies, toxicity studies, and eco-toxicity studies are required. Evaluation of microbiological pesticides follows tired approach. Tier 1 consists of the evaluation of the studies on acute toxicity, such as oral/ dermal/ inhalation/ intravenous tests on experimental animals. When Tier 1 evaluation identifies a risk, Tier 2 and/or 3 evaluations are required.

The requirements and guidelines were established in 1997, more than 20 years ago. We need to update the guidelines and harmonize them with international standards.

The US experience with test methods for micro-organisms

by Shannon Borges (Environmental Protection Agency (EPA), Washington DC, United States) [PPT 13]

Data requirements for microbial pesticides parallel those for other types of pesticides, but some required studies are specialised because of the unique properties of microbials. Microbial pesticides have specific sets of testing guidelines for certain toxicology (human health) and nontarget organism data requirements. While these guidelines are well established, certain ones are clearly applicable, while others present greater challenges in conduct and interpretation. Relatively few issues are encountered with product analysis and toxicology guidelines. Many Tier 1 nontarget organism data requirements are addressed by means other than guideline studies, and while certain guidelines present few issues, others are more complex in their interpretation and use. Challenges are particularly noted in testing with freshwater fish and invertebrates, nontarget insects, and honey bees. Some clarifications in methods or alternative approaches may be appropriate, though the issues need closer examination to determine a best path forward. Best practices for conducting these studies at this time include consultation with EPA prior to conducting studies and ensuring that the studies are scientifically sound.

The Canadian experience with test methods for micro-organisms

by Brian Belliveau, Pest Management Regulatory Agency (PMRA), Ottawa, Canada [PPT 14]

Health Canada's Pest Management Regulatory Agency has been regulating microbial pest control agents (MPCA's or microbials) and their associated end-use products for over 30 years. Since this time it has faced many challenges guiding industry on the most appropriate test methodologies for assessing the potential effects of different types of microorganisms (bacteria, fungi, viruses, protozoa) on human health and safety as well as on non-target organisms. Primary guidance to industry currently consists of PMRA's own microbial registration guidelines (Regulatory Directive DIR2001-02), the US EPA's more advanced OCSPP Harmonized Test Guidelines Series 885 for microbials, various OECD test guidelines and EGBP guidance documents as well as Environment & Climate Change Canada's guidance on testing pathogenicity and toxicity of microbial substances to aquatic and terrestrial organisms. PMRA

also advocates for the use of OECD data evaluation templates for microbials, which were developed to guide industry on test methods/protocols as well as regulators who are responsible for assessing the test data. These evaluation templates contain detailed guidance taken from US EPA test guidelines for microbials and chemicals, OECD test guidelines for chemicals as well as guidance from PMRA's DIR2001-02 guidelines and ECCC's guidance document on organism testing. In general, PMRA's experiences with evaluating studies conducted using existing test methods/guidance tools have been largely positive. However, a number of challenges or weaknesses remain and are common to both test methods for assessing human health and environmental safety, including lack of viability checks by the testing laboratories, inadequate study duration to assess infectivity potential and inadequate dose levels. Revisions to existing guidance tools could address some of these common problems, but in some cases new guidance or test methods are needed where there is little or inadequate existing guidance (e.g., bees/pollinators).

Annex 4 – Slides of Speakers' Plenary Presentations

Please refer to the separate publication for full Annex 4: ENV/JM/WRPR(2019)2/ANN

[PPT 1] Presentation on the OECD and the work of OECD-EGBP and general introduction to the seminar on 'Test Methods for Micro-organisms'
Jeroen Meeussen (European Union Minor Uses Coordination Facility)

[PPT 2] Background and feedback from the OECD Survey on Data Requirements and Test Guidelines for Micro-organisms, and challenges for human toxicology
Marloes Busschers (Charles River's-Hertogenbosch, The Netherlands)

[PPT 3] Test methods and the evaluation of micro-organisms: The EU experience
José V. Tarazona (Pesticides Unit, European Food Safety Authority (EFSA), Parma, Italy)

[PPT 4] Ecological risk assessment for microbial pesticides
Mark Whittaker (Applied Insect Science (APIS), Ripon, United Kingdom)

[PPT 5] Test methods for micro-organisms and non-target organisms: Aquatic and terrestrial
Bilgin Karaoglan (German Federal Environment Agency UBA, Dessau-Roßlau, Germany)

[PPT 6] Pollinators and test methods for micro-organisms
Emily McVey, Jacoba Wassenberg (Board for the Authorisation of Plant Protection Products and Biocides (Ctgb), Ede, The Netherlands)

[PPT 7] Microbes and Daphnia effects: False toxicity due to study design?
Maria Pilar Herrero (Valent BioSciences LLC, United States)

[PPT 8] The U.S. experience with long-term Daphnia testing
Shannon Borges (Environmental Protection Agency, Washington DC, United States)

[PPT 9] Experience with long-term Daphnia toxicity studies (OECD TG 211) for microbials and proposals for the amendment of the study design
Bilgin Karaoglan (German Environment Agency (Unweltbundesamt), Germany)

[PPT 10] How to develop and adapt OECD Test Guidelines for mirco-organisms
Magdalini Sachana, Anne Gourmelon (OECD, Paris, France)

[PPT 11] The Australian approach on test methods for micro-organisms
Alan Norden (Australian Pesticides and Veterinary Medicines Authority (APVMA, Kingston, Australia)

[PPT 12] Biological Pesticides in Japan
Hidetaka Kobayashi, Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan)

[PPT 13] The US experience with test methods for micro-organisms
Shannon Borges (Environmental Protection Agency (EPA), Washington DC, United States)

[PPT 14] The Canadian experience with test methods for micro-organisms
Brian Belliveau (Pest Management Regulatory Agency PMRA, Ottawa, Canada)