GUIDELINES FOR THE REGISTRATION OF MICROBIAL, BOTANICAL AND SEMIOCHEMICAL PEST CONTROL PRODUCTS FOR USE IN ANIMALS

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ABBREVIATIONS

ADI	Acceptable daily intake
CFU	Colony-forming unit
EGBP	Expert group on biopesticides (OECD)
EPPO	European and Mediterranean Plant Protection Organization
EU	European Union
EC	European Commission
FRAC	Fungicide resistance action committee
GAP	Good agriculture practice
GEP	Good Experimental Practice
GLP	Good Laboratory Practice
GMO	Genetically modified organism
GRAS	Generally recognized as safe
HPLC	High performance liquid chromatography
HRAC	Herbicide resistance action committee
IPM	Integrated Pest Management
IPPC	International Plant Protection Convention
IRAC	Insecticide resistance action committee
ISPM	International Standards for Phytosanitary Measures
IVM	Integrated Vector Management
MPCA	Microbial pest control agent
MPCP	Microbial pest control product
OECD	Organisation for Economic Co-operation and Development
PPE	Personal protective equipment
RNA	Ribo-nucleic acid
QA	Quality assurance
QC	Quality control
QPS	Qualified presumption of safety
QSAR	Quantitative structure–activity relationship models
SCLP	Straight chain lepidopteran pheromones
SOP	Standard operating procedure
TDI	Tolerable daily intake
TGAS	Technical grade active substance
TTC	Threshold of toxicological concern
US EPA	United States Environmental Protection Agency

DEFINITIONS

Active ingredient: The part of the product that provides the pesticidal action *[definition from the International Code of Conduct on Pesticide Management (FAO/WHO, 2014)]*.

Biocontrol: A pest control strategy that uses living natural enemies, antagonists or competitors of the organism being protected and other self-replicating biotic entities *[adapted from revised ISPM Pub. No. 3, 2005 (IPPC, 2005)]*.

Biological pesticide: See biopesticide.

Biopesticide: A generic term generally applied to a substance derived from nature, such as a microorganism or botanical or semiochemical, that may be formulated and applied in a manner similar to a conventional chemical pesticide and that is normally used for short-term pest control *[adapted from ISPM Pub. No. 3, 1996 (IPPC, 2005)]*.

Integrated Vector Management (IVM): The rational decision-making process for the optimal use of resources for disease vector control. IVM aims to improve efficacy, cost– effectiveness, ecological soundness and sustainability of disease vector control interventions for control of vector-borne diseases *[definition from the International Code of Conduct on Pesticide Management (FAO/WHO, 2014)]*.

Traditional product, remedy or active substance: Material used to reduce pests and obtained usually from plants, mainly derived by composting or similar processing or through similar means.

Note: more definitions specific to the three classes of biopesticides covered by this document can be found at the beginning of each relevant Chapter 2, 3 and 4.

1. INTRODUCTION

1.1 International context

Currently, disease vector control are based predominantly on the use of conventional (synthesized) chemical pesticides. However, concerns remain about the impactof chemical pesticides on human and animal health and the environment. The development of alternative vector control approaches such as Integrated Vector Management (IVM) have been encouraged to address these concerns. Biological pest control agents can contribute to IVM as they generally pose little health or environment risk and can have good compatibility with many beneficial invertebrates used in IVM.

There is no globally agreed definition of biological pest control agents or so-called "biopesticides", but for the purposes of these guidelines these terms will include products with active substances that are based on microbials, botanicals or semiochemicals. These substances are distinguished from conventional chemical pesticides by a combination of their active substance material and/or nature, and their use.

In most countries, microbials, botanicals and semiochemicals are evaluated and registered following the same system as for conventional chemical pesticides. However, this approach can pose an unnecessarily high and inappropriate regulatory burden. This is because many, if not most, of the data requirements and evaluation criteria are not relevant to biological pest control agents (e.g. the data requirements for chemical identity are not relevant for a microorganism but appropriate studies on taxonomy are critical). Further, the level of risk resulting from the use of biological pest control agents is often lower than for conventional chemical pesticides, so higher tier testing is usually unnecessary.

Both international organizations and individual nations or regions have therefore begun to develop separate registration guidance for biological pest control agents. These include the Organisation for Economic Co-operation and Development (OECD, 2017a), the European Union (EC, 2017), the United States Environmental Protection Agency (US EPA, 2017), Brazil, China, Ghana, India, Kenya and South-East Asia (FAO Bangkok, 2012). The OECD member countries consider biopesticides to require a different registration approach to the oneused for conventional chemical pesticides and, through the OECD Expert Group on Biopesticides (EGBP) (formerly Biopesticide Steering Group (BPSG)), they are developing a harmonized approach specific to biopesticide registration.

Therefore, the Authority may wish to consider including specific provisions for biological pest control agents in existing legislation regulating chemical pesticides, or developing separate and specific legislation or regulation for biological pest control agents. Harmonization of the different approaches is important for streamlining and facilitating the research, development, commercialization and use of biopesticides for pest control. Using similar data requirements and evaluations should make it easier for applicants to submit applications to different countries and for regulatory agencies to benefit from each other's reviews.

1.2 Objectives

The purpose of this document is to provide practical guidance to facilitate best practice in the registration of microorganisms, botanicals and semiochemicals for control of ectoparasites in animals. The document focuses primarily on data requirements for registration and evaluation

approaches. It provides the Authority with a framework for registering biopesticides, identifies aspects where they differ from chemical pesticides, and indicates where the Authority should pay special attention.

In keeping with the principles and processes of the *FAO/WHO Guidelines for the registration of pesticides* (FAO/WHO, 2010) and *Guidelines on data requirements for the registration of pesticides* (FAO/WHO, 2013), this guidance aims to ensure that evaluations and decisions with regard to registration of microorganism, botanical and semiochemical products provide an appropriate level of protection of human and animal health and the environment.

1.3 Scope

These guidelines cover:

- Descriptions of the **basic data requirements** for field trial permits and the registration of microorganisms (Chapter 2), botanicals (Chapter 3) and semiochemicals (Chapter 4) for control of ectoparasites in animals.
- Guidance for the **evaluation of registration dossiers** for the above pest control products and uses.

These guidelines do **not** cover:

- Registration of invertebrates or macro-organisms used for biological control, as in most jurisdictions these are regulated by plant health legislation.
- Microbials, botanicals and semiochemicals derived from or based on genetically modified organisms (GMOs), as they represent a special consideration and should be addressed separately.
- Pest control agents based on so-called "RNA interference" technology or on "clustered regularly interspaced short palindromic repeats (CRISPR)" or other gene editing techniques.
- Substances for consideration as botanical active substances that are referred to as analogues, mimics, natural-identical synthesized molecules and biosimilars, which are out of scope as botanical active substances.
- Substances referred to as natural-identical synthesized molecules except when they are semiochemical active substances only.
- Semiochemicals when used as attractants or in traps for monitoring and not as pesticides, which are usually exempt from registration.
- Production of traditional remedies or products which often represent an important, cheap and locally available source of pest control agents, but which can present unacceptable risks to humans, animals and the environment. This guidance considers it acceptable for traditional products to be produced by individuals for their personal use, but not acceptable for these products or their active substance to be sold.

Biological pest control agents can be subject to the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (2011). This is an international agreement which aims to share the benefits arising from the utilization of genetic resources in a fair and equitable way. For countries signed up to this agreement, its measures and obligations can apply to many biological pest control agents. This guideline will not consider matters related to the Protocol but due attention should be paid to it.

1.4 Factors specific to biological pest control agents to be considered

A number of factors that are unique to biological pest control agents should be considered in their evaluation and registration. This will help to eliminate unnecessary barriers to registration while ensuring a high level of protection of humans, animals and environmental. The factors to consider are as follows:

- Many of the active substances used in biological pest control agents are well known and studied, so information about them is readily available. As a result, large parts of a dossier may consist of information from published literature and in-house studies conducted by the producer. Such information can be useful and, if it is of good quality and is consistent with current thinking and methodology, should be evaluated in the same way as other information. Evaluators should be aware that names of microbial and botanical species may have changed for taxonomic reasons.

- Waivers for the submission of certain data, IF JUSTIFIED, can reasonably be granted to support the non-provision of certain data. In the registration of biological pest control agents, waivers are most frequently requested for data on residues, environmental fate and ecotoxicology.

- Exchangeability of data is acceptable in certain cases, for example for certain groups of microorganisms that are known to have common properties.

- For some biological pest control agents, there may be no distinction between the active substance material and the product. In other words, the active substance and the product are the same material. In such cases, data are only needed on the product.

- Biological pest control agents are often formulated with materials that are inert or of no toxicological concern. In such cases the active substance will represent the worst case situation, so risk assessment can reasonably be based on the active substance alone.

- Biological pest control products are often a mixture of different active substances. Where this is the case, it should be clearly indicated during the registration process and on the product label.

- Suitable or validated testing methods for biological pest control agents are often unavailable, so in-house studies or external expert studies done by independent testing facilities can be used.

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1.5 Biological control agent specific registration issues

1.5.1 Labelling of biological pesticide products

Biological control agents have characteristics that make them different from chemical pesticides and the product labels should reflect this including (but not only):

Description and quantification of the active ingredient (a.i.) in the formulation: the label should provide a description and quantification of the active substance in the formulated product as follows:

- Microbials: the content of the active substance can be expressed, for example, as colony forming unit (CFU) per kilogram or litre and/or amount of relevant secondary

compound (metabolite) or in terms of biopotency (e.g. *Bacillus thuringiensis* is expressed in terms of Billions of International Units, or BIU). The label may also give information on the amount of other material such as spent fermentation media.

- Botanicals: the active substance content can be expressed as the amount of botanical source material, the lead component, or biopotency.
- Semiochemicals: the active substance content is usually expressed as the amounts of each of the active substances or the amount of the combined active substance (e.g. xx g of moth pheromone).

- *Formulation:* details should be provided on the type of formulation.

- *Safety advice*: the label should contain safety advice (and pictograms) for humans, animals and the environment, as well as appropriate personal protection equipment (PPE).

- *Effectiveness:* the label should indicate the expected effect and the expected level of this effect (e.g. pest control, pest reduction, pest suppression).

- *Directions for use:* the label should provide advice on how to mix, prepare and apply the product for each target pest and situation, as well as advice on application equipment, water volumes, adjuvants, and conditions under which the product should not be used.

- *Directions for storage*: the label should specify storage conditions that align with the test conditions for the (real-time) storage study and any specific conditions that are required (e.g. refrigeration).

- *Integrated vector management*: it is good practice for the label to recommend use of the product as part of IVM and to indicate compatibility with other control measures, if known.

- *Resistance:* it is good practice for the label to recommend that products with active substances that have different modes of action be used in rotation to reduce the chance of pest, disease or weed resistance developing. However, it should be noted that many biological pest control agents have multiple modes of action, so it is reasonable to expect that resistance will not develop.

2. MICROBIALS

2.1 Definitions

To facilitate consistency, these definitions harmonize with other international sources such as OECD, US EPA and EU.

Antibiosis: A relationship between two or more species in which one species is actively harmed (for example, by toxins produced by the other species).

Antigenic: Any substance that, as a result of coming in contact with appropriate cells, induces a state of sensitivity and/or immune responsiveness after a latent period (days to weeks) and which reacts in a demonstrable way with antibodies and/or immune cells of the sensitized subject in vivo or in vitro.

Antimicrobial agents: Naturally occurring semi-synthetic or synthetic substances that kill or inhibit the growth of microorganisms. Examples are:

- antibiotics, which are active against bacteria, and
- anticoccidials, which are active against coccidia, single cell protozoan parasites.

CFU: Colony-forming unit; one or more cells that grow to form a single visible colony.

Colonization: Proliferation and persistence of a microorganism in an environment, such as on external (skin) or internal body surfaces (intestine, lungs). For colonization, the microorganism should at least persist for a longer period than expected in a specific organ. The population of microorganisms may decline, but at a slower rate than normal clearance; it may be a steady population or it may be a growing population. Colonization can be related to harmless and functional microorganisms as well as to pathogenic microorganisms. The possible occurrence of effects is not indicated.

Contaminant or impurity: Any microorganism or substances it produces that are present in a product, other than the specified microorganism (or substances it produces) of the microbial pest control agent (MPCA); an alternate/mutant form of the MPCA is considered to be a microorganism impurity.

Ecological niche: Unique environmental position occupied by a particular species, perceived in terms of actual physical space occupied and function performed within the community or ecosystem.

Establishment: Colonization.

Host: An animal (including humans) that harbours or nourishes another organism (parasite).

Host specificity: The range of different host species that can be colonized by a microbial species or strain. A host-specific microorganism colonizes or has adverse effects on one or only a small number of different host species. A non-host-specific microorganism might colonize or have adverse effects on a broad range of different host species.

Impurity: See Contaminant.

Infection: The introduction or entry of a pathogenic microorganism into a susceptible host, whether or not it causes pathological effects or disease. The organism must enter the body of the host, usually the cells, and be able to reproduce to form new infective units. Simply ingesting a pathogen does not imply infection.

Infective or Infectivity: The ability of a microorganism to invade and persist in a viable state and to multiply within or on an organism, with or without disease manifestation. The nature of an infection can vary widely with respect to severity, location and number of organisms involved.

Invasion: The entry of a microorganism into the host body (e.g. actual penetration of the integument, gut epithelial cells, etc.). "Primary invasiveness" is a property of pathogenic microorganisms.

Metabolite: See Relevant secondary compound (metabolite).

Microbial or Microorganism: A microorganism active substance.

Microbial pest control agent (MPCA): See microorganism active substance.

Microbial pest control product (MPCP): A product containing an MPCA that is registered or labelled with instructions for direct use or application for pest control purposes.

Microorganism active substance: A microorganism (protozoan, fungus, bacterium, virus, or other microscopic self-replicating biotic entity) (revised ISPM Pub. No. 3. IPPC, 2005) and any associated metabolites, to which the effects of pest control are attributed (OECD, 2008).A microorganism active substance may contain viable and/or non-viable microorganisms. It can contain relevant metabolites/toxins produced during cell proliferation (growth), material from the growth medium, provided none of these components have been intentionally altered.

Multiplication: The ability of a microorganism to reproduce and increase in numbers during an infection.

Mycotoxin: A fungal toxin.

Non-viable microorganism: A microorganism that is not capable of replication or of transferring genetic material.

Non-viable residue: A residue that is not capable of replication or of transferring genetic material.

Pathogenicity: The ability of a microorganism to cause disease and/or inflict damage on the host. Many pathogens cause disease by a combination of (i) toxicity and invasiveness or (ii) toxicity and colonizing ability. However, some invasive pathogens cause diseases that result from an abnormal reaction of the host's defence system.

Relevant secondary compound (metabolite): Any secondary compound (metabolite) that is of toxicological concern for human or animal health and/or the environment; in this way, some toxins can be considered a relevant secondary compound (metabolite).

Secondary compound: A compound produced by a microorganism that is not essential for growth, development or reproduction of a microorganism.

Symbiosis: A type of interaction between organisms where one organism lives in intimate association with another, which is favourable for both organisms.

Technical grade of MPCA: Microbial material used for manufacture of microbial pestcontrol products. It is the purest preparation of the MPCA resulting from a typical production process, and contains no additives except for purposes of MPCA growth or replication, or typical purification and preparation. It may be commercially distributed to manufacturers of microbial pest control products either in its pure form or augmented with preservatives, stabilizers, and diluents; or it may be a hypothetical stage in the manufacture of the microbial pest control product.

Viable microorganism: A microorganism that is capable of replication or of transferring genetic material.

Viable residue: A residue that is capable of replication or of transferring genetic material.

Viroid: Any of a class of infectious agents consisting of a small strand of RNA not associated with any protein. The RNA does not code for proteins and is not translated; it is replicated by host cell enzymes. Viroids are known to cause several diseases.

Virulence: Measurement of the degree of disease-producing ability of a microorganism as indicated by the severity of the disease produced. Measure of the dosage (inoculum size) required to cause a specific degree of pathogenicity. It is measured experimentally by the median lethal dose (LD_{50}) or median infective dose (LD_{50}).

2.2 Types of data and information (data requirements)

This section outlines the data and information required to support the registration of a microbial pesticide. The data requirements for microbial pest control agents (MPCA) and products (MPCP) are listed in Annex 1.

These registration requirements for microbial products are based on, and structured similarly to, the standard requirements for the registration of chemical pesticides. However, they are specifically adapted to MPCAs and cover all relevant aspects of these products. This adaptation of the chemical pesticide registration requirements is necessary because of the fundamentally different nature of microbial products. The adaptations for microorganisms are described here.

2.1.1 Introduction

For many microorganisms, the production process from inoculation with the starter material to formulated product may be entirely enclosed and it is therefore not possible to have samples of the active substance (MPCA). In these circumstances it is acceptable for testing to be done with the product (MPCP) only.

It is also important that evaluators who examine the information and data on MPCAs and MPCPs consider both the test results and the test guidelines followed. Existing test methods for

chemical pesticides may not be directly applicable to MPCAs and MPCPs, so modified methods are usually needed. A number of test guidelines or guidance on the evaluation of microbials for pest control, have been developed by the US EPA, the OECD (OECD, 2008; OECD, 2011; OECD, 2012) and the EU, and these are referred to in the guidance provided below as appropriate.

In addition to the microbial cells, microorganisms have the potential to produce secondary compounds (also may be called secondary metabolites). These:

- may be present in the product and/or can be produced *in situ*;
- may or may not contribute to the activity of the MPCA; and
- may or may not be of toxicological concern.

Secondary compounds (metabolites) need be addressed in the dossier only when they are known, from literature or studies, to be of toxicological concern, when there would be human, animal or environmental exposure, and/or when they are the principle mode(s) of action. The evaluation can follow the approach used for botanical substances (which are usually mixtures of substances) as outlined in Chapter 3, with relevant (toxic) secondary compounds being considered similar to "components of concern" for botanicals.

For the more general parts of the dossier, when a high similarity within a species has been demonstrated, data for different strains of the same species can be used.

2.1.2 Intended use

- The data requirements are the same as those used for registration of chemical pesticides. No adaptations are required.

2.1.3 Identity, characterization, biological properties and analytical methods

Generally, the following information is needed for MPCA and MPCP in order to make regulatory decisions:

Technical material and product

- *Identity:* detailed taxonomic description and species affiliation of the MPCA to *strain* level.

- *Production:* details of the production method(s) including quality control measures for levels of any human or animal pathogens. OECD has developed guidance proposing acceptable levels for human or animal pathogens in products (OECD, 2011).

- *Composition:* amount of microorganism, to be provided in terms of g/kg or g/L(also in % w/w) and cell number (CFU) or biopotency by bioassay. Any spent fermentation media and secondary compounds (metabolites) should be quantified if relevant.

- *Biological properties*: information on the MPCA's biology, biogeography and ecology including:
    - 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; whether the species is indigenous.
- Natural occurrence of the microorganism including geographical distribution, hosts, habitat, ecological niche, level of natural occurrence.
- Life cycle of the microorganism and information regarding closely related species.
- Information on the target host range, effect of environmental parameters on growth, infectivity, dispersal and colonization ability are useful.
- Information on target organism(s), including mode of action and available information on host specificity.
- Potential of the microorganism to produce secondary compounds (metabolites) that are of concern for human health, animal health and/or the environment and, if there are, then information on their mode of action and any toxins and/or degradation products.
- Physiological properties, especially effect of environmental parameters on growth.
- Genetic stability (mutation rate of traits related to the mode of action).
- Information on whether the microorganisms will produce antibiotics that will interfere with human and veterinary medicines.

- *Storage stability:* accelerated high temperatures studies are usually not suitable, so real-time studies at an appropriate and justified storage temperature are used; useful guidance on this is provided by OECD (OECD, 2016). The conditions used in the study may then be reflected on the label.

- *Analytical methods:* many existing testing methods are not suitable for microorganisms. Where suitable methods are not available, new methods may need to be developed and these may need to be validated. It is accepted that some techniques are highly specialized and it may not be possible to have them validated externally to a recognized standard. In this case, the results should be validated by a second laboratory that can be in another company or be the same company but not under same laboratory management. The in- house methodology needs to be made available and the second laboratory must be able to reproduce the validation data from the first laboratory to within acceptable limits.

- *Technical equivalence*: technical equivalence needs to be adapted for a microorganism: the approved (reference) source needs to be demonstrated to be equivalent in one or more of the following cases:
  - Change of location of manufacturing plant,
  - Scale up of fermentation vessel,
  - Change of manufacturing process, such as change of production equipment or propagation conditions (e.g. temperature or ingredients).

  The aim is to ensure that the new source is equivalent to the approved source for the following parameters:
  - Identity of the microorganism
  - Composition of material for production (e.g. inoculum, culture media)
  - Content of the active microorganism (determined in relevant units)
  - Content of relevant secondary compounds (metabolites)
  - Content of microbial contaminants.

2.1.4 Pathogenicity

To be able to assess risks to human and animal health for a MPCA and MPCP proposed for

registration there should be data for the microorganism on their pathogenic potential, their ability to infectand pattern of clearance. Plus, toxicological effects from secondary compounds (metabolites),if relevant, should be assessed.

Toxicity of technical material and/or formulated product

Generally, the following information is needed for MPCA/MPCP in order to make regulatory decisions:

- *Acute toxicity (single exposure toxicity/pathogenicity study):* basic studies, using protocols adapted for microorganism, should include infectivity and pathogenicity and toxicity from oral, intratracheal, intraperitoneal and other relevant route of exposure and skin and eye irritation. In some cases it may be possible to present a reasoned case for non-provision of study data.

- *Higher tier studies:* for the MPCA repeat dose, sub-chronic or chronic studies are not usually necessary. However, if adverse effects are noted in the acute studies these may need to be further investigated. When relevant secondary compounds (metabolites) are confirmed to be present and/or the MPCP contains co-formulants that are toxic, additional studies should be considered.

- *Sensitization*: the available test methods for microbial material can be unreliable; therefore this test is not required at present. When secondary compounds (metabolites) are expected or confirmed to be present, sensitization testing will be required following a suitable method as for conventional chemical pesticides.

- *Genotoxicity*: data is required if relevant secondary compounds (metabolites) are present.

- *Reports of adverse effects:* data should be provided of records of any reported incidence of adverse effects in production facilities or in the literature and any studies done to establish that the MPCA does not cause unacceptable adverse effects for humans and animals.

2.1.5 Residues

To allow the authority to make an assessment of residues for microorganism-based products, information on the following is needed:

- Microorganisms approved for use are not human or animal pathogens, meaning there is no adverse mammalian exposure and so residue studies arenot required. A short rationale for waiver of data based on information showing that MPCA is not hazardous to mammals should be provided.

- If relevant secondary compounds (metabolites) are produced *in situ*, a rationale for a waiver based on a theoretical calculation should be made. This calculation would determine if the MPCA is unlikely to occur on treated food/feed stuffs in amounts considerably higher than under natural conditions. This should include a consideration of the potential persistence and likelihood of multiplication of the MPCA in or on animals, food/feed stuff.

- If there are secondary compounds (metabolites) of toxicological concern and/or they are the principle mode of action, then information on the likely exposure to these relevant secondary compounds (metabolites) should be provided and residue studies on these

relevant secondary compounds (metabolites) may be needed.

2.1.6 Environment

Depending on the composition of the MPCA/MPCP, information following one of the options below is needed in order to make regulatory decisions:

- *Indigenous MPCA species:*
  - The amount of MPCA released into the environment is **similar to or below** the levels that commonly occur in the natural environment and there **are no secondary compounds** (metabolites) present in the MPCP or if they are not relevant, or if they can reasonably be expected not to be expressed *in situ* in quantities likely to cause toxicity: short rationale for waiver of data should be provided.
  - The amount of MPCA released into the environment is **significantly above** the levels that commonly occur in the natural environment and there **are no secondary compounds** (metabolites) present in the MPCP or if they are not relevant, or if they can reasonably be expected not to be expressed *in situ* in quantities likely to cause toxicity: information should be provided to confirm that the microorganism will not establish and persist above natural levels in the environment. If this cannot be confirmed, then additional studies on environmental persistence will be required.Methodology may need to be adapted as appropriate.
  - The amount of MPCA released into the environment is **similar to or below** the levels that commonly occur in the natural environment and there **are relevant secondary compounds** (metabolites) present in the MPCP, or if they can reasonably be expected to be expressed *in situ* in quantities likely to cause toxicity: data from studies with the MPCA or MPCP (as appropriate) for the soil, air and/or water compartments. Methodology may need to be adapted as appropriate.
  - The amount of MPCA released into the environment is **significantly above** the levels that commonly occur in the natural environment and there **are relevant secondary compounds** (metabolites) present in the MPCP or if they can reasonably be expected to be expressed *in situ* in quantities likely to cause toxicity: data from studies with the MPCA or MPCP (as appropriate) should be provided for non-target organisms found in the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate.
  - There is no information and relevant secondary compounds (metabolites) cannot be excluded or the MPCA are used in different ecological compartments other than those in which they naturally occur: data from studies with the MPCA or MPCP (as appropriate) should be provided for the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate.

- *Non-indigenous MPCA species:* a non-indigenous MPCA species may represent a higher risk because they could establish and displace or compete with indigenous microorganism species. Therefore, information for the MPCA or MPCP (as appropriate) should be provided on the potential for survival and persistence of the microorganisms in the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate. Where non indigenous MPCA species are involved, clearance by the relevant Authorities (DVS, Public Health and KEPHIS) will be required before registration.

2.1.7 Ecotoxicology

Depending on the composition of the MPCA and MPCP, information following one of the options below is needed in order to make regulatory decisions:

- *Indigenous MPCA*
  - The amount of MPCA released into the environment is **similar to or below** the levels that commonly occur in the natural environment and there **are no secondary compounds** (metabolites) present in the MPCP or if they are not relevant, or if they can reasonably be expected not to be expressed *in situ* in quantities likely to cause toxicity: short rationale for waiver of data on effects on non-target organisms shouldbe provided.
  - The amount of MPCA released into the environment is **significantly above** the levels that commonly occur in the natural environment and there **are no secondary compounds** (metabolites) present in the MPCP or if they are not relevant, or if they can reasonably be expected not to be expressed *in situ* in quantities likely to cause toxicity: information should be provided to confirm that the microorganism will not establish and persist above natural levels in the environment. If this cannot be confirmed, then studies on non-target organisms will be required. Methodology may need to be adapted as appropriate.
  - The amount of MPCA released into the environment is **similar to or below** the levels that commonly occur in the natural environment and there **are relevant secondary compounds** (metabolites) present in the MPCP, or if they can reasonably be expected to be expressed *in situ* in quantities likely to cause toxicity: data from studies with the MPCA or MPCP (as appropriate) against non-target organisms will be required. Methodology may need to be adapted as appropriate.
  - The amount of MPCA released into the environment is **significantly above** the levels that commonly occur in the natural environment and there **are relevant secondary compounds** (metabolites) present in the MPCP, or if they can reasonably be expected to be expressed *in situ* in quantities likely to cause toxicity: data from studies with the MPCA or MPCP (as appropriate) should be provided for non-target organisms found in the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate.
  - There is no information and relevant secondary compounds (metabolites) cannot be excluded or the MPCA are used in different ecological compartments other than the one(s) where they naturally occur: data from studies with the MPCA or MPCP (as appropriate) should be provided for non-target organisms found in the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate.

- *Non-indigenous MPCA species:* a non-indigenous MPCA species may represent a higher risk because non-target organisms may have never been exposed to them. Therefore, information for the MPCA or MPCP (as appropriate) should be provided on the potential for effects of the microorganism on non-target organisms found in the relevant soil, air and/or water compartments. Methodology may need to be adapted as appropriate. Where non indigenous MPCA species are involved, clearance by the relevant Authorities (DVS, Public Health and KEPHIS) will be required before registration.
- *Insect pathogenic MPCA:* information from good quality literature or studies of the pathogenicity of the insect pathogenic MPCA for bees, in relevant environmental compartments, should be provided.

2.1.8 Efficacy

In general, data from good quality and representative field trials is needed to ensure that the product is effective when used according to label instructions.

- Data from carefully designed small-scale laboratory and/or growth chamber studies can form a component of the overall data package to reduce the number of field trials. A minimum of three large-scale field trials for a target pest should be sufficient if the information is of good quality and demonstrates consistent effects.
- For some general areas such as non-target effects, in practice it may be possible touse information in lieu of actual data.
- Data from field trials done in areas with a comparable climate can be used.
- It is good practice to provide guidance to end users on any restrictions that may apply (e.g. do not use at low temperatures), on how to apply the product, and on how to use the product as part of IVM.
- Sufficient information should be provided on the likely performance of the MPCP and on how best to use the product so that it will perform as effectively and consistently as possible.

2.2 Evaluation of the dossier

2.2.1 Introduction

This section provides background on the testing of microbial pest control agents, outlines factors to consider, and highlights areas that need particular attention in the evaluation of data and information on MPCAs and MPCPs.

It should first be noted that the information provided by applicants for registration of MPCAs and MPCPs can come from different sources including good quality literature, in-house studies, and/or GLP studies for the particular species or strain. In addition, as previously noted, MPCAs by their nature are different to conventional chemical pesticides so many of the testing methods used for chemical pesticides need to be adapted. Good guidance for testing microorganisms has been produced by the OECD, the EU and the US EPA, and applicants for product registration may have used these.

In practice, microorganisms are usually well identified, which enables the Authority to predict their properties and behaviour. This is particularly true for human and animal health. However, if the MPCA under consideration is taxonomically similar to a clinically or significant microorganism, its properties and effects should be examined in detail.

Some common microbial species have been used for many years for control of pests without unacceptable adverse effects, and no such effects are expected, given their nature. Therefore, for some MPCAs and MPCPs, evaluators should accept a reduced set of data requirements.

In addition, many common microbial species have already been evaluated by countries, and these assessments can be a useful source of information on the approach used and decisions taken. The conditions and criteria for these common species of MPCA and MPCP to be considered for reduced data requirements are:

- Full and unequivocal taxonomic identification to species with strain designation, deposition

of the strain in an internationally recognized culture collection, and an accession number.

- Confirmation of the MPCA production process including quality control steps, to clearly demonstrate that the active substance contains colony forming unit (CFU) only and no secondary compounds (metabolites).
- Confirmation that the active substance is formulated only with inert (non-toxic) co-formulants in the product.
- Confirmation of CFU viability/potency as appropriate, in the final product following storage.
- Confirmation of formulated product-relevant physical-chemical and technical properties.
- Confirmation that human and animal pathogen contaminants do not exceed accepted levels in the product.

2.2.2 Intended use

- The data requirements are the same as those used for registration of chemical pesticides. No adaptations are required.

2.2.3 Identity, characterization, biological properties and analytical methods

- *Identity*: to properly assess microorganisms, the taxonomy is vital. The MPCA must be identified correctly using the best available molecular taxonomic techniques and the strain compared to the type species and other strains of the same species in a good quality (large) taxonomic library. This is important to allow assessors to confirm that the strain being registered is not closely related to a human or animal pathogen and to allow read-across to other strains of the same species to support reasoned cases (based on information for other strains of the same species).

- *Production:* there are no impurities per se for MPCA, but the levels of any human or animal pathogens should be minimal:
  - Microorganism production has the potential to have contaminant microorganisms so it is important that the assessor can confirm that quality control procedures during production are adequate so that the product contains acceptable (minimal) amounts of human or animal pathogenic microbial contaminants. If this is not possible, then the applicant should provide details and results of testing to confirm lack of human or animal pathogen contaminants for example following OECD guidance for this.
  - The absence of significant secondary compounds (metabolites) can be confirmed from the production and downstream process (e.g. if spores are washed there should be no secondary compounds present) or if this is not possible, applicants should have provided details and results of testing, by a suitable method such as high performance liquid chromatography (HPLC), that confirm if any types and if possible amounts of, relevant secondary compounds (metabolites) are present.

  Composition: microorganisms are produced *in vivo* or by specific fermentation processes. The type of production method and the downstream processing method will alter the type of active substance and determine whether it contains cells, spent fermentation media and/or secondary compounds (metabolites).
  - Assessors need to confirm that sufficient detail of the production process is provided to allow them to confirm that the description and specification declared for the active substance is reasonable. It should be possible to confirm: the amount of microorganism, in terms of g/kg or g/L (also in % w/w) and cell number (CFU) or biopotency by bioassay; and any spent fermentation media. Secondary compounds (metabolites) should be quantified if relevant.

This production process must be kept confidential.

- For some MPCA, the specification is based on biopotency by means of a suitable bioassay. Assessors should be aware that due to the complexity of interactions in host-pathogen, cell and spore counts often have considerable variation and the precision is difficult to standardize.
- It is usually accepted that the specification is given as a range rather than an absolute figure.

- *Biological properties*: information that is provided on the MPCA's biology, biogeography and ecology is usually from good quality literature.
  - Applicants will have provided information on the MPCA's biology, biogeography and ecology. In addition, (in-house) studies done to determine for example, the target host range, effect of environmental parameters on growth, infectivity, dispersal and colonization ability are useful to support risk assessment in other areas of the dossier.
  - Information should be provided detailing documented evidence if available on the potential for production of relevant secondary compounds (metabolites). This should include consideration of whether the microorganisms produce antibiotics that will interfere with human and veterinary medicines. If this cannot be excluded, the use of the product could be severely restricted or refused. If secondary compounds (metabolites) are expected to be toxic, then information on their presence or lack of in the MPCA/MPCP should be provided. If relevant secondary compounds (metabolites) are present, this will affect the mammalian and environmental risk assessments and more data will be needed to confirm that use of the product would not present an unacceptable risk.

- *Storage stability:* accelerated high temperatures studies are usually not suitable, so real-time studies at an appropriate and justified storage temperature are used. The conditions used in the study will then be reflected on the label.

- *Analytical methods:* many existing testing methods are not suitable for microorganisms. Where suitable methods are not available, new methods may need to be developed and these may need to be validated. It is accepted that some techniques are highly specialized and it may not be possible to have them validated externally to a recognized standard. In this case, the results should be validated by a second laboratory that can be in another company or be the same company but not under same laboratory management. The in- house methodology needs to be made available, and the second laboratory must be able to reproduce the validation data from the first laboratory to within acceptable limits.

Technical equivalence: the assessors can consider the new source as technically equivalent in Tier I and therefore no Tier II assessment is required when the strain or isolate is established as identical and the following criteria are fulfilled:

- Content of the active microorganism (determined in relevant units) is higher than or equal to (within the minimum–maximum range) the reference source, and
- Content of relevant secondary compounds (metabolites) is lower than or equal to the reference source, and
- Composition of material for production is the same, and
- Content of microbial contaminants is lower than or equal to the reference source.

However, higher levels can be accepted as long as the content of microbial contaminants in the product is within the agreed limits for microbial contamination for the MPCP.

If the above criteria are not fulfilled, the MPCA can be considered under a Tier II assessment to determine if the changes in composition (chemical and/or microbiological) are with or without increased risk to human health, animal health and the environment. Additionalinformation can be found in EU guidance (EC SANCO, 2014a).

2.2.4 Pathogenicity

In practice, microorganisms are usually well identified, which enables a regulatory authority to predict their properties and behaviour. This is particularly true in the categories of human and animal health.

In some cases it may be possible, based on the nature and mode of action of the microorganism and lack of relevant secondary compounds (metabolites), to accept a reasoned case for non-provision of study data. This will need to be considered on a case-by-case basis. However, it is more usual for studies to be conducted.

It is generally expected that MPCA acute studies result in no endpoints of concern. If the study shows there is mammalian pathogenicity, it is unlikely that the authority would want the product approved. If there is toxicity in acute tests, then additional testing such as repeated doses should be requested.

If there are endpoints of concern from the skin and eye irritation, then guidance to protect operators and workers should be provided and restrictions on the use of the product should be placed on the label with suitable warning phrases. Depending on the type of formulation, it may be advisable to indicate that there can be the potential for microorganisms to provoke a sensitizing reaction.

2.2.5 Residues

Microorganisms approved for use are not human or animal pathogens, meaning there is no demonstrated hazard. Therefore, there is generally no concern about human or animal exposure nor is there a need for exposure studies.

If the MPCA proliferates (increases in number and amount), a risk assessment should be made based on the absence of toxic effects due to any relevant secondary compound (metabolite). If the secondary compounds (metabolites) are of toxicological concern and/or the principle mode of action, then information on the relevant secondary compound (metabolite) should be provided. The approach taken can follow that used for botanicalsubstances (that are usually mixtures of substances) as outlined in Chapter 3 with “relevant (toxic) secondary compounds (metabolites)” being considered similar to “components ofconcern” for botanicals.

2.2.6 Environment

The nature of microorganisms and the specificity of their relationship to their environment mean that based on the taxonomy, biology and ecology of a MCPA, minimal environmental information is likely to be required. For some species and strains of MPCAs, there may be significant amounts of good quality literature on related strains or species or in-house studies such as decline of populations in the environment that can be provided to justify non-provision of study data.

If, based on the nature of the microorganism, it is not possible to exclude environmental concerns, then for either the microorganism and/or the relevant secondary compounds (metabolites) it can be useful to consider if they are likely to be present at levels below those documented in the relevant environmental compartment. If they are, then a reasoned case can be made to justify why they will not represent a significant environmental risk.

Assessors should particularly consider if sufficient information has been provided to allow a risk assessment to be made for non-indigenous MPCAs, and indigenous MPCA that are used in different ecological compartments than those where they naturally occur.

2.2.7 Ecotoxicology

The nature of microorganisms and the specificity of their relationship to their hosts which is usually highly specific, means that based on the taxonomy, biology and ecology of a MCPA, minimal non-target species information are likely to be required. For some species and strains of MPCAs there may be significant amounts of good quality literature on related strains or species or in-house studies such as specificity to host or decline of populations in the environment that can be provided to justify non-provision of study data.

If, based on the nature of the microorganism, it is not possible to exclude non-target species concerns then for either the microorganism and/or the relevant secondary compounds (metabolites) it can be useful to consider if they are likely to be present at levels below those documented in the relevant environmental compartment. If they are, then a reasoned case can be made to justify why they will not represent a significant non-target organism risk.

Insect pathogenic MPCA: these microorganisms are a special case and attention needs to be paid to them for their potential effects on bees. Information from good quality literature or studies of the pathogenicity of the organism for bees should be provided.

Assessors should particularly consider if sufficient information has been provided to allow a risk assessment to be made for non-indigenous MPCAs, and indigenous MPCA that are used in different ecological compartments than those where they naturally occur.

2.2.8 Efficacy

It is in principle agreed that provision of efficacy data is useful to protect users from unrealistic claims by the manufacturers and to protect the microbial industry from poor quality products. The aim of efficacy testing is to demonstrate that the MPCP gives users a sufficient benefit that outweighs any negative effects.

Microorganisms have multiple modes of action, so the levels of effects in trials may be hard to assess and may be lower than those expected for conventional chemical pesticides. The efficacy testing should demonstrate that the MPCP gives users a sufficient benefit, for example in terms of pest control or resistance management, that outweighs any negative effects. As a minimum, there should be a statistically significant improvement, at an acceptable level of probability, of an appropriate measure of pest control, of sufficient magnitude to be worthwhile from a user's perspective.

All trials should in principle include an untreated control. In most trials, an appropriately justified reference product should also be included. Because of the variability of the conditions under which pest control products are used, the inclusion of a reference treatmentis necessary

in order to allow a meaningful evaluation of efficacy under the conditions of the trial and to permit comparison between different trials in a series. However, it is not required that acceptable efficacy must be relative to the standard but compared to the untreated controls where available.

In principle, data from good quality and representative field trials will be required. Data from carefully designed small-scale laboratory and/or growth chamber studies may form a component of the overall data package provided to the Authority, and the number of field/glasshouse trials can therefore be reduced.

It should be noted that although there are various areas to be addressed, for some areas such as non-target plant effects, in practice it may be possible to use information in lieu of actual data for some of these areas.

It should be recognized that MPCP may provide full control, partial control or contribute to control. Reduced performance should not in itself be grounds for refusal of authorization, if the applicant reasons why the demonstrated efficacy might be "sufficient". Such reasons might be: offering alternative modes of action (relevant to resistance management), valuable uses, resistance management, chemical residue management or specific compatibility in, for example, IVM systems. As a minimum, there should be a statistically significant improvement, at an acceptable level of probability, of an appropriate measure of pest control, of sufficient magnitude to be worthwhile from a user's perspective.

It is good practice to provide information that provides guidance to end users on any restrictions that may apply (e.g. do not use at low temperatures), how to apply the product andhow to use the product as part of IVM.

In general, applicants and evaluating officials should concentrate on ensuring that users can be provided with accurate information on the likely performance of the MPCP and advise on how best to use the product so that it will perform as effectively and consistently as possible.

3. BOTANICALS

3.1 Definitions

To facilitate consistency, these definitions harmonize with other international sources such as OECD, US EPA and EU.

Botanical active substance: A botanical substance that consists of one or more components found in plants and obtained by subjecting plants or parts of plants of the same species to a process such as pressing, milling, crushing, distillation and/or extractions. The process may include further concentration, purification and/or blending, provided that the chemical nature of the components is not intentionally modified or altered by chemical and/or microbial processes.

Component of concern: Any component which has an inherent capacity to cause an adverse effect on humans, animals or the environment and is present or is produced in a pest product in sufficient concentration to present risk of such an effect.

Chemical fingerprint: A spectroscopic and/or chromatographic profile that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a sample and consistency from sample to sample.

Lead component concept: The technical grade may have one or more components that can be used as analytical lead substances.

Natural exposure: Levels of substances present in the environment taking into account in what way exposure levels have been altered (e.g. agriculture), and in situations relevant forthe respective environmental compartment.

Plants: Living plants and parts thereof, including seeds and germplasm *[definition from the IPPC (IPPC, 2011)]*.

Pure active substance: This term does not typically apply to most botanical active substances because of their complex nature.

Reference specification: The specification on which the risk assessment in the original dossier was based and for which a regulatory decision has been taken.

Technical grade: A botanical substance produced from the defined source(s) and by the described manufacturing processes, and which is the “active substance”. For botanical active substances, the technical grade will be in most cases a mixture of components from the plant and in addition all components that result from the cultivation, harvest, post-harvest storage and primary processing and manufacturing. It may be difficult to identify and characterize all individual components. Some of these components may be considered as components of concern which may be considered in the same way as “relevant impurities” in chemical pesticides.

3.2. Types of data and information (data requirements)

This section outlines the data and information required to support the registration of a botanical pest control agent, also called a botanical, plant extract, or botanical active substance. As for microbial pest control products, these requirements are based on, andstructured similarly to, the standard requirements for the registration of chemical pesticides. However, they need to be specifically adapted to botanicals and to cover all relevant aspectsof these products.

Guidance on the data, information, and procedures for registration of botanicals, and the subsequent evaluation of this registration package (dossier) by the Authority, has been published by both the EU (EC SANCO, 2014b) and the OECD (OECD, 2017b).

This section draws from and interprets the EU and OECD guidance, and, in some cases, quotes directly from guidance from these two organizations. No separate list of data requirements is provided.

3.2.1 Introduction

To defend themselves against herbivores (including insects) and pathogens, plants produce a variety of components (also called "secondary plant compounds") including volatiles such as various alcohols, terpenes and aromatic compounds. As these properties have been known and observed for a very long time, it is a logical progression that some of these compounds have been identified as candidates for pest control uses.

The term "botanical" covers an extremely heterogeneous group of substances ranging from simple plant powders to unprocessed and processed plant extracts. Furthermore, botanicals may be highly refined (i.e. one single active substance) or represent a complex mixture of components of which all or only some are biologically active.

Pest control agents derived from plant material represent a special situation for registration. Botanicals differ from synthesized chemicals in their origin. Synthesized chemicals are produced by chemical reactions whereas botanicals are obtained by processing material of biological origin.

The production of substances of botanical origin is influenced by the geographical areas and climatic conditions (e.g. time of sunshine, rain, soil) and differs each year. Therefore, the nature and concentrations of substances vary naturally and affect the quantitative and qualitative composition of the botanical. For this reason, botanicals are likely to have a larger variation in their qualitative and quantitative composition than synthesized chemicals. Whileit is good practice to ensure a consistent and good quality of botanical material produced, it is common knowledge that plant quality varies from crop to crop, so some degree of variation can be accepted during evaluation.

In addition, the way of processing and purifying the botanical has an impact on the complexity and composition of the extracted material. Therefore, certain physical parameters related to the processing method can be regarded as important for characterizing a botanical.

Studies carried out on botanicals are usually conducted with the technical grade mixture, although use of single components (where more appropriate) for a study can also be considered. Studies conducted with single components of concern could be useful for supporting the evaluation to predict how the botanical might behave.

A lead component approach can be followed if appropriate. There can be different "lead components" used for different sections of the risk assessment. The lead component(s) that is/are used should be justified in terms of its/their properties and quantities in particular, with regard to representativeness of biological activity. Lead components may be the most frequently occurring substances as demonstrated from the "chemical fingerprint". Alternatively, they may be substances which have been identified to be the source of potentialeffects. In some cases, it may be difficult to identify the component(s) responsible for an adverse effect. In such cases, the weight of evidence that supports a particular component being of concern should also be accepted.

In this guidance, the term *batches* is replaced by "samples" to take into account situations when the production process does not allow sampling of distinct batches (e.g. continuous production). Often, botanical active substances are not produced in batches.

The data requirements for registration of botanicals are similar to those required for chemical pesticides, with the adaptations recommended below. For botanicals that lack a comprehensively reported history of use and those whose intended use levels will significantly exceed historical use or background exposure levels, the conventional chemical pesticide data requirements will apply, with options for scientifically justified deviations fromcertain data requirements.

3.2.2 Intended use

- No adaptation of chemical pesticide requirements is required.

3.2.3 Identity, characterization, physical, chemical, biological properties and analytical methods

Technical material and product

The following information about botanical pest control products is needed:

- *Identity:* detailed taxonomic description of the botanical material including:
  - Scientific name of source material (and, where relevant, variety, subspecies and/or chemotype); synonyms and any common name(s)
  - Ecology and biogeography
  - Part of plant used
  - Growth stage(s) of plant used.

- *Source of botanical material*: the process for obtaining the botanical raw material must be fully described, including details on:

- Cultivation: wild harvest or cultivation details; geographical origin(s); ecology/habitat or cultivation practices; usual agronomic conditions.
- Harvest: time of year of harvest; part of plant used; growth stage at harvest; method of harvest; time to storage (e.g. including any drying in the field).
- Post-harvest storage: storage conditions prior to any primary processing.
- Primary processing: the botanical raw material may be from more than one source to allow blending to manage the variability of raw material. All the sources of botanical material used will need to be described for their cultivation, harvest and storage (as above); preparation of botanical materials prior to any extraction; conditions of storage of the botanical material prior to manufacturing process.
- For sources from secondary or waste material where cultivation, harvest andstorage may not be available, information is required on the methods used to guarantee consistent quality and composition of the final product.
- If production of technical grade material leads to variation in the material produced, then this variation should be adequately characterized.

- *Manufacturing and production*: the detailed manufacturing and production process will form part of the botanical active substance specification. Therefore, details of the process for manufacture and the production process must be fully described. Provision of Standard operating procedures (SOPs) is preferred. The information should be sufficiently detailed to allow the assessor to fully understand the entire processes and should include:
    - Information on substances entering the manufacturing process and any special precautions such as control of light, humidity and temperature.
    - Information on the method(s) of manufacturing.
    - Extraction: temperatures; method and solvents (or mixture of solvents); the number of extractions; any purification processes; standardization criteria; further processing (e.g. concentrating or purifying).

- *Composition/specification*: the technical grade should be defined by a suitable method (e.g. HPLC, spectrophotometry as appropriate) using a suitable reference sample or standard. This characteristic profile is then the *chemical fingerprint* of the technical grade.If required, an applicant will need to provide reference samples and analytical standards used for the botanical active substance identification to a reference laboratory.

  Based on the taxonomy and/or current knowledge of the botanical source, the following groups can be distinguished. The requirements regarding the specification for the different groups are detailed below.

  Group 1: botanical active substances that are already known to have no unacceptable effects on humans, animals and the environment and are based on materials with known specifications e.g. food grade (FAO/WHO, 2017; FFC, 2017).
  - Data to demonstrate that each sample of botanical active substance is similar in its composition and comparable to the specification, with variation within defined acceptable margins. Five samples should be assessed and acceptable ranges for the profile of components quantitatively provided. The acceptable variability between samples may be different for different botanicals or chemical classes. It is not necessary to identify each component. However, if known, the components from the specification should be identified and declared.

Group 2: botanical active substances based on a material with an established specification and for which the taxonomy and current knowledge indicates that the botanical active substance may contain components of possible concern for humans, animals and/or the environment (EFSA, 2012a).

- In addition to the requirements indicated under Group 1, the components of possible concern should be identified and quantified.

Group 3: botanical active substances that are not based on a material with an established specification. In this case, complete identification and characterization of the technical grade is in principle needed.

- Complete identification and characterization is in principle needed.
- For identified components (e.g. sugars, chlorophyll) known to be of no concern,further validation of the analytical methods is not necessary.
- For identified components of possible concern for humans, animals and/or the environment, these components should be quantified.
- As no international agreed standards are currently available for these types of active substances: for other components in the technical grade another threshold for "significance" (e.g. $\geq$ 1 g/kg) could be taken if adequately justified. Any component $\geq$ 10% of the peak area of the main component and/or any component with a threshold of 10 g/kg and all components in total accounting for at least 80% of the total mass need to be identified and quantified, not necessarily using formally validated analytical methods.

Where necessary, and depending on the cultivation, storage and processing conditions, information on maximum levels for possible components of concern, including e.g. heavy metals, mycotoxins, pesticide residues, solvents, enzymes and other substances introduced during the manufacturing process, should be provided.

- *Analytical methods:* botanicals by their nature are complex mixtures, so testing methods may require adaptation. Some techniques are highly specialized and it may not be possible to have them validated externally to a recognized standard.

- *Technical equivalence*: for a botanical active substance, this is when a new source has the same or less harmful effects compared to the reference specification, and it is manufactured by essentially the same process, then the new source can be considered (eco)toxicologically equivalent to the reference specification.

  This is needed under the following circumstances:
  - When technical material comes from a new or different source or manufacturer other than the applicant of the reference specification.
  - When the production is switched from a pilot scale to an industrial scale commercial production, the latter is regarded as a different source.
  - When there is a change of the manufacturing location, and/or the addition of one or more alternative manufacturing locations (production sites).
  - When there is a change in the method of manufacturing: as the method of manufacture (e.g. process or quality of starting materials) is part of the technical grade specification, a change in the method of manufacturing is considered a new specification.

Information should be presented to demonstrate that the new source material is technically equivalent to the reference specification.

3.2.4 Toxicity

Toxicity of technical material and/or formulated product

Generally, the following adaptions to the information forbotanical active substances is needed in order to make regulatory decisions:

- Where there is sufficient documented knowledge, this should be used to avoid unnecessary animal testing. Extrapolating from one botanical active substance to another with respect to the same component(s) of toxicological concern (read-across) can be considered when accompanied by evidence of their composition with respect to the particular components of concern.

- Reference values and good quality assessments from other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed:
    - When available data show that similar exposures to known levels of the botanical by the same routes have occurred in large population groups for many years without adverse effects being reported e.g. in epidemiological studies.
    - When adverse effects are sufficiently characterized, no animal testing is required. If there is no indication of concern and studies indicate no toxicological concern, then a scientific justification can be provided to confirm no unacceptable risks.

- If it is reasonable to expect there may be a concern, then the results of suitable studies (acute and if necessary longer-term studies) should be provided.

3.2.5 Residues

Generally, the following information for botanical activesubstances is needed in order to make regulatory decisions:

- *Botanical active substances that are food or feed:* for botanical active substances listed as food and feed, information on the nature and magnitude of residues is usually not necessary. A reasoned case for a waiver should be provided. For these botanical active substances, normally no maximum residues are set.

- *Botanical active substances that are not food or feed*: for botanical active substances not listed as food and feed:
    - Information on the nature and magnitude of residues is needed and may often be addressed by a reasoned case.
    - Where natural or documented exposures are being considered to address consumer exposure, the registrant should present in detail a consumer risk assessment that compares anticipated exposures from the intended use to the “background” exposures.

- If components of toxicological concern are present in the technical grade and the information provided is insufficient: supervised field residue studies can be performed using formally validated analytical methods, or other suitable studies may be used, as appropriate.
- In general, metabolism or processing studies are only considered necessary if concerns remain on the nature and/or magnitude of the residues. However, since it is often not possible to radiolabel complex botanicals it may not be technically feasible to perform studies based on radioactive detection.
- If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of toxicological concern, then the chemical pesticide data requirements on metabolism apply.
- When residues on food or feed cannot be excluded, an exposure assessment for consumers will be required.

3.2.6 Environment

The data requirements will depend on the nature of the botanical, its intended uses, exposure levels and whether there is information on the botanical from documented use which may be relevant for environmental fate assessment.

In principle the standard approaches outlined in the *FAO/WHO Guidelines on data requirements for the registration of pesticides* (FAO/WHO, 2013) should be followed. Where these approaches are not appropriate or technically feasible, the following aspects could be considered.

Generally, the following information for botanical active substances is needed in order to make regulatory decisions:

- Details of any known pathways for their breakdown and decomposition in animals and the environment.
- Reasoned cases relating to "natural exposure" can be used to waive data requirements, taking into account good agricultural practice and exposure due to public health; estimated exposures of the (components of the) botanical should be compared to the natural exposure situations in the relevant environmental compartments (water, soil, air).
- The nature of the compound and its behaviour needs be taken into account: e.g. for highly volatile compounds such as essential oils, a calculation based on the substance's volatility may be used to replace the need for certain studies/requirements, e.g. by providing estimates of rapidity and likely extent of volatilization losses and gains by re-deposition.
- If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of ecotoxicological concern, then the standard data requirements apply.

3.2.7 Ecotoxicology

The activity, the mode of action and the exposure route of the botanical should be taken into account in order to focus on non-target organisms expected to be the most at risk, and to avoid animal testing when unnecessary. Due to the diversity and complexity of botanicals, the non-target organisms potentially affected vary substantially and therefore a general testing strategy cannot be provided in this guidance. The applicant should propose a relevant testing strategy in line with the proposed use(s) and the relevant exposure situations. Available ecotoxicological information, including studies and publications, should be analysed and considered. Good quality assessments from other regulatory frameworks may be taken into account.

The data requirements will depend on the nature of the botanical, its intended uses, exposure levels and whether there is information on the botanical from documented use which may be relevant for ecotoxicological assessment.

Generally, the following information for botanical active substances is needed in order to make regulatory decisions:

- Where natural or documented exposures are being considered to address exposure of non-target organisms, the registrant should present detailed non-target organisms risk assessments that compare anticipated exposures from the intended use to the natural exposures.
- If components of concern have been identified and ecotoxicological data are necessary, the ecotoxicological assessment should focus on these specific components. This will be the case for substances in Group 2.
- If components of concern have not been identified (Group 3) and ecotoxicological data are necessary, identification and further testing (ecotoxicology) is in principle needed, following chemical pesticide guidelines. It is recognized that it may be difficult to identify the active principle responsible for an unacceptable effect. However, the information submitted needs to be sufficient to assess if the botanical fulfils the relevant approval criteria.

3.2.8 Efficacy

In general, data from good quality and representative field trials is needed to ensure that there is a benefit for users when the products are used according to label instructions.

- Data from carefully designed small-scale laboratory and/or growth chamber studies can form a component of the overall data package provided to the authority and the number of field trials can therefore be reduced.
- A minimum of three large-scale field trials for a target should be sufficient if the information is of a good quality and demonstrates consistent effects.
- For some general areas such as non-target effects, in practice it may be possible to use information in lieu of actual data.
- In principle, it should be possible to extrapolate trials data from those done in areas where there is a comparable climate and in this way limit the amount of additional trials that are required.
- It is good practice to provide information that provides guidance to end users on any restrictions that may apply (e.g. do not use at low temperatures), how to apply the product and how to use the product as part of IVM.
- In general, there should be sufficient information provided so that the authority canensure users can be provided with good information on the likely performance of the product and

to formulate advice on how best to use the product so that it will perform as effectively and consistently as possible.

3.3 Evaluation of the dossier

3.3.1 Introduction

This section provides background on the testing of botanicals, outlines factors to consider, and highlights areas that need particular attention in the evaluation of data and information. As for microbial pest control agents, the information provided on botanicals can be from good quality literature, in-house studies, or GLP studies for the species or strain as relevant. Botanical active substances by their nature are different to conventional chemical pesticidesso many testing methods will need adaptation. Guidance published by the OECD (OECD, 2017a), the EU (EC, 2017) and the US EPA (US EPA, 2017) provide some suitable approaches and protocols, and applicants may have used them.

In considering what levels of exposure to botanical active substances are common for humansanimals and the environment, the following questions should be addressed:

- What is the nature and the level of "common background exposure"?
- Is there a history of safe use and, if so, for what use and how is it documented?
- Have adverse effects been reported and, if so, what was the nature and level of exposure?
- Which part of the plants was used and in which way was it processed?

If argumentation (i.e. a scientific rationale or reasoned case) is based on historical documented use, a comparison should be provided of the exposure for the intended use compared to the documented use. The chemical composition of the botanical should becomparable to those historically used, taking into consideration natural variation.

Extrapolating from one botanical to another with respect to the same or similar component(s) of (eco)toxicological concern (read-across) can be considered when accompanied by evidence of their composition with respect to the particular substance of concern.

Intended use

- No adaptations are required.

3.3.2 Identity, characterization, physical, chemical, biological properties and analytical methods

The identity, source and manufacturing are an integral part of the definition of the botanical active substance, and therefore details must be comprehensive and must also remain confidential.

- *Identity*: there should be a good description of the taxonomy of the species that is the source material.
- *Source of botanical material*: there should be good records presented, including SOPs for agronomic practices as appropriate.
- *Manufacturing and production*: the process for obtaining the botanical raw material must be fully described including details and provision of SOPs for production and manufacturing. This information will be confidential.

- Where necessary, and depending on the cultivation, storage and processing conditions, information on maximum levels for possible components of concern, including e.g. heavy metals, mycotoxins, pesticide residues, solvents, enzymes and other substances introduced during the manufacturing process, should be assessed.

- *Composition/specification*: based on the taxonomy and/or current knowledge of the botanical source, the botanical active substance dossier will have been developed following the data requirements for one of more of the suggested Groups (1, 2 or 3).
  - Five samples should be assessed following principles for batch analyses of active substances and acceptable ranges for the profile of components quantitatively provided. The acceptable variability between samples may be different for different botanicals or chemical classes. This will need to be assessed on a case-by-case basis.
  - The use of the technical grade/chemical fingerprint should have been fully justified and demonstrated that safety tests were conducted using suitable material.
  - If the characterization indicates that the botanical active substance is reasonably expected to contain components of possible concern for humans, animals and/or the environment, it/they should be identified and quantified.
  - If the botanical active substance is from an unknown plant source, complete identification and characterization should have been provided or a justification made for non-provision.
  - Data on the chemical composition of the botanical active substance should have been provided with emphasis on the concentrations of components of relevance for the safety assessment, such as: components that should be classified according to their chemical structure (e.g. flavonoids, terpenoids, alkaloids); components that characterize the quality, chemical fingerprint, production process and/or biological activity of the preparation (lead components); and components that provide reasonsfor concern due to their chemical, physiological or (eco)toxicological properties.

  Technical equivalence: if the technical grade is variable and beyond acceptable ranges,this may constitute a new source for the botanical active substance and this should be assessed for technical equivalence to a proposed specification.
- *Analytical methods:* botanicals by their nature are complex mixtures, so testing methods can be expected to have been adapted. Some techniques will be highly specialized and it may not have been possible to have them validated externally to a recognized standard. This is acceptable for botanical active substances.
- *Technical equivalence*: for the evaluation of equivalence of different sources against the reference specification, the following criteria should be considered in the Tier I approach. The new source is deemed to be equivalent to the reference specification if:
  - No new components are present and
  - The variability is within the reference specification.

  Decision-making – Tier I

  On the basis of the above criteria the conclusions might be that:
  - The new source is equivalent to the reference specification; therefore, no further consideration is needed.
  - Equivalence of the new source to the reference specification cannot be established based on the Tier I criteria alone; therefore, a Tier II evaluation is required.
  - The new source is not equivalent to the reference specification. In this case, an appropriate risk assessment must be conducted for the new specification to determine whether plant protection or public health products containing the technical material will represent an equal or lower risk compared to the reference specification.

For the evaluation of equivalence of different sources against the reference specification, the following criteria should be considered in the Tier II approach:

- If some new components have been identified where further toxicological and ecotoxicological testing is needed, the information provided should be assessed based on information that is already available, bridging information based on a similar botanical, expert judgement or on a case-by-case basis.

Decision-making – Tier II

In taking a decision the options available are:

- The new source presents no greater hazard hence is equivalent to the reference source.
- The new source is not equivalent to the reference specification because it presents a greater hazard.

3.3.3 Toxicity

Botanicals are not *per se* non-toxic, and risk mitigation measures may be necessary to avoid or minimize risk for human and animal health.
Depending on the botanical active substance and its uses, where there is sufficient documented knowledge this should be used to avoid unnecessary animal testing. Evaluators can accept extrapolating from one botanical active substance to another with respect to the same component(s) of toxicological concern (read-across) when this has been accompanied by evidence of their composition with respect to the particular components of concern. The application of non-testing methods (e.g. the use of reliable (Q)SAR models) could have been considered.

To assess potential risks, it may be possible that applicants have used data derived from biocidal use, medical use or epidemiological studies, or any other data on possible adverse health effects, either anecdotal or on the basis of case reports of intoxication (e.g. data related to toxicity on livestock animals). Reference values and good quality assessments from other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed.

When available data have been presented showing that similar exposures to known levels of the botanical active substance by the same routes have occurred in large population groups formany years without adverse effects being reported e.g. in epidemiological studies, these can be used. However, it is advised that applicants discuss this approach at an early stage with the pesticide board.

If there is no indication of concern, then a scientific justification can be sufficient to confirm no unacceptable risks. However, if it is reasonable to expect there may be a concern, then the results of suitable studies (acute and longer-term studies if adverse findings arise from acute studies) should have been presented and are to be assessed.

- *Components of concern:* in cases where components or components of concern with known toxic properties are present in the technical grade under evaluation, the significance of overall exposure should be assessed and compared with existing health- based guidance values such as the acceptable/tolerable daily intake (ADI/TDI).Consideration of exposure to the component(s) of concern in relation to the Threshold of Toxicological Concern (TTC) values may also be helpful. Guidance on the applicabilityof the TTC concept can be found in the EFSA journal (EFSA, 2012b).
  - If components of concern *have been* identified and toxicological data in addition to those for the technical grade are deemed necessary, hazard identification should focus on these specific components.

- If components of concern *have not been* identified and toxicological data in addition to those for the technical grade are deemed necessary, complete identification and characterization is in principle needed. It is recognized that it may be difficult to identify the active principle responsible for an adverse effect. However, the information submitted is required to be sufficient to assess if the botanical active substance fulfils the relevant approval.

3.3.4 Residues

As secondary plant compounds found in botanicals can be common in nature, human, animal and environmental exposure of many of them can be frequent in the natural environment. Quantification of this exposure may be complex. However, there are some substances for which there are already available well documented exposure assessments.

It is acknowledged that if the proposed botanical is considered to be the same material that is reasonably expected to be or to become a component of food, this provides considerable reassurance for consumer exposure. Food grade material is difficult to define, however, and therefore the applicant should have provided a reasoned case/evidence to the way the material complies with relevant food legislation, confirming that technical material is the same as that supplied to the food industry, and explaining the extent to which the material is used in food. The same approach applies to animal feed.

For many botanical active substances, residue data may not be required if it has been determined that detectable residues on the consumable commodity are unlikely to occur, or that residue levels are unlikely to exceed natural exposure and that the residues are not of toxicological concern. Where natural or documented exposures are being considered to address consumer exposure, the registrant should present in detail a consumer risk assessment that compares anticipated exposures from the intended use to the "background" exposures.

If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of toxicological concern, then the standard data requirements on metabolism apply.

If information provided on the nature and/or magnitude of the residues because of the lack of metabolism studies or processing studies is still considered insufficient, it might be necessary to account for these in the risk assessment (e.g. applying a higher safety factor, using available knowledge on metabolic pathways).

When residues on food or feed cannot be excluded, an exposure assessment for consumers will be required.

3.3.5 Environment

Arguments relating to "natural exposure" may have been used and need to be considered carefully. Taking into account good agricultural practice and exposure due to public health, estimated exposures of the (components of the) botanical should be compared to the natural exposure situations in the relevant environmental compartments (water, soil, air). The risk can be considered acceptable when estimated exposures are lower than or similar to the natural exposure situations and no unacceptable effects occur. If any estimated exposure(s) is higher

than natural exposure situations, more information may be needed to allow assessment of the relevant exposure levels addressing any persistence, transformation and mobility in the environment. The information to be submitted might be reduced to just the relevant environmental compartment.

The nature of the compound and its behaviour can also be taken into account. For example, for highly volatile compounds such as essential oils, a calculation based on the substance's volatility may be used to replace the need for certain studies/requirements, e.g. by providing estimates of rapidity and likely extent of volatilization losses and gains by re-deposition.

In general, botanicals are complex mixtures comprising a number of components therefore the whole technical grade is regarded as the active substance. However, there might be components with different properties. Therefore, studies conducted with single active components may provide more reliable information on fate and behaviour properties, however, single active components may also behave differently than the entire botanical active substance and provide mainly supporting information. If it is necessary and technically feasible with reasonable efforts to synthesize and radiolabel the active component(s) and/or known components of environmental concern, then the standard data requirements apply.

Components from botanicals are found in plants and it is to be anticipated that there will be common pathways for their breakdown and decomposition in animals and the environment; therefore, data on environmental fate could be waived.

While the whole technical grade is regarded as the botanical active substance, there might be components with different properties. Therefore, studies conducted with single active components may be needed to provide more reliable information on fate and behaviour properties. However, single active components may also behave differently than the entire botanical active substance and provide mainly supporting information.

3.3.6 Ecotoxicology

The risk can be considered acceptable when estimated exposures are lower than or similar to the natural exposure situations and no unacceptable effects occur on relevant non-target organisms. The activity, the mode of action and the exposure route of the botanical should be taken into account in order to focus on non-target organisms expected to be the most at risk, and to avoid animal testing when unnecessary. Due to the diversity and complexity of botanicals, the non-target organisms potentially affected vary substantially and, therefore, a general testing strategy cannot be provided in this guidance. The applicant should have made a relevant testing strategy in line with the proposed use(s) and the relevant exposure situations. Available ecotoxicological information, including studies and publications, should be analysed and considered. Good quality assessments from other regulatory frameworks maybe taken into account.

If any estimated exposure(s) is higher than natural exposure situations, more information is needed to assess the possible effect on exposed non-target organisms. It is recognized that it may be difficult to identify the active principle responsible for an unacceptable effect. However, the information submitted needs to be sufficient to assess if the botanical fulfils the relevant approval criteria.

3.3.7 Efficacy

It is in principle agreed that provision of efficacy data is useful to protect users from unrealistic claims by the manufacturers and to protect the microbial industry from poor quality products. For botanical products, it is necessary to demonstrate that it is sufficiently effective to justify the corresponding (label) claims.

Botanicals have multiple modes of action, so the level of effects in trials may be hard to assess and lower than that expected for conventional chemical pesticides. The efficacy testing should demonstrate that the botanical product gives users a sufficient benefit that it outweighs any negative effects. As a minimum there should be a statistically significant improvement, at an acceptable level of probability, of an appropriate measure of pest control of sufficient magnitude to be worthwhile from a user's perspective. In general, data from good quality and representative field trials will be required. Data from carefully designed small scale laboratory and/or growth chamber studies may form a component of the overall data package provided to the authority and the number of field/glasshouse trials can therefore be reduced.

All trials should include an untreated control. In most trials an appropriately justified reference product should also be included. Because of the variability of the conditions under which pest control products are used, the inclusion of a reference treatment is necessary in order to allow a meaningful evaluation of efficacy under the conditions of the trial and to permit comparison between different trials in a series. However, it is not required that acceptable efficacy must be relative to the standard but compared to the untreated controls where available. Variation in efficacy of botanical products when used for pest control may bemore than expected for a conventional chemical pesticide.

It should be recognized that botanical products may provide full control, partial control or contribute to control. Reduced performance should not in itself be grounds for refusal of authorization, if the applicant reasons why the demonstrated efficacy might be "sufficient". Such reasons might be offering an alternative mode of action (relevant to resistance management), valuable uses, resistance management, chemical residue management or specific compatibility in for example IVM systems. As a minimum there must always be a statistically significant improvement, at an acceptable level of probability, of an appropriate measure, of sufficient magnitude to be worthwhile from a user's perspective.

In principle, it should be possible to extrapolate trials data from those done in areas where there is a comparable climate and in this way limit the amount of additional trials that are required.

It should be noted that although there are various areas to be addressed, for some areas such as non-target plant effects, in practice it may be possible to use information in lieu of actual data for some of these areas.

In general, applicants and evaluating officials should concentrate on ensuring that users can be provided with accurate information on the likely performance of the botanical product and advice on how best to use the product so that it will perform as effectively and consistently as possible.

4. SEMIOCHEMICALS

4.1 Definitions

To facilitate consistency, these definitions harmonize with other international sources such as OECD, US EPA and EU.

Dispenser: A device able to release semiochemicals at controlled release rates.

Natural exposure level: The level of exposure that might occur in the environment by a high population of emitting organisms independently from the use of the products thus expected to be experienced by humans, animals and other non-target organisms.

Semiochemicals: Substances or mixtures of substances emitted by plants, animals, and other organisms that evoke a behavioural or physiological response in other individuals of the same or other species. Different types of semiochemicals are:

- **Allelochemicals** produced by individuals of one species that modify the behaviour of individuals of a different species (i.e. an interspecific effect). They include allomones (emitting species benefits), kairomones (receiving species benefits) and synomones (both species benefit).
- **Pheromones** produced by individuals of a species that modify the behaviour of other individuals of the same species (i.e. an intraspecific effect).
- **Straight-chained lepidopteran pheromones** (SCLPs) are a group of pheromones consisting of unbranched aliphatics having a chain of 9 to 18 carbons, containing up to three double bonds, ending in an alcohol, acetate or aldehyde functional group. This structural definition encompasses the majority of known pheromones produced by insects in the order Lepidoptera, which includes butterflies and moths.

Technical grade active substance (TGAS): A material containing an active substance that is used to manufacture the products. It may contain impurities produced as by-products of the manufacturing process and isomers but does not contain co- formulants.

4.2 Data requirements for registration of semiochemicals

Semiochemicals are active substances used in products and have a non-toxic, target specific, mode of action and are of natural occurrence. They are generally effective at very low rates, often comparable to levels that occur naturally. Theymay be volatile and can dissipate and/or degrade rapidly in the environment. It can be expected that many semiochemical products pose low risk to human health, animal health and the environment. The regulatory approach for semiochemicals should take into account their specific properties and inherent differences from chemical pesticides (OECD, 2002; ECSANTE, 2016).

This section draws from and interprets the OECD and EU guidance, and, in some cases, quotes directly from guidance from these two organizations. No separate list of data requirements is provided.

4.2.1 Introduction

Pesticide products containing semiochemicals may be formulated and dispensed using techniques that can reduce exposure levels and/or increase their effectiveness. For example, controlled release technology is critical to slow down and extend effective pheromone release over the optimum time period.

It is important to differentiate between different types of application techniques used for semiochemicals:

1. Retrievable dispensers
    a. Passive dispensers (extruded or reservoir). The semiochemical diffuses continuously from the device into the air where the active substance becomes diluted.
    b. Active dispensers. The semiochemical is released discontinuously from the device into the air where the active substance becomes diluted.
2. Passive non-retrievable products
    a. Dispensers (extruded or reservoir). The semiochemical diffuses continuously from the device (such as biodegradable dispensers) into the air where the active substance becomes diluted.
    b. Dosable matrix dispensers. The semiochemical is embedded in a matrix, such as a sticky polymeric material. They are not discrete units; application is *in situ* by attaching the polymeric mass onto animals or elsewhere at the site of use.
    c. Capsule suspension products. The semiochemical is formulated as a microencapsulation.
    d. Granular products (non-WDG). The semiochemical is formulated in a granular form.

Any uses of semiochemicals not mentioned above should be evaluated on a case-by-case basis with the possibility of extending the list of types of application techniques/formulated products. Dispenser units as described under 1b, should be considered as the packaging containing a formulated product. All other current examples above are considered part of the formulated product.

<u>Natural exposure levels in relation to applied levels</u>
For the purposes of modifying pest behaviour, releases of semiochemicals are unlikely to exceed natural emissions of high density target populations and are dependent on olfactory and other receptor systems that are tuned to natural emission rates.

The following approach is recommended to estimate the levels of exposure that might occur naturally in the environment from a high density population of emitting organisms, independent from the use as pesticides (= natural exposure level). This natural exposure can be compared with the exposure resulting from the intended use of the pesticide products. This approach applies when the exposureroute is by the vapour phase only (retrievable dispensers and dosable matrix). When oral or contact exposure to pesticide product is possible e.g. to sprayed droplets and granules, then a risk assessment in relation to these routes of exposure should be considered.

When use of the product results in similar exposure (within one order of magnitude by the same route) to the natural exposure level of the semiochemical(s), no further information is needed except identity, characterization and analytical methods.

To estimate the natural exposure level, follow Step I. This method estimates natural exposure levels a semiochemical from available experimental data. The realistic reference value obtained can then be compared with the use rate of the product.

Step I: *Method to estimate the release of semiochemicals from a high population of the source organism (natural exposure level).*

In-field measurements of concentration in the air compartment or total release rate of semiochemicals (e.g. due to severe outbreaks of the pest) are usually not available. These values may however be estimated using available data on the number of sources of release ofa semiochemical in a given area, and release rates from each source, using this equation.

Equation 1: Formula for calculation of estimated value

PRR = RIO × NRO
Where,
PRR (Population Release Rate) is the release rate of the semiochemical from a justified high population of the source organism in nanograms per hectare and hour (ng/ha/h).
RIO (Release of an individual organism) is the release rate of the semiochemical by an individual organism in one hour (ng/h).
NRO (Number of Releasing Organisms) is the number of releasing organisms per hectare or similar unit.

Quantification of releasing organisms can be done by different means of estimating the population density e.g. monitoring traps and damage assessments.

Step II*: Comparison between natural exposure level and related exposure from the pesticide product.*

The release rate resulting from the product should be calculated using the same units and in an analogous way as in equation 1 in Step I.

Where the exposure (by the same route) caused by the use of the product is not lower, similar or comparable to natural exposure levels (PRR) of the semiochemical(s), Step III should be used to calculate exposure levels. It is important that exposure levels from the pesticide product and PRR are expressed in the same units.

Step III*: Mathematical modelling to predict the final concentrations derived from the application of semiochemical based pesticide products.*

The fixed steady one-cell model (or fixed box model) can be used to predict the concentration of semiochemicals in the air compartment associated with a treated area. This model is commonly used to obtain estimations of pollution concentration related to diffuse emissions, scattered along a given surface, as in case of a city or a field. This model has been designed for outdoor applications. It may be used with refined parameters for other situations.

The data requirements to be followed for semiochemicals are similar to those of chemical pesticides, with the adaptations recommended below. As mentioned above, no separate list of data requirements is provided in this guidance.

4.2.2 Intended use

- No adaptations are required.

4.2.3 Identity, characterization, physical and chemical properties and analytical methods

Technical material and product

Semiochemical based products can be a single active substance or mixtures of two or more active substances. The specificity of semiochemicals to elicit an effect in the target organisms means that the ratio of the active substances in any mixtures must be precisely controlled.

Generally, the following information for semiochemicals is needed in order to make regulatory decisions:

- *Identity*: as the active substances are essentially similar to conventional chemical pesticides no semiochemical specific provisions are required and the provisions in Guidelines on data requirements for the registration of chemical pesticides can be applied but with some deviations as indicated below:
  - For data requirements related to additives and significant manufacturing impurities: when impurities in SCLPs are themselves also SCLPs, the practice should be to sum up these individual SCLP impurities and specify them as a single impurity.
  - Where a semiochemical is constituted by isomers, the ratio of isomers in the TGAI needs to be specified. It should be noted that the specification defined does not need tobe the same as in the natural semiochemical as natural ratios can vary.
- *Manufacturing and production*: as very small quantities of active substances are required to be used in the end-use product, production can be infrequent and/or active substances can be stored for long periods of time before being formulated. As such, there can often be few production batches prepared and sometimes only one batch may be available. In general, semiochemicals are synthesized, nature-identical substances and data requirements can follow those for chemical pesticides.
- *Physical and chemical characteristics*: these should be addressed as far as needed for specific purposes following chemical pesticide guidelines but with some deviations as indicated below:
  - Detailed information about the formulated product should be provided and the dispensers should be fully described. Some dispensers may be considered part of the product (application techniques 1a, 2b, c, d, and e);for these products, changes related to the dispenser and not impacting the release rate per unit per hour should be considered as non-significant formulation changes. Applicants should justify with information why they consider such a change as non- significant.
  - The biology of the target organism(s), including information on the nature and specificity of the communication with the target organism and information on possible effects or their absence on non-target organisms, should be fully described and used to justify the risk assessment strategy. The mode of action of a semiochemical product should be explained in terms of its function in modifying the behaviour of the target organism.
  - Details on the product, the method of application and factors affecting the way the product should be used (e.g. weather, landscape, adjacent fields, building structures) should be fully described. This description should also include the numbers of dispensers per unit area, how this relates to the release rateper unit area per hour, and

how often the dispensers need replacing during the season. In addition, a rationale for their placement within the site, as related to the factors described above, should also be provided.

- The application rate per treatment for retrievable dispensers (application techniques 1a & 1b), and dosable matrix dispensers (application technique 2b) should be expressed as a 24-hour average active substance release rate per unit area per hour (for example ng/ha/h). The total time the dispensers will be deployed during the season should be described as the duration of the treatment and interval at which individual dispensers may require changing.
- For other non-retrievable application techniques (application techniques 2a, 2c and 2d), the application rate should be defined both as active substance ng/ha/h and g/ha combined with the number of applications per season. Where there is more than one application, the interval between treatments must be provided. In terms of assessment, the focus should be on the release rate per ha per hour: assessors should be aware that the same release rate per ha per hour may be achieved by different combinations of number of dispensers per ha and/or release rate per dispenser.
- The total time the dispensers will be deployed during the season should be described.

- *Composition/specification*: in general, five representative batches from recent and current industrial scale production of the active substance should be provided and analysed for content of pure active substance, impurities, additives and each further component other than additives, as appropriate. For semiochemicals, production can be insufficient to allow five batches within a reasonable timeframe. At the time of submission, it is recommended that applicants provide data for as many batches as possible, including laboratory and pilot production.
- *Analytical methods:* in general, semiochemicals are synthesized, nature-identical substances and data requirements can follow those for chemical pesticides. However, use should be made of the appropriate methods for volatile compounds.
- *Technical equivalence*: in general, semiochemicals are synthesized, nature-identical substances and data requirements can follow those for chemical pesticides. However, use should be made of the appropriate methods for volatile compounds.

4.2.4 Toxicity

Toxicity of technical material and/or formulated product

In general, the following information is needed:

- Information is needed on the specific properties of semiochemicals and the way they are used as pesticide products, so non-testing strategies can be considered to provide sufficient information to perform risk assessments.

- When the exposure route to semiochemicals is by the vapour phase only, e.g. when retrievable dispensers (application techniques 1a and 1b), non-retrievable dispensers (application techniques 2a), or dosable matrix (application techniques 2b) are used, and where the exposure caused by the use of the product is similar (within one order of magnitude) to natural exposure levels of the semiochemical (or a group of related semiochemicals), no further information is required.

- When the above conditions are not fulfilled, hazard identification and an exposure assessment should be provided. When oral or contact exposure might occur, information should be provided to allowfor a risk assessment based on these routes of exposure. At a

minimum, acute toxicity testing would be required.

Residues

For semiochemicals, residue data may not be required if it has been determined that quantifiable residues on the consumable commodity are unlikely to occur or that residuelevels are unlikely to exceed natural exposure levels during outbreaks of the pest. This can be demonstrated by a scientific rationale: detailed information about the formulated product and the dispensers should be made in sufficient detail to understand the proposed release method and rate.

If it is not possible to confirm lack of exposure, then residue testing may be required following the conventional chemical guidance.

4.2.5 Environment

In general, the following information is needed:

- Detailed information about the formulated product and the dispensers in sufficient detail to understand the proposed release method and rate. Exposure levels in soil, groundwater, surface water, sediment and air should be considered but depending on the application technique all compartments may not be exposed: information should be provided to detail the nature of the environmental exposure. It may be possible to use data derived from uses such as biocidal use, medical and veterinary use, cosmetic use, food and food additives to justify acceptable exposure.

- Information on the specific properties of semiochemicals and the way they are used as pesticide products means non-testing strategies can be used to provide sufficient information to perform risk assessments in the environment. The nature of the compound and its behaviour can be taken into account. For example, for highly volatile compounds such as SCLPs, a calculation based on the substance's volatility may be used to replace the need for certain studies/requirements, e.g. by providing estimates ofthe rapidity and likely extent of volatilization losses and gains from / to soil and natural surface water systems by re-deposition.

- Information to confirm when the release in the environment is by the vapour phase only and where the release caused by the use of the product is similar to natural release rates of the semiochemical (or a group of related semiochemicals when justified) to justify that no further information is needed.

When these conditions are not fulfilled, an exposure assessment should be provided. When release into the environment is via other routes than the vapour phase e.g. by sprayed droplets (including off-target spray drift), treated seeds and granules, then an exposure assessment should be provided. When exposure calculations are necessary, for vapour phase exposure see step II above; for other exposure routes the standard approaches should be followed.

4.2.6 Ecotoxicology

In general, the following information is need:

- Detailed information on the activity, the mode of action and the exposure route of the semiochemical active substance in order to focus on non-target organisms expected to be the most at risk such as arthropods related to the target species, and to avoid animal testing when unnecessary. Due to the diversity and complexity of semiochemical active substances, the non-target organisms potentially affected vary substantially and therefore a general testing strategy cannot be provided in this guidance. The applicant should propose a relevant testing strategy in line with the proposed use(s) and the relevant exposure situations. Available ecotoxicological information, including studies and publications, should be analysed and considered.

- When the exposure of non-targets is by the vapour phase only and where the release caused by the use of the product is similar to natural release rates of the semiochemical (or a group of related semiochemicals when justified), no further information is needed.

- When these conditions are not fulfilled, an exposure assessment should be provided. When release into the environment is via other routes than the vapour phase e.g. by sprayed droplets (including off-target spray drift) and granules, then an exposure assessment should be provided.

- The application of this guidance to specific cases will depend on the nature of the semiochemical active substance, its intended uses and resulting exposure levels in water, sediment and soil or on animals or in food items of non-target species. It may be possible to use data derived from dossiers provided for other uses such as biocidal use, medical and veterinary use, cosmetic use, food and feed additives. Good quality assessments and threshold values from such other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed and any dataaccess issues have been addressed by the applicant.

4.2.7 Efficacy

In general, data from good quality and representative field trials are needed to ensure that there is a benefit for users when the products are used according to label instructions.

Information on the efficacy of the product should be provided to confirm that the label claims are justified. However, efficacy field trials for semiochemicals are complex and may be difficult to replicate on a large scale. Therefore it is essential to provide as much information on the biology of the target and the mode of action of the semiochemical where possible.

Information on the mode of action, in combination with the recommended application technique, will determine the appropriate trial design (e.g. plot size, timing and placement of dispensers). It is useful to provide as much preliminary and small scale studies as possible to reduce the number of large-scale field trials. Where feasible, some data from large-scale field trials should be provided.

It should be recognized that semiochemical pesticide products may provide full control, partial control or contribute to control. Often the measure of benefit isnot in lethal dose to the target pests, but in reduction of effects to the host species. They may also have more variable performance than would be expected for a conventional pesticide product. The effective dose can be reduced with continual usage of the semiochemical pesticide product, and therefore establishing a minimum effective dose is inappropriate. In most cases, there is no linear dose–response relationship. However, a rationale for the chosen dose should still be provided, and this may include preliminary, laboratory studies examining emission rates of target pests, effects on biology etc. Any reduced performance should not in itself be grounds for refusal of authorization.

4.3 Evaluation of the dossier

4.3.1 Introduction

This section provides background on the testing of semiochemicals, outlines factors to consider, and highlights areas that need particular attention in the evaluation of the registration dossier. As for microbials and botanicals, the data and information submitted by registrants can be from good quality literature, in-house studies, or GLP studies for the species.

Semiochemicals by their nature or use are different to conventional chemical pesticides, so some testing methods will need adaptation. Guidance documents produced by the OECD (OECD, 2002), the EU (EC SANTE, 2016) and the US EPA (US EPA, 2017) provide suitable approaches and protocols, and applicants may have used them.

The specific properties of semiochemicals and the way they are used as pesticide products means non-testing strategies may provide sufficient information to perform risk assessments.

Information on the biology of the target organism(s) and information on the specificity of the communication between organisms and resulting lack of effects on non-target organisms is key information for the assessment of semiochemicals. Information to demonstrate this may have been gathered from efficacy trials or fundamental investigations on emitting and receiving species.

When use of the product results in similar exposure (within one order of magnitude by the same route) to the natural exposure level of the semiochemical (or a group of related semiochemicals, when justified), the risk characterization can be concluded. No further information is needed with the exception of identity, characterization and analytical methods.

Intended use

- No adaptations are required.

4.3.2 Identity, characterization, physical, chemical, biological properties and analytical methods

- *Identity*: there should be a good description of the chemical composition of the semiochemical(s), following chemical pesticide guidelines except for impurities which for SCLP they can be grouped and considered as one impurity.
- *Manufacturing and production*: as there can often be few production batches prepared and

sometimes only one batch may be available, this should be accepted by the evaluators.

- *Physical and chemical properties:* the authority will assess the following changes to the data requirements specific to semiochemicals:
  - There is sufficient information about the target organism and the effect of the semiochemical, the formulated product and the dispensers and their intended usepattern to allow the intended use and therefore relevant areas for the risk assessment tobe well understood. For example, the focus should be on the release rate per ha per hour: assessors should be aware that the same release rate per ha per hour may be achieved by different combinations of number of dispensers per ha and/or release rate per dispenser.
- *Composition/specification*: evaluation of the laboratory and pilot production and representative batches from recent and current industrial scale production of the active substance for content of pure active substance, impurities, additives and each further component other than additives, as appropriate. The evaluators should accept that for semiochemicals it may not be possible for there to be data from five batches available.
- *Analytical methods:* evaluation to confirm that the applicant has used the appropriate methods especially for volatiles.
- *Technical equivalence:* evaluation to confirm that the applicant has used the appropriate methods especially for volatiles.

4.3.3 Toxicity

When evaluating the data, evaluators should pay attention to aspects that are specific to semiochemicals: in particular, when the exposure route to semiochemicals is by the vapour phase only and where the exposure caused by the use of the pesticide product is similar (within one order of magnitude) to natural exposure levels of the semiochemical, no further information is required.

When the above conditions are not fulfilled, hazard identification and an exposure assessment should have been provided and assessed as for chemical pesticides, with particular consideration of the methodology that it was adapted for volatile substances.

Residues

For semiochemicals, residue data are unlikely to be required if it has been determined that quantifiable residues on the consumable commodity are unlikely to occur or that residuelevels are unlikely to exceed natural exposure levels during outbreaks of the pest. A scientific rationale should have been presented and contain sufficient detail from good quality sources to support this approach.

4.3.4 Environment

When the release in the environment of the semiochemical is by the vapour phase only and where the release caused by the use of the product is similar to natural release rates of the semiochemical (or a group of related semiochemicals when justified), no further information is needed. The evaluator should accept a scientific rationale for this approach.

Where the use levels are significantly above natural background levels or the release is not by the vapour phase only, exposure levels in soil, groundwater, surface water, sediment and air should be considered but, depending on the application technique, all compartments may not

be exposed: the information provided should allow assessment of the nature of the environmental exposure. It may be possible to accept data derived from uses such as biocidal use, medical and veterinary use, cosmetic use, food and food additives to justify acceptable exposure.

4.3.5 Ecotoxicology

When the exposure of non-targets is by the vapour phase only and where the release caused by the use of the product is similar to natural release rates of the semiochemical (or a group of related semiochemicals when justified), the evaluator shouldaccept that no further information is needed.

Where the use levels are significantly above natural background levels or the release in not by the vapour phase only, exposure levels for non-target organisms in the relevant compartment should be considered but, depending on the application technique, all compartments may not be exposed. The information provided should allow assessment of the nature of the environmental exposure. It may be possible to accept data derived from uses such as biocidal use, medical and veterinary use, cosmetics use, food and food additives to justify acceptable exposure.

4.3.6 Efficacy

The assessor needs sufficient information on the efficacy of the product to confirm that the label claims are justified. However, efficacy field trials for semiochemicals are complex and may be difficult to replicate on a large scale. Therefore it is essential to accept information on the biology of the target and the mode of action of the semiochemical where possible. Assessors should make use of preliminary and small-scale studies to reduce the number of large-scale field trials needed but, if feasible, some data from large-scale field trials should be available.

It should be recognized that semiochemical pesticide products may provide full control, partial control or contribute to control. Often, the measure of benefit isnot in lethal dose to the pest, but in reduction of effects to the host species.They may also have more variable performance than would be expected for a conventional chemical pesticide product. The effective dose can be reduced with continual usage of the semiochemical pesticide product and therefore establishing a minimum effective dose is inappropriate. In most cases, there is no linear dose–response relationship. However, a rationale for the chosen dose should still have been provided, and this may include preliminary, laboratory studies examining emission rates of target pests, effects on biology, etc. Any reduced performance should not in itself be grounds for refusal of authorization.

Annex 1: Data requirements for registration of microbials

This Annex is composed of two parts:

A. Microbial pesticides: recommended data requirements for registration of the active substance (MPCA)

B. Microbial pesticides: recommended data requirements for registration of the formulated products (MPCP)

Each part lists several tables on the various study areas.

Note: the numbering of the data points in the tables below follows a logical order. However, in a very few instances, it may appear that the numbers are out of sequence. In view of international harmonization, the data point numbers are in line with the format of the OECD Guidance Documents for Pesticide Registration (OECD, 2006).

A. Microbial pesticides: recommended data requirements for registration of the active substance (MPCA)

The tests listed in this Annex1.A (in the various Tables A1 to A7 below) are generally conducted with the MPCA itself but, depending on the type of MPCA, its production method, stability and/or formulation, testing may be done only on the Technical Grade Active Ingredient (TGAI) or MPCP, as appropriate. A reasoned case may be made for the non-submission of some studies or data and addressed instead by provision of scientific information from good quality sources.

If the MPCA contains relevant (toxic) secondary compounds (metabolites), then the data requirements for chemical pesticides may need to also be fulfilled.

Table A1. Identity, composition, physical and chemical properties

Codes used: CR = conditionally required, R = required, NR = not required

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
1	**Identity of Microbial Pest ControlActive (MCPA)**			
1.1	**Applicant (name, address, contact,telephone and telefax numbers)**	R	NR	
1.2	**Manufacturer(s) (name, address, contact, telephone and telefax numbers)**	R	NR	
1.3	**Scientific information**			
1.3.1	Scientific name of microorganism to species level or a level sufficient to show taxonomic relation to known microorganisms, especially pathogens	R	TGAI	
1.3.2	Accession no. of sample in a recognizedculture collection	R	TGAI	
1.3.3	Test procedures and criteria, using best available technology, to characterize thestrain or serotype	R	TGAI	
1.3.4	For mutant or genetically modified strains,indicate all known differences between the modified microorganism and the parentwild strain(s)	R	TGAI	
1.3.5	Include any trade names, common names,developmental code names	R	TGAI/MPCA	
1.3.6	Indigenous or non-indigenous at thespecies level to the intended area of application.	R	TGAI	
1.4	**Composition of Technical Grade ofMPCA/Active Substance**			

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
1.4.1	Concentration of microorganism (and relevant secondary compound (metabolite), if appropriate) in terms of g/kg or g/L (alsoin % w/w) and CFU or biopotency units	R	MPCA	
1.4.2	Composition of microbial material used formanufacture of end use products in terms of g/kg or g/L for each active ingredient including microbial and non-microbialimpurities	R	MPCA	
1.4.3	Methods of production and quality criteria for the production and storage of the activemicroorganism. Including quality control measures and information on human/mammalian pathogens	R	MPCA	
1.4.4	Quality control data (measures of quality criteria) from 3–5 production batches,including storage stability data.	CR	MPCA	
1.4.5	The formation, presence and/or impact ofunintentional ingredients (theoretical discussion)	R	MPCA	
1.4.6	Physical and chemical properties, if MPCAis produced as a manufacturing product that is stored prior to formulation of end- use products: physical state; density; viscosity or surface tension; explosivity, corrosive character, oxidizing properties;technical characteristics as appropriate	R	MPCA	
1.4.7	International regulatory status of microorganism	CR	MPCA	
1.4.8	Sample of MPCA and analytical standard of secondary compound (metabolite) (ifrequested)	CR	MPCA	

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
2	**Biological Properties of the MicrobialPest Control Agent**			
2.1	**Origin of the isolate; method of isolation; preservation and maintenanceof 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 morphological, physiological, pesticidal or resistance characteristics of the MPCA which differ from classicaldescription of the species**	R	TGAI	
2.2	**Natural occurrence of the microorganism including geographic distribution, hosts, habitat, ecologicalniche, level of natural occurrence**	R	TGAI	
2.3	**Information on target organism(s),including mode of action**	R	TGAI/ MPCA	
2.4	**Available information on host specificity; possible effects on speciesclosely related to the target pest**	R	TGAI/MPCA	
2.5	**Life cycle of the microorganism including various forms that may occur**	R	TGAI/MPCA	
2.6	**Among closely related species provideinformation on:**			
2.6.1	Potential of the microorganism to producesecondary compounds (metabolites) that are of concern for human health, animal health and/or theenvironment	R	TGAI	
2.6.2	Information regarding closely related species	R	TGAI	

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
2.6.3	Physiological properties, especially effect of environmental parameters on growth	R	TGAI/ MPCA	
2.6.4	Description of any plasmids or other extra chromosomal genetic elements involved inpesticidal activity, pathogenicity, toxicity, etc.	R	TGAI	
2.6.5	Genetic stability (mutation rate of traitsrelated to the mode of action)	R	TGAI	
2.6.6	Detailed discussion of relationship ofmicroorganism to any known human and animal dermatophyte	R	TGAI	
2.6.7	Resistance/sensitivity to antibiotics/anti-microbial agents used in human orveterinary medicine	R	TGAI/MPCA	
3	**Further information on the Microbial Pest Control Agent (Function, Mode ofAction, Handling)**			
3.1	**Function, e.g. fungicide**	R	MPCA	
3.2	**Placeholder**			
3.3	**Field of use, e.g. forestry**	R	MPCA	
3.4	**Information on target targetorganism(s)**	R	MPCA	
3.4.1	Details of existing and intended uses	R	MPCA	
3.4.2	Details of harmful organisms against which protection is afforded	R	MPCA	
3.4.3	Effects achieved	R	MPCA	
3.5	**Mode of action**			
3.5.1	Information on mode of action	R	MPCA	
3.5.2	Information on secondary compounds (metabolites), any toxins and/or degradation products			

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
3.6	Information on the possible occurrenceof the development of resistance or cross-resistance	R	MPCA	
3.7	A material safety data sheet for theMicrobial Active Substance	R	MPCA	
3.8.1.2	Detailed instructions for safe disposal	R	MPCA	
3.9	Procedures for the decontamination ofwater in case of an accident	R	MPCA	
3.10	Other/special studies	CR	MPCA	
3.11	Measures to render microorganismharmless, in case of an accident	R	MPCA	

Table A2. Analytical methods

Suitable methodology for working with MPCA may not be available or require specialist know-how; therefore, validation of methods may have to be done in-house. In this case, the in-house methodology needs to be made available and the second laboratory must be able to reproduce the validation data from the first laboratory to within acceptable limits.

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct applicationto animals**	**Test substance**	**Testnote**
4	**Analytical methods and validation**			
4.1.5	Method to preserve and maintain the masterseed stock; criteria for an acceptable level of consistency and integrity of seed stock	CR	TGAI/MPCA	
4.2.8	Production process for Technical Grade	CR	TGAI	
4.3	**Quality control and post-registrationmonitoring methods**	CR	MPCA	
4.4.	**Storage stability test, data and determination of shelf life, if MPCA isstored**	CR	MPCA	
4.5	**Post-registration monitoring methods to determine and quantify residues of viable or non-viable microorganism and secondary compounds (metabolites)(especially toxins)**			
4.5.1	Food (where relevant)	NR	MPCA	
4.5.2	Feed (where relevant)	NR	MPCA	
4.5.3	Animal tissue (where relevant)	NR	MPCA	
4.5.4	Soil (where relevant)	NR	MPCA	
4.5.5	Water (where relevant)	NR	MPCA	
4.5.6	Air (where relevant)	NR	MPCA	
4.5.7	Analytical methods for amount or activity of proteinaceous products (where relevant)	CR	MPCA	

Table A3. Toxicology

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct application to animals**	**Test substance**	**Testnote**
5	**Toxicological and Exposure Data**			
5.1	**Summary: potential of microbial pest control agent to be hazardous with consideration of its pathogenic potential, its ability to infect and patternof clearance, and its toxicological effects**	R	MPCA	
5.2	**Occupational health surveillance reporton workers during production and testing of MPCA**	R	MPCA	
5.3.	**Basic studies**			
5.3.9	Acute oral infectivity, toxicity and pathogenicity	R	MPCA	
5.4	**Acute intratracheal/inhalation infectivity, toxicity and pathogenicity**	R	MPCA	
5.5	**Acute intravenous/intraperitonealinfectivity**	CR	MPCA	
5.6	**Cell culture study, for viruses and viroids or specific bacteria and protozoawith intracellular replication**	CR	MPCA	
5.7	**Genotoxic potential, especially for fungiand actinomycetes**	CR	MPCA	
5.8	**Toxicity studies on secondary compounds (metabolites) (especiallytoxins)**	CR	MPCA	
5.8.1	Published reports of adverse effects, especially clinical cases and follow-up studies	R	MPCA	
5.10	**Other/special studies**	CR	MPCA	
5.11	**Summary of mammalian toxicity andoverall evaluation**	R	MPCA	

Table A4. Metabolism and residues

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct application to animals**	**Test substance**	**Testnote**
6	**Metabolism and residues data**			
6.1.1	Rationale for waiver of residue data basedon information showing that MPCA is not hazardous to mammals	R	MPCA	
6.1.2	Rationale for waiver based on a substantiated estimation that MPCA isunlikely to occur on treated food/feed stuffs in concentrations considerably higher than under natural conditions.	NR	MPCA	
6.1.3	Summary of residue behaviour and overall evaluation	R	MPCA	

Table A5. Environmental fate

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct application to animals**	**Test substance**	**Testnote**
7	**Fate and behaviour in the environment**			
7.1	**Sufficient information on the origin, properties, survival and residual secondary compounds (metabolites) of the microorganism to assess its fate andbehaviour in the environment**			
7.1.1	Persistence and mobility in soil	NR	MPCA	
7.1.2	In water	NR	MPCA	
7.1.3	In air	NR	MPCA	
7.13	**Other special studies**	CR	MPCA	

Table A6. Ecotoxicology

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct application to animals**	**Test substance**	**Testnote**
8	Ecotoxicological studies on the MPCA(effects on non-targets)			
8.1	Avian toxicity	NR	MPCA	
8.2	Fish toxicity	NR	MPCA	
8.3	Toxicity to aquatic species other thanfish and aquatic species field testing	NR	MPCA	
8.4	Effects on algal growth and growth rate	NR	MPCA	
8.5	Effects on aquatic plants	NR	MPCA	
8.6	Effects on terrestrial plants	NR	MPCA	
8.7	Effects on bees	NR	MPCA	
8.8	Effects on non-target terrestrialarthropods	NR	MPCA	
8.9	Effects on earthworms	NR	MPCA	
8.10	Effects on soil microorganisms	NR	MPCA	
8.11	Other/special studies	CR	MPCA	

Table A7. Summary of information for the MPCA

		Use pattern		
Data point	**Information, test or study on the ActiveSubstance (technical)**	**Direct application to animals**	**Test substance**	**Testnote**
9	**Summary and evaluations of environmental impact: summarize all data relevant to environmental impactand assess environmental risk**	NR	MPCA	

B. Microbial pesticides: recommended data requirements for registration of the formulated products (MPCP)

Table B1. Identity and physical and chemical properties

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
1	**Identity of the Microbial Pest ControlProduct**			
1.1	**Applicant (name, address, contact,telephone and telefax numbers)**	R	MPCP	
1.2.1	Manufacturer(s) of the preparation and producer of the microbial pest control agent	R	MPCP	
1.2.2	Producer of the MPCA	R	MPCP	
1.3	**Trade name or proposed trade name andmanufacturers code number(s), for the preparation and similar preparations (differences to be specified)**	R	MPCP	
1.4	**Placeholder**			
1.5	**Physical state of MPCP**	R	MPCP	
1.6	**Function (herbicide, insecticide, etc.)**	R	MPCP	
1.6.1	Biological function category	R	MPCP	
1.7	**Other/special studies**			
1.7.1	Concentration of MPCA in MPCP, measured in terms of g/kg or g/L of the MPCP and in CFU or biopotency: indicate scientific name and strain designation, anddevelopment stage (e.g. spore)	R	MPCP	

1.7.2	Composition in terms of g/kg or g/L and % w/w of each ingredient in MPCP, including technical grade, additives, microbial and non-microbial impurities	R	MPCP	
1.7.3	Quality criteria for the production and storage of the MPCP, including range of content of MPCA, presence of human or non-target animal pathogens, maximum acceptable level for microbial impurities andknown mammalian toxins	R	MPCP	
1.7.4	Quality control data (measures of quality criteria) from 3–5 production batches, including product stored for duration of shelflife if it is metabolically active	R	MPCP	
1.7.5	The formation, presence and/or impact ofunintentional ingredients (theoretical discussion)	R	MPCP	
2	**Physical, chemical and technicalproperties of the MPCP**			
2.1	**Appearance**	R	MPCP	
2.2	**Storage stability and shelf-life**	R	MPCP	
2.3	**Explosivity, oxidizing properties, flash point, flammability, spontaneous ignition, acidity, alkalinity, pH, viscosity, surfacetension – as appropriate**	CR	MPCP	
2.4	**Technical characteristics of the MPCP –as appropriate**			
2.4.1	Wettability			
2.4.2	Persistent foaming	CR	MPCP	
2.4.3	Suspensibility and suspension stability	CR	MPCP	
2.4.4	Dilution stability	CR	MPCP	
2.4.5	Sieve test	CR	MPCP	
2.4.6	Particle size distribution	CR	MPCP	
2.4.7	Emulsion characteristics	CR	MPCP	
2.4.8	Flowability, pourability and dustability	CR	MPCP	

2.4.9	Density	CR	MPCP	
2.7	**Other/special studies**	CR	MPCP	
3	**Data on application**			
3.1	**Pest to be controlled and available information on mode of action**	R	MPCP	
3.2	**Available information on the developmentof resistance in target pest and appropriate mitigation strategy**	R	MPCP	
3.3	**Application rate in terms of mass/vol of MPCP per unit area/volume (e.g. kg/ha).Content of microorganism in material used (diluted spray, bait, treated seed)**	R	MPCP	
3.4	**Application rate in terms of units of microorganism per unit area/volume**	R	MPCP	
3.5	**Method of application (incl. type ofequipment and volume of diluent)**	R	MPCP	
3.6	**Number, timing and conditions of applications, related to: host/pest phenology, duration of protection, application of other pesticides, pre-harvest interval**	R	MPCP	
3.7	**Precautions to avoid phytotoxic/ phytopathogenic effects on protected hosts**	R	MPCP	
4	**Further information on the product**	R	MPCP	
4.1	**Packaging: description**			
4.2	**Specifications of packaging and measuresof its suitability**	R	MPCP	
4.3	**Label instructions regarding cleaningequipment and protective clothing**	R	MPCP	

4.4	**Procedures to clean equipment and protective clothing; measures of their effectiveness**	R	MPCP	
4.5	**Necessary waiting periods for re-entry;recommended protective measures to reduce occupational exposure**	R	MPCP	
4.6	**Label instructions regarding: safehandling and storage**	R	MPCP	
4.7	**Recommendations regarding: handling,storage, transport, fire: specify risks, specify procedures to minimize hazardsand the generation of waste**	R	MPCP	
4.8	**Label instructions regarding: cleanup ofspills**	R	MPCP	
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**	R	MPCP	
4.10	**Procedures for destruction/disposal ofMPCP and its packaging**	R	MPCP	

Table B2. Methods of analysis

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
5	**Methods of analysis**			
5.1	**Quality control and post-registrationmonitoring methods**	CR	MPCP	
5.2	**Storage stability test and determination ofshelf life (methods of analysis)**	CR	MPCP	
5.3	**Production process for MPCP**	CR	MPCP	

Table B3. Efficacy data

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
6	**Efficacy data**	R	MPCP	
6.1	**Performance assessment: laboratory orgrowth chamber**	R	MPCP	
6.2	**Performance assessment: field studies**	R	MPCP	
6.3	**Toxic or pathogenic effects on the host which is protected**	R	MPCP	
6.4	**Compatibility with products in authorizedtank mixes and with other products that are applied under expected conditions of use. Recommended interval between application of MPCP and chemicalpesticide, to avoid loss of efficacy**	CR	MPCP	
6.5	**Contribution to risk reduction**	R	MPCP	

Table B4. Toxicology

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
7	**Toxicological studies and exposure dataand information for MPCP**			
7.1	**Acute toxicity**			
7.1.1	Acute oral toxicity	CR	MPCP	
7.1.2	Acute percutaneous (dermal) toxicity	CR	MPCP	
7.1.3	Acute inhalation toxicity to rats	CR	MPCP	
7.1.4	Skin irritation	R	MPCP	
7.1.5	Eye irritation	R	MPCP	
7.1.6	Skin sensitization	NR	MPCP	
7.2	**Operator, bystander and worker exposure – monitoring**	NR	MPCP	
7.3	**Operator and bystander exposure –hypersensitivity**	NR	MPCP	
7.4	**Safety data sheet for each additive**	R	MPCP	
7.5	**Supplementary information**	CR	MPCP	
7.6	**Summary and evaluation of all healtheffects**	R	MPCP	

Table B5. Metabolism and residues

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
8	**Metabolism and residues data: rationale towaive residue studies**	CR	MPCP	

Table B6. Environmental fate

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
9	**Fate and behaviour in the environment**			
9.1	**Sufficient information on the origin, properties, survival and residual secondary compounds (metabolites) of the microorganism to assess its fate andbehaviour in the environment**			
9.1.1	Persistence and mobility in soil	CR	MPCP	
9.1.2	In water	CR	MPCP	
9.1.3	In air	CR	MPCP	
9.2	**Other special studies**	CR	MPCP	

Table B7. Ecotoxicology

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
10	**Rationale to waive additional testing, basedon adequacy of information provided for MPCA, to permit an assessment of the impact of the MPCP on non-target organisms**			
10.1	**Effects on birds**	CR	MPCP	
10.2	**Effects on aquatic organisms**	CR	MPCP	
10.3	**Effects on bees**	CR	MPCP	
10.4	**Effects on terrestrial arthropods other thanbees**	CR	MPCP	
10.5	**Effects on earthworms**	NR	MPCP	
10.6	**Effects on soil microorganisms**	NR	MPCP	
10.7	**Additional studies**	CR	MPCP	

Table B8. Summary

		Use pattern		
Data point	**Information, test or study of the product**	**Direct applicationto animals**	**Test substance**	**Testnote**
11	**Summary and evaluation of environmentalimpact: summarize all data relevant to environmental impact and assess environmental risk**	R	MPCP	

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Additional information of relevance to the registration of pesticides

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The FAO Pesticide Registration Toolkit is a decision support system for pesticide registrars in lower and middle-income countries. It assists registrars in the evaluation for authorization of pesticides and review of registered pesticides.

The Toolkit can best be considered as a web-based registration handbook intended for day-to-day use by pesticide registrars. It supports and facilitates informed decision-making by registrars, but is not an automated system that suggests decisions for registrars. Registrars can use the Toolkit to support several of their regular tasks.

With respect to **biological pesticides**, the Toolkit can be used as an aid to look for, among other information, "Data requirements and testing guidelines" as well as for "Assessment methods". Once these guidelines are published, its content will be reflected in the FAO Pesticide Registration Toolkit.