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ANNEXES 1 to 2

ANNEXES

to the

Commission Regulation (EU) .../...

amending Regulation (EU) No 283/2013 as regards the information to be submitted for active substances and the specific data requirements for micro-organisms

ANNEX I

‘Introduction

Information to be submitted, its generation and its presentation

A dossier shall be submitted in accordance with Part A if the active substance is:

(a) a chemical substance (including both semiochemicals and extracts from biological material), or

(b) a metabolite produced by a micro-organism where:

– the metabolite is purified from the micro-organism; or

– the metabolite is not purified from a producing micro-organism which is no longer capable of replication or of transferring genetic material.

A dossier shall be submitted in accordance with Part B if the active substance is:

(a) a micro-organism, either as a single strain or as a qualitatively defined combination of strains, or

(b) a micro-organism, either as a single strain or as a qualitatively defined combination of strains, and one or more metabolites produced by the micro-organism that are claimed to be part of the plant protection action (i.e. when the application of the metabolite(s) purified from the micro-organism would not cause the claimed plant protection action).

1 For the purposes of this Annex, the following definitions apply:

(1) **‘efficacy’** means a measure concerning the overall effect of the application of a plant protection product on the agricultural system in which it is used (i.e. which includes positive effects of treatment in performing the desired plant protection activity and negative effects such as development of resistance);

(2) **‘relevant impurity’** means a chemical impurity that is of concern for human health, animal health or the environment;

(3) **‘effectiveness’** means the capacity of the plant protection product to produce a positive effect regarding the desired plant protection activity;

(4) **‘toxicity’** means the degree of injury or damage in an organisms caused by a toxin or a toxic substance;

(5) **‘toxin’** means a (organic) substance that is produced in nature and is able to injure or damage a living organism.

The information submitted shall meet the requirements set out in points 1.1 to 1.14.

1.1. The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this Annex.

1.2. Any information including any known data on potentially harmful effects of the active substance, its metabolites and impurities on human and animal health or on their potential presence in groundwater shall be included.

1.3. Any information including any known data on potentially unacceptable effects of the active substance, its metabolites and impurities on the environment, plants and plant products shall be included.

1.4. The information shall include all relevant data from the scientific peer reviewed open literature on the active substance, relevant metabolites, where relevant, breakdown or reaction products and plant protection products containing the active substance and dealing with side-effects on human and animal health, the environment and non-target species. A summary of this data shall be provided.

1.5. The information shall include a full and unbiased report of the studies conducted as well as a full description of them. Such information shall not be required, where a justification is provided showing that:

(a) it is not necessary owing to the nature of the plant protection product or its proposed uses, or it is not scientifically necessary; or

(b) it is technically not possible to supply.

1.6. The simultaneous use of the active substance as a biocide or in veterinary medicine shall be reported. If the applicant for the active substance in the plant protection product is identical to the one responsible for the notification of the active substance as a biocide or as a veterinary medicine, a summary of all relevant data submitted for approval of the biocide or the veterinary medicine shall be submitted. Where relevant, that summary shall include toxicological reference values and MRL proposals, taking into account any possible cumulative exposure due to different uses of the same substance based on scientific methods accepted by the competent authorities of the Union, together with a summary of the residues and toxicology data and information on the use of the plant protection product. If the applicant for the active substance in the plant protection product is not identical to the one responsible for the notification of the active substance as a biocide or in veterinary medicine, a summary of all available data shall be submitted.

1.7. Where relevant, the information shall be generated using test methods, which are included in the list referred to in point 6.

In the absence of suitable internationally or nationally validated test guidelines, test protocol discussed with and accepted by the competent authorities of the Union shall be used. Any deviations from test guidelines shall be described and justified.

1.8. The information shall include a full description of the test methods used.

1.9. The information shall include a list of endpoints for the active substance, where relevant.

1.10. Where relevant, the information shall be generated in accordance with Directive 2010/63/EU of the European Parliament and of the Council[1].

1.11. The information on the active substance, taken together with the information concerning one or more plant protection products containing the active substance and together, if appropriate, with the information concerning safeners and synergists and other components of the plant protection product, shall be sufficient to:

(a) permit an assessment of the risks for humans, associated with handling and use of plant protection products containing the active substance;

(b) for chemical active substances: permit an assessment of the risks for human and animal health, arising from residues of the active substance and its relevant

[1] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

metabolites, impurities and, where relevant, breakdown and reaction products remaining in water, air, food and feed;

(c) for active substances that are micro-organisms: permit an assessment of the risks for human and animal health, arising from residues of the metabolites of concern in water, air, food and feed;

(d) for chemical active substances: predict the distribution, fate and behaviour in the environment of the active substance and metabolites, breakdown and reaction products where they are of toxicological, or environmental significance, as well as the time courses involved;

(e) permit an assessment of the impact on non-target species (flora and fauna), including the impact on their behaviour, which are likely to be exposed to the active substance, its relevant metabolites and, where relevant, breakdown and reaction products, where they are of toxicological, pathogenic or environmental significance. Impact can result from single, prolonged or repeated exposure and can be direct or indirect, reversible or irreversible;

(f) evaluate the impact on biodiversity and the ecosystem;

(g) identify non-target species and populations for which risks arise because of potential exposure;

(h) permit an evaluation of short and long-term risks for non-target species, populations, communities and processes;

(i) classify the chemical active substance as a hazard in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council[2];

(j) specify the pictograms, the signal words and relevant hazard and precautionary statements for the protection of human and animal health, non-target species and the environment, which are to be used for labelling;

(k) establish, where relevant, an acceptable daily intake (ADI) level for humans;

(l) establish, where relevant, acceptable operator exposure levels (AOEL);

(m) establish, where relevant, an acute reference dose (ARfD) for humans;

(n) identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of poisoning or infection in humans;

(o) for chemical active substances: establish the isomeric composition and the possible metabolic conversion of the isomers, where relevant;

(p) establish residues definitions appropriate for risk assessment, where relevant;

(q) establish residues definitions appropriate for monitoring and enforcement purposes, where relevant;

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

(r) permit a risk assessment of consumer exposure, including, where relevant, a cumulative risk assessment deriving from exposure to more than one active substance;

(s) permit an estimation of the exposure to operators, workers, residents and bystanders including, where relevant, the cumulative exposure to more than one active substance;

(t) establish, where relevant, maximum residue levels and concentration/dilution factors in accordance with Regulation (EC) No 396/2005 of the European Parliament and of the Council[3];

(u) permit an evaluation to be made as to the nature and extent of the risks for humans, animals (species normally fed and kept by humans or food producing animals) and of the risks for other non-target vertebrate species;

(v) identify measures necessary to mitigate the risks identified for human and animal health, the environment and/or non-target species;

(w) for chemical active substances: decide whether or not the active substance has to be considered as persistent organic pollutant (POP), persistent, bio accumulative and toxic (PBT) or very persistent and very bio accumulative (vPvB) in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;

(x) decide whether or not the active substance is to be approved;

(y) for chemical active substances: decide whether or not the active substance has to be considered as a candidate for substitution in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;

(z) decide whether or not the active substance has to be considered as a low-risk active substance in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;

(aa) specify conditions or restrictions to be associated with any approval.

1.12. Where relevant, tests shall be designed and data analysed using appropriate statistical methods. Details of the statistical analysis shall be reported transparently.

1.13. Exposure calculations shall refer to scientific methods accepted by the European Food Safety Authority, where available. Additional methods, when used, shall be justified.

1.14. For each section of this Annex, a summary of all data, information and evaluation made shall be submitted. This shall include a detailed and critical assessment in accordance with Article 4 of Regulation (EC) No 1107/2009.

2. The requirements set out in this Annex constitute the minimum set of data to be submitted. Member States may set out additional requirements at national level to address specific circumstances, specific exposure scenarios and specific patterns of use other than those taken into account for approval. The applicant shall pay careful attention to environmental, climatic and agronomic conditions when tests are set up

[3] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC (OJ L 70, 16.3.2005, p. 1).

subject to the approval by the Member State where the application has been submitted.

3. Good laboratory practice (GLP)

3.1. Tests and analyses shall be conducted in accordance with the principles laid down in Directive 2004/10/EC of the European Parliament and of the Council[4] where testing is done to obtain data on the properties or safety with respect to human or animal health or the environment.

3.2. By way of derogation from point 3.1:

(a) for active substances that are micro-organisms, tests and analyses done to obtain data on the properties and safety with respect to other aspects than human health may be conducted by official or officially recognised testing facilities or organisations which satisfy at least the requirements set out in points 3.2 and 3.3 of the Introduction of the Annex to Commission Regulation (EU) No 284/2013[5];

(b) for tests and analyses made to obtain data for minor crops required under points 6.3 and 6.5.2 of Part A:

– the field phase may have been conducted by official or officially recognised testing facilities or organisations which satisfy the requirements as laid down in points 3.2 and 3.3 of the Introduction of the Annex to Regulation (EU) No 284/2013;

– the analytical phase, if not realised in accordance with the principles of good laboratory practice ('GLP principles'), shall be conducted by laboratories accredited for the relevant method in accordance with the European standard EN ISO/IEC 17025 'General requirements for the competence of testing and calibration laboratories';

(c) studies conducted before the date of application of this Regulation, although not fully compliant with GLP principles or with current test methods, may be integrated into the assessment if carried out in accordance with scientifically validated test guidelines, thereby avoiding repeating animal tests, especially for carcinogenicity and repro-toxicity studies. This derogation from point 3.1 shall apply in particular to studies with vertebrate species.

4. Test material

4.1. A detailed description (specification) of the test material used shall be provided. Where tests are done using the active substance, the test material used shall comply with the specification that will be used in the manufacture of plant protection products to be authorised, except for radio-labelled chemicals or the purified chemical active substance.

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4 Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20.2.2004, p. 44).

5 Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (OJ L 93, 3.4.2013, p. 85).

4.2. Where studies are conducted using an active substance produced in the laboratory or in a pilot plant production system, the studies shall be repeated using the active substance as manufactured, unless the applicant shows that the test material used is essentially the same, for the purposes of toxicological, pathological, ecotoxicological, environmental and residue testing and assessment. In cases of uncertainty, bridging studies shall be submitted to serve as a basis for a decision as to the possible need for repetition of the studies.

4.3. Where studies are conducted using an active substance of different purity or which contains different impurities or different levels of impurities to the technical specification or where the active substance is a mixture of components, the significance of the differences shall be addressed either by data or scientific case. In cases of uncertainty, appropriate studies using the active substance as manufactured for commercial production shall be submitted to serve as a basis for a decision.

4.4. In the case of studies in which dosing extends over a certain period (for example, repeated dose studies), the same batch of active substance shall be used, if stability permits. Whenever a study implies the use of different doses, the relationship between dose and adverse effect shall be reported.

4.5. For chemical active substances, when tests are conducted using a purified chemical active substance (≥ 980 g/kg) of stated specification, the purity of such test material shall be as high as can be achieved using the best available technology and shall be reported. A justification shall be provided in cases where the degree of purity achieved is less than 980 g/kg. Such justification shall demonstrate that all technically feasible and reasonable possibilities for the production of the purified chemical active substance have been exhausted.

4.6. For chemical active substances, where radio-labelled test material of the chemical active substance is used, radio-labels shall be positioned at sites (one or more as necessary) to facilitate elucidation of metabolic and transformation pathways and to facilitate the investigation of the distribution of the active substance and of its metabolites, reaction and breakdown products.

5. Tests on vertebrate animals

5.1. Tests on vertebrate animals shall be undertaken only where no other validated methods are available. Alternative methods shall include in vitro methods, *in-silico* methods. Reduction and refinement methods for in vivo testing shall also be encouraged to keep the number of animals used in testing to a minimum.

5.2. The principles of replacement, reduction and refinement of the use of vertebrate animals shall be taken into account in the design of the test methods, in particular when appropriate validated methods become available to replace, reduce or refine animal testing.

5.3. Study designs shall be carefully considered from ethical point of view, taking into account the scope for reduction, refinement and replacement of animal tests. For example, by including one or more additional dose groups or time points for blood sampling in one study, it may be possible to avoid the need for another study.

6. For purposes of information and of harmonisation the list of test methods and guidance documents relevant to the implementation of this Regulation shall be published in the *Official Journal of the European Union*. That list shall be regularly updated.’

ANNEX II

‘PART B

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INTRODUCTION TO PART B

(i) This Introduction to Part B complements the Introduction to this Annex with points which are specific for active substances that are micro-organisms.

(ii) For the purpose of Part B, the following definitions apply:

(1) **'strain'** means a genetic variant of an organism in its taxonomic rank (species) that is made up of the descendants of a single isolation in pure culture and usually is made up of a succession of cultures ultimately derived from an initial single colony;

(2) **'non-viable micro-organism'** means a micro-organism that is not capable of replication or of actively transferring genetic material. However, it may still be able to transfer genetic material passively;

(3) **'colony-forming unit' ('CFU')** means a measurement unit used to estimate the number of bacterial or fungal cells in a sample, which have the ability to multiply under controlled growing conditions, with the consequence that one or more cells reproduce and multiply to form a single visible colony;

(4) **'International Unit' ('IU')** means a quantity of a substance that produces a specific effect when tested in accordance with an internationally accepted biological procedure;

(5) **'Microbial Active Substance as Manufactured'** (**'MASAM')** means the outcome of the manufacturing process of the micro-organism(s) intended to be used as active substance in plant protection products, consisting of the micro-organism(s) and any additives, metabolites (including metabolites of concern), chemical impurities (including relevant impurities), contaminating micro-organisms (including relevant contaminating micro-organisms) and the spent medium/rest fraction resulting from the production process or, in case of a continuous manufacturing processes a strict separation between the manufacturing of the micro-organism(s) and the production process of the plant protection product is not possible, a non-isolated intermediate;

(6) **'additive'** means a component added to the active substance that is a micro-organism during its manufacturing, to preserve microbial stability and/or facilitate handling;

(7) **'purity'** means the content of the micro-organism in relevant unit in the MASAM and the maximum content of substances of concern in case they are identified;

(8) **'relevant contaminating micro-organism'** means a pathogenic/infective micro-organism unintentionally present in the MASAM;

(9) **'seed stock'** means a microbial strain starter culture used to manufacture the MASAM or the final plant protection product;

(10) **'spent medium/rest fraction'** means the fraction of the MASAM, excluding the micro-organism(s), metabolites of concern, additives, relevant contaminating micro-organisms, and relevant impurities consisting of remaining or transformed starting materials;

(11) **'starting material'** means substances used in the manufacturing process as substrate and/or buffering agent for the production process of the MASAM;

(12) **'ecological niche'** means an ecological function and actual physical spaces occupied by a particular species within the community or ecosystem;

(13) **'host range'** means the range of different biological host-species that can be infected by a microbial species or strain;

(14) **'infectivity'** means the ability of a micro-organism to cause an infection;

(15) **'infection'** means the non-opportunistic introduction or entry of a micro-organism into a susceptible host, where the micro-organism is able to reproduce to form new infective units and persist in the host, whether or not the micro-organism causes pathological effects or disease;

(16) **'pathogenicity'** means the non-opportunistic ability of a micro-organism to inflict injury and damage to the host upon infection;

(17) **'non-opportunistic'** means a condition under which a micro-organism exerts an infection or inflicts an injury or damage when the immune system of the host is not impaired by an unrelated cause;

(18) **'virulence'** means the degree of pathogenicity that a pathogenic micro-organism is able to exert in the host;

(19) **'virulence factor'** means a factor that enhance the pathogenicity/virulence of a micro-organism;

(20) **'metabolite of concern'** means a metabolite produced by the micro-organism under assessment, with known toxicity or known relevant antimicrobial activity, which is present in the MASAM at levels that may present a risk to human health, animal health or the environment, and/or for which it cannot be adequately justified that *in-situ* production of the metabolite is not relevant for the risk assessment;

(21) **'*in-situ* production'** means the production of a metabolite by the micro-organism after application of the plant protection product containing that micro-organism;

(22) **'background level of a metabolite'** means a level of a metabolite that is likely to occur in relevant European environments (including also sources different than those of plant protection) and/or in food and feed (e.g. plant edible parts), when the micro-organisms are in conditions to grow, reproduce and to produce such metabolite in presence of a host or availability of carbon and nutrient sources, under consideration of high host densities and nutrients;

(23) **'antimicrobial resistance' ('AMR')** means the intrinsic or acquired ability of a micro-organism to multiply in the presence of an antimicrobial agent at concentrations which are relevant for therapeutic measures in human or veterinary medicine, making that substance therapeutically ineffective;

(24) **'antimicrobial agent'** means any antibacterial, antiviral, antifungal, anthelmintic or antiprotozoal agents that is a substance of natural, semi-synthetic, or synthetic origin that at *in vivo* concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target;

(25) **'acquired antimicrobial resistance'** means a non-intrinsic and acquired novel resistance enabling a micro-organism to survive or multiply in the presence of an antimicrobial agent at concentrations higher than that which inhibits wild type strains of the same species;

(26) **'intrinsic antimicrobial resistance'** means all inherent properties of a microbial species that limit the action of antimicrobial agents thereby allowing them to survive and multiply at relevant therapeutic concentrations of an antimicrobial agent. Inherent properties of micro-organisms are considered not transferable and can include structural characteristics like lack of drug targets, the impermeability of cellular envelopes, activity of multidrug efflux pumps, or metabolic enzymes. An antimicrobial resistance gene is considered intrinsic if it is located on a chromosome in the absence of mobile genetic element and shared by the majority of wild type strains of the same species;

(27) **'relevant antimicrobial activity'** means the antimicrobial activity caused by relevant antimicrobial agents;

(28) **'relevant antimicrobial agents'** means all antimicrobial agents important for therapeutic use in humans or animals, as described in the latest available versions at the time of submission of the dossier:

– in a list adopted by means of Commission Regulation (EU) 2021/1760[6] in accordance with Article 37(5) of Regulation (EU) No 2019/6 of the European Parliament and of the Council[7], or

– by the World Health Organisation[8] in the lists of Critically Important Antimicrobials, Highly Important Antimicrobials and Important Antimicrobials for Human Medicine;

(29) **'viroid'** means 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.

(iii) The information from scientific peer-reviewed literature as provided for under point 1.4 of the Introduction shall be provided at the relevant taxonomic level of the micro-organism (e.g. strain, species, genus). An explanation on why the chosen taxonomic level is considered relevant for the addressed data requirement shall be provided.

(iv) Other available sources of information, such as medical reports, may also be provided and submitted in a summary.

(v) Where appropriate or specifically indicated in the data requirements, test guidelines as described in Part A shall be used also for this Part, upon adaptation in such a way that they are appropriate for chemical compounds present in the MASAM.

(vi) Where testing is done, a detailed description (specification) of the material used and its impurities, in accordance with point 1.4, shall be provided. Where studies are conducted using micro-organisms produced in the laboratory or in a pilot scale production system, the studies shall be repeated using the MASAM, unless it can be demonstrated that the test material used is essentially the same for the purposes of the testing and assessment.

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6 Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by establishing the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans (OJ L 353, 6.10.2021, p. 1).

7 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7. 1.2019, p.43).

8 https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1.

(vii) If the active substance is a genetically modified micro-organism, a copy of the evaluation of the data concerning the risk assessment, as stated in Article 48 of Regulation (EC) No 1107/2009, shall be submitted.

(viii) The assessment of pathogenicity/ infectivity of micro-organisms shall be based on a weight of evidence approach, taking into account that:

– tests on animals may not always be suitable for extrapolation to humans due to differences between humans and test animals (e.g. immune system, microbiome), and

– micro-organisms might have narrow host range, as a result of which it cannot always be assumed that a micro-organism that does not cause disease in the animals tested has the same result in humans, and vice-versa.

(ix) The information on the micro-organism shall be sufficient to permit an evaluation to be made as to the risk concerning to anti-microbial resistance.

(x) Until validated methods for testing dermal and respiratory sensitization of micro-organisms become available, all micro-organisms shall be considered as potential sensitizers.

1. IDENTITY OF THE APPLICANT, THE ACTIVE SUBSTANCE AND MANUFACTURING INFORMATION

1.1. Applicant

The name and address of the applicant shall be provided, as well as the name, address, telephone number and e-mail address of a contact point.

1.2. Producer

The following information shall be provided:

(a) the name and address of the producer of the active substance;

(b) the name and address of each manufacturing plant in which the active substance is produced or will be produced;

(c) a contact point (preferably a central contact point), including name, telephone number and e-mail address.

Where, following approval of the micro-organism, there are changes in the address or number of producers, the information required shall again be submitted.

1.3. Identity, taxonomy and phylogeny of the micro-organism

The information provided shall allow an unambiguous identification and characterisation of the micro-organism.

(i) The micro-organism shall be deposited at an internationally recognised culture collection. The contact details of the culture collection and accession number shall be submitted.

(ii) The micro-organism shall be identified as unequivocally belonging to a certain species, based on the latest scientific information, and named at strain level, including any other designation which may be relevant to the micro-organism (e.g. isolate level, if relevant for viruses). Its scientific name and taxonomic grouping shall be stated. This includes traditional Linnean taxonomy (kingdom, phylum, class, order, family, genus, species, and strain) as well as established rank-free phylogenetic taxa in between these Linnean ranks and any other denomination relevant to the micro-organism (e.g. serovar, pathovar, biovar).

(iii) All known synonymous, alternative, superseded names shall be provided. If code names have been used during development these shall also be provided.

(iv) A phylogenetic tree including the micro-organism shall be provided. The scale of the phylogenetic tree shall be selected to include relevant strains and species (e.g. in case of use of read-across among related strains or species to address data requirements). Superseded names of included micro-organisms or taxonomic groupings may be indicated in the phylogenetic tree.

(v) It shall be indicated whether the micro-organism is a wild type, a mutant (either spontaneous or induced) or whether it has been genetically modified. If the micro-organism is a mutant or has been modified, all known differences in properties, including genetic differences, between the modified micro-organism and the parent wild strain shall be provided. The technique used for the modification shall be reported.

1.4. Specification of the microbial active substance as manufactured

1.4.1. Content of the active substance

The minimum and maximum content of the micro-organism in the MASAM shall be derived from the analysis of five representative batches as indicated under point 1.4.3 and reported. The content shall be expressed in:

– where possible, the dry weight of the pure micro-organism (if this value cannot be determined, a conversion factor shall be proposed to convert the unit of MASAM to the unit of dry weight of pure micro-organism), and

– appropriate microbial unit that most accurately reflects plant protection action, such as number of active units, colony forming units, or international units per volume or weight or any other manner that is relevant to the risk assessment on the micro-organism. A rationale for the relevance of the microbial unit used in the context of the tests to be conducted shall be provided. The use of such unit shall be consistent along studies and literature data provided. In case of provision of literature data with different units, recalculation based on the units used shall be provided.

In case it is claimed that one or more metabolites present in the MASAM are part of the plant protection action, the content of these metabolites shall be indicated as provided for in point 1.9 of Part A.

1.4.2. Identity and quantification of additives, relevant contaminating micro-organisms and relevant impurities

Data on additives, relevant contaminating micro-organisms, relevant impurities and metabolites of concern, present in the MASAM shall be directly derived from the analysis of five representative batches as indicated under point 1.4.3 and reported.

1.4.2.1. Identity and quantification of additives

The identity, minimum and maximum content in g/kg of each additive in the MASAM shall be provided.

1.4.2.2. Identity and content of relevant contaminating micro-organisms

The identity and maximum content of relevant contaminating micro-organisms in the MASAM, expressed in the appropriate unit, shall be reported.

1.4.2.3. Identity and quantification of relevant impurities

The identity and maximum content of chemical impurities present in the MASAM and which are relevant due to undesirable toxicological, ecotoxicological or environmental properties, shall be reported in g/kg, including also metabolites of concern produced by the micro-organism as impurities in the manufacturing batch.

1.4.3. Analytical profile of batches

At least five representative batches from recent and current production of the micro-organism shall be analysed. All of the representative batches shall bear a date within the last five years of manufacture. Manufacturing dates of the representative batches and batches size shall be reported.

Where the active substance is produced in different manufacturing plants, the information required under this point shall be provided for each of the plants separately.

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

1.5. Information on manufacturing process and control measures for the active substance

1.5.1. Production and quality control

Information on how the micro-organism is produced in bulk shall be provided for all the steps of the manufacturing process. Such information shall include relevant descriptions of:

– starting materials,

– culture media sterilisation (e.g. autoclave),

– initial inocula level for the culture media (e.g. number of conidia/g of dry culture media),

– culture and media conditions (e.g. pH, temperature, water activity (a_w)),

– phase of the growth curve and growth stage of the micro-organism during the production process,

– ratio vegetative cells / (endo)spores,

– fermentation process,

– purification and cellular dehydration,

– other technical parameters (e.g. centrifugation protocols).

The type of manufacturing process (e.g. continuous or batch process) shall be indicated.

Both production method/process and product shall be subject to a continuous quality control, and the quality assurance criteria shall be submitted. In particular, the possible occurrence of spontaneous changes of characteristics of the micro-organism shall be monitored. It shall be indicated where in the process the quality assurance steps are implemented and it shall be described how the samples for quality assurance screening are taken.

The techniques used to ensure a uniform product, and the assay methods for its standardisation, maintenance and purity, to prevent the presence of relevant contaminating micro-organisms and relevant impurities in the MASAM shall be described and specified.

Information on possible loss of activity of starting cultures shall be provided along with corresponding methods to assess it. If relevant, any method aiming at preventing the micro-organism from losing its effects on the target organism shall be described.

1.5.2. Recommended methods and precautions concerning handling, storage, transport or fire

A safety data sheet pursuant to Article 31 of Regulation (EC) No 1907/2006 shall be provided for the MASAM.

1.5.3. Procedures for destruction or decontamination

Methods to dispose safely of the MASAM or, where necessary, to render the micro-organism non-viable prior to disposal of the MASAM and methods to dispose of contaminated packaging and other materials shall be described (e.g. chemical methods or autoclaving).

Information that makes it possible to establish the effectiveness and safety of these methods shall be provided.

1.5.4. Measures in case of an accident

Information on procedures for rendering the MASAM harmless in the environment (e.g. water or soil) in case of an accident shall be provided.

2. BIOLOGICAL PROPERTIES OF THE MICRO-ORGANISM

2.1. Origin, occurrence and history of use

2.1.1. Origin and isolation source

The geographical location and environmental compartment (e.g. substrate, host organisms), from which the micro-organism was isolated, shall be stated. The method of isolation and the selection procedure of the micro-organism shall be reported.

2.1.2. Occurrence

The geographical distribution of the micro-organism shall be described.

The environmental compartment(s) where the micro-organism is already expected to occur shall be described (e.g. soil, water, rhizosphere, phyllosphere, host organism).

When relevant, food or feed commodities where the micro-organism is already expected to occur shall be described.

The information referred to in this point shall be provided at the most relevant highest taxonomic level (e.g. strain, species, genus) and the choice of the relevant highest taxonomic level shall be justified.

2.1.3. History of use

Previous and current known uses of the micro-organism (e.g. research, commercial, uses evaluated for recommending the Qualified Presumption of Safety[9] status) shall be described. The description shall include both plant protection and other uses (e.g. uses and/or assessments under other regulatory frameworks, bioremediation, uses in food and feed).

The information referred to in this point shall be provided at the most relevant highest taxonomic level (e.g. strain, species, genus). The choice of the relevant highest taxonomic level shall be justified.

2.2. Ecology and life cycle of the micro-organism

The known life cycle(s) of the micro-organism (e.g. parasitic, saprophytic, endophytic, pathogenic) and its ecological niche(s) shall be described, along with all forms that may occur and the type of reproduction.

For bacteriophages, information shall be provided on, if applicable, lysogenic and lytic properties.

For fungi and bacteria, information shall be provided, if applicable, on:

– external conditions for resting stages, information on resistance of spores against adverse environmental conditions, survival time of the spores and conditions for germination, and/or

– formation of biofilm.

2.3. Mode of action on the target organism and host range

All available information on modes of action against the target organism(s) shall be described.

[9] https://zenodo.org/record/3336268#.X5mJIdBKg2z.

The type of intended biological control (e.g. inundative or inoculative) shall be specified.

In case of a pathogenic or parasitic mode of action on the target organism, information on the site of infection and mode of entry into the target organism, the infective dose and the susceptible stages of the target organism shall be given. The results of any experimental studies shall be reported.

In case of a toxic or antimicrobial effect on the target organism caused by a metabolite of concern produced by the micro-organism under assessment and identified as required by point 2.8, information on exposure route to the target organism and the mode of action of the metabolites of concern shall be described.

All known host organisms of the micro-organism shall be listed at the relevant taxonomic level. Available information on possible density of host organisms, supporting the indication on natural occurrence of the micro-organisms, shall be provided.

2.4. Growth requirements

The conditions required for growth and proliferation of the micro-organism shall be described (e.g. host, nutrients, pH, osmotic potential, humidity). The minimum, optimum and maximum temperature required for growth and proliferation shall be reported. The generation time under favourable growth conditions shall be reported.

2.5. Infectivity

In case any pathogenic mode(s) of action is described under point 2.3, virulence factors and (if applicable) environmental factors affecting them shall be indicated and described. The results of any relevant experimental studies and/or data/information from the existing literature at the relevant taxonomic level shall be reported.

2.6. Relationship to known pathogens

Where the micro-organism is closely related to any known pathogens to humans, animals, crops or other non-target species, the applicant shall:

– list the pathogens and the type of known diseases caused,

– describe the known virulence factors belonging to the pathogens,

– describe the known virulence factors belonging to the micro-organism which is the active substance,

– describe the phylogenetic relationship between the micro-organism and the related pathogens identified,

– describe the way or means to distinguish the active micro-organism from pathogenic species.

2.7. Genetic stability and factors affecting it

Where the micro-organism is a non-virulent variant of a plant pathogen virus, the likelihood of regaining virulence through mutation after application under the proposed conditions of use shall be reported, including the information on measures that can be taken to reduce the likelihood of this occurrence and the effectiveness of such measures.

2.8. Information on metabolites of concern

The applicant shall identify and list under this point the metabolites of concern produced by the micro-organism, including a summary of the information submitted under points 5.5.1, 8.8.1, 6.1, 7.4.1 and 7.4.2 used to identify or to exclude metabolites as being of concern, unless the micro-organism is a virus.

Metabolites of concern may be identified based on the scientific literature, or on observation of toxicity, ecotoxicity or antimicrobial activity in studies conducted with the micro-organism and closely related strains. The absence of the gene(s) encoding the identified metabolite(s) of potential concern evidenced by employing appropriate genomics methods (e.g. whole genome sequencing), shall be considered to prove the absence of such hazard for that metabolite(s).

All the available information (e.g. scientific literature, experimental studies) on the metabolites and the related identified hazards (e.g. the toxicological characterization) and, where relevant, the exposure to the metabolite shall be submitted under the relevant points of the dossier (i.e. points 5.5, 6.2 and 7.4.3 if relevant for human and animal health and points 7.4.3 and 8.8 if relevant to the non-target organism for which a hazard due to a metabolite was identified).

2.9. Presence of transferrable antimicrobial resistance genes

Where the micro-organism is a bacterium, information on any resistance to relevant antimicrobial agents shall be reported at strain level, and information on whether the antimicrobial resistance genes are acquired, transferrable and functional shall be reported. The information provided shall be sufficient to perform an evaluation as to the risks for human and animal health due to a possible transfer of relevant antimicrobial resistant genes.

3. FURTHER INFORMATION

3.1. Function and target organism

The biological function shall be specified as:

– control of bacteria,

– control of fungi,

– control of viruses,

– control of insects,

– control of mites,

– control of molluscs,

– control of nematodes,

– control of plants,

– other (shall be specified).

3.2. Field of use envisaged

The field(s) of use, existing and proposed, for plant protection product containing the micro-organism shall be specified from among the following:

– field use, such as agriculture, horticulture, forestry and viticulture,

– protected crops (e.g. in greenhouses),

– non-cultivated areas,

– home gardening,

– houseplants,

– stored food/feed items,

– other (shall be specified).

3.3. Crops or products protected or treated

Details of existing or intended use in terms of crops, groups of crops, plants or plant products protected shall be provided.

3.4. Information on possible development of resistance of the target organism(s)

Available information on the possible occurrence of the development of resistance or cross-resistance of the target organism(s) shall be provided. Where possible, appropriate management strategies shall be described.

3.5. Literature data

A summary on the systematic review of the scientific peer-reviewed literature shall be provided, including indication on bibliographic databases employed, criteria for relevance and reliability assessment in relation to the data requirements and search strategies, etc.

The summary shall list the references used for the dossier compilation and for which points the respective references are relevant.

4. ANALYTICAL METHODS

Introduction

Analytical methods shall be used in the context of the generation of data for the risk assessment on human toxicology or ecotoxicology. Analytical methods shall also support post-approval stages, for instance, in monitoring quality of the manufacturing process and compliance of manufacturing batches with the agreed specification, where relevant (Section 1), by monitoring residues on crops (Section 6), if applicable. The method used shall be justified.

Descriptions of methods shall be provided and include details of equipment, materials and conditions used. The applicability of any internationally recognised method shall be reported.

As far as practicable, these methods shall be as simple as possible, involve a minimum cost and require commonly available equipment. Data on specificity, linearity, accuracy and repeatability, as laid down in points 4.1 and 4.2 of Part A, are also required for analytical chemistry methods used to analyse relevant impurities, metabolites of concern and additives included in the MASAM.

On request by the rapporteur Member State, the following shall be provided:

(i) samples of the MASAM;

(ii) if technically possible, analytical standards of metabolites of concern and all other components included in the residue definition (in case of non-provision of such a sample a justification shall be provided);

(iii) if available, samples of reference substances for the relevant impurities.

4.1. Methods for the analysis of the MASAM

The following methods shall be described providing validation data:

(a) methods for the identification of the micro-organism required in accordance with points 1.3(ii) and 1.3(iv), including the most appropriate molecular analytical and phenotypic methods, based on unique identifiers to distinguish the strain from other strains belonging to the same species; with information on appropriate test procedures and criteria used for identification (e.g. morphology, biochemistry, serology and molecular identification);

(b) methods for the characterisation of the micro-organism, including the most appropriate molecular analytical methods and phenotypic methods, as required by Section 2 with information on appropriate test procedures and criteria used for identification (e.g. morphology, biochemistry, serology and molecular identification);

(c) methods for providing information on possible variability of seed stock/active micro-organism and its storability (including loss of activity and methods to assess it), as required by Section 1;

(d) methods to differentiate a mutant of the micro-organism from the parent wild strain, e.g. including the most appropriate molecular analytical methods as required by Section 1;

(e) methods for the establishment of purity of seed stock from which batches are produced and methods to control that purity, e.g. including the most appropriate molecular analytical methods as required by Section 1;

(f) methods to determine the content of the micro-organism in the manufacturing batch, and methods to detect and enumerate relevant contaminating micro-organisms, as required in Section 1, to allow verifying the compliance of the material/batch with a maximal threshold of relevant contaminating micro-organism;

(g) methods for the determination of relevant impurities, metabolites of concern, and additives, in the manufacturing material as required by Section 1.

4.2. Methods to determine the density of the micro-organism and quantify residues

The methods used to determine and quantify:

– the density of the micro-organisms, where relevant, as required in points 5.3, 5.4, 6.1, 7.3.2 and 8,

– the residues of metabolites of concern, where relevant, as required in points 2.8, 5.5, 6 and 8.8,

– the residues of relevant impurities and additives, where relevant;

on and/or in crops, foodstuffs, feeding stuffs, animal and human body tissues and fluids and in relevant environmental compartments shall be described.

5. EFFECTS ON HUMAN HEALTH

Introduction

(i) The information provided, taken together with that provided for one or more plant protection products containing the micro-organism, shall be sufficient to perform an evaluation as to the risks for human and animal (i.e. species normally fed and kept by humans or food-producing animals) health:

(a) directly and/or indirectly associated with the handling and use of plant protection products containing the micro-organism;

(b) handling treated products; and

(c) arising from residues or impurities remaining in food and water.

In addition, the information provided shall be sufficient to:

– permit a decision to be made as to whether or not the micro-organism is to be approved,

– specify appropriate conditions or restrictions to be associated with the approval,

– specify risk and safety phrases for the protection of human and animal health and the environment to be included on packaging (containers),

– identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of infection or another adverse effect in humans.

(ii) All adverse effects found during investigations shall be reported. Investigations which may be necessary in order to evaluate the probable mechanism involved, and to assess the significance of these effects shall also be performed.

(iii) For all studies actual achieved dose of the micro-organisms or of the metabolite of concern in appropriate units per kg body weight (e.g. CFU/kg), or in any other appropriate units shall be reported. Justification for the chosen unit shall be provided.

(iv) Available information on the identity and biological properties of the micro-organism (Sections 1 and 2) as well as health and medical reports may be sufficient for an assessment of the infectivity and pathogenicity potential of the micro-organism.

(v) Further studies may be required to complete the evaluation of the effects on human health, and the type of these additional studies shall be decided on a case-by-case approach based on expert judgment, depending on the available information provided in particular as regards the biological properties of the micro-organism. Pending the acceptance of specific guidelines at international level, the information required shall be generated using available test guidelines.

(vi) Additional studies (see point 5.4) shall be conducted if available information (see point 5.2) or tests under point 5.3 require further investigation or have shown adverse health effects. The type of study to be performed depends on the effects observed.

5.1. Medical data

5.1.1. Therapeutic and first aid measures

Therapeutic regimes and first aid measures for use in the event of ingestion, inhalation or contamination of eyes and skin shall be described. Available information based on practical experience or on theoretical grounds shall be provided.

Where available and without prejudice to Article 10 of Directive 98/24/EC[10], practical data and information relevant to the recognition of the symptoms of infection or pathogenicity and on the effectiveness of therapeutic measures shall be submitted.

For micro-organisms excluding viruses, antimicrobial agents with effectiveness against the micro-organism shall be listed. In case of identification of metabolite(s) of concern, as required in point 2.8, the effectiveness of known antagonists of such metabolite(s) shall be reported.

5.1.2. Medical surveillance

Available reports of occupational health surveillance programmes shall be submitted. These reports may refer to the strain under assessment, to closely related strains or to metabolites of concern, and shall be supported with information on the design of the programme, on use of appropriate protective measures including personal protective equipment, on exposure to the micro-organism or the metabolites of concern. These reports shall, where available, include data on effects on individuals exposed to the micro-organism or the metabolites of concern in manufacturing plants or after application of the micro-organism (e.g. agricultural or research workers). These reports shall, where available, also cover sensitisation and/or allergenic responses.

In the case of adverse effects, attention shall be paid to whether the individual's susceptibility may have been affected by any pre-disposing conditions, e.g. underlying disease, medication, compromised immunity, pregnancy or breast-feeding.

5.1.3. Information on sensitisation/ allergenicity

Due to the unavailability of an adequate method to assess sensitising potential of micro-organisms, they shall be considered as sensitizers until a validated test is available and the possible absence of sensitising potential is demonstrated on a case-by-case basis.

5.1.4. Direct observation

Available reports from the open literature on the micro-organism or closely related members of the taxonomic group and relating to clinical cases of infections in humans shall be submitted together with reports of any follow-up studies undertaken. Such reports are of particular value and shall contain descriptions of the nature and level of exposure, as well as the clinical symptoms observed, first aid and therapeutic measures applied and measurements and observations made.

In the case of adverse effects, attention shall be paid to whether the individual's susceptibility may have been affected by any pre-disposing conditions, e.g.

[10] Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (OJ L 131, 5.5.1998, p. 11).

underlying disease, medication, compromised immunity, pregnancy or breast-feeding.

5.2. Assessment on potential infectivity and pathogenicity of the micro-organism to humans

Studies to determine the potential infectivity and pathogenicity of the micro-organism shall be performed as set out in points 5.3.1 and 5.4, unless the applicant demonstrates, by following a weight of evidence approach, that no such effects are to be expected. The weight of evidence approach may be based on the information provided under points 2.1, 2.3, 2.4, 2.6 and 5.1, and/or be retrieved from any other reliable sources (e.g. Qualified Presumption of Safety[11]). A summary shall be taking into consideration this information to demonstrate absence of infectivity and pathogenicity to humans, in order to justify the non-submission of the studies required in points 5.3.1 and 5.4.

5.3. Infectivity and pathogenicity studies on the micro-organism

5.3.1. Infectivity and pathogenicity

Unless the applicant can demonstrate absence of infectivity and pathogenicity based on a weight of evidence approach as set out in point 5.2, studies, data and information shall be provided and evaluated as required from points 5.3.1.1 to 5.3.1.3. These shall be sufficient to permit the identification of effects following a single exposure to the micro-organism, and in particular to establish or indicate:

– the infectivity and pathogenicity of the micro-organism,

– the time course and characteristics of the effects with full details of observed changes (clinical and behavioural) and possible gross pathological findings at post-mortem,

– the relative hazards associated with the different routes of exposure, and

– analyses throughout the studies in order to evaluate the clearance of the micro-organism.

If these studies are performed, the applicant shall:

– adapt the observation period to the biological properties or the micro-organism administered, in particular its incubation time, rate of clearance and timing for observation of adverse effects,

– estimate, during the infectivity and pathogenicity studies, the micro-organism clearance in the organs which is relevant for microbial examination (e.g. liver, kidneys, spleen, lungs, brain, blood and site of administration),

– take into account the potential differential species susceptibility (i.e. relevance of the chosen test species) of the micro-organism (e.g. based on literature) when the study results and their relevance for humans are evaluated.

5.3.1.1. Oral, infectivity and pathogenicity

The oral infectivity and pathogenicity following a single exposure to the micro-organism shall be reported.

[11] https://doi.org/10.2903/j.efsa.2021.6377.

A study in test animals in accordance with relevant guidelines shall be performed, unless the applicant can demonstrate absence of oral infectivity and pathogenicity based on a weight of evidence approach as set out in point 5.2.

5.3.1.2. Intratracheal/ intranasal infectivity and pathogenicity

The intratracheal/ intranasal infectivity and pathogenicity following a single exposure to the micro-organism shall be reported. Expert judgement may support the evaluation on which of the two exposure routes is the most appropriate to be investigated, based on biological properties of the micro-organism and available information described in points 5.1 and 5.2.

A study in test animals in accordance with relevant guidelines shall be performed, unless the applicant can demonstrate absence of intratracheal/ intranasal infectivity and pathogenicity based on a weight of evidence approach as set out in point 5.2.

5.3.1.3. Intravenous/ intraperitoneal or subcutaneous single exposure

The intravenous/Intraperitoneal or subcutaneous test shall be considered a highly sensitive assay to elicit in particular infectivity. The worst-case scenario – micro-organism bypassing the dermal barrier and entering the body in a high concentration – may be used to assess the results of oral and intratracheal/intranasal testing in case of uncertainties.

The choice on which is the most appropriate exposure routes to be investigated shall be based on biological properties of the micro-organism and available information required in points 5.1 and 5.2.

A study in test animals in accordance with the relevant guidelines shall be performed, unless the applicant can demonstrate absence of intravenous/intraperitoneal or subcutaneous infectivity and pathogenicity based on a weight of evidence approach as set out in point 5.2.

5.3.2. Cell culture study

This information shall be reported for intracellular replicating micro-organisms, such as viruses, viroids or, where relevant, bacteria and protozoa, unless the information provided in accordance with Sections 1, 2 and 3 clearly demonstrates that the micro-organism does not replicate in homoeothermic (warm-blooded) organisms.

If this information is required, a cell culture study shall be performed in human cell or tissue cultures of different organs. Selection may be based on expected target organs after infection. If human cell or tissue cultures of specific organs are not available, other mammal cell and tissue cultures shall be used. For viruses, particular attention shall be given on the ability to interact with the human genome.

5.4. Specific infectivity and pathogenicity studies on the micro-organism

In case, based on expert judgment, available information (see point 5.2) or effects observed in the single dose infectivity and pathogenicity studies (see point 5.3.1) require further investigation, specific infectivity and/or pathogenicity studies shall be carried out, in particular in case of close relatedness to micro-organisms which are pathogenic to humans and animals.

If these studies are required, they shall be designed on an individual basis, in the light of the particular parameters to be investigated and the objectives to be achieved.

5.5. Information and toxicity studies on metabolites

5.5.1. Information on metabolites

All the available information (e.g. scientific literature, studies results) on the toxicological characterization of the metabolites and the related identified hazards to human and animal health, collected or generated to identify the metabolites of concern listed under point 2.8 and relevant to human and animal health, shall be submitted. This information concerns metabolites for which a hazard to human or animal health is identified and, where relevant, other metabolites which are considered of no concern and which are therefore not requiring further risk characterization.

For those metabolites for which a hazard to human or animal health is identified, an estimation of human exposure shall be provided under points 6.1 and 7.4.1.

5.5.2. Additional toxicity studies on metabolites of concern

For metabolite(s) of concern, identified based on information provided on hazard to (see point 5.5.1) and exposure of (see points 6.1, 7.4.1 and 7.4.2) humans or animals and listed under point 2.8, toxicological reference value(s) shall be set based on the available toxicological information for each metabolite of concern. The reference values shall allow risk assessments to be performed for operators, workers, bystanders, residents and consumers, as appropriate, unless a risk assessment can be made by other means (e.g. a qualitative assessment or using the Threshold of Toxicological Concern (TTC) concept). Further exposure information may be required, if deemed necessary based on expert judgement.

If reference values cannot be set based on already existing information or reported effects need further investigation, additional studies may be required and shall be performed on a case-by-case basis (for example short-term toxicity studies and genotoxicity studies). If any toxicity studies on metabolites are conducted, the requirements set out in Part A for the specific type of study shall be followed.

For organisms which have not been extensively studied, i.e. where the amount of published information is not sufficient to conclude on the production of metabolites of concern, a repeated-dose toxicity study on relevant fractions of the MASAM shall be conducted in accordance with the provisions set out in Part A for the same type of study. The decision to require further studies shall be based on the type of any toxic effects observed and on expert judgement.

6. RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Introduction

Data on residues as required in point 6.2 shall be provided, unless:

– based on a weight of evidence approach concerning the information submitted in accordance with Sections 2, 3, 5 and 7, it can be justified that possible metabolites of concern identified (see point 2.8) are not hazardous to humans as a result of the intended use, or

– it is possible to conclude, through estimation of consumer exposure to residues of metabolites for which a hazard to human health was identified (see point 5.5.1) that the risk for consumers is acceptable.

6.1. Estimation of consumer exposure to residues

An estimation of consumer exposure shall be provided for metabolites for which a hazard to human health was identified based on information submitted in accordance with point 5.5.1, considering the intended use.

The estimation shall include, for the metabolites for which a hazard to human health was identified, a calculation of the expected residue levels of these metabolites on edible parts of treated crops using worst-case estimates, taking into account the critical good agricultural practice(s), ecology of the micro-organism, such as its lifestyle (e.g. saprotroph, parasite, endophyte), host range, life cycle, population growth requirements and the conditions which trigger the production and the properties of the metabolite of concern.

The estimation of exposure to residues of metabolites, for which a hazard to human health was identified may also be supported by direct measurements of the metabolite, e.g. to show the absence of the metabolite on edible parts at time of harvest. When determining the need for direct measurements, the possibility and relevance of exposure to the metabolite produced after application on the edible parts (*in-situ* production) shall be taken into consideration. This may include a comparison between the background level of the metabolite and the elevated level of it due to treatment with the plant protection product containing the active substance. Read across approaches shall be justified.

An estimation of exposure to metabolites, for which a hazard to human health was identified, may be supported by the direct measurements of the density of the micro-organism on edible parts of treated crops, e.g. if it cannot be adequately justified that *in-situ* production of the metabolite is not relevant for the consumers. Such measurements shall be performed under normal conditions of use and in accordance with good agricultural practice.

The estimation shall take into consideration, depending on the case, the whole crop life-cycle (e.g. pre-harvest, and post-harvest), in order to allow a proper assessment of the risk to consumers. A weight of evidence approach shall be employed. Where relevant, adequate justification for read-across shall be provided (e.g. between different substances, members of a species, climatic conditions).

Based on the exposure estimation, an indicative consumer risk assessment shall be performed to demonstrate that the anticipated exposure to metabolites, for which a hazard to human health was identified, does not constitute an unacceptable dietary consumer risk.

6.2. Data generation on residues

For those metabolites of concern identified under point 2.8 and for which it was not adequately demonstrated that the risk to consumers is acceptable based on the information provided under point 6.1, relevant studies of a data package on residues as provided in Section 6 of Part A shall be required. The studies shall be performed with a representative plant protection product aiming at analysing and, if possible, at quantifying the different metabolites of concern identified as described in point 2.8.

If a data package on residues is required:

– half of the supervised residues trials shall be residue decline trials which shall include, unless it can be demonstrated that only non-viable micro-organisms are present at the time of harvest, at least one post-harvest measurement,

– information on levels of the micro-organism and concentrations of the metabolite(s) of concern shall be provided,

– based on the residue trials, a consumer risk assessment shall be performed to demonstrate that the exposure does not constitute an unacceptable consumer risk.

7. ENVIRONMENTAL OCCURRENCE OF THE MICRO-ORGANISM, INCLUDING FATE AND BEHAVIOUR OF METABOLITES OF CONCERN

Introduction

(i) This Section sets out requirements that make it possible to determine ecological implications of the micro-organism, considering its occurrence in the relevant environmental compartments and to assess the potential exposure of humans and non-target organisms to the active substance, and where relevant to metabolites of concern. Information on the biological properties and ecology of the micro-organism as well as its intended use, i.e. information submitted in accordance with Sections 1 to 6, is the main source of information. This may be complemented with literature data, laboratory investigation or field measurements.

(ii) The information provided for the micro-organism and one or more preparations containing the micro-organism shall be sufficient to permit an assessment of the exposure of non-target organisms to the micro-organism. In addition, sufficient information shall be provided to permit an assessment of metabolites of concern, in case they are identified under point 2.8.

(iii) The information provided shall be sufficient to identify measures necessary to minimise impact on non-target species and the environment.

7.1. Predicted environmental density of the micro-organism

7.1.1. Soil

The predicted environmental density of the micro-organism in soil following treatment with the product under the proposed conditions of use shall be estimated, unless the applicant properly justifies absence of hazard under Section 8.

7.1.2. Water

The predicted environmental density of the micro-organism in surface water following treatment with the product under the proposed conditions of use shall be estimated, unless the applicant properly justifies absence of hazard under Section 8.

7.2. Exposure to micro-organisms known to be pathogenic either for plants or for other organisms

For micro-organisms not occurring in the relevant European environments at the relevant highest taxonomic level and which are known to be pathogenic either for plants or for other organisms (see points 2.2 and 2.3), the host organisms in which proliferation of the micro-organism is expected shall be indicated. If non-target organisms indicated under Section 8 may be exposed to the host organisms colonised by the pathogen, information on the likelihood and, if applicable, level of exposure shall be provided.

Such information may be provided based on the biological properties (see Section 2), literature data and/or studies required under Section 8.

7.3. Refined exposure assessment

7.3.1. Qualitative exposure assessment

A qualitative assessment of the exposure to the micro-organism shall be carried out if:

– adverse effects are observed on non-target organisms (see Section 8) after exposure to environmentally relevant concentrations, based on the predicted environmental density of the micro-organism calculated as provided for in point 7.1, or information is not sufficient to conclude about it, or

– under consideration of the information provided for in point 7.4 a potential risk is identified for humans or non-target organism(s), or information is not sufficient to conclude about it.

If required to provide supporting indications for the risk assessment, a qualitative assessment of the exposure to the micro-organism shall be provided employing a weight of evidence approach. Such qualitative assessment shall take into consideration the predicted environmental densities calculated under point 7.1, and may be based on the ecology of the micro-organism, such as its lifestyle (e.g. saprotroph, parasite, endophyte), host range and possible host densities, life cycle, population growth requirements or available monitoring data at the relevant highest taxonomic level. Adequate justification for using read-across shall be provided (e.g., among strains of the same species).

7.3.2. Experimental exposure data

If under consideration of the information provided under points 7.1, 7.2, 7.3.1 and 7.4 a potential risk is identified for humans or non-target organism(s) or information is not sufficient to conclude about it, the population density of the micro-organism shall be determined in relevant environmental compartment(s) (e.g. soil, water, plant surfaces).

The experimental data shall include population densities measured in a time course including pre-application and immediately post-application, aiming at demonstrating the potential decline of population density.

7.4. Fate and behaviour of metabolite(s) of concern

7.4.1. Predicted environmental concentration

In case of identification of metabolites which are present in the MASAM and for which a hazard to human health or non-target organisms was identified (see points 5.5.1 and 8.8.1), the predicted environmental concentration of the metabolite in the relevant environmental compartment (i.e. soil, surface water, groundwater or air) shall be provided. If the applicant cannot adequately demonstrate that *in-situ* production of the metabolite is not relevant for the risk assessment, provisions set out in point 7.4.2 shall be followed.

No predicted environmental concentration calculations are needed for metabolites for which a hazard to human health or non-target organisms was identified that are produced *in situ* but are not present in the MASAM.

7.4.2. Qualitative exposure assessment

In case of identification of metabolites for which a hazard to human health or non-target organisms was identified (see points 5.5.1 and 8.8.1), a qualitative exposure assessment shall be performed on such metabolites where the information provided under point 7.4.1 is not sufficient to conclude on acceptable risk to non-target organisms or on no-risks to human health.

If required, the assessment may be based on existing knowledge on the ecology of the micro-organism, such as its lifestyle, host range, life cycle, population growth

requirements, available monitoring data at the relevant highest taxonomic level and the conditions, which trigger the production of the metabolite, and on the properties of the metabolite. A weight of evidence approach shall be employed. Adequate justification for using read-across shall be provided (e.g. between different substances, members of a species, climatic conditions).

7.4.3. Experimental exposure data

Experimental exposure data shall be provided for the metabolites of concern identified under point 2.8 for which the information provided under points 7.4.1 and 7.4.2 is not sufficient to conclude on acceptable risk to non-target organisms, or on no-risks to human health.

In such cases, sufficient information on the concentration of the metabolite of concern in the relevant environmental compartments (e.g. soil, surface water, groundwater, air, flowers, leaves, roots, host organisms) shall be provided to permit an assessment. The study shall be conducted in accordance with the relevant provisions of Part A for the relevant type of study.

8. **ECOTOXICOLOGICAL STUDIES**

Introduction

(i) This Section sets out requirements for the data to allow:

– for the assessment of potential adverse effects on non-target organisms likely to be exposed to the micro-organism and relevant associated metabolites of concern, and

– for the identification of the relevant tests to be carried out on specific non-target organisms, based on information regarding intrinsic properties, so as to limit testing to what is necessary to conclude the risk assessment.

Attention shall be paid to microbiological species which are not known to occur in the relevant European environments. The information provided shall be sufficient to determine the physiological and ecological host range (in conjunction with the analysis of key biological traits of the micro-organisms) in order to assess impacts on non-target organisms.

(ii) The information provided at the most relevant highest taxonomic level, taken together with that for one or more preparations containing the micro-organism, shall be sufficient to permit an assessment of the impact on non-target species, likely to be at risk from exposure to the micro-organism. When submitting this information the applicant shall take into account that the impact on non-target species can result from single, prolonged or repeated exposure and can be reversible or irreversible. The information provided shall be sufficient to:

– decide whether or not the micro-organism can be approved,

– specify appropriate conditions or restrictions to be associated with any approval,

– permit an evaluation of short- and long-term risks for non-target species populations, communities, and processes, as appropriate, and

– specify any precautions deemed necessary for the protection of non-target species.

(iii) In general, the duration of experimental studies shall be long enough to permit time for incubation, infection and manifestation of adverse effects in non-target organisms depending on the biological properties of the micro-organism. The provided studies shall take into consideration the maximum recommended application rate or the expected environmental concentration, the exposure that may arise from the intended uses and the potential of the micro-organism to proliferate in the environment or in the host.

In order to distinguish between pathogenicity of the living micro-organism and toxic effects triggered by its metabolites of concern, appropriate controls shall be included in addition to the no-dosed control group, such as inactivated forms of the living micro-organisms, and/or sterile filtrate/supernatant controls.

(iv) If pathogenicity/infectivity studies are required for any of the non-target organisms groups indicated in points 8.1 to 8.6, the choice of the appropriate species of that non-target organisms group shall be based on the biological properties of the micro-organism (including the specificity of the host range, mode of action and ecology), the proposed use pattern(s) of the plant protection

product (e.g. treated crops, frequency, timings, use patterns such as spraying or brushing) and consider relevant guidelines, where available.

Additional studies may be conducted if tests referred to in points 8.1 to 8.6 have shown adverse effects in one or more non-target organisms and may include studies on additional species.

(v) All known adverse effects on the environment shall be reported. Additional studies may be necessary to investigate the probable mechanisms involved and to assess the significance of these effects.

(vi) It may be necessary to conduct separate studies for metabolites of concern identified under point 2.8, which constitute a relevant risk to non-target organisms. The study on non-target organisms shall be conducted in accordance with the relevant provision of Part A.

(vii) In order to facilitate the assessment of the significance of test results obtained, the same species, recorded origin or, where possible, strain of each relevant non-target species shall be used in the various tests performed.

8.1. Effects on terrestrial vertebrates

A summary on potential infectivity and pathogenicity of the micro-organism to terrestrial vertebrates (e.g. mammals, birds, reptiles, and amphibians) shall be provided, based on the information already provided under Sections 1, 2, 3, 5 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies shall be performed unless the applicant demonstrates, by following a weight of evidence approach, that pathogenicity/infectivity of the micro-organism to non-target terrestrial vertebrates can be assessed based on the summary provided.

If these studies are required:

– gross necropsy shall be performed and

– for micro-organisms with pathogenic mode of action or viruses (e.g. entomopathogens) that are expected to proliferate significantly in the environment following an application, the oral dose administered in the studies may be justified based on the information submitted under points 7.1 and 7.2.

8.2. Effects on aquatic organisms

8.2.1. Effects on fish

A summary on potential infectivity and pathogenicity of the micro-organism to fish shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies shall be performed unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to fish can be assessed based on the summary provided; or

– exposure of fish to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.2.2. Effects on aquatic invertebrates

A summary on potential infectivity and pathogenicity of the micro-organism to aquatic invertebrates shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies shall be performed unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to aquatic invertebrates can be assessed based on the summary provided, or

– exposure of aquatic invertebrates to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.2.3. Effects on algae

A summary on potential infectivity and pathogenicity of the micro-organism to algae shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant studies on pathogenic/infective effects on algae growth and growth rate shall be performed if the micro-organism is known to have an herbicidal mode of action or to be closely related to a plant pathogen, unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to algae can be assessed based on the summary provided, or

– exposure of algae to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.2.4. Effects on aquatic macrophytes

A summary on potential infectivity and pathogenicity of the micro-organism to aquatic macrophytes shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant studies on pathogenic/infective effects on aquatic macrophytes shall be performed if the micro-organism is known to have an herbicidal mode of action, or to be closely related to a plant pathogen, unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to aquatic macrophytes can be assessed based on the summary provided, or

– exposure of aquatic macrophytes to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.3. Effects on bees

A summary on potential infectivity and pathogenicity of the micro-organism to bees shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies, including adult and larval stages, shall be performed, unless the applicant demonstrates, by following a weight of evidence approach, that:

– the micro-organism is not pathogenic/infective to bees based on the summary provided, or

– exposure of bees to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. field studies under representative conditions in accordance with the proposed conditions of use for use) shall be performed.

8.4. Effects on non-target arthropods other than bees

A summary on potential infectivity and pathogenicity of the micro-organism to non-target arthropods other than bees shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies shall be performed unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to non-target arthropods other than bees can be assessed based on the summary provided, or

– exposure of non-target arthropods to the micro-organism is expected to be none based on information provided under Section 7.

If studies are required, they shall be performed on two arthropod species other than bees playing a role in biological control and comprising different taxonomic groups (orders), where possible, for which agreed testing protocols are available, and the applicant shall provide a justification for number and taxonomy of the tested species. Moreover, these tests may require conditions affecting growth or viability of the micro-organism (e.g. high osmotic potential of the test matrices).

Where adverse effects are observed in such studies, further relevant studies (e.g. extended laboratory tests or field studies under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.5. **Effects on non-target meso- and macro-organisms in soil**

A summary on potential infectivity and pathogenicity of the micro-organism to non-target soil meso- and macro-organisms shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant pathogenicity/infectivity studies shall be performed unless:

– pathogenicity/infectivity of the micro-organism to non-target soil meso- and macro-organisms can be assessed based on the summary provided, or

– exposure of meso- and macro soil organisms to the micro-organism is expected to be none based on information provided under Section 7.

If studies are required, they shall be performed on two non-target meso- and macro-organisms species chosen based on the biological properties of the micro-organism under evaluation, where possible, for which agreed testing protocols are available.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.6. Effects on non-target terrestrial plants

A summary on potential infectivity and pathogenicity of the micro-organism to non-target terrestrial plants shall be provided, based on the information already provided under Sections 1, 2, 3 and 7 and that information which may be retrieved from any other reliable source.

Relevant studies on pathogenic/infective effects on non-target terrestrial plants shall be performed if the micro-organism is known to have an herbicidal mode of action or to be closely related to a plant pathogen, unless the applicant demonstrates, by following a weight of evidence approach, that:

– pathogenicity/infectivity of the micro-organism to non-target terrestrial plants can be assessed based on the summary provided, or

– exposure of non-target plants to the micro-organism is expected to be none based on information provided under Section 7.

Where adverse effects are observed in such studies, further relevant studies (e.g. under representative conditions in accordance with the proposed conditions of use) shall be performed.

8.7. Additional studies on the micro-organism

Further data may need to be submitted on potential pathogenicity/infectivity of the micro-organism on non-target species different from those assessed to fulfil the requirements set out in points 8.1 to 8.6.

The data may also consist of a summary including the information already provided under Sections 2, 3, 5 and 7 and those which may be retrieved from any other source, or from additional infectivity and pathogenicity studies.

***8.8.* Information and toxicity studies on metabolites**

8.8.1. Information on metabolites

All the available information (e.g. scientific literature, studies results) on the toxicological characterization of the metabolites and the related identified hazards relevant to non-target organisms, collected or generated to identify the metabolites of concern listed under point 2.8 and relevant to non-target organisms, shall be submitted. This information shall concern metabolites for which a hazard to non-target organisms is identified and, where relevant, other metabolites which are considered of no concern and which therefore do not require further risk characterization.

For those metabolites for which a hazard to non-target organisms is identified, an estimation of exposure of the relevant non-target organisms shall be provided under point 7.4.1.

8.8.2. Additional toxicity studies on metabolites of concern

For metabolite(s) of concern, identified based on information provided on hazard to (see point 8.8.1) and exposure of (see points 7.4.1 and 7.4.2) non-target organisms and listed under point 2.8, further relevant information on their toxicity to the non-target organisms, which are relevant (e.g. based on exposure, and indication of toxicity) among those described in points 8.1 to 8.6, shall be provided. In case it is necessary to generate experimental data, relevant studies on ecotoxicology as provided for in Section 8 of Part A shall be submitted.'