Evaluation Manual

for the Authorisation of Biopesticides according to Reg. (EC) No 1107/2009

Part II: Botanicals

Version 2.0, December 2022

Board for the Authorisation of
Plant Protection Products and Biocides

ctgb

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Document history

Version	Date	Amended paragraph(s)	General description of changes
Pre-separation history of the Botanicals section			
1.0	July 2017		**All aspects:** Initial Biopesticides EM
1.1	June 2018	7	**Efficacy:** Implementation of new EPPO standard "*principles of efficacy evaluation for low-risk plant protection products"* PP1/(296). (All efficacy-related paragraphs updated).
1.2	July 2021	7 2	**Efficacy:** - Implementation of new EPPO standard "*General principles for efficacy evaluation of plant protection products with a mode of action as plant defence inducers"* PP1/(319). **Chemistry:** - Rework of the General Introduction to align with Green Deal principles and to expand EM functionality. - Preliminary addition to Botanicals-section: an alternative to the pragmatic approach regarding characterization of Group 3 botanicals (see SANCO/11470/2012 – rev.8, section 7) is presented. Use of a broader spectrum of scientifically supported methods for UVCB-characterization is now actively encouraged by Ctgb.
1.3	November 2021		No changes regarding the Botanicals section
1.4	July 2022		No changes regarding the Botanicals section
Post-separation history of the Botanicals section			
2.0	December 2022	**-**	Initial version of the separated EM Biopesticides – Part II, dedicated to the assessment of botanicals, in accordance with Part A of Regulations (EU) No 283/2013 and (EU) No 284/2013, and additional interpretation according to SANCO/11470/2012 – rev.8.

General introduction

REGULATORY FRAMEWORK AND OUTLINE OF THE BIOPESTICIDES EVALUATION MANUAL

In this Manual we consider *biopesticides*, i.e., plant protection products (PPPs) that contain micro-organisms (including viruses), botanicals, or semiochemicals as active substance. Due to their inherent differences with conventional chemical active substances, these groups of substances have customized data requirements and guidances, which logically justifies a separate Evaluation Manual.

It is important to note that, in reference to biopesticides, Regulation (EC) No 1107/2009 only distinguishes between microbial and chemical active substances, and low-risk and non-low-risk substances and products; the text makes no mention of the term biopesticides. Although the domain of biopesticides is a great repository of low-risk products, the two concepts are not synonymous. A biopesticide is not necessarily considered as 'low-risk' according to Art. 47 of the Regulation, and not all products based on chemical active substances are automatically ineligible for a low-risk status.

This Biopesticides Evaluation Manual (Biopesticides EM) particularly describes the Dutch evaluation of biopesticides in the EU framework under (EC) No 1107/2009. Naturally, the EU Data Requirements, Uniform Principles, and relevant guidances provide the abstract foundation to this EM. The actual outline of the evaluation is however mostly shaped by the interpretation of these strata of rules and guidelines.
Ideally, interpretation is a constantly evolving product of growing experience, critical reflection and, to an increasing extent, necessity (see below); it adds a less solidified layer to the core framework and thus allows budding innovation to take root, and amendments to be easier to integrate. The purpose of the EM is to keep track of the ongoing developmental process thus avoiding something necessarily progressive to become unnecessarily elusive.

The perspectives described in this EM can be used for both the approval procedure for microbial, botanical, and semiochemical active substances, and for zonal and interzonal applications for the authorisation of biopesticidal products (i.e., Core registration reports).

The layout of the Biopesticides EM follows the regulatory division applied to biopesticides and presents three sections, dealing with microbial, botanical, and semiochemical active substances, respectively.

STRATEGIC SHIFTS PROMPTED BY THE EUROPEAN COMMISSION'S GREEN DEAL

Since the last update of this EM, the European Commission has set out the course towards achieving the goals of the European Green Deal. To underline its importance: the Green Deal is a massively spirited charge toward securing a sustainable future and a higher level of well-being for all. Not only does the initiative serve most of the EU's raisons d'être set out in the Treaty of Lisbon, it also reflects a powerful Zeitgeist that is steadily gaining momentum.

A prominent aspiration of the Deal is a significant reduction of the use of chemical pesticides within this decade. As such, the new course set out by the Commission directly affects the position that Competent Authorities should hold towards biopesticides in particular. After all, a substantial phaseout of chemical PPPs will leave a gap in the crop protection puzzle that requires filling up with at least several pieces, one of which is decidedly biopesticides-shaped.

It is acknowledged, however, that the current assessment practice regarding biopesticides is not in the right gear to serve the acute objectives of the Green Deal, that is, by facilitating registration of ever more innovative, efficaceous, and safe biopesticides.

Of course, there are multiple impeding factors, not all of which are even causally related to the assessment. Even then, laying down a perfectly balanced set of interpretations on evaluation systematics would not straighten out all bumps in the procedure.
Still, multifaceted challenges are most frequently tackled with the necessary kit of partial solutions.

Therefore to begin with, a principal issue that is within the actual scope of this EM is the absence of a truly comprehensive, clear-cut, and unambiguous set of guidelines for any of the three biopesticide groups currently recognized. Too often, the incompleteness, incompatibility, and non-specificity of the allotted framework results in substantial variation among dossiers, a lot of which is a product of necessary *ad hoc* choices from both applicants and evaluators.
For the current EM-version, Ctgb started out to define a more predictable direction for the micro-organisms-related specification-, product properties-, and analytical methods-sections, as these had been lacking in sufficiently detailed substantiation for some time.

When proving effective, these introductory amendments may prelude a possible revaluation of the EM as a unique supporting document with the potential to fulfill a broader range of functions critical to the improvement of biopesticide assessment that the higher-tier regulatory texts could *by design* not address – at least not in a responsive, specific, and, if needed, purposefully aligned way.

Botanicals

1. INTRODUCTION

The relevant EU Guidance document for botanicals is the Guidance document on botanical active substances, SANCO/11470/2012. In this guidance, a botanical active substance is defined as follows:

A 'botanical active substance' 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/altered by chemical and/or microbial processes.

The botanical active substances that are covered by the guidance are:

- Plant powders
- Unprocessed plant extracts
- Processed plant extracts
- Highly refined plant extracts
- Complex mixtures of plant extracts

Not included in the guidance are extracts from genetically modified organisms and chemically derived analogues of plant extracts (which can be referred to as mimics, natural-identical synthesized molecules and biosimilars).

The approval criteria and legal frame work for botanical active substances are also described in the guidance document. In principle, plant protection products (PPPs) containing botanical active substances have to be approved under Regulation (EC) No 1107/2009 and a dossier has to be compiled according to the data requirements as laid down in parts A of Regulation (EU) No 283/2013 (active substance) and Regulation (EU) No 284/2013 (plant protection product). The evaluation should take into account the uniform principles for the evaluation and authorisation of plant protection products as described in Commission Regulation (EU) No 546/2011.

For many botanicals there is a long historical use and exposure is known. If the use and exposure are documented in peer reviewed open literature or from other reliable sources these data can be used for the dossier. In case a botanical is used in another regulatory context than the approval for the use as active substance in a PPP, such as in human nutrition, animal feeding, cosmetics, as a fertiliser, in pharmacopoeia, or as a biocide, these data may also be used for the dossier.

For all botanicals that are subject to application all available relevant knowledge and information in literature should be provided. The literature search should be carried out in accordance with the EFSA Guidance on the submission of scientific peer-reviewed open literature (EFSA Journal 2011; 9(2): 2092). Literature retrieved from this search should be reported in the relevant sections of the dossier.

2. PHYSICAL CHEMICAL PROPERTIES AND ANALYTICAL METHODS

The Method of manufacture should be reported in detail. All steps should be described including, amount of solvent, pressure, temperature, time, type of filter/distillation/extraction.

The 5-batch analysis has to reflect the practical production. Therefore, It should contain a number of products taken from at least 2 crop seasons and, if applicable, several sources of starting material.

Especially for Group 3 botanicals (i.e., '*Botanical active substances that are not based on a material with an established specification*'; see guidance document SANCO/11470/2012 – rev.8, Section 7), the criteria for characterization of the botanical extract may in specific cases be disproportionately difficult, if not impossible, to satisfy.
The approach presented in the guidance requires the identification and quantification of at least 80 % w/w of the extract. This pragmatic threshold solely exists because there has been no way to characterize a complex mixture to a degree that only its active components and components of concern are identified – note here that the regulatory framework has no interest for constituents that are neither active nor (eco)toxicologically relevant.
Due to scientific developments in the field of metabolomics, there may now however be a way to address the analytical core challenge involved – notably in cases where proportionally applied conventional methodology is not fit for purpose. Although the existing framework does not yet accommodate these methods, Ctgb holds that only familiarization and experience-building could enable eventual implementation. Addition of these innovative methods is therefore encouraged, if only for the fact that there is no other feasible way to obtain the data they promise to generate.
In this, Ctgb maintains an assertive interpretation of EFSA's opninion on the use of 'omics methods in risk asessment, that recognizes the methods' indispensable value in the field of risk assessment, and identifies the need to employ them in order to generate confidence in the support they may provide.

For the determination of the phys-chem properties of both the botanical and the plant protection product, referral is made to the regular Evaluation Manual (chapter 2). Preferably, all phys-chem data for the main components should be submitted. Especially since botanicals are often complex mixtures, and it may not be feasible to test all properties of the complete mixture.

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

3. MAMMALIAN TOXICOLOGY

Botanical active substances are not per se non-toxic and it should be ensured that the botanical active substance does not lead to any harmful effects on the health of operators, worker, bystanders or residents under the conditions of use.

Botanical active substances should not lead to any harmful effects. The approach to address this depends on the intended use with corresponding exposure levels and whether there is information available on the botanical active substance from document uses, e.g. biocide, food or medicinal use, which may be relevant for the exposure assessment. The guidance document on botanical active substances states that 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. In accordance with Regulation (EU) 1107/2009 the deliberate administration of an active substance to humans with the purpose of determining no effect levels is prohibited. However, if data is available from e.g. clinical studies if the botanical active substance is used in human medicine these data are considered acceptable.

When available data on background exposure show similar exposure levels compared to the plant protection use than further animal testing should be avoided. This would be the case when similar exposures to known levels of the botanical active substance by the same routes have occurred in large population groups for many years without adverse effects being

reported e.g. in epidemiological studies. It is advised to discuss the proposed background exposure level with the rapporteur member state prior to submission of the dossier. When comparing the exposure levels from the plant protection use to the background exposure all relevant exposure groups, i.e. operators, workers, bystanders and residents, should be taken into account. To this end typical exposure models, such as the EFSA AOEM, can be applied as is done for chemical active substances.

For botanical active substances lacking a substantially reported history of use or for botanical active substances whose intended use levels will significantly exceed historical use or background exposure levels the assessment has to rely on basically the same set of data as for synthesized chemical active substances (default approach) with options for scientifically justified deviations from data requirements. At the moment there is no EU agreement on what the minimum data requirements would be for botanical active substances for which background exposure levels are exceeded or not available. It is recommended to discuss the test strategy with the rapporteur member state prior to dossier submission.

In case the botanical active substance contains components of concern with known toxic properties the significance of overall exposure to the component of concern should be assessed and compared with existing health-based guidance values. If no specific health based reference value is available consideration of exposure to the component of concern in relation to the Threshold of Toxicological Concern (TTC) values may also be helpful to avoid unnecessary animal testing.

4. RESIDUES

Assessment of the possible residues of botanical active substance is required to make sure that there is no risk for the consumers after the exposure via food to the plant protection product containing a botanical active substance.

In particular cases, evaluation of residues could be waived, based on relevant argumentation provided by the applicant:

It is acknowledge that if the proposed botanical active substance 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. The applicant is asked to provide a reasoned case/evidence to the way the material complies with relevant food legislation, confirming that technical material is the same as that is supplied to the food industry. The same applies to “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 when the residues are not of toxicological concern. The (scientific) rationale including a comparison between the residue levels arising from the use as a plant protection product and levels from the naturally occurrence or other use, should be demonstrated by the applicant.

Food or feed

In case of botanical active substances listed as food and feed (Annex I of Regulation No 396/2005), information on nature and magnitude of residues is usually not necessary. For those botanicals, normally no MRLs are set and they are included in Annex IV of Regulation (EC) No 396/2005).

Not food or feed
Though occurring naturally, for botanical active substances as a minimum, information on the nature and magnitude of residues on plants and processed products is needed for the consumer risk assessment. Further information e.g. concerning the nature and magnitude of residues in livestock or in succeeding crops may often be addressed by a reasoned case.

If MRLs are in place or needed, residue data will be needed to show compliance with these MRLs. If relevant toxicological endpoints are established and residues on food and/or feed cannot be excluded, a consumer risk assessment will be required. It is advised to discuss this approach at an early stage with the rapporteur member state.

5. FATE AND BEHAVIOUR

The aim of the environmental risk assessment is to ensure that botanical active substances for use in plant protection products do not have any unacceptable effects on the environment. Botanical active substances are not *per se* non-toxic and often risk mitigation measures may be necessary to avoid risk for the environment.

The application of the guidance to specific cases will depend on the nature of the botanical active substance, its intended uses, exposure levels and whether there is information on the botanical active substance from documented use (e.g. as plant protection product, biocide, in food or medicine) these may be relevant for the exposure and effect assessment.

In the fate and behaviour assessment the aim is to identify areas of potential unacceptable effect on the environment and to assess whether the exposure levels do not result in unacceptable effects. The natural occurring exposure levels should be compared with the exposure levels resulting from use of the product in the different environmental compartments (i.e., soil, water and air).

Components from botanical active substances occur naturally in plants and it is to be anticipated that there will be common pathways for their breakdown and decomposition in plants and the environment. Further guidance on the assessment of fate and behaviour of botanical active substances in the environment may be developed by the European Food Safety Authority in the future.

For the application of botanicals in protected crops an emission percentage of 0.1% should be used, as the "Guidance document on clustering and ranking emission of active substrates of plant protection products and transformation products from protected crops (greenhouses and crops grown under cover) to relevant environmental compartments" has no scenario for botanical active substances. Alternatively, if the botanical consists of components with known endpoints, the greenhouse emission model (GEM) should be used for the assessment.

6. EFFECTS ON NON-TARGET SPECIES

The aim of the ecotoxicological risk assessment is to ensure that botanical active substances for use in plant protection products do not have any acute or long-term unacceptable effects on non-target species. Botanical active substances are not *per se* non-toxic to non-target organisms, therefore risk mitigation measures may be necessary.

The risk from botanical active substances used in plant protection products can be considered acceptable if the estimated exposure is lower or similar to the natural exposure and no unacceptable effects occur on the non-target organisms. If the estimated exposure is higher than the natural exposure, additional data must be submitted to assess the possible effects on

the non-target organisms. The guidance document on botanical ative substances does not provide a general testing strategy, but instead recommends that applicants propose a relevant testing strategy in line with the mode of action, proposed use(s) and the relevant exposure situation, avoiding animal testing when unnecessary.

7. EFFICACY

For efficacy it is important to know if a botanical is low-risk or not. Botanical products that do not receive low-risk status should be evaluated as conventional products.The data requirements for efficacy for a low-risk product can differ markedly from those for a conventional product and are described here. At the start of the efficacy evaluation the status of the product (low-risk or not) is however not known with certainty. In some cases a product based on a low-risk substance may not receive low-risk status as mitigation measures need to be prescribed due to the risk assessment.

In most cases however the outcome of the evaluation should be predictable. Where there is doubt the applicant is advised to contact the Ctgb to discuss the low-risk status of the product, and the approach for the efficacy dossier.

Efficacy evaluation

General EPPO standards

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

In addition to this standard, specific guidance exists for products with a predominant mode of action as plant defence inducers (elicitors), PP1/(319). Preliminary and supporting trials for these types of product can differ from other modes of action.

Specific EPPO standards

The EPPO standards database includes many standards on specific plant pathogen combinations. It should be noted that these have mostly been written with conventional products in mind. However as the mode of action and method of application of botanicals is usually quite similar to conventional products, these should in most cases be usefull for botanicals.

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

IPM and spray programmes.

Biopesticides are often used in an integrated pest management system. Most EPPO standards however assume that only one product is used in a testing programme, as multiple products may complicate the interpretation of trial results. It is relevant to note that the new EPPO standard for plant defence inducers/elicitors (PP1/(319)) includes several paragraphs with guidance on how to test efficacy in mixtures, or in spray programmes with other products. If properly motivated some of these principles may also apply to other low-risk products.

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

For a more detailed description please refer to chapter 9 (extrapolation possibilities for effectiveness) of PP1/196. In addition some further context is provided below, consisting of an explanation of extrapolations in general, followed by a section specifically for low-risk products.

Principles of extrapolation
The regular extrapolation principles (non low-risk) are described in EPPO Standard PP 1/257 "Efficacy and crop safety extrapolations for minor uses". Extrapolations are either based on extrapolation tables, or on expert judgement. Extrapolation tables that can be used are available from the EPPO website. For the Dutch situation additional possibilities exist; Dutch national extrapolation tables are available in our Evaluation Manual as an appendix of Chapter 8 Efficacy (also available in English). This national document has not been approved by EPPO, however it can be reffered to using expert judgement.

It should also be noted that the Netherlands take a flexible approach to the requirement in PP 1/257 that extrapolations are from major to minor crops only. For Dutch labels extrapolations may also be possible to major crops.

Extrapolation for low-risk products
The above-mentioned extrapolation tables have mostly been written for conventional crop protection products. For low-risk botanicals different extrapolations may be possible using expert judgement. The possibility for extra extrapolations depend for a large part on the mode of action of the botanical. It is therefore important that the applicant clearly describes the mode of action of the active substance and the reasoning behind the extrapolations.
Where multiple modes of action are claimed the relative importance of the different modes of action should be described.`It is advisable to contact Ctgb or schedule a PSM if more information is required.

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

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

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

literature.

In some cases target organisms may develop resistance to some strains of a micro-organism, but not to other strains of the same species. This differs from conventional PPPs where often cross resistance exists between many active substances.