Evaluation Manual

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

Part III: Semiochemicals

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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 Semiochemicals section			
1.0	July 2017		**All aspects:** Initial Biopesticides EM
1.1	June 2018	6	**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	6	**Efficacy:** - An update for the efficacy section on semiochemicals was made as several EPPO standards for this section were released or updated. (PP1/264(2), PP1/314(1), PP1/323(1)).
1.3	November 2021		No changes regarding the Semiochemicals section
1.4	July 2022		No changes regarding the Semiochemicals section
Post-separation history of the Semiochemicals section			
2.0	December 2022	**-**	Initial version of the separated EM Biopesticides – Part III, dedicated to the assessment of semiochemicals, in accordance with Part A of Regulations (EU) No 283/2013 and (EU) No 284/2013.

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.

Semiochemicals

1. INTRODUCTION

The information in this section is taken from the EU guidance document on semiochemical active substance and plant protection products (SANTE/12815/2014 – rev.5.2).
Semiochemical 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 Part A to Regulation (EU) No 283/2013 (active substance) and Part A to Regulation (EU) No 284/2013 (Plant Protection Product; PPP). 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.

Semiochemicals are substances or mixtures of substances emitted by plants, animals, and other organisms that evoke a behavioural or physiological response in individuals of the same or other species. To be used as PPP, semiochemicals can for example be used in conjunction with dispensing devices, as granular product, or as seed treatment product.
Different types of semiochemicals are:

- Allelochemicals produced by individuals of one species that modify the behaviour of individuals of a different species (i.e. an interspecific effect). They include allomones (emitting species benefits), kairomones (receptor species benefits) and synomones (both species benefit).
- Pheromones produced by individuals of a species that modify the behaviour of other individuals of the same species (i.e. an intraspecific effect; for example straight-chained lepidopteran pheromones).

In plant protection products or biocides these semiochemicals can have different functions.

(Determined in the Netherlands: C-302.I.5)
Semiochemicals can act as attractant, repellent, or disruptor (for example mating disruptors). Depending on the function, and the target organism, either an authorisation as a plant protection product, a biocide, or no authorisation is required. The following decision table can be used.

Decision table for semiochemical products.

Types of semiochemicals in the product	***Extra function of the product***	***Plant Protection Product (PPP)***	***Product to protect against harmful organisms or to prevent effects of these organisms (BPR)***
Attractant	*None*	*Authorisation is not required*	*No authorisation required**
	Mechanical control	*Authorisation is not required*	*BPR authorisation required***
	Insecticide or other function	*PPP authorisation is required (semiochemical is not an active ingredient)*	*BPR authorisation requried*
Repellent	-	*PPP authorisation is required (semiochemical is an active ingredient)*	*BPR authorisation required*
(mating) Disruptor	-	*PPP authorisation is required (semiochemical is an active ingredient)*	*BPR authorisation required*

** Including traps for insects and pests without the intention to influence the population.*
*** The intention is to limit the population.*

Calculations of the natural exposure levels are provided in the EU guidance document that also provides methods to compare naturally occurring exposures levels with levels achieved by a product containing semiochemical. When based on the use of plant protection product a similar exposure is achieved (within one order of magnitude by the same route) to the natural exposure level of the semiochemical, the risk characterisation is concluded. No further information is needed with the exception of identity, characterisation and analytical methods. If the exposure levels of the product are higher than the naturally exposure the guidance document provides per application method the data required. The exposure and requirement per aspect will be briefly described in the following paragraphs.

The OECD Series on Pesticides Number 12 Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control will be updated with the EU guidance document on semiochemicals which will result in an update OECD guidance document. The update of the OECD guidance is expected to be available end 2017.

The guidance document on the assessment of new substances falling into the group of Straight Chain Lepidopteran Pheromones (SCLPs) (SANCO/5272/2009 – rev.3) can be used in order to add a new SCLP to the group of approved active substances, using a simplified procedure for the assessment. Currently this GD is being updated to be in line with current legislation and the EU guidance on semiochemicals. The list of SCLPs already approved can be found in the Commission review report (SANCO/2633/08 – rev.14).

For all semiochemicals 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. IDENTITY, PHYSICAL CHEMICAL PROPERTIES

For the determination of the phys-chem properties of both the semiochemical and the plant protection product, referral is made to the regular Evaluation Manual (chapter 2). All properties required for CLP labelling should be addressed. For the technical properties a waiver is not allowed.

3. MAMMALIAN TOXICOLOGY

For semiochemicals it should be ensured that they do not have any harmful effects on the health of consumers (see section 3.4), operators, workers, bystanders or residents.

To ensure this the semiochemicals can be divided into two groups.
- Group 1: the only exposure route is via the vapour phase, e.g. retrievable dispensers (category 1A and 1B), non-retrievable dispensers (category 2A) and dosable matrix (category 2B). In addition, the exposure (by the same route) caused by the plant protection product use is within one order of magnitude to natural exposure levels of the semiochemical.
- Group 2: the exposure cannot be related to a natural background exposure level further hazard identification.

For group 1 no further hazard or risk characterisation would be required. However, for group 2 further hazard identification and risk assessment would be needed.

For the hazard identification the dossier should comply with the data requirements as laid down in Part A to Regulation (EU) No. 283/2013. In general data requirements can be fulfilled

by submitting studies, a reasoned approach and/or relevant literature. Reference values or good quality assessments from other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed and any data access issues have been addressed by the applicant. Extrapolating from one semiochemical active substance to another (read-across) will be considered when accompanied by evidence of comparable relevant properties. This approach has been followed for the well-defined group of SCLPs. If no information from other regulatory frameworks or structurally similar semiochemicals is available further toxicity testing may be required to derive reference values.

For the exposure assessment the following exposure scenarios should be taken into account:

	Retrievable dispensers		**Non-retrievable application techniques**				
	Passive	**Active**	**Passive dispensers**	**Dosable matrix**	**Capsule suspension**	**Granular application**	**Seed treatment**
	1A	**1B**	**2A**	**2B**	**2C**	**2D**	**2E**
Operator exposure contact	Y	N	Y	Y	Y	Y	Y
Operator exposure inhalation	Y	N	Y	Y	Y	Y	Y
Worker exposure contact	Y	N	Y	Y	Y	Y	N
Worker exposure inhalation	Y	Y	Y	Y	Y	Y	N
Bystander exposure contact	N	N	N	N	Y	Y	N
Bystander exposure inhalation	Y	Y	Y	Y	Y	Y	Y
Resident exposure contact	N	N	N	N	Y	Y	N
Resident exposure inhalation	Y	Y	Y	Y	Y	Y	Y

Y = Yes, N = No

Vapour exposure can be estimated using the approach described in the guidance document on semiochemicals (Chapter 6, step II). For other exposure routes standard approaches as is done for chemicals, e.g. the EFSA AOEM, can be applied.

4. RESIDUES AND MRLS IN OR ON TREATED PRODUCTS, FOOD AND FEED

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

In general, for semiochemicals residue data may not be required if it has been determined that quantifiable residues (limit of quantification according to Regulation (EC) No 396/2005) on the consumable commodity are unlikely to occur or that reside levels are unlikely to exceed natural exposure levels during outbreaks of the pest (see Section 2.4.1 of Guidance Document on Annex IV; SANCO/11188/2013 – rev.2 or later). This can be demonstrated by a scientific rationale. In this case, an application for inclusion in Annex IV of Regulation (EC) No 396/2005 should be done by the applicant and the same time as it is applied for the approval of the active substance.

When the exposure route for the commodity is by the vapour phase only or when those

conditions are not fulfilled it is referred to Guidance document on semiochemical active substances and plant protection products.

If MRLs are in place or needed, residue data addressing the data requirements will be needed to show compliance with these MRLs or to propose new MRLs.

5. ENVIRONMENTAL FATE AND BEHAVIOUR AND EFFECTS ON NON-TARGET SPECIES

As described in the introduction when use of the plant protection product results in similar exposure (within one order of magnitude by the same route) to the natural exposure level of the semiochemical, the risk characterisation is concluded for the aspects fate and behaviour and effects on non-target organisms. No further information is needed. The guidance document provides information and examples how to compare natural background exposure with the product exposure.

If the exposure levels of the product are higher than the naturally occurring exposure levels the following exposure routes for the environment and non-target species should be taken into account.

The following table is taken from the guidance document.

Table 3.5-01 Compartment for which exposure is expected

	Retrievable dispensers		Non-retrievable application techniques				
	Passive	Active	Passive dispensers	Dosable matrix	Capsule suspension	Granular application	Seed treatment
	1A	1B	2A	2B	2C	2D	2E
Soil	N	N	N	N	Y	Y	Y
Groundwater	N	N	N	N	Y	Y	Y
Surface water	Y*	Y*	Y*	Y*	Y	Y	Y
Sediment	Y*	Y*	Y*	Y*	Y*	Y*	N
Air	Y	Y	Y	Y	Y	Y	Y
Birds and mammals	Y	Y	Y	Y	Y	Y	Y
Aquatic organisms	Y*	Y*	Y*	Y*	Y	Y	Y
Reptiles and amphibians	Y*	Y*	Y*	Y*	Y	Y	Y
Non target athropods (above ground)	Y	Y	Y	Y	Y	Y	Y**
Soil invertebrates	N	N	N	N	Y	Y	Y
Pollinators	Y	Y	Y	Y	Y	Y	Y

Y = Yes; N = No

* FOCUS (2008) air guidance regarding short range deposition estimations to surface water bodies should be followed.

** Unless information is provided that the active substance is not systemic so not taken up by the roots (e.g. use of the Briggs equation to calculate transpiration stream concentration factor on the transpiration stream concentration).

The guidance document on botanical active substances does not provide a general testing strategy for non-target organisms, 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.

6. EFFICACY EVALUATION OF SEMIOCHEMICALS

The data requirements for efficacy for a low-risk product can differ markedly from those for a conventional product. At the start of the efficacy evaluation the status of the product (low-risk or not) may however not yet be known. In some cases a product based on a low-risk substance may not receive low-risk status. In most cases however this 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.

Evaluation of the efficacy dossier

General EPPO standards

An EU guidance document on semiochemical actives and plant protection products is available (SANTE/12815/2014 – rev.5.2). This document also covers some efficacy aspects. For more detailed guidance on efficacy requirements however, reference should be made to 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 plant protection products, EPPO standard 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 product This evaluation manual does not repeat the content of this EPPO standard, but provides some further context.

The low-risk standard PP1/(296) is also used for low-risk products that are not semiochemicals. As such it does not go into much detail about pheromone specific issues, and partly refers to other standards on this subject.

Guidance specific for mating disruption pheromones is available in EPPO standard PP1/264(2). Many of the principles in this standard are also relevant for semiochemicals that have a different mode of action than mating disruption.
Trial setup may depend for a large part on behaviour and mobility of pests, and how these are affected by the semiochemical. It is possible that for a certain pheromone only incomplete guidance is available. It is advisable to contact Ctgb or schedule a PSM if more information is required. 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.

In addition to this general standard on mating disruptors several specific EPPO standards are available. These should be used for products where the relevant uses are claimed:
PP1/314(1); *Evaluation of mating disruption techniques against Lepidopteran pests in grapevine, pome and stone fruits under field conditions.*
PP1/323(1); *Evaluation of mating disruption techniques against Lepidopteran pests in grapevine, pome and stone fruits under semi-field conditions.*

Extrapolations

Pheromones are very different from conventional products and as such, conventional extrapolation tables are not relevant. Semiochemicals are often pest specific and act by modifying behaviour. The plant species is not relevant in relation to the product's performance. For that reason extrapolation is possible to other crops in which the same pest appears. In the case of semiochemicals that have multiple targets, extrapolation to a group of related species may be possible if properly motivated.