EUROPEAN COMMISSION
HEALTH & FOOD SAFETY DIRECTORATE-GENERAL

Food safety, sustainability, and innovation
Pesticides and Biocides

SANTE/12815/2014 rev. 11
January 2024

GUIDANCE DOCUMENT ON SEMIOCHEMICAL ACTIVE SUBSTANCES AND PLANT PROTECTION PRODUCTS

Revision history

When	What
Rev. 5.2 of 19 May 2016	First noted version
Rev. 11 of January 2024	Amendment adding a list of candidate substances for approval as semiochemicals, as well as their target species (amended by PAFF July-December 2023 and Biopesticides WG September/November 2023) and reviewing technical equivalence assessment (amended by PAI WG in November 2023).

Contents

1. Introduction

In order to facilitate the development, registration and use of semiochemicals as plant protection products, the OECD Working Group on Pesticides (WGP) developed guidance and rationales for their specific registration requirements. Harmonisation of requirements is very important for facilitating the research, development, commercialisation, and use of semiochemicals for plant protection. Using similar registration requirements in different countries should make it easier for applicants to submit applications to different countries and make it possible for regulatory agencies to benefit from each other's reviews.

It was considered appropriate to develop an EU Guidance Document which aims to provide practical solutions on how procedures and data requirements can be applied to facilitate the approval of semiochemicals at EU-level and the authorisation of plant protection products containing these active substances at Member State level.

In developing a regulatory approach for semiochemicals their specific properties should be taken into account. They are often target specific and act by modifying behaviour, may be used at concentrations close to those present in nature, and may dissipate and/or degrade rapidly. For these reasons it is expected that many semiochemical products can pose low risk to human health and the environment. Efficacy, environmental and health studies have demonstrated that such substances may provide effective pest control at low volumes, and at minimal risk.

Guidance for addressing the data requirements, taking into account the specific properties, uses and application techniques of semiochemicals, is provided in this document. This guidance document has been built on 'OECD-12' and experience gained since then.

Semiochemicals exist in nature for wide range of organisms, acting usually in a species-specific way. Recently the renewal of approval[1] for Straight Chain Lepidoptera Pheromones (SCLP) was granted.

A scientific literature review was carried out by one Member State, listing chemical compounds which act as semiochemicals for different classes assigned to the arthropods (Insecta, Arachnida, Diplopoda) which could be harmful to crops (pests). This expert review was based on the methodical screening of publicly available scientific publications[2] and expert judgement for classification of the findings, which was based on different level of molecular similarities and structural analogies with the SCLP group as defined (in 2021): 3 different groups of semiochemicals were identified with more or less similarities to the initial definition of the SCLP group.

The main results of this scientific review are listed in Appendixes I to III of this document, presenting several groups of compounds sorted according to their structural similarities with the SCLP group definition, in view of informing potential applicants and risk assessors about the opportunities of these compounds in plant protection and the possibilities for potential applications of new active substances or plant protection product authorisations.

[1] COMMISSION IMPLEMENTING REGULATION (EU) 2022/1251 of 19 July 2022 renewing the approval of the active substances Straight Chain Lepidopteran Pheromones (acetates) as low-risk active substances, and Straight Chain Lepidopteran Pheromones (aldehydes and alcohols) in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011, OJ, L191, 20.07.2022, p. 35

[2] https://www.pherobase.com/

2. Implementation schedule

This amended document has been finalised in the Standing Committee on Plants, Animals, Food and Feed on 31 January 2024 with immediate application as there are no direct effects on regulatory processes.

3. Scope

For the purpose of this Guidance Document, 'semiochemical active substances' refers to active substances that are emitted by plants, animals, and other organisms and are used by these organisms for communication. Substances referred to as natural-identical synthesized molecules are also covered by this Guidance Document.

Semiochemicals are not considered as active substances, when they are used only to attract arthropods which subsequently receive a lethal dose of an insecticide or are killed by other means, as in a bait. Further, semiochemicals used in traps to attract arthropods only for the purpose of monitoring are exempt from registration.

Currently, safeners, synergists, adjuvants and co-formulants are out of the scope of this Guidance Document.

4. Definitions

In the framework of this Guidance Document the following definitions apply:

Active substances are substances, including micro-organisms, which have general or specific action against harmful organisms or on plants, parts of plants or plant products.

Dispenser is a device able to release semiochemicals at controlled release rates.

Impurity means any component other than the pure active substance and/or variant which is present in the technical material or formulated product (including components originating from the manufacturing process or from degradation during storage).

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

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.

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).

- Straight-chained lepidopteran pheromones (SCLPs) are a group of pheromones consisting of unbranched, aliphatics having a chain of nine to eighteen carbons, containing up to three double bonds, ending in an alcohol, acetate or aldehyde

functional group. This structural definition encompasses the majority of known pheromones produced by insects in the order Lepidoptera, which includes butterflies and moths. This group is currently approved at EU level[3]. To note is that in the approval there is no restriction as regards the taxonomic classification of the pest it can be used against, which implies that the approved active substances can be used in a PPP against any kind of target pest if efficacy is proven.

- Straight Chain Arthropod Pheromones (SCAPs) are a group of pheromones structurally compliant with the SCLPs definition, except that triple bonds are possible i.e. consisting of unbranched aliphatics having a chain of nine to eighteen carbons, containing up to three unsaturated bonds, ending in an alcohol, acetate or aldehyde functional group. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which include also taxonomic orders beyond Lepidoptera (for instance Coleoptera, Diptera, Hemiptera, Acarida, Hymenoptera, Thysanoptera). This group is referred in the Appendix I as a non-exhaustive list of candidate compounds that could potentially be approved in the same group as SCLP, subject to confirmation by the rapporteur Member States as regards their toxicological similarities with the group of SCLP or subject to a peer review under Article 7 of Regulation (EC) No 1107/2009. To note that some compounds are already approved at EU level[4] but in different mixtures: it should however facilitate further their authorisations by Member States.

- Other Chained Arthropod Pheromones (OCAPs) are a group of pheromones structurally similar to SCLPs definition, i.e. consisting of acyclic, branched or unbranched aliphatics, containing a five to thirty carbons**,** zero to three unsaturated bonds and having zero to several functional alcohol, ester, aldehyde, ketone or epoxide groups. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which include also taxonomic orders beyond Lepidoptera (for instance Coleoptera, Diptera, Hemiptera, Acarida, Thysanoptera, Hymenoptera). This group is referred in the Appendix II to this amended guidance document as a non-exhaustive list of candidate compounds that could potentially be approved as a group of semiochemicals for which structural similarities with SCLP would mean toxicological similarities with the group of SCLP. This assumption is subject to confirmation by an application under Article 7 of Regulation (EC) No 1107/2009.

- Other Arthropod Pheromones (OAPs) are a group of pheromones not directly structurally related to SCLPs definition, i.e. consisting of branched or unbranched aromatic or aliphatic (straight or cyclic) hydrocarbons and containing two to thirty carbons zero to several unsaturated bonds and having zero to several functional alcohol, ester, aldehyde, ketone or epoxide groups. This structural definition encompasses the majority of known pheromones produced by and acting on a variety of organisms which encompasses different taxonomic orders assigned to Coleoptera, Diptera, Hymenoptera, Thysanoptera and Hemiptera. This group is referred in the Appendix III to this amended guidance document as a non-exhaustive list of candidate compounds that could potentially be approved as a group of semiochemicals for which structural relation with SCLP could potentially be identified, subject to confirmation by an application under Article 7 of Regulation (EC) No 1107/2009.

Technical grade active substance (TGAS) is a material containing an active substance that is used to manufacture plant protection products. It may contain impurities produced as by-

[3] OJ, L191, 20.07.2022, p. 35
[4] OJ, L191, 20.07.2022, p. 35

products of the manufacturing process, isomers and additives but does not contain co-formulants.

<table>
<tr><th>Group</th><th>Molecular Structure</th><th>Chain Length or Carbon Content</th><th>Number of unsaturated bonds</th><th>Type of chemical Functions</th><th>Position of chemical functions</th><th>Responding Orders</th></tr>
<tr><td>SCLPs</td><td>Acyclic, aliphatic (Straight)</td><td>Chain of 9 – 18 carbons</td><td>$\leq$ 3 (only double bonds)</td><td rowspan="2">Alcohol, acetate or aldehyde</td><td rowspan="2">Terminal (end of chain)</td><td>Lepidoptera</td></tr>
<tr><td>SCAPs</td><td></td><td></td><td>$\leq$ 3</td><td>Lepidoptera +Coleoptera, Diptera, Hemiptera, Thysanoptera, Hymenoptera, Acarida, etc.</td></tr>
<tr><td>OCAPs</td><td>Acyclic, branched or unbranched aliphatics</td><td>5-30 carbons</td><td rowspan="2">$\geq$ 0</td><td>Alcohol, ester, aldehyde, ketone or epoxide</td><td rowspan="2">Any</td><td rowspan="2">Coleoptera, Diptera, Hemiptera, Thysanoptera, Hymenoptera, Acarida, etc.</td></tr>
<tr><td>OAPs</td><td>Branched or unbranched aromatic or aliphatic</td><td>2-30 carbons</td><td>Various functional groups</td></tr>
</table>

5. Approval of semiochemical active substances and legal framework

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). The legal framework will also be the basis for the peer review and decision making process and therefore the data requirements and the protection goals as laid down in the Uniform Principles Part I (Regulation (EU) No 546/2011) have to be respected.

To note is that point 1.5 of the introductions of the Annexes of Regulations (EU) No 283/2013 and No 284/2013 allow to provide justifications in cases where experimental data would not be necessary owing to the nature of the active substance or the representative uses of the plant protection product containing it.

5.1. Pre-submission meeting

Applicants have the right to request a pre-submission consultation with the Competent Authority in line with the provisions of Article 32a of the General Food Law[5] and the Implementing Regulation (EU) No 2019/1381[6] on the transparency and sustainability of the EU risk assessment in the food chain. Applicants should assume that the Competent Authority is unfamiliar with the product specific technology and biology of the target organism. The main

[5] Regulation (EC) No 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 031 1.2.2002, p. 1

[6] OJ L 231, 6.9.2019, p.1

objective of pre-submission meetings is to discuss the information requirements and regulatory approach. Although the data requirements are laid down in legislative documents, applicants may need additional guidance how to interpret these data requirements and whether studies, published literature and/or a reasoned approach can be accepted. It is up to the applicant to submit the relevant information.

Information is recommended to include the following:

- The standard Good Agricultural Practices (GAP) table for active substances (see Appendix IV) and a draft label;
- The biology of the target organism(s), including information on the nature and specificity of the communication with the target organism, mating and flight behaviour, spatial distribution within the crop;
- Details on the product, the method of application and factors affecting the way the plant protection product should be used (e.g. weather, landscape, adjacent fields/structures);
- The mode of action of a semiochemical plant protection product in terms of its function in modifying the behaviour of the target organism;
- The possible effects or their absence on non-target organisms;
- The (reference) specification of the 'semiochemical active substance' (see chapter 7);
- The composition of the product listing all the ingredients, their amounts, and where appropriate their proportions;
- A summary on the health, environmental and efficacy data and related risk assessments.

It should be noted that the Member States competent authorities cannot be definitive on data/information requirements which are ultimately dependent on the full evaluation and peer review.

Information that normally should be considered confidential is listed in Article 63 of Regulation (EC) No 1107/2009.

If applicable and when available, the information should also include:

- International regulatory status;
- Other relevant information (e.g. from biocidal use, medical and veterinary use, cosmetic use, food and feed additives), such as summaries of other available evidence on the health, environmental and efficacy data and related risk assessments;
- Ranges of levels of the concerned active substance that occur in the environment. Extrapolation from other substances is possible, when justified;
- Safety Data Sheets (SDS).

5.2. Dossier preparation - general

All information necessary for hazard identification and exposure assessment should be provided. To note is that point 1.5 of the introductions of the Annexes of Regulations (EU) No 283/2013 and No 284/2013 allow to provide justifications in cases where experimental data would not be necessary owing to the nature of the active substance or the representative uses of the plant protection product containing it.

Applicants are advised to follow up all action points agreed in any pre-submission meeting and that the necessary information and assessments are included in the dossier.

In general data requirements can be fulfilled by submitting studies, a reasoned approach and/or relevant literature. If applicants submit relevant literature they should make clear reference to the specific data requirements which are considered to be addressed by this literature. Where scientific literature is provided it should have been searched and selected

without bias and determined as 'reliable'. In this respect the EFSA guidance on submission of scientific peer reviewed open literature applies (EFSA 2011; see also Article 8(5) of Regulation (EC) No 1107/2009).

When providing technical reports/studies on the properties or safety on the semiochemical active substance with respect to human or animal health, the environment or efficacy, the tests and analyses shall be conducted in accordance with the principles of Good Laboratory Practice (GLP) and Good Experimental Practice (GEP) as appropriate according to the provisions in Article 3(19) & (20) of Regulation (EC) No 1107/2009. However, the GLP- and GEP-requirement is accepted as not applying to studies reported in literature where the journal has a published peer-review policy.

It should be noted that, if studies are conducted, the test methods should be those specified in the modified Commission Communications 2013/C 95/01 and 2013/C 95/02. Any other methods used or deviations from the methods should be justified. Where the identity of the test substance or material has not been adequately specified, or its stability in dosing vehicles or solvents used is questionable, the impact on the validity/reliability and usefulness of the test or study has to be assessed.

In the introduction to the Annex to the data requirements (Regulation (EU) No 283/2013) it is indicated that:
"*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 one of the following conditions is fulfilled:*
(a) it is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary;
(b) it is technically not possible to supply.
In such a case a justification shall be provided."

For a number of semiochemical active substances these conditions may be particularly relevant.

Under Part A Section 1 point 1.11 in the data requirements (Regulation (EU) No 283/2013) it is stated that '*At least five representative batches from recent and current industrial scale production of the active substance shall be analysed for content of pure active substance, impurities, additives and each further component other than additives, as appropriate'*. […] *For plant extracts and semiochemicals (such as pheromones), justified exemptions can be made'*.
This means that a smaller number of batches tested might be acceptable. However, a sound justification is to be provided in such cases (see chapter 7)

Extrapolating from one semiochemical active substance to another (read-across) can be considered when accompanied by evidence of comparable relevant properties.

Application of non-testing methods (e.g. the use of validated (Q)SAR models) could also be taken into account when doing the assessment.

5.3. Dossier preparation - specific

The specific properties of semiochemicals and the way they are used as plant protection products means that point 1.5 of Introductions to the Annexes of Regulations (EU) No 283/2013 and 284/2013 are applicable, i.e. experimental data would not be necessary owing to the nature of the active substance or the representative uses of the plant protection product containing it, in the field of health and environment if scientifically justified.

Information on the biology of the target organism(s) and information on the specificity of the communication between organisms and resulting lack of effects on non-target organisms is key information for the assessment of semiochemicals. Information to demonstrate this can be gathered from efficacy trials or fundamental investigations on emitting and receiving species. As a first indication of their efficacy and specificity the Appendixes I, II and III are reporting the available scientific literature and peer-reviewed articles but any complementary information or data shall be provided. The lists reported in Appendixes I, II and III should be considered as non-exhaustive lists and only illustrative. Application for a new semiochemical complying with one of the definition of the new groups but not included in any of the Appendixes is acceptable to be considered.

Data requirements for human health and environmental risk assessment also depend on the type of plant protection product and on its realistic conditions of use. In this context, it is important to differentiate between different types of application techniques:

1. Retrievable dispensers

1A) Passive dispensers (extruded or reservoir). The semiochemical diffuses continuously from the device into the air where the active substance becomes diluted.

1B), Active dispensers: the semiochemical is released discontinuously from the device into the air where the active substance becomes diluted.

2. Passive non-retrievable dispensers

2A) Dispensers (extruded or reservoir). The semiochemical diffuses continuously from the device (such as biodegradable dispensers) into the air where the active substance becomes diluted.

2B) Dosable matrix dispensers: the semiochemical is embedded in a matrix, such as a sticky polymeric material. They are not discrete units; application is *in-situ* by attaching the polymeric mass onto plants or elsewhere at the site of use.

2C) Capsule suspension products: the semiochemical is formulated as a microencapsulation.

2D) Granular products (non-WDG): the semiochemical is formulated in a granular form.

2E) Seed treatment products

2F) Sprayable matrix

Some examples of dispenser types are provided in Appendix V.

Any uses of semiochemicals in plant protection products not mentioned above should be evaluated on a case-by-case basis with the possibility of extending the list of types of application techniques/formulated products. Dispenser units 1(B) should in most of the cases be considered as the packaging containing a formulated product. All other current examples above are considered part of the formulated product.

This document provides guidance on options for addressing data requirements when completing dossiers for semiochemical active substances and products which is explained in more detail in the following chapters.

Further guidance on the risk assessment of semiochemicals may be developed by the European Food Safety Authority in the future.

5.4. Classification and labelling

Where a classification according to Regulation (EC) No 1272/2008 is applicable, relevant data should be submitted. Details are to be discussed between the applicant, the rapporteur Member State (RMS) and European Chemicals Agency (ECHA).

6. Natural exposure levels in relation to applied levels

Semiochemicals are active substances in plant protection products generally considered as naturally occurring, non-toxic and with a target-specific mode of action. They are generally effective at very low rates, often comparable to levels that occur naturally. They may be volatile and can dissipate and/or degrade rapidly in the environment. When compared to conventional hydraulic spraying application techniques, plant protection products containing semiochemicals may be formulated and dispensed using techniques that can reduce exposure levels.

For the purposes of modifying pest behaviour, releases of semiochemicals are unlikely to exceed natural emissions of high density target populations and are dependent on olfactory and other receptor systems that are tuned to natural emission rates. For example, male Lepidoptera typically respond to a discrete range in ambient pheromone concentration, with the consequence that a high rate of pheromone release may be less effective than an intermediate rate of release. Controlled release technology is critical to slow down and extend effective pheromone release over the appropriate time period.

The following approach is recommended to estimate the levels of exposure that might occur naturally in the environment from a high density population of emitting organisms, independent from the use of plant protection products and thus, expected to be experienced by humans and other non-target organisms (= natural exposure level). This natural exposure should be compared with the exposure resulting from the intended use of the plant protection products. This approach applies when the exposure route is by the vapour phase only (retrievable dispensers and dosable matrix). When oral or contact exposure to the plant protection product is possible e.g. to sprayed droplets, treated seeds and granules then a risk assessment in relation to these routes of exposure is needed.

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 (or other semiochemicals, when justified), the risk characterisation is concluded. No further information is needed with the exception of identity, characterisation and analytical methods (see chapter 7 and 10).

Information should be provided regarding the natural exposure levels: the following method (Step 1) is recommended for this. This method is for estimating natural exposure levels of a given semiochemical from available experimental data.

The calculation method can be used to obtain a realistic reference value which can then be compared with the use rate of the plant protection product. It is in the applicant's interest that good quality justified information is provided.

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

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

Equation 1: Formula for calculation of estimated value

$$\boldsymbol{PRR = RIO \times NRO}$$

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

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

When the number of releasing organisms is not known, an equation such as the following can be used to estimate the population.

Equation 2: Formula for calculation of estimated value

$$\boldsymbol{NRO} = \frac{\boldsymbol{YLD}}{\boldsymbol{MPY}} \times \frac{\%\boldsymbol{INF}}{\mathbf{100}} \times \boldsymbol{OCC}$$

Where,
NRO Number of Releasing Organisms) is the number of releasing organisms per hectare.
YLD (Yield), is the total yield of the crop in one cropping cycle (Kg/ha).
MPY (Mass per yield unit), is the average mass of a standard unit (Kg) of the crop.
% INF (Infestation rate), is the percentage of harvested units affected by the target organism (%, dimensionless).
OCC (Occupancy), is the number of releasing individuals per individual plant part (dimensionless).

This formula may be adapted for other scenarios, such as when the pest does not affect the harvested unit. The input data for the equation should preferably be taken from official sources e.g. FAO or peer-reviewed scientific literature.

6.2. Step II: Comparison between natural exposure level and related exposure from the plant protection product

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

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

6.3. Step III: Mathematical modelling to predict the final concentrations derived from the application of semiochemical based plant protection products

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

There are other models but in general they are used to calculate concentrations in much bigger areas, for point sources like leakages or other kind of massive releases.

The fixed-box model is described in detail in Appendix V. The variables in the model equation have been standardized to a constant in order to provide a simple expression where the key parameter is the release rate of semiochemical per area unit. This operation is also rationalized in Appendix V.

7. Identity, physical and chemical properties

7.1. Active substance

For all submissions data requirements on identity should be addressed.

Physical and chemical properties should be addressed as far as needed for specific purposes (e.g. analytical methods, to perform a risk assessment, classification and labelling).

In point 1.10 of Part A of Annex of Regulation (EU) 283/2013, it is stated that additives and significant manufacturing impurities should be described and their concentrations should be provided. It is further stated that relevant manufacturing impurities have to be assessed for their toxicological and ecotoxicological properties (e.g. by validated (Q)SAR models for genotoxic end-points). When impurities in semiochemicals are themselves also semiochemicals the practice should be to sum up these individual impurities and specify them as a single impurity. Impurities occurring in significant[7] amounts and/or being of (eco-) toxicological relevance that are not themselves semiochemicals are to be specified individually.

Confidentiality may apply to some extent, according to Article 63 of Regulation (EC) No 1107/2009.

Deviations from the standard data requirements may occur in the following area:
Under point 1.11 of Part A of Annex of Regulation (EU) 283/2013, it is stated that at least "*five representative batches from recent and current industrial scale production"* of the active substance shall be analysed for content of pure active substance, impurities, additives and each further component other than additives, as appropriate. "*For plant extracts and semiochemicals (such as pheromones), justified exemptions can be made"*.

This deviation is to take into account situations, when production is insufficient to allow 5 batches within a reasonable timeframe. At the time of submission, it is the interest of the applicant to provide data for as many batches as possible, including laboratory and pilot production. It is recognised that sometimes only one batch may be available.

Where a semiochemical is constituted by isomers, the ratio of isomers in the TGAS needs to be specified (as defined by the data requirements). Note that the specification defined does not need to be the same as in the natural semiochemicals. It should also be noted that typically

[7] See definitions in SANCO/3030/99 rev.5

an individual species only emits single enantiomers, as living cells are a chiral environment and biochemistry usually only produces one enantiomer. Structural isomer production by an organism is possible and the natural ratios emitted can vary. This situation (particularly that of enantiomers) should be accounted for when considering the characterisation of exposure and risk.

7.2. Plant protection product

Detailed information about the formulated product should be provided. The dispensers should be described.

When a dispenser is considered part of the plant protection product (cases 1A, 2A, 2C, 2B, 2D, 2E), changes related to the dispenser and not impacting the release rate per ha per hour, should be considered as non-significant formulation changes. Applicants should justify with information why they consider such a change as non-significant.

8. Technical equivalence

The *"Guidance Document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 (SANCO/10597/2003 – rev. 10.1, 13 July 2012 or later)"* is applicable to semiochemicals.

In the particular case of semiochemicals being SCLPs, and in supplement to the Guidance Document (SANCO/10597/2003), some specific rules can be applied: when impurities in SCLP active substances are themselves also SCLPs the practice should be to sum up these individual SCLP impurities and specify them as a single impurity, as they are of comparable (low) risk as the SCLP AS. Nevertheless, a fully validated analytical method should be provided for each individual SCLP impurity.

Regarding the assessment of impurities, the following applies:

- For SCLP impurities, a global specification should be set corresponding to the sum of individual SCLP impurities. However, a higher specified content compared to the reference specification does not preclude considering the new source equivalent at Tier I.
- For all other impurities, if equivalence cannot be confirmed at Tier I, an assessment at Tier II is required. Relevant impurities have to be specified.

Following their renewal in 2022, all SCLP active substances are currently specified individually on a single-compound basis. In consequence, the assessment of the technical equivalence for new sources should be performed on the individual SCLP (single compound as specified) and not on mixtures that were previously called ‘blends’ (SCLPs produced separately, then mixed (blended) or mixtures of single SCLPs produced together in one manufactured batch with or without subsequent).

The reference specifications to be taken into account in the assessment of the technical equivalence, correspond to the sources of SCLPs specifications that were considered fully validated in the RAR (see Vol 1 and “Vol4_ALLBatches_amendment_January_2021.xlsx”) or those set after re-approval in 2022.
In the case where no fully validated reference specifications are available in the RAR, the minimum purity of the active substance as well as the maximum content of the relevant impurity as indicated in the review report should be taken into account for the assessment of

technical equivalence. In these cases, Tier II assessment is required for all impurities except the (sum of) SCLP impurities.

When checking the technical equivalence for semiochemicals, isomer ratios do not have to match the reference specification in order to be considered equivalent.

9. Biological properties and data on application

The biology of the target organism(s), including information on the nature and specificity of the communication with the target organism and information on possible effects or their absence on non-target organisms, should be fully described and used to justify the risk assessment strategy. The mode of action of a semiochemical plant protection product should be explained in terms of its function in modifying the behaviour of the target organism.

Details on the product, the method of application and factors affecting the way the plant protection product should be used (e.g. weather, landscape, adjacent fields/structures) should be fully described. This description should also include the numbers of dispensers per ha, how this relates to the release rate per ha per hour, and how often the dispensers need replacing during the season. In addition, a rationale for their placement within the field/orchard, as related to the factors described above, should also be provided. Further information is available in EPPO guideline 1/264(1) Mating disruption pheromones (rev. 1 or later).

In the standard good agricultural practice (GAP) table the application rate per treatment for retrievable dispensers (categories 1A & 1B), and dosable matrix dispensers (category 2B) should be expressed as a 24-hour average active substance release rate per hectare per hour (for example ng/ha/h). The total time the dispensers will be deployed during the season should be described as the duration of the treatment and interval at which individual dispensers may require changing. For details see Appendix IV.

In the GAP for other non-retrievable application techniques (categories 2A, 2C, 2D, 2E, 2F) the application rate should be defined both as active substance ng/ha/h and g/ha combined with the number of applications per season. Where there is more than one application, the interval between treatments must be provided. For details see Appendix IV.

In term of authorisations, Member States should focus on the release rate per ha per hour. Member States must be aware that the same release rate per ha per hour may be achieved by different combinations of number of dispensers per ha and/or release rate per dispenser.

10. Analytical methods

With regards to the analytical methods for the active substance in the TGAS and in the formulation, the data requirements (Regulation (EU) No 283/2013 and (EU) No 284/2013) apply. Applicants are reminded to use the appropriate methods for volatile compounds.

Where the exposure (by the same route) caused by the use of the plant protection product is similar (within one order of magnitude) to natural exposure levels of the semiochemical (or a group of related semiochemicals when justified), the risk characterisation is concluded. For that compartment no further information as regards analytical methods for post authorisation monitoring purposes is needed, though analytical methods supporting any pre authorisation experiments provided in submissions apply and must be provided according to the data requirements (Regulation (EU) No 283/2013 and (EU) No 284/2013).

Although semiochemical impurities are specified not individually, but as a sum, analytical methods to quantify each individual impurity in the TGAS are to be provided as much as technically possible.

11. Mammalian toxicology

The aim of the human health risk assessment is to ensure that semiochemical active substances for use in plant protection products do not have any harmful effects on the health of consumers (via residues), operators, workers, bystanders or residents.

When the exposure route is by the vapour phase only (retrievable dispensers – categories 1A & 1B, non-retrievable dispensers – category 2A and dosable matrix – category 2B) and where the exposure (by the same route) caused by the use of the plant protection product is similar (within one order of magnitude) to natural exposure levels of the semiochemical (or a group of related semiochemicals when justified) the risk characterisation is concluded (see step I, chapter 6). When these conditions are not fulfilled the following hazard identification, a full exposure assessment and subsequent conclusion on the risk assessment is necessary.

When oral or contact exposure to the plant protection product is possible e.g. to sprayed droplets, treated seeds and granules then risk assessment in relation to these routes of exposure is always needed.

11.1. Hazard identification

Data Requirements and read-across
The application of this guidance to specific cases will depend on the nature of the semiochemical active substance, its intended uses, exposure levels and whether there is information on the semiochemical active substance from documented exposure. It may be possible to use data derived from uses such as biocidal use, medical and veterinary use, cosmetic use, food and food additives or epidemiological studies, or any other data on possible adverse health effects on the basis of case reports of intoxication (e.g. data related to toxicity on livestock animals). Reference values and good quality assessments from other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed and any data access issues have been addressed by the applicant. The aim is to identify areas of potential adverse effect on human health or whether the exposure levels do not result in harmful effects under the proposed realistic conditions of use.

As manufacturing impurities (>1g/kg TGAS) that are not semiochemicals will not have natural exposure levels, their hazard characterisation is necessary (e.g. by scientifically validated (Q)SAR models for genotoxic end-points).

Limitations regarding the use of human data according to Regulation (EU) No 1107/2009 apply. According to recital 13 and Article 8 (2) of Regulation (EU) No 1107/2009 no tests and studies involving the deliberate administration of the active substance or the plant protection product to humans with the purpose of determining a human 'no observed effect level' of an active substance should be contained in the dossier. However, this should not prevent the use of available data from e.g. clinical studies if the semiochemical active substance is used in human medicine.

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 and could be tentatively applied for other groups of semiochemicals based on the structural similarities with the approved SCLPs.

Application of non-testing methods (e.g. the use of scientifically validated (Q)SAR models for genotoxic end-points) will also be taken into account when provided.

It should be noted, however, that any read-across hypothesis based on structural similarity will require some form of validation as foreseen by the “OECD Guidance on Grouping of Chemicals, Second Edition. Series on Testing and Assessment, No. 194” and the “Read-Across Assessment Framework (RAAF), ECHA-17-R-01-EN”.

11.2. Exposure assessment

When step I is not fulfilled or when the exposure route is not by the vapour phase only exposure for operators, workers, bystanders and residents may occur, depending on the application technique (see table 1).

When exposure calculations are necessary, for vapour phase exposure see step II (chapter 6), for other exposure routes follow standard approaches. This means sufficient information should be provided and an assessment of potential occupational and bystander exposure during and following application of a product will be based on the proposed use pattern.

Table 1: Groups for which exposure may be expected

	Retrievable dispensers		Non-retrievable dispensers					
	Passive	Active	Passive dispensers	Dosable matrix	Capsule suspension	Granular application	Seed treatment	Sprayable matrix
	1A	1B	2A	2B	2C	2D	2E	2F
operator exposure contact	Y	N	Y	Y	Y	Y	Y	Y
operator exposure inhalation	Y	N	Y	Y	Y	Y	Y	Y
worker exposure contact	Y	N	Y	Y	Y	Y	N	Y
worker exposure inhalation	Y	Y	Y	Y	Y	Y	N	Y
bystander exposure contact	N	N	N	N	Y	Y	N	Y
bystander exposure inhalation	Y	Y	Y	Y	Y	Y	Y	Y
resident exposure contact	N	N	N	N	Y	Y	N	Y
resident exposure inhalation	Y	Y	Y	Y	Y	Y	Y	Y

Y = Yes; N = No

12. Residues and MRLs in or on treated products, food and feed

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 residue 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 at the same time as is applied for the approval of the active substance.

When the exposure route for the commodity is by the vapour phase only (retrievable dispensers – categories 1A & 1B, non-retrievable dispensers – category 2A and dosable matrix –category 2B) and where the exposure (by the same route) caused by the use of the plant protection product is similar (within one order of magnitude) to natural exposure levels of the semiochemical (or a group of related semiochemicals when justified) the risk characterisation is concluded (see step I, chapter 6). When these conditions are not fulfilled information addressing the data requirements may be necessary. It is advised to discuss this approach at an early stage with a rapporteur member state. Where relevant the rapporteur may consult other competent authorities.

When consumer exposure following contact of the commodity with the plant protection product is possible e.g. to sprayed droplets, then risk assessment in relation to this route of exposure is always needed.

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.

13. Environmental fate and behaviour

The aim of the environmental risk assessment is to ensure that semiochemical active substances for use in plant protection products do not have any unacceptable effects on the environment.

When the release in the environment is by the vapour phase only (retrievable dispensers – categories 1A & 1B, non-retrievable dispensers – category 2A and dosable matrix – category 2B) and where the release (by the same route) caused by the use of the plant protection product is similar (within one order of magnitude) to natural release rates of the semiochemical (or a group of related semiochemicals when justified) the risk characterisation is concluded (see step I, chapter 6). When these conditions are not fulfilled the following exposure assessment should be provided (depending on the application techniques; see table 2).

When release into the environment is via other routes than the vapour phase e.g. by sprayed droplets (including off-target spray drift), treated seeds and granules then an exposure assessment regarding these is always needed.

The Regulation requires exposure levels in soil, groundwater, surface water, sediment and air to be considered. Depending on the application techniques all compartments may not be exposed (see table 2).

The application of this guidance to specific cases will depend on the nature of the semiochemical active substance, its intended uses, exposure levels and whether there is

information on the semiochemical active substance from documented exposure. It may be possible to use data derived from uses such as biocidal use, medical and veterinary use, cosmetic use, food and food additives. Good quality assessments and endpoints from such other regulatory frameworks may be taken into account if the basis for the derivation of these endpoints can be assessed and any data access issues have been addressed by the applicant.

When exposure calculations are necessary, for vapour phase exposure see step II (chapter 6), for other exposure routes the standard approaches should be followed.

The information to be submitted must be sufficient to address any concern identified and might be reduced to the relevant environmental compartment. The nature of the compound and its behaviour can also be taken into account. For example, for highly volatile compounds such semiochemicals, a calculation based on the substance's volatility may be used to replace the need for certain studies/requirements, e.g. by providing estimates of the rapidity and likely extent of volatilisation losses and gains from / to soil and natural surface water systems by re-deposition. Potential for long range atmospheric transport should be addressed following FOCUS (2008) air guidance.

14. Effects on non-target species (excluding man and domesticated animals)

The aim of the ecotoxicological risk assessment is to ensure that semiochemical active substances for use in plant protection products do not have any acute or long-term unacceptable effects on the non-target species, including beneficial organisms and bees.

14.1. Hazard identification

When the exposure route is by the vapour phase only (retrievable dispensers – categories 1A & 1B, non-retrievable dispensers – category 2A and dosable matrix – category 2B) and where the exposure (by the same route) caused by the use of the plant protection product is similar (within one order of magnitude) to natural exposure levels of the semiochemical (or a group of related semiochemicals when justified) the risk characterisation is concluded (see step I, chapter 6). When these conditions are not fulfilled hazard identification, exposure assessment and subsequent conclusion on the risk assessment is necessary.

When the exposure of non-target organisms is via other routes (e.g. contact, dietary) than the vapour phase e.g. by sprayed droplets (including off-target spray drift), treated seeds and granules then risk assessment in relation to these routes of exposure is always needed.

The application of this guidance to specific cases will depend on the nature of the semiochemical active substance, its intended uses and resulting exposure levels in water, sediment and soil or on plant surfaces or in food items of non-target species.

It may be possible to use effects data derived from dossiers provided for other uses such as biocidal use, medical and veterinary use, cosmetic use, food and feed additives. Good quality assessments and threshold values from such other regulatory frameworks may be taken into account if the basis for the derivation of these thresholds can be assessed and any data access issues have been addressed by the applicant. The aim is to identify areas of potential unacceptable effect on the non-target species or whether the exposure levels do not result in unacceptable effects under the proposed conditions of use.

As manufacturing impurities (>1g/kg TGAS) that are not semiochemicals will not have natural exposure levels the hazard characterisation is necessary for them (e.g. by validated (Q)SAR models as already described in section 7).

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

14.2. Exposure assessment

When step I is not fulfilled or when the exposure route is not by the vapour phase only, exposure for non-target organisms may occur, depending on the application technique (see table 2).

When exposure calculations are necessary, for vapour phase exposure step II (chapter 6) should be applied, for other exposure routes the standard approaches should be followed.

Table 2: Compartment for which exposure may be expected

	Retrievable dispensers		Non-retrievable application dispensers					
	Passive	Active	Passive dispensers	Dosable matrix	Capsule suspension	Granular application	Seed treatment	Sprayable matrix
	1A	1B	2A	2B	2C	2D	2E	2F
soil	N	N	N	N	Y	Y	Y	Y
groundwater	N	N	N	N	Y	Y	Y	Y
surface water	Y*	Y*	Y*	Y*	Y	Y	Y	Y
sediment	Y*	Y*	Y*	Y*	Y*	Y*	N	Y*
air	Y	Y	Y	Y	Y	Y	Y	Y
birds and mammals	Y	Y	Y	Y	Y	Y	Y	Y
aquatic organisms	Y*	Y*	Y*	Y*	Y	Y	Y	Y
reptiles and amphibians	Y*	Y*	Y*	Y*	Y	Y	Y	Y
non target arthropods (above ground)	Y	Y	Y	Y	Y	Y	Y**	Y
soil invertebrates	N	N	N	N	Y	Y	Y	Y
pollinators	Y	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).

15. Efficacy

Regulation (EC) No 1107/2009 (Article 4(3)) requires that a plant protection product shall be sufficiently effective and it shall not have any unacceptable effects on the plants or plant products. It also states that an active substance alone or associated with a safener or synergist shall only be approved where this has been established for one or more representative uses for the associated plant protection product(s). This is required to be evaluated in accordance with the Uniform Principles (Article 29(6)).

Data to demonstrate efficacy should be provided in the form of a biological assessment dossier. Data from efficacy trials conducted according to agreed guidelines (including relevant EPPO guidelines) are required.

In addition, guidance document SANCO/10054/2013 – rev. 3 (or later) provides guidance how to address data requirements on efficacy for the dossier to be submitted for the approval of a new active substance contained in a plant protection product. It is recognised, however, that deviations from the guidance may be required in some cases to account for the specific properties of semiochemical plant protection products. Where this is the case, detailed descriptions and explanations for the methodologies used should be provided. The explanation may require relating the methodology to the mode of action and potential factors affecting its effectiveness under field conditions.

The mode of action of a semiochemical product should be explained in terms of its function in modifying the behaviour of the target pest. This information can form the basis of reasoned cases to address several areas of the efficacy assessment, not only related to performance and proposed label claims, but also to address crop safety and any other unintended non-acceptable side effects.

It should be recognised that semiochemical plant protection products may provide full control, partial control or contribute to control. Often the measure of benefit is not in lethal dose to the pest, but in reduction of damage to the harvestable portion of the crop. They may also have more variable performance than would be expected for a conventional chemical plant protection product. The effective dose can be reduced with continual usage of the semiochemical plant protection product and therefore establishing a minimum effective dose is inappropriate. In most cases there is no linear dose-response relationship. However, a rationale for the chosen dose should still be provided, and this may include preliminary, laboratory (or glasshouse) studies examining emission rates of target pests, effects on biology etc. Any reduced performance should not in itself be grounds for refusal of authorisation, if the applicant reasons why the demonstrated efficacy might be sufficient to deliver a benefit, in accordance with EPPO 1/214 ‘Principles of acceptable efficacy’ (rev. 3 or later). Such reasons might be offering an alternative mode of action (relevant to resistance management), in comparative assessment, reduce residues of chemical plant protection products or compatibility with specific growing systems. As a minimum there must be a demonstrable statistically significant improvement, at an acceptable level of probability, of an appropriate measure of either pest control, crop damage or crop yield, of sufficient magnitude to be beneficial from an agronomic perspective.

It is recognised that efficacy field trials for semiochemicals are complex and may be difficult to replicate and on a large scale. It is essential to provide as much information on the biology of the target and the mode of action of the semiochemical where possible. These factors, in combination with the recommended application technique, will determine the appropriate trial design (e.g. plot size, timing and placement of dispensers), and should form the basis of the product label recommendations for use and claims. The more preliminary and small scale studies provided, the greater the scope to reduce the number of field trials (EPPO and other

agreed guidelines provide more information, in particular EPPO guideline 1/264 (rev. 1 or later) 'Mating disruption pheromones'. Although this is written for mating disruption, a number of the principles on trials design and assessments are applicable to other types of semiochemicals).

The experimental design may include whenever possible untreated plots as an indication of population pressure and/or plots receiving a commercial standard treatment with another plant protection product of known efficacy as a basis for comparison with the semiochemical treatment. Currently also cage techniques are discussed for efficacy evaluation of substances which are used for the confusion method.

Resistance to semiochemicals is currently not foreseen, but the applicant should make a case based on the proposed use.

16. Other developments

Article 22 of Regulation (EC) No 1107/2009 introduces the new category of "low-risk active substances" which are active substances that present “considerably less of a risk than other substances". Specific criteria are laid down in Annex II.5 to identify a substance as low risk.
If 'semiochemical active substances' can be considered as “low-risk” active substances according Article 22 of Regulation (EC) No 1107/2009 will be the result of the decision based on an application and assessment according to the criteria fixed in Annex II of Regulation (EC) No 1107/2009. The plant or animal origin of a substance does not confer this status automatically.

17. References

Acín, P.; Rosell, G.; Guerrero, A.; Quero, C. 2010: Sex pheromone of the Spanish population of the beet armyworm *Spodoptera exigua*. *J. Chem. Ecol.* 36(2): 778-786

Akey, D.H.; Henneberry, T.J. 1998: Beet armyworm (Lepidoptera: Noctuidae) behaviour and effects on insecticide efficacy in open and closed cotton flowers and boll abscission or damage from flower infestation. *J. Econ. Entomol.* 91(1): 263-266

Backmän, A.C. 1997: Pheromone release by codling moth females and mating disruption dispensers. *IOBC wprs Bull.* 20(1): 175-180

Backmän, A.C.; Bengtsson, M.; Witzgall, P. 1997: Pheromone release by individual females of codling moth, Cydia pomonella. *J. Chem. Ecol.* 23(3): 807-814

Banuri, T. 1997: Pakistan: Environmental impact of cotton production and trade. *Trade Knowledge Network Project – REPORT. International Development Research Center – Ottawa, Canada*

Collins, R.D.; Rosenblum, L.; Cardé, R.T. 1990: Selection for increased pheromone titre in the pink bollworm moth, *Pectinophora gossypiella* (Lepidoptera: Gelechiidae). *Physiol. Entomol.* 15(1): 141-147

Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, 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 (2013/C 95/01)

Commission communication in the framework of the implementation of 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 (2013/C 95/02)

Commission Regulation (EC) No 2229/2004 of 3 December 2004 laying down further detailed rules for the implementation of the fourth stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC (OJ L 379, 24.12.2004)

Commission 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)

Commission Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009)

Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products (OJ L 155, 11.6.2011)

Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, 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)

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)

EEA (European Environment Agency). 2009: Europe's onshore and offshore wind energy potential. EEA Technical Report. No. 6/2009

EPPO Standards (PP1): https://pp1.eppo.int/standards/PP1-264-2

European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance Straight Chain Lepidopteran Pheromones. EFSA Journal 2014;12(1):3524. [537 pp.] doi:10.2903/j.efsa.2013.3058.

Flint, H.M.; Yamamoto, A.; Parks, N.J.; Nyomura, K. 1990: Aerial concentrations of gossyplure. The sex pheromone of the pink bollworm (Lepidoptera: Gelechiidae), in cotton fields treated with long-lasting dispensers. Environ. Entomol. 20(1): 175-180

FOCUS AIR (2008): https://esdac.jrc.ec.europa.eu/public_path/projects_data/focus/air/docs/FOCUS_AIR_GROUP_REPORT-FINAL.pdf

Guidance document on criteria for inclusion of active substances in Annex IV of Regulation (EC) No 396/2005 (SANCO/11188/2013)

Guidance document on Data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products (SANCO/10054/2013)

Guidance Document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009 (SANCO/10597/2003 – rev. 10.1, 13 July 2012 or later)

EFSA: Guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009; EFSA Journal 2011;9(2):2092; https://www.efsa.europa.eu/en/efsajournal/pub/2092

Health Canada, Pest Management Regulatory Agency. 2013. Regulatory Directive 2013-03: "Value Assessment of Pest Control Products" https://publications.gc.ca/site/eng/9.577495/publication.html

OECD: Guidance for Registration Requirements for Pheromones and Other Semiochemicals Used for Arthropod Pest Control (OECD Environment, Health and Safety Publications, Series on Pesticides No. 12)

Mitchell, E.R. and Mayer, M.S. 2001: Spodoptera exigua: Mating disruption, measurement of airborne concentration of pheromone, and use of specialist receptor cell responses for comparison to female pheromone emission. J. Environ. Sci. Health. B36(4): 467-488

Peters, C. 2010: Precision Pipfruit Production. *Victoria Fruitgrowers Meeting Nov 2010 – APAL Australia.* https://apal.org.au/

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)

Symonds, M.R.E.; Johnson, T.L.; Elgar, M.A. 2011: Pheromone production, male abundance, body size and the evolution of elaborate antennae in moths. *Ecol. Evol.* 2(1): 227-246

Ünlü, L. 2007: The estimation of field infestation ratio of blind bolls of *Pectinophora gossypiella* Saunders and *Earias insulana* Boisd. *J. Entomol.* 4(1): 33-39

Vossen, P.M.; Jolly, D.; Meyer, R.; Varela, L.; Blodgett, S. 1994. Disease, insect pressures make organic production risky in Sonoma County. *California Agriculture* 48(6): 29-36

Appendix I – candidate list of Strain Chain Arthropod Pheromones (SCAPs)
https://food.ec.europa.eu/document/download/84756f63-408c-4498-bf96-d56e03a006f5_en

Appendix II – candidate list of Other Chain Arthropod Pheromones (OCAPs)
https://food.ec.europa.eu/document/download/59e92f1c-1ae7-4267-959a-d2b8d091ae37_en

Appendix III – candidate list of Other Arthropod Pheromones (OAP)
https://food.ec.europa.eu/document/download/d4e27a8f-b9a0-474d-8338-797a0781cf8f_en

Appendix IV - Good agricultural practice table[8]

			GAP rev. , date: year-month-day
PPP (product name/code):	product name / code	Formulation type:	type [a, b]
Active substance 1:	active substance 1	Conc. of as 1:	conc. [c]
Active substance 2:	active substance 2	Conc. of as 2:	conc. [c]
Active substance.…:	active substance ...	Conc. of as ….:	conc. [c]
Safener:	safener	Conc. of safener:	conc. [c]
Synergist:	synergist	Conc. of synergist:	conc. [c]
Applicant:	company	Professional use:	☐
Zone(s):	northern/central/southern/interzonal [d]	Non professional use:	☐
Verified by MS:	yes/no		
Field of use:	herbicide, fungicide, insecticide etc		

[8] For full details see Template to notify intended zonal applications under Article 33 and Article 43 of Regulation (EC) No 1107/2009 (SANCO/12544/2014 rev. 0, 12 December 2014 or later)

1	2	3	4	5	6	7	8	8A	10	11	12	13	14
Use-No. (e)	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F, Fn, Fpn G, Gn, Gpn or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**				**Application rate**			**PHI** (days)	**Remarks:**
					Method / Kind	Timing / Growth stage of crop & season	Max. number a) per use b) per crop/ season	Duration of treatment window (min)	kg or L or number of product / ha a) max. rate per appl. b) max. total rate per crop/season	g or kg as/ha a) max. rate per appl. b) max. total rate per crop/season	ng as/ha/h a) min b) max		
Zonal uses (field or outdoor uses, certain types of protected crops)													
1					*specify dispenser type: continous, discontinuous, retrievable or not*			*time during which the dispensers are deployed (includes changing of empty dispensers)*					*Range of number of dispensers per ha and the release rate per dispenser*
2													
Interzonal uses (use as seed treatment, in greenhouses (or other closed places of plant production), as post-harvest treatment or for treatment of empty storage rooms)													
3													
4													
Minor uses according to Article 51 (zonal uses)													
5													
6													
Minor uses according to Article 51 (interzonal uses)													
7													
8													

Remarks table heading:

(a) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(b) Catalogue of pesticide formulation types and international coding system CropLife International Technical Monograph n°2, 6th Edition Revised May 2008

(c) g/kg or g/l

(d) Select relevant

(e) Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1

(f) No authorization possible for uses where the line is highlighted in grey, Use should be crossed out when the notifier no longer supports this use.

Remarks columns:

1 Numeration necessary to allow references

2 Use official codes/nomenclatures of EU Member States

3 For crops, the EU and Codex classifications (both) should be used; when relevant, the use situation should be described (e.g. fumigation of a structure)

4 F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

5 Scientific names and EPPO-Codes of target pests/diseases/ weeds or, when relevant, the common names of the pest groups (e.g. biting and sucking insects, soil born insects, foliar fungi, weeds) and the developmental stages of the pests and pest groups at the moment of application must be named.

6 Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated.

7 Growth stage at first and last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

8 The maximum number of application possible under practical conditions of use must be provided.

9 Minimum interval (in days) between applications of the same product

10 For specific uses other specifications might be possible, e.g.: g/m³ in case of fumigation of empty rooms. See also EPPO-Guideline PP 1/239 Dose expression for plant protection products.

11 The dimension (g, kg) must be clearly specified. (Maximum) dose of a.s. per treatment (usually g, kg or L product / ha).

12 If water volume range depends on application equipment (e.g. ULVA or LVA) it should be mentioned under “application: method/kind”.

13 PHI - minimum pre-harvest interval

14 Remarks may include: Extent of use/economic importance/restrictions

Appendix V - Examples of Semiochemical-based Plant Protection Product

In principle, a classification of semiochemical-based plant protection products can be made according to their retrievability, the mode of controlled release and/or their formulation type. Some examples can be found in the following table:

	Retrievable dispensers		**Non-retrievable dispensers**		
	Passive	Active	Capsule suspension	Sprayable matrix	Dosable matrix
Typical unitary load (mass a.i.)	*ca*. 1-2%	*ca*. 10%	< 0.1%	< 10 %	ca. 1-2%
Density of devices per surface (units per ha)	100-1,000	1-5	>>1,000,000	>>1,000,000	100-1,000
Exposure in deployment/app	Very low	None	Low	Low	Low
Exposure in-use (residual)	Constant	Instantaneous	Constant	Constant	Constant
Chance of exposure (time)	Whole day	Night period	Whole day	Whole day	Whole day

Examples and main features for those types of products are briefly presented:

1. Retrievable dispensers

A) Passive dispensers. The diffusion of the active ingredient occurs by equilibrium of permeation from the device into the air where the active ingredient becomes diluted.

Extruded Dispensers: The active ingredient is embebbed in a matrix, that is usually made from polymeric material. The dispensers are discrete units.

Figure 1: Pictures of different examples of retrievable-passive-extruded dispensers.

Reservoir Dispensers: The active ingredient is kept inside a container. The compound migrates through the walls of this container to the outer surface where it diffusses passively.

Figure 2: Pictures of different examples of retrievable-passive-reservoir dispensers.

The general features for retrievable passive dispensers are:

- Passive emission
- High number of emission points needed (50-1000 dispensers/ha)
- Emission rate per dispenser (400-700 mg/ha/day = 20-275 g A.I. per ha / season)
- Small area of influence per dispenser
- Pheromone released during the whole day
- Release dependent on weather conditions

Typical kinetics release profile for three representative examples in real field conditions are provided for two products of the Checkmate®. The active ingredient loss rate could be estimated as approximately constant and it is indicated by the value of the slope of the regression line included in each graph hereunder (mg/day).

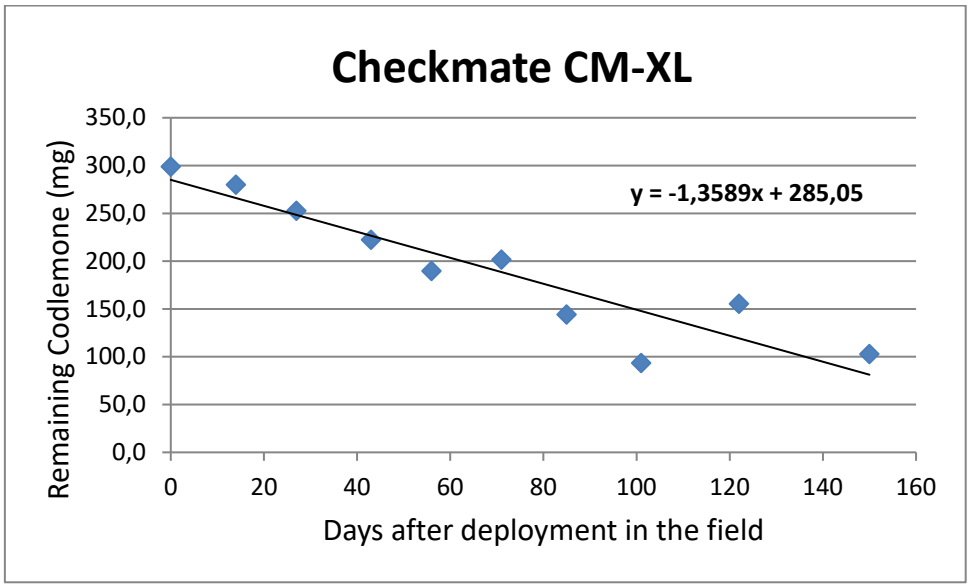


Figure 3: Release profile for Checkmate® CM-XL passive dispensers (Mating disruption of *Cydia pomonella*).

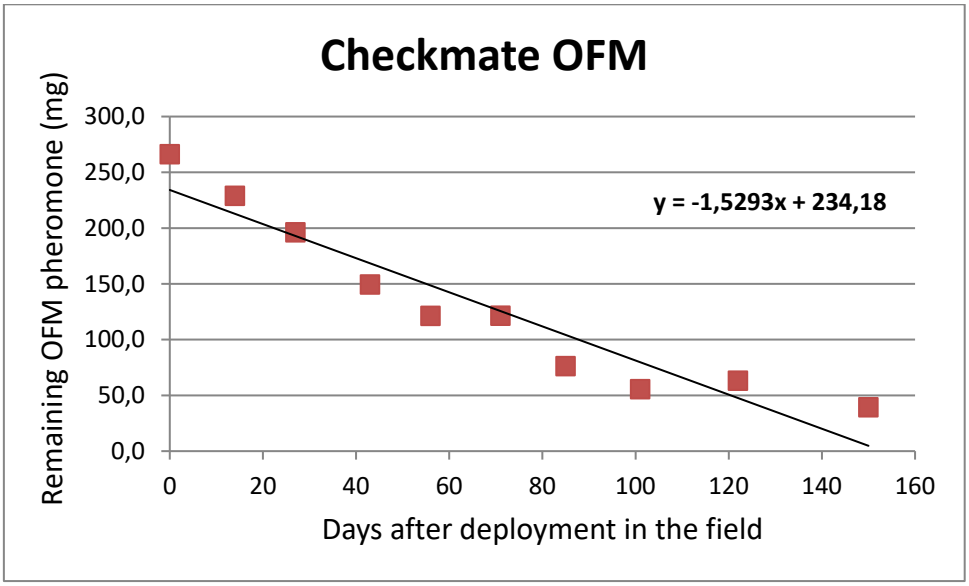


Figure 4: Release profile for Checkmate OFM passive dispensers (Mating disruption of *Grapholita molesta*).

The application rate for these products varies depending on the pest. For example, in the case of CheckMate®, typical values for different species are provided in the following table:

Pest species	**Checkmate**	**mg/unit**	**units/ha**	**g/ha/year**
Cydia pomonella	CM-XL	270	300	81.0
Grapholita molesta	OFM	250	270	67.5
Anarsia lineatella	PTB	200	375	75.0
Planococcus ficus	VMB-XL	150	620	93.0

The following table shows some application rate data on passive dispenser products.

PPP	Target pests	Crops (major)	Application rate g as/ha/y sum of single SCLPs	Dispenser/ha
ISONET L	*Lobesia botrana*	Grapes	86	500
ISOMATE OFM ROSSO	*Grapholita molesta, Grapholita funebrana*	Stone fruits Pome fruit	240	500-600
ISOMATE C LR combi product	*1. Part: Cydia pomonella* *2. part: Leaf rollers*	Pome fruit	240	1000
ISOMATE C-PLUS	*Cydia pomonella*	Pome fruit	190	800-1000
ISOMATE C TT	*Cydia pomonella*	Pome fruit	190	500
ISOMATE C/OFM combi product	*1. Part: Cydia pomonella* *2. part: Grapholita molesta*	Pome fruit	190	800-1000
ISONET L PLUS combi product	*1. part: Lobesia botrana* *2. part: Eupoecilia ambiguella*	Grapes	180	500
ISONET LE combi product	*1. part: Lobesia botrana* *2. part: Eupoecilia ambiguella*	Grapes	190	500
ISONET Z	*Zeuzera pyrina, Synanthedon tipuliformis*	Pome fruit	21	300
ISONET A	*Anasia lineatella*	Stone fruits	134	1000
ISOMATE A/OFM combi product	*1. Part: Anasia lineatella* *2. part: Grapholita molesta*	Stone fruits	274	1000
ISOMATE RSB	*Chilo suppressalis*	Rice	75	50-100

B) <u>Active retrievable dispensers:</u> The diffusion of the active ingredient occurs by turbulence-enhanced equilibrium of permeation from the device into the air where the active ingredient becomes diluted.

Figure 5: An example of retrievable-active dispensers in use.

This technology works by periodical releasing of pheromone at the time of the day where the pest is active (usually during night period). Pheromone is actively loaded into the air, where it gets diluted. As an example, in the case of Checkmate Puffer CM this means a liberation of 2mg-10mg of active ingredient per shot. The total amount of pheromone employed by surface unit and year is approximately the same when compared to passive dispensers.

Values of application rates for different species are provided in the following table:

Pest species	Checkmate Puffer	g/unit	units/ha	g/ha/year
Cydia pomonella	CM	55.5	2	111.0
Grapholita molesta	OFM	48	2	96.0
Anarsia lineatella	PTB	64.8	3	194.4
Lobesia botrana	LB	28	2.5	70.0

<u>General features</u>

- Aerosol Formulation contains the active ingredient.
- Active emission after activation.
- Emission rate per dispenser (300-500 mg/ha/day= up to 110 g/ha/season)
- Large area of influence per device
- Low number of emissions points (1,25 - 5 devices/ha)
- Completely retrievable.
- Pheromone released during flight activity. System is active during the night when the exposure of humans is unlikely.
- Constant release at defined time intervals.

2. Non-retrievable Dispensers

A) <u>Capsule suspension products:</u> The active ingredient is formulated as a microencapsulation. Suspension of the concentrate in water and spraying into the field distribute millions of microdispensers that subsequently behave as passive dispensers.

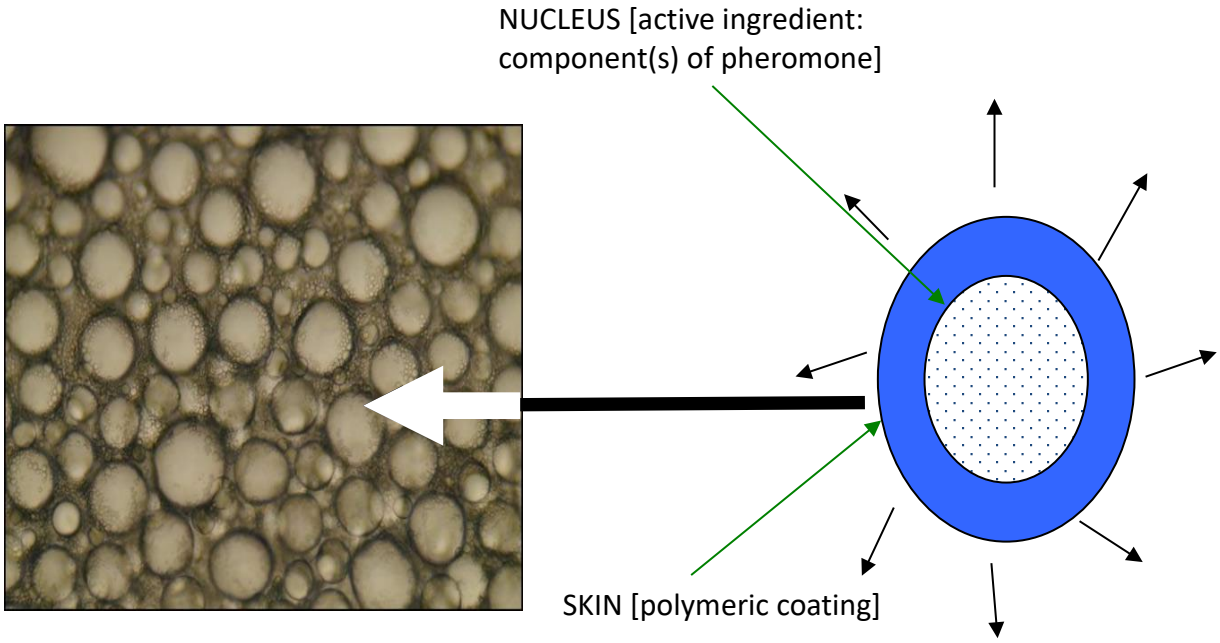


Figure 6: Scheme showing the structure of microcapsules, an example of a non-retrievable-capsule-suspension product. Microcapsule diameter is <200 micron.

Figure 7: Capsule suspension products are applied with standard spraying equipment. After application millions of microcapsules behave as passive dispensers each.

General features

- Capsule Suspension (CS) formulation
- Different microencapsulation processes. Sex pheromone components may be a limiting factor for the use of some processes.
- Sex pheromone components contained inside polymers which are the walls of the microcapsule.
- Microcapsule diameter: ≤ 200 µm
- As in any other passive dispenser, microcapsule release rates also depends on weather conditions.

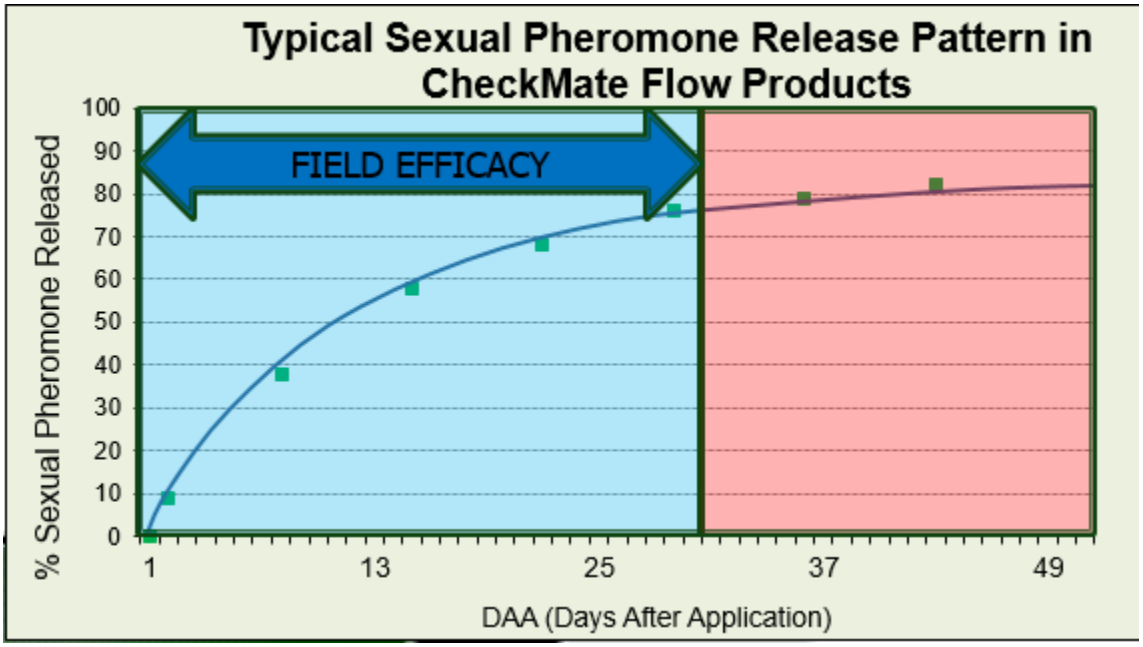
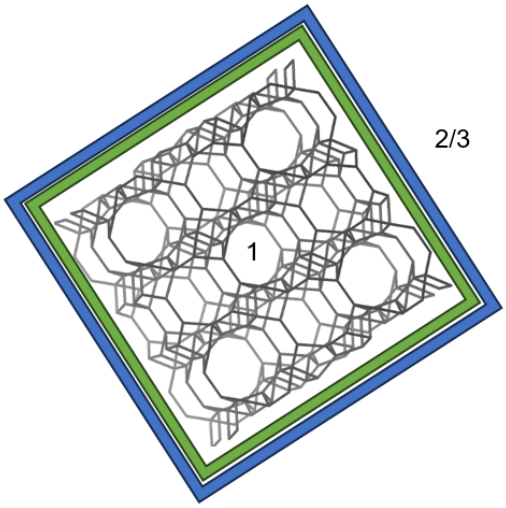


Figure 8: Release pattern for semiochemical capsule suspension products after application.

For this kind of product, the amount of active substance is again depending on the species. Typical application rate values are provided for different products CheckMate-F® as representative examples:

	Checkmate F	**g a.s./L**	**mL/ha**	**g/ha/year**
Cydia pomonella	CM-F	140	100	140.0
Grapholita molesta	OFM	230	50	115.0
Anarsia lineatella	PTB	175	150	157.5

B) **Sprayable matrices:** Similar to non-retrievable dosable dispensers, the active ingredient is embedded within a solid matrix. When mixed into a tank, it forms a suspension that, upon being sprayed onto the field, disperses millions of micro-dispensers. These micro-dispensers then act as passive dispensers, gradually releasing the active ingredient over time.



1 – Core carrier material is solid and has a natural background
2/3 – inert mineral / biodegradable co-formulants/additives.

Figure 7: Scheme showing the structure of sprayable matrix, an example of a non-retrievable-sprayable-matrix product (e.g. WP, WG, SC). Particle size diameter is <70 micron.

C) Dosable matrix dispensers: Like for extruded passive dispensers the active ingredient is embebbed in a matrix, which in this case is made of a sticky polymeric material. They are not discrete units, so dosifying happens in-situ by sticking the polymeric mass directly into the plants.

Final considerations:

It is important to remark that this document shows a general description of the way of application of Semiochemical-based Plant Protection Products. The rates given there are typical values and it has to be considered that the successful applications of these techniques are influenced by environmental factors like, *e.g.*:

- Wind (especially if constant and recurrent)
- Evaporation (seasonal increases in summer)
- Plot shape and size (surrounding area)
- Plot location (slopes, basins, hills)
- Tree height and vegetation (high, unevenness, failing)
- Specific local conditions (traffic roads, rivers, houses…)

These factors affect the diffusion of the volatile compound originating the need of slight tuning in the application rates that at the end are kept in the same magnitude order.

Appendix VI – Fixed steady one-cell model

The essential hypotheses of the fixed steady one-cell model are:

- The base of the box is a rectangle with W and L dimensions, having one of its sides parallel to the wind direction. Normally L is referred to the source's dimensions according to the wind direction.
- The atmospheric turbulence produces a complete and total blending of the pollutants up to the blending height H. No flux is produced higher to this. The result is that a homogeneous *c* concentration can be assumed inside the defined volume of air.
- The wind blows with a direction x with a speed u. This speed and direction are constant and independents to time, place or height above the ground.
- The concentration of pollutants that enters the source area (x=0) from the exterior with the wind is constant and equal to b (background concentration).
- The rate of emission of substances per unit area is q (*e.g.* in g/s·m^2). This rate is constant and does not vary with the wind.
- No contaminant enters or leaves through the sides of the box that are perpendicular neither to the wind direction nor from the upper side (blending height).

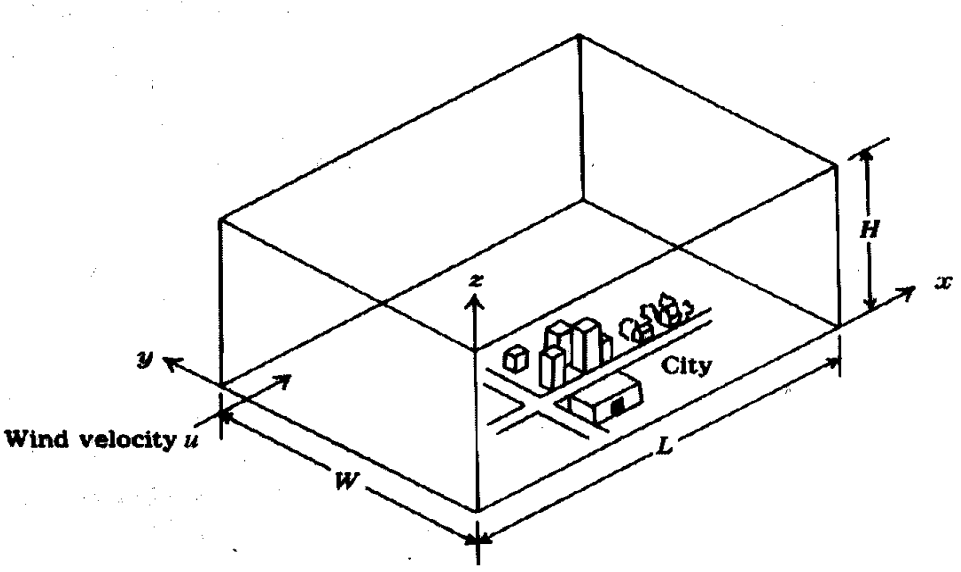


Figure 1: Rectangular city, showing meaning of symbols used in the fixed-box model (Source: *de Nevers*, Air Pollution Control Engineering 2nd Ed. McGraw-Hill, 2000).

Steady state equilibrium is assumed to be obtained (the concentration does not vary with time):

- In this model the substance is assumed to be stable.
- The amount of air that enters equals the amount that exits in the cell.

The chemical mass balance is reduced to entrances, emissions and exits. For estimating the concentration in air due to the emission of the products in a field a square parcel having a homogeneous distribution of emissions has been considered. The objective is to quantify the increase of substance contents in the air when wind flows on the parcel with a constant wind speed and direction (Figure 1).

Assuming all the conditions above, equation 3 to obtain the concentration inside the box is as follows:

Equation 3:

$$c = b + \frac{qL}{uH}$$

For our purpose we could set reasonable values to all the parameters but the release rate of the semiochemical q per surface unit (ng/ha/h). These values are:

- Background could be considered negligible (b= 0 mg/m^3)
- The base of the box is a square of one hectare (W=L=100m)
- Wind speed is set at 3m/s (u= 3m/s), this is an extremely low average value for any of the European areas according to climatic standards. So this assumption is reflecting a worst case scenario (EEA, 2009).
- The mixing height is set at 5m (H= 5m), this value is likely expected to be bigger but a precautionary approach is taken considering that the semiochemical is not diffusing above a reasonable work height where exposure may occur.

By fixing these values and applying the conversion factors to use suitable units we obtain the following simple expression in equation 4 that estimates final airborne concentration in ng/m^3 from the release rate of the semiochemical due to application in ng/ha/h.

Equation 4:

c (ng/m^3)= 0.185·q (ng/ha/h)

When designing a plant protection product it is intended to achieve a target range of concentration in the treated area. Since degradation will usually occur in the field, the release rate of the plant protection product is established so that it compensates degradation. Since degradation is not considered in the model, the model will predict (all other parameters being equal) a higher concentration and thus be more conservative.

In Appendix IV representative examples are provided to demonstrate the validity of the predictions obtained by the model on one side, and to illustrate the procedure of background exposure calculation and comparison on the other.

Appendix VII – examples supporting the aforementioned proposals

The calculations given in this appendix are examples only based on information available for SCLPs at the time of writing. They should not preclude other calculations if justified by and based on additional scientific data.

The codling moth sex pheromone example (*Cydia pomonella*)

Regarding Step I: Natural exposure level estimation
There are no measurements of pheromone concentration of natural exposure levels for severe codling moth outbreaks, but a reasoned calculation can be made starting with the fact that the average release rate from individual females has been determined to be 9 ng/h (Bäckman et al., 1997). Infestation degree has been reported to be up to 100% of the fruit infested, no specification of the mean number of worms found per fruit is reported but it has to be at least one to provide a total infestation (Vossen, 1994). The genetic potential of apple tree in standard growing conditions is *ca.* 135 metric tonnes per hectare, and a common weight for commercial apples could be taken as approximately 200g (Peters, 2010). The combination of these last data provide a number of $6.75 \cdot 10^5$ apples/ha that may lead to $3.4 \cdot 10^5$ calling codling moth females per hectare, which means an average release rate of $3.1 \cdot 10^6$ ng/ha/h that is equal to 3.1 mg/ha/h. Note that average release from the dispensers was 12 mg per hectare and hour (mg/ha/h).
The two values, 3 and 12 mg/ha/h, are within the same order of magnitude so we can conclude that the exposure scenario derived from the use of mating disruption at that release rate does not significantly differ from the one expected in a severe outbreak of the pest.

Regarding Step II: Mathematical prediction
In this case there are actual data of the airborne concentration of codling moth pheromone in a mating-disruption-treated apple orchard (Bäckman, 1997). Measurement made by means of calibrated EAG quantitation provided a value of 1.1 ng/m^3 in a field where average release from the dispensers was 12 mg per hectare per hour (mg/ha/h).
The mathematical model forecasts a value of 2.2 ng/m^3 for this release rate (See Appendix III), showing a good fitness with respect to the real measured concentration (note that degradation has not been taken into account). It can be considered that both values are within the same order of magnitude.

The pink bollworm sex pheromone example (*Pectinophora gossypiella*)

Regarding Step I: Natural exposure level estimation.
There are no measurements of pheromone concentration of natural exposure levels for severe pink bollworm outbreaks, but a reasoned calculation can be made starting with the fact that the average titre value from pheromone gland of virgin females has been determined to be 24 ng (Collins et al. 1990). Considering this amount of sex pheromone to be liberated in 24 hours and omitting peak release we can assume a release of *ca.* 1 ng/h per female as reasonable approach. Infestation degree has been reported to be up to 60% of the bolls infested, and the mean number of worms found per boll is reported to be as high as 4.86 (Ünlü, 2007). The yield of cotton in standard growing conditions is *ca.* 1,500 metric tonnes per hectare, and the accepted average weight of a cotton boll is approximately 3.5 g (Banuri, 1998). The combination of these last data provide a number of $4.3 \cdot 10^8$ bolls/ha that may lead to $6.27 \cdot 10^8$ calling pink bollworm moth females per hectare, which means an average release rate of $6.27 \cdot 10^8$ ng/ha/h that is equal to 627

mg/ha/h. Note that average release from the dispensers was 42 mg per hectare and hour (mg/ha/h).
We can conclude that the exposure scenario derived from the use of mating disruption at that release rate is below the background exposure and does not significantly differ from the one expected in a severe outbreak of the pest. Even for this estimation the amount of the natural background in that case is *ca.* 15-fold higher with respect to the measured in a mating disruption treatment.

Regarding Step II: Mathematical prediction
There are actual data of the airborne concentration of cotton bollworm pheromone in a mating-disruption-treated cotton field (Flint et al., 1990). Measurement made by means of calibrated EAG quantitation provided a maximum value of 2.0 ng/m^3 in a field where the average release from the dispensers was 41.6 mg per hectare and hour (mg/ha/h).
The mathematical model forecasts a value of 7.7 ng/m^3 for this release rate (See Appendix III), showing a good fitness with respect to the real measured concentration (note that degradation has not been taken into account). It can be considered that both values are within the same order of magnitude.

The beet armyworm sex pheromone example (*Spodoptera exigua*)

Regarding Step I: Natural exposure level estimation.
There are no measurement of pheromone concentration of natural exposure levels for severe beet armyworm outbreaks, but a reasoned calculation can be made starting with the release rate of a single female has been determined to be *ca*. 2.1 ng/gland, that can be converted to *ca.* 0.09 ng/h per female as a reasonable approach (Acín et al. 2010). Infestation degree has been reported to be up to 20% of the bolls infested, and the mean number of worms found per boll is reported to be typically one per boll (Akey and Henneberry, 1998). The yield of cotton in standard growing conditions is *ca.* 1,500 metric tonnes per hectare, and the accepted average weight of a cotton boll is approximately 3.5 g (Banuri, 1998). The combination of these last data provide a number of $4.3 \cdot 10^8$ bolls/ha that may lead to $4.3 \cdot 10^7$ calling beet armyworm moth females per hectare, which means an average release rate of $3.87 \cdot 10^6$ ng/ha/h that is equal to 4 mg/ha/h. According to the publication on the experiments performed by Mitchell and Mayer (2001), the average release from the dispensers to achieve complete mating disruption was 3 mg per hectare in eight hours. This value equates to 0.4 milligrams of the corresponding pheromone per hectare and hour (mg/ha/h).
The two values, 4 and 0.4 mg/ha/h, are within one order of magnitude, even for this approach the natural background would be tenfold the amount produced by the mating disruption treatment. Therefore, we can conclude that the exposure scenario derived from the use of mating disruption at that release rate does not significantly differ from the one expected in a severe outbreak of the pest.