参考資料３

Unclassified **ENV/JM/MONO(2017)33**

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

10-Jan-2018

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2017)33
Unclassified

GUIDANCE DOCUMENT ON SEMIOCHEMICAL ACTIVE SUBSTANCES AND PLANT PROTECTION PRODUCTS

Series on Pesticides
No. 93

English - Or. English

JT03425264

OECD Environment, Health and Safety Publications
Series on Pesticides
No. 93

GUIDANCE DOCUMENT
ON SEMIOCHEMICAL ACTIVE SUBSTANCES AND PLANT PROTECTION PRODUCTS

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INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2017

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FOREWORD

This document provides guidance to both industry and regulatory authorities on how procedures and data requirements can be applied to facilitate the submission of a complete data package/dossier for semiochemical active substances in plant protection products, and the subsequent evaluation of this data package/dossier by the regulatory authorities. In 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 synthesised molecules are also covered by this Guidance Document.

The document provides a summary of the legal frameworks and registration procedures for semiochemical active substances and plant protection products in several OECD member countries It also describes various information elements that are considered necessary for assessing the safety of these substances. 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. 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.

The document has been developed within the framework of the OECD Expert Group on Bio-Pesticides (EGBP), a sub-group of the OECD Working Group on Pesticides (WGP) that helps member countries to harmonise the methods and approaches used to assess biological pesticides and to improve the efficiency of control procedures. The EU served as the initial author of the guidance document, which has been reviewed and further developed by the EGBP. The EGBP includes representatives from OECD member countries and the regulated industry.

The present guidance document received final approval of the OECD EGBP on the 30th of November 2016 and of the OECD WGP by written procedure on the 30th of October 2017

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public.

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INTRODUCTION

1. In developing a regulatory approach for reviewing and approving the use of semiochemicals, their specific properties should be taken into account. Semiochemicals 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.

2. Since the early 2000's, the OECD Working Group on Pesticides (WGP) has worked to help member countries harmonise the methods and approaches used to assess and register biological pesticides, including semiochemicals. 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. Further, harmonisation of requirements is very important for facilitating the research, development, commercialisation, and use of semiochemicals for plant protection.

3. The early work focused on developing guidance documents for the registration requirements for semiochemicals[1] (2002) - hereafter referred to as "*OECD 12*", followed by guidance for industry data submissions for semiochemicals and their active substances[2] (2003) and guidance on the format and presentation of the documentation to be prepared by regulatory authorities who receive industry data submissions[3](2003).

4. In several jurisdictions, during the review of straight chained lepidopteran pheromones it became apparent that guidance document OECD 12 was no longer sufficient for the review process and there was a need for a more updated guidance. In response, in May 2016, the EU published a new document entitled "*Guidance Document on Semiochemical Active Substances and Plant Protection Products*[4]". Following this publication, the EGBP worked together with the EU to develop the following Guidance Document. While based largely on the EU publication, the following guidance more broadly reflects the practices across OECD countries, such as the legal frameworks and registration procedures that concern semiochemical active substances. The guidance is also based on OECD 12, but takes into account the experiences gained by governments since that document was published.

[1] OECD Guidance for Registration Requirements for Pheromones and Other Semiochemicals Used for Arthropod Pest Control Series on Pesticides **No. 12**

[2] OECD Guidance For Industry Data Submissions for Pheromones and Other Semiochemicals and their Activie Substances (Dossier Guidance for Pheromones and Other Semiochemicals), Series on Pesticides No. 16 (2003)

[3] OECD Guidance for Country Data Review Reports for Pheromones and other Semiochemicals and their Active Substancs (Monograph Guidance for Pheromones and other Semiochemicals) Series on Pesticides No. 17 (2003)

[4] EU Guidance Document on Semiochemical Active Substances and Plant Protection Products, SANTE/12815/2014 rev. 5.2, May 2016

SCOPE

5. 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 synthesised molecules are also covered by this Guidance Document.

6. 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.

7. Furthermore, safeners, synergists, adjuvants and co-formulants are also outside the scope of this Guidance Document.

DEFINITIONS

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

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

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

11. 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).

12. 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 humans and other non-target organisms are expected to be impacted by such exposure level.

13. 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.

14. Different types of semiochemicals include:

- Allelochemicals produced by individuals of one species that modify the behaviour of individuals of a different species (i.e., an interspecific or interspecies 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 or interspecies 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 and 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.

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

REGISTRATION OF SEMIOCHEMICAL ACTIVE SUBSTANCES AND LEGAL FRAMEWORKS

16. Semiochemical active substances are regulated slightly differently in different countries and regions. This section provides an overview of the regulatory frameworks in Australia, Canada, the EU, Japan, New Zealand and the United States.

Australia

17. The Australian Pesticides and Veterinary Medicines Authority (APVMA) assess and registers agricultural and veterinary chemical products. A number of products of biological origin fall within the Australian Government, Agricultural and Veterinary Chemicals Code Act 1994 (the Agvet Code) definition of an agricultural chemical product and therefore must be registered by the APVMA. The definition of an agricultural chemical product includes not only plant protection products, but also biocides and other products. The APVMA's guidelines refer to these products by the term 'biological agricultural product'. APVMA define four major categories of biological chemical products:

- Category 1: biological chemicals (e.g., pheromones, hormones, growth regulators, enzymes and vitamins)
- Category 2: plant and other extracts (e.g., plant extracts, oils)
- Category 3: microbial agents (e.g., bacteria, fungi, viruses, protozoa)
- Category 4: other living organisms (e.g., microscopic insects, plants and animals plus some organisms that have been genetically modified).

18. As the Australian regulator, the APVMA recognises the need for flexibility in determining the data requirements for biological products, and the APVMA's 'Guideline for the regulation of biological agricultural products' (http://apvma.gov.au/node/11196) allows for these products to be evaluated on a case-by-case basis as well as providing specific guidance for when reduced information requirements apply.

Canada

19. At the federal level in Canada, pesticides are regulated under the Pest Control Products Act (PCPA). All products, organisms and substances that are within the definition of "pest control product" as described in the PCPA must be registered before they are imported, manufactured or used in the country. The registration requirement does not apply to pesticides that are exempt by regulation (e.g., pesticide devices that do not pose unacceptable risks to people or the environment). For pest control products containing pheromones and other semiochemicals, Regulatory Proposal PRO2002-02, Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals, offers general guidance to prospective applicants and registrants. Regulatory Proposal PRO2002-02 outlines the general principles for the regulation of pheromones and other semiochemicals that affect the behaviour of arthropods and are used in pest control products. (Semiochemicals used in traps to attract and monitor arthropods are exempt from registration). The proposed data set is reduced relative to conventional pesticides. Further reductions in data requirements are proposed for the family of chemicals which make up the straight-chained lepidopteran pheromones (SCLPs). For regulatory purposes, SCLPs are pheromones with a well-defined unbranched aliphatic structure, which is characteristic of most known pheromones produced by members of the order Lepidoptera, including moths and butterflies. In developing a regulatory approach for semiochemicals, the inherent differences between these products and conventional pesticides were taken into consideration. Semiochemicals act by modifying the behaviour of the pest species rather than killing it, are more target specific than conventional insecticides, are used at concentrations close to those occurring in nature, and dissipate rapidly. For these reasons it is expected that most semiochemical products will pose low potential risk to human health and the environment. Applicants are encouraged to make use of the pre-submission consultation process to help determine what information is needed in support of registration. Prior to initiating any original testing, applicants are encouraged to consult with the Pest Management Regulatory Agency (PMRA) on proposed protocols. Pre-submission advice will include information to assess:

a. *Human health and safety*: Hazard information requirements, including acute inhalation and genotoxicity, must be addressed for all semiochemicals that are not SCLP, regardless of the application method and whether exposures to workers and the public are expected to be similar to natural background levels. Short and long term studies may be waived for SCLPs and possibly for other well-characterised semiochemicals. Dietary, occupational and bystander exposure information may also be required for some semiochemicals depending on whether emissions are expected to be above certain specified levels described in Regulatory Proposal PRO2002-02.

b. *Environmental risks*: Hazard information requirements must be addressed for terrestrial wildlife, aquatic animals, plants and beneficial insects. The types of studies required will, however, depend on various factors, such as the method of application (e.g., fixed dispenser versus broadcast spray), formulation (e.g., granular) and site of application (e.g., aquatic versus terrestrial). Information to address the environmental fate of a pheromone or semiochemical may also be required if the potential for environmental exposure is expected to exceed natural background levels or if ecotoxicity data or public literature indicates a hazard to biota. For potential effects to non-target insects, a discussion of available information may be sufficient. For semiochemicals that are SCLPs, environmental chemistry and fate and environmental toxicology data (with the exception of aquatic toxicology data where exposure is expected) may be waived due to the existing body of evidence for this specific group of pheromones. Further information is available in Regulatory Proposal PRO2002-02.

c. *Value:* In Canada, a weight of evidence approach is used to support proposed label claims, and value information from several sources may be submitted, including efficacy trials, scientific rationales, published literature, and history of use in other jurisdictions (Health Canada, Pest

Management Regulatory Agency 2013; 2014). The PMRA's approach to the value has been updated since the publication of PRO2002-02, and a pre-submission consultation is recommended.

EU

20. 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.

Pre-submission meeting

21. Applicants are encouraged to request a pre-submission consultation with the Competent Authority, particularly if they are not familiar with the regulatory system. Applicants should assume that the Competent Authority is unfamiliar with the product specific technology and biology of the target organism. The main 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.

22. It is recommended that the information include the following:

- The standard Good Agricultural Practices (GAP) table for active substances (see Appendix I) 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 section on Identity, physical and chemical properties);
- 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.

23. 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.

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

25. 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).

Dossier preparation

26. All information necessary for hazard identification and exposure assessment should be provided. 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.

27. 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).

28. 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.

29. It should be noted that 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.

30. 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.*"

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

32. Under 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’.

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

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

Classification and labelling

35. 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).

Japan

36. For all 'botanical active substances' it should be made clear that the plant material has been produced with sustainable, reproducible methods and that the Nagoya Protocol on Access to genetic resources and fair and equitable sharing of benefits, adopted by the Conference of the parties to the Convention on Biological Diversity (2010 in Nagoya), has been respected.

37. Japan has no specific regulations and guidelines for the approval of botanical active substances. Therefore, in principle, for the evaluation and registration of botanical active substances, a complete set of data which is the same with that required for chemical substances under Notification No.12- Nousan 8147 would be required. This Notification provides information about whether data requirements can be exempted when certain criteria are met (e.g., if there is enough information on the health effect of the active ingredients due to long history of safe consumption as food, certain data requirements can be waived).

New Zealand

38. The two main pieces of legislation covering the regulation of pesticides in New Zealand are:

a Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 administered by Ministry for Primary Industries (http://www.mpi.govt.nz/importing/agricultural-compounds-and-veterinary-medicines); and

b Hazardous Substances and New Organisms (HSNO) Act 1996 administered by the NZ Environmental Protection Authority (http://www.epa.govt.nz/Pages/default.aspx).

39. The ACVM Act authorises agricultural compounds (which includes agricultural chemicals, biological, botanical and chemical), veterinary medicines, animal feeds, fertilisers etc. either by registration of trade name products, or exempting product groups from the requirement of registration. The HSNO Act approves hazardous substances (which includes agricultural chemicals), and the approval can cover one or more trade name products.

United States

40. All pesticides are regulated within the United States (US) under the Federal Insecticide, Fungicide, and Rodenticide Act. The regulatory approaches proposed by OECD in this Guidance Document are similar to those conducted by the U.S. Environmental Protection Agency (US EPA). There are two major exceptions. First, this Guidance focuses solely on bioactive substances obtained from botanical sources, whereas the US EPA addresses bioactive pesticidal substances obtained from any natural source (plant, animal, or geological). Secondly, the US EPA makes a distinction between natural

substances that have a toxic mode of action and those substance that do not have a toxic mode of action. If a natural substance has a toxic mode of action against a target pest, the US EPA considers it to be a Conventional Chemical pesticide and is assessed for safety to human health and the environment as any synthetic chemical.

41. Naturally-occurring substances that have a non-toxic mode of action may be considered to be reviewed and assessed under a reduced data set, when compared to Conventional Chemicals, and considered to be Biochemical pesticides if they meet the following three statutory criteria, as described in 40 CFR 158.2000(a) (https://www.gpo.gov/fdsys/granule/CFR-2012-title40-vol25/CFR-2012-title40-vol25-sec158-2000):

(i) It is a naturally-occurring substance, or if not naturally-occurring, is structurally-similar and functionally identical to a substance that occurs in nature;
(ii) It has a history of exposure to humans and the environment with minimal toxicity;
(iii) It has a non-toxic mode of action against the target pest.

42. It is noted here that the US EPA makes a further distinction between toxicity and lethality; many Biochemical pesticides can have a lethal mode of action against the target pest without being toxic. For example, some plant oils may act via a suffocating mode of action, of via a physic-chemical mode of action, such as membrane disruption or desiccation.

43. A 12-member Biochemical Classification Committee reviews all new active ingredients that are proposed to the US EPA as Biochemical pesticides to determine whether they meet the three statutory criteria described above.

44. Other similarities in this OECD Guidance Document to current practice at the US EPA relate to (i) reducing some of the data requirements, via the submission of historical data in the open technical literature (e.g., scientific journal articles) in lieu of guideline studies, (ii) comparison of application rates of the active substances vs. background levels already present in the environment, (iii) bridging of existing toxicological information from similar substances, and (iv) current exposures to humans and the environment via other uses of naturally occurring active substances.

45. This Guidance Document also proposes a tiered approach (see below) to hazard assessment similar to that already in practice at the US EPA for Biochemicals:

46. For new Straight-Chain Lepidopteran (SCLP) Pheromone active ingredients, only product chemistry data are required.

For all other arthropod pheromone active ingredients, product chemistry and all Tier I mammalian toxicity data are required, but no ecological effects/non-target organism data are required.

For all other new biochemical active ingredients (non-pheromone semiochemicals and other naturally occurring substances), product chemistry, all Tier I mammalian toxicity, and all Tier I ecological effects/non-target organism data are required.

For new end use products containing active ingredients that are present in registered end use products, only mammalian acute toxicity studies are required.

47. This OECD Guidance Document goes further into details of product chemistry data requirements, hazard assessments for mammalian toxicology and non-targets, residues, fate and behaviour in the environment, endocrine disruption and risk assessments, all of which are very similar to currently conducted practice in the Agency.

48. To be registered as a Biochemical pesticide, the natural substance:

(i) must be a substance that meets all three Biochemical Classification criteria (described above);
(ii) must contain only approved inerts; and,
(iii) cannot contain a Conventional Chemical active ingredient.

49. Biochemical pesticide data requirements are as follows (see http://www.ecfr.gov/):

40 CFR 158.2030 Product Chemistry
40 CFR 158.2050 Human Health
40 CFR 158.2060 Non-target Organism & Environmental Fate

50. OCSPP Harmonized Guideline study protocols (see http://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic):

Series 830 Product Chemistry
Series 870 Human Health
Series 850 Non-target Organism & Environmental Fate

To register semiochemical active substances and plant protection products the applicant has to submit a dossier according to the data requirements. Subsequently, an evaluation and risk assessment need to be performed by the competent authority. In the next chapter more detailed information is provided how to address the issue of exposure levels, and the different sections of the data requirements.

NATURAL EXPOSURE LEVELS IN RELATION TO APPLIED LEVELS

51. Semiochemicals are active substances in plant protection products with a non-toxic, target-specific, mode of action and of natural occurrence. 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.

52. 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.

53. 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.

54. 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 a group of related semiochemicals, when justified), the risk characterisation is concluded. No further information is needed with the exception of identity, characterisation and analytical methods (see sections on Identity, physical and chemical properties and Analytical methods).

55. 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.

56. 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.

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

57. 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.

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

59. 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

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

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).

60. 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).

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

61. 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.

62. 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.

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

63. 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.

64. 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.

65. The fixed-box model is described in detail in Appendix III. The variables in the model equation have been standardised 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 rationalised in Appendix III.

IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES

Active substance

66. For all type of submissions, the data requirements on identity should be addressed.

67. 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).

68. Additives and significant manufacturing impurities should be described and their concentrations should be provided. In addition, 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 SCLPs are themselves also SCLPs the practice should be to sum up these individual SCLP impurities and specify them as a single impurity. This may be appropriate for other semiochemicals, when justified.

69. Confidentiality may apply to some extent.

70. At the time of submission, it is in the interest of the applicant to provide data for as many representative batches as possible, including laboratory and pilot production. It is recognised that sometimes only one batch may be available.

71. Where a semiochemical is made up of 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 semiochemical natural ratios can vary.

Plant protection product

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

73. 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 products

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- Water Dispersible Granules). The semiochemical is formulated in a granular form.

2E) Seed treatment products

74. Some examples of dispenser types are provided in Appendix II.

75. 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 be considered as the packaging containing a formulated product. All other current examples above are considered part of the formulated product.

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

TECHNICAL EQUIVALENCE

77. As regards the assessment of the equivalence of technical materials, the following applies:

- When impurities in SCLPs are themselves also SCLPs the practice should be to sum up these individual SCLP impurities and specify them as a single impurity. This may be appropriate for other semiochemicals, when justified. When checking the technical equivalence for SCLPs, isomer ratios do not have to match the reference specification in order to be considered equivalent.

BIOLOGICAL PROPERTIES AND DATA ON APPLICATION

78. 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. Information to demonstrate this can be gathered from efficacy trials or fundamental investigations on emitting and receiving species. 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.

79. 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 hectare, how this relates to the release rate per hectare 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).

80. 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 I.

81. In the GAP for other non-retrievable application techniques (categories 2A, 2C, 2D & 2E) 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 I.

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

ANALYTICAL METHODS

83. With regards to the analytical methods for the active substance in the TGAS and in the formulation, the standard data requirements apply. Applicants are reminded to use the appropriate methods for volatile compounds.

84. 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 standard data requirements.

MAMMALIAN TOXICOLOGY

85. The specific properties of semiochemicals and the way they are used as plant protection products means non-testing strategies can be used to provide sufficient information to perform risk assessments in the field of human health.

86. Data requirements for human health 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.

87. 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.

88. 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, section on Natural exposure levels in relation to applied levels). When these conditions are not fulfilled the following hazard identification, a full exposure assessment and subsequent conclusion on the risk assessment is necessary.

89. 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.

Hazard identification

Data Requirements and read-across

90. 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.

91. 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).

92. Limitations regarding the use of human data apply in most jurisdictions. In general, 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.

93. 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.

94. 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.

Exposure assessment

95. 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).

96. When exposure calculations are necessary, for vapour phase exposure see step II (section on Natural exposure levels in relation to applied levels), 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 is expected

	Retrievable dispensers		Non-retrievable dispensers				
	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

*Types of application techniques: see paragraph 73

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

97. For semiochemicals, residue data may not be required if it has been determined that quantifiable residues on the consumable commodity are unlikely to occur or that residue levels are unlikely to exceed natural exposure levels during outbreaks of the pest. This can be demonstrated by a scientific rationale.

98. 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 on section Natural exposure levels in relation to applied levels). 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.

99. 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.

100. 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.

ENVIRONMENTAL FATE AND BEHAVIOUR

101. The specific properties of semiochemicals and the way they are used as plant protection products means non-testing strategies can be used to provide sufficient information to perform risk assessments in the field of environment.

102. Data requirements for 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.

103. 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.

104. 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, section on Natural exposure levels in relation to applied levels). When these conditions are not fulfilled the following exposure assessment should be provided (depending on the application techniques; see table 2).

105. 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.

106. Exposure levels in soil, groundwater, surface water, sediment and air should also need to be considered. However, depending on the application techniques all compartments may not be exposed (see table 2).

107. 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.

108. When exposure calculations are necessary, for vapour phase exposure see step II (section on Natural exposure levels in relation to applied levels), for other exposure routes the standard approaches should be followed.

109. 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 as SCLPs, a calculation based on the substance’s volatility may be used to replace the need for certain studies/requirements, e.g., by providing estimates of the rapidity and likely extent of volatilisation losses and gains from / to soil and natural surface water systems by re-deposition. Within the EU, the potential for long range atmospheric transport should be addressed following FOCUS (2008) air guidance.

EFFECTS ON NON-TARGET SPECIES (EXCLUDING MAN AND DOMESTICATED ANIMALS)

110. 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.

Hazard identification

111. 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, section on Natural exposure levels in relation to applied levels). When these conditions are not fulfilled hazard identification, exposure assessment and subsequent conclusion on the risk assessment is necessary.

112. 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.

113. 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.

114. 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.

115. 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 on Identity, physical and chemical properties).

116. 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.

Exposure assessment

117. 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).

118. When exposure calculations are necessary, for vapour phase exposure step II (section on Natural exposure levels in relation to applied levels) should be applied, for other exposure routes the standard approaches should be followed.

Table 2: Compartment for which exposure is expected

	Retrievable dispensers		Non-retrievable application techniques				
	Passive	**Active**	**Passive dispensers**	**Dosable matrix**	**Capsule suspension**	**Granular application**	**Seed treatment**
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 arthropods (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

* Within the EU, 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).

EFFICACY

119. Different jurisdictions have different approaches and requirements as regards efficacy. In general, it is required that a plant protection product shall be sufficiently effective and it shall not have any unacceptable effects on the plants or plant products. In general, these approaches or requirements also state that an active substance shall only be approved where this has been established for one or more representative uses for the associated plant protection product(s). This should be evaluated in accordance with the relevant legislation.

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

121. It is recognised, however, that deviations from agreed guidelines 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.

122. 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.

123. 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. 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.

124. 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.

125. 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.

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

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APPENDIX I - GOOD AGRICULTURAL PRACTICE TABLE

			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 (specific to EU) [d]	Non professional use:	☐
Verified by MS:	yes/no		
Field of use:	herbicide, fungicide, insecticide etc		

1	2	3	4	5	6	7	8	8A	10	11	12	13	14
Use - No. **(e)**	**Member country (ies)**	**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		
Field or outdoor uses, certain types of protected crops (In the EU: the zonal uses)													
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													
Use as seed treatment, in greenhouses (or other closed places of plant production), as post-harvest treatment or for treatment of empty storage rooms (In the EU: the Interzonal uses)													
3													
4													

1	2	3	4	5	6	7	8	8A	10	11	12	13	14
Use - No. **(e)**	**Member country (ies)**	**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		
Minor uses													
5													
6													

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

APPENDIX II - EXAMPLES OF SEMIOCHEMICAL-BASED PLANT PROTECTION PRODUCTS

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

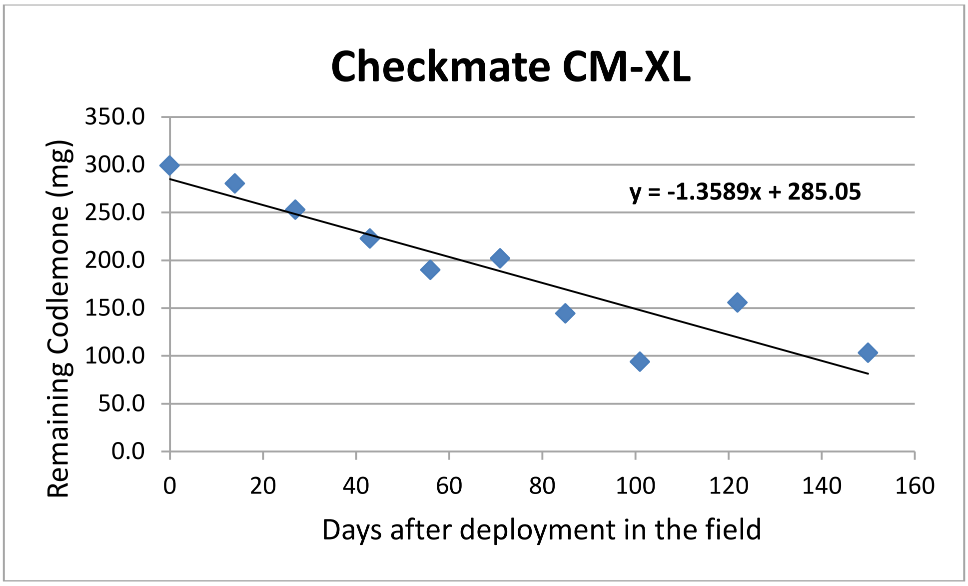

Figure 3: Release profile for Checkmate® CM-XL passive dispensers (Mating disruption of *Cydia pomonella*).

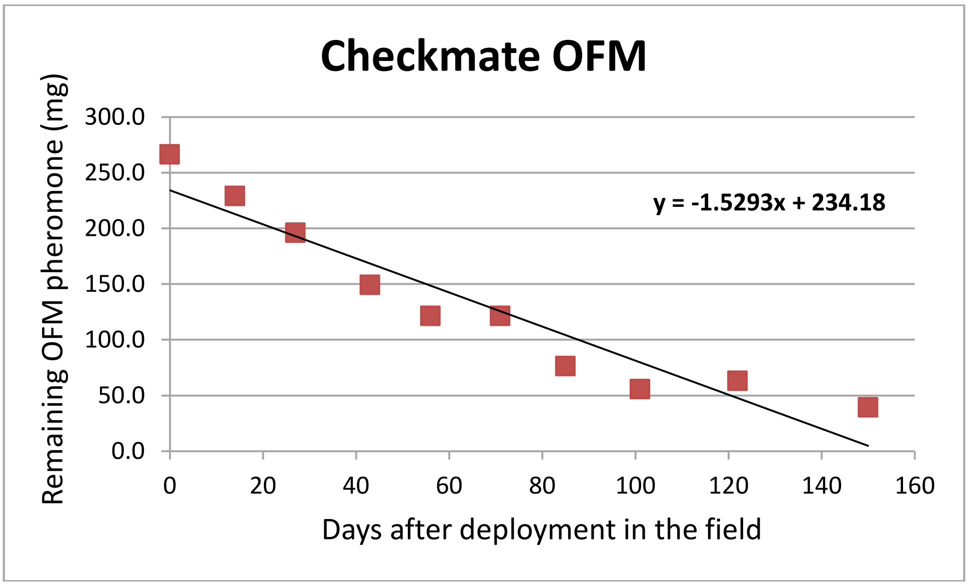

Figure 4: Release profile for Checkmate OFM passive dispensers (Mating disruption of *Grapholita molesta*).

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) Active retrievable dispensers: 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

General features

- 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) Capsule suspension products: 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.

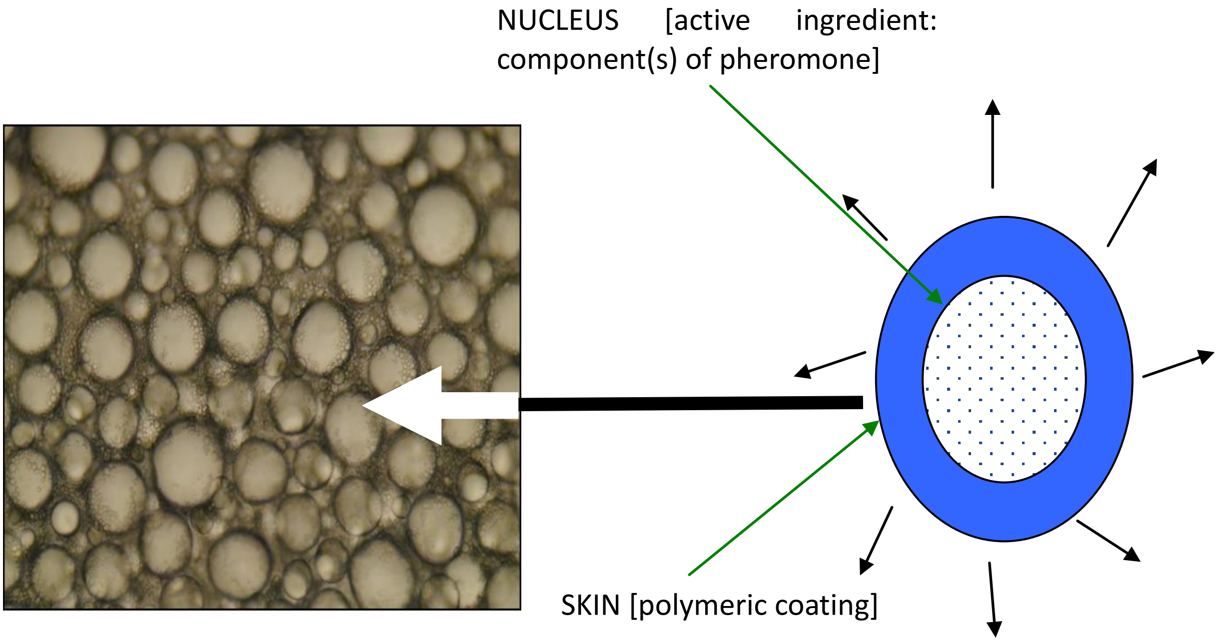

Figure 6: Scheme showing the structure of microcapsules, an example of a non-retrievable-capsule-suspension product. Microcapsule diameter is <200 micron.

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.

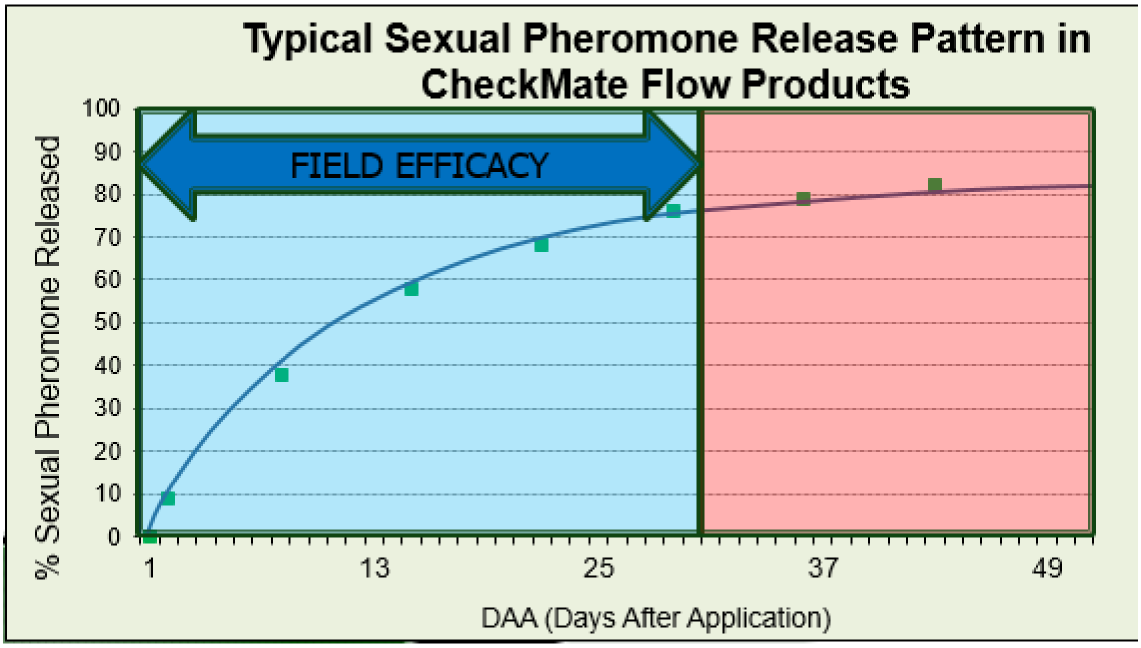

Figure 8: Release pattern for semiochemical capsule suspension products after application.

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) <u>Dosable matrix dispensers:</u> 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.

Figure 9: Examples of dosable matrix dispensers

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 III – 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 $g/s \cdot m^2$). 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).

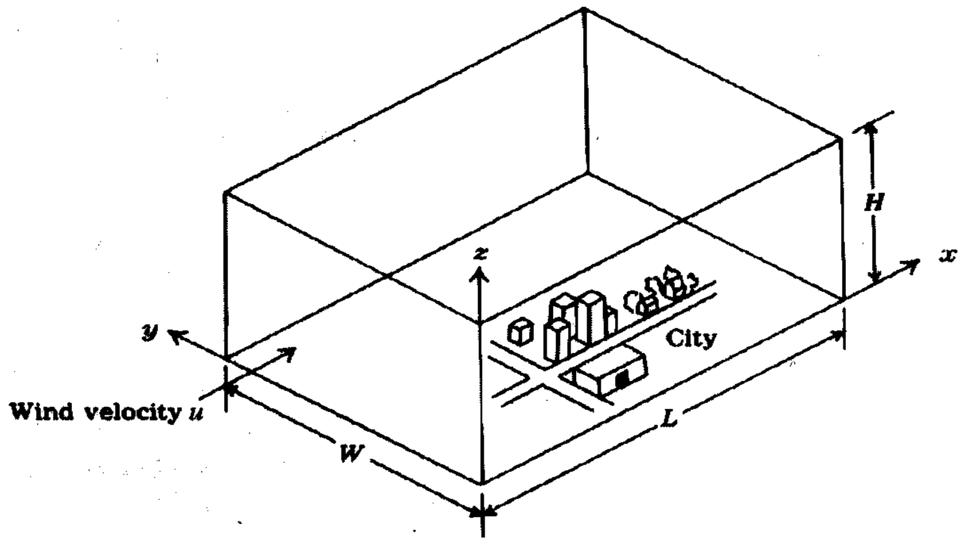

Figure 1: Rectangular city, showing meaning of symbols used in the fixed-box model (Source: *de Nevers*, Air Pollution Control Engineering 2nd Ed. McGraw-Hill, 2000).

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 IV – 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.