# Evaluation Manual for the Authorisation of plant protection products according to Regulation (EC) No 1107/2009

## EU part

## Plant protection products

## Chapter 1 General Introduction and Generic Aspects

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ctgb

**Board for the Authorisation of plant protection products and biocides**

# Chapter 1 General Introduction and Generic Aspects

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**Changes in the Evaluation Manual**

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| 2.1 | October 2016 | | Initial version |
| 2.2 | November 2017 | 1 | PBT/vPvB guidances added |
| | | 5 | Updated link low risk criteria |

## GENERAL INTRODUCTION

The EU Evaluation Manual describes the data requirements and how these are evaluated in the EU framework under Regulation (EC) No 1107/2009.The described risk assessment in the Evaluation Manual can be used for both the approval procedure for active substances as well as for zonal and interzonal applications for the authorization of plant protection products (i.e. core registration reports).

Substances that are approved under Regulation (EC) No 1107/2009 and were approved under Directive 91/414/EEC are included in Commission Implementing Regulation (EU) No 540/2011.

The Evaluation Manual describes the procedures following the data requirements as laid down in Commission Regulation (EU) No 283/2013 for active substances and in Commission Regulation (EU) No 284/2013 for plant protection products (PPP). These data requirements apply for active substances submitted after 31 December 2013 and for plant protection products submitted after 31 December 2015.

A guidance is available on the interpretation of the transitional measures for the data requirements for chemical active substances according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013 (SANCO/11509/2013 – rev. 5.2).

For further information on the former data requirement as laid down in Commission Regulation (EU) No 544/2011 for active substances and in Commission Regulation (EU) No 545/2011 for PPP. Ctgb refers to the Evaluation Manual for Authorisation of plant protection products according to Regulation (EC) No 1107/2009 versions 1.0 and 1.1 and version Evaluation Manual for Authorisation of plant protection products according to Regulation (EC) No 1107/2009 versions 2.0.

The Evaluation Manual contains per aspect the data requirements and risk assessment if required for this aspect.

This chapter also concerns generic background information that is useful for evaluation of substances and formulations that does not pertain to a specific section.

## 1. POP, PBT AND VPVB

Point 3.7 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance. The texts in the regulation specifically addresses criteria for approval of active substance and the criteria for persistent organic pollutant (POP), persistent bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative substance (vPvB).

In summary, an active substance, safener or synergist shall not be approved if it has been shown to be a POP, a PBT substance, or a vPvB.

A substance is considered a POP when the $DT_{50}$ in water is >2 months and it fulfils the bioaccumulation and long-range environmental transport criterion described in section 3.7.1.2 and 3.7.1.3 of Annex II.

A substance is considered a PBT substance if it fulfils the PBT criterion described in section 3.7.2.1-3.7.2.3 of Annex II.

A substance is considered a vPvB if it fulfils both the vPvB requirements described in section 3.7.3.1 and 3.7.3.2 of Annex II.

There is a working document, the DG SANCO Working Document on "Evidence Needed to Identify POP, PBT and vPvB Properties for Pesticides" 25/09/2012 rev. 3 and an ECHA guidance document, the Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment. Version 3.0, June 2017, that can be consulted in order to determine if an active substance is P, B and T or vP and vB.

## 2. ENDOCRINE DISRUPTION

Point 3.6.5 and point 3.8.2 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance.

Under Regulation (EC) No 1107/2009 it is stated that only active substances, safeners or synergists shall be approved if they are not considered to have endocrine disrupting properties in humans unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005. In addition, an active substance shall not be approved if they considered to have endocrine disrupting properties that may cause adverse effects on non-target organisms unless the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible.

Currently, there are no specific criteria for determining the potential endocrine properties of compounds. The development of such criteria has been challenging as from a toxicological point of view, the significance of various adverse effects, gender and life stage must be assessed and different types of combined actions need to be considered.

In Regulation (EC) 1107/2009 it is stated that by 14 December 2013, the Commission shall present a draft on these specific scientific criteria. The approval of these criteria however is now expected to be delayed until somewhere in 2014. However, no formal criteria have been established, internationally or at EU level, for identifying substances with endocrine disrupting properties. The Commission presented on 15 June 2016 a draft legal acts, under the Plant Protection Products legislation which set the criteria to identify endocrine disruptors. The drafts will now need to be adopted according to their relevant procedures, which in this case involves Parliament and Council.

Until the draft is adopted substances that are of have to be classified as carcinogenic category 2 and toxic for reproduction category, will be considered to have endocrine disrupting properties. In addition, substances that are or have to be classified as toxic for reproduction category 2 and which have toxic effect on the endocrine organs, may also be considered to have endocrine disrupting properties.

The data requirements for endocrine disruption are specifically mentioned in section 5.8 (other toxicological studies, 5.8.3), section 8.1 (effects on birds and other terrestrial vertebrates 8.1.5) and 8.2 (effects on aquatic organisms 8.2.3) of Commission Regulation (EU) 283/2013.

Data requirement 5.8.3 states that when there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required to elucidate the mechanism of action. Studies required shall be designed on an case-by-case basis taking into account Union or internationally agreed guideline, in the light of the particular parameters to be investigated and the objectives to be achieved.

For other terrestrial vertebrates (data requirement 8.1.5) and aquatic organisms (data

requirement 8.2.3) consideration shall be give whether the active substance is a potential endocrine disruptor according to Union or internationally agreed guidelines. This may be done by consulting the mammalian toxicology section for terrestrial vertebrates and by taking into account available information on toxicity profile and mode of action. If the active substance is identified as a potential endocrine disruptor, the type and conditions of the study to be performed shall be discussed with the national competent authorities.

An EFSA scientific report of the Endocrine Active Substances Task Force is available which provides additional information on endocrine disruption. Additionally there is also an EFSA scientific opinion on the hazard assessment of endocrine disruptors providing more information on endocrine disruption. There is also an OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters that can be used as test guideline for the testing endocrine disruption. Both the EU DG's health and environment, EFSA and the OECD have excellent websites where the latest information on endocrine disruption can be found.

## 3. NEGLIGIBLE EXPOSURE

Point 3.6.3 – 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance.

Under Regulation (EC) No 1107/2009 is stated that an active substance, safener or synergist shall only be approved if on the basis of the assessment it does not have to be classified as carcinogenic category 1A or 1B, as toxic for reproduction category 1A or 1B, or is considered to have endocrine disrupting properties. An exemption is made when the exposure to humans and under realistic proposed conditions of use can be considered as negligible. In addition, for endocrine disrupting properties the exposure of non-target organisms to that active substance in a plant protection product has to be considered negligible as well.

A draft guidance on negligible exposure is available, this guidance document describes the rationale recommended to be followed during the approval/non approval decisions of active substances, safeners, and synergists under Regulation (EC) No 1107/2009 concerning points 3.6.3 to 3.6.5 and 3.8.2 of Annex II.

## 4. CANDIDATES FOR SUBSTITUTION AND COMPARATIVE ASSESSMENT

Substances which demonstrate a less favourable toxicological profile but which still satisfy the criteria for approval may be approved as candidates for substitution. As stated in Article 24 of Regulation (EC) No. 1107/2009 candidates for substitution are approved for a period not exceeding seven years.

Point 4 of Annex II of Regulation (EC) No 1107/2009 defines the criteria of when an active substance should be considered a candidate for substitution. An active substance shall be approved as a candidate for substitution pursuant to Article 24 where any of the following conditions are met:

- its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories,
- it meets two of the criteria to be considered as a PBT substance,
- there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones),
- it contains a significant proportion of non-active isomers,
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in

accordance with the criteria laid down in point 3.6.3,
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4,
- if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.

Products containing active substances approved as candidates for substitution (CfS) are subject to comparative assessment by Member States. Such products are withdrawn if that assessment identifies alternative products or methods of control which are significantly safer and can be used without significant drawbacks. Article 50 and Annex IV of Regulation (EC) No 1107/2009 gives further details on this comparative assessment.

If a substance is a CfS, this will be indicated on the EU Pesticide Database.

If a product contains a CfS, a comparative assessment will be carried out:
-for new product applications for authorization
-for product renewals
-for extensions of product authorizations, for which the comparative assessment will only be carried out for the requested extension

During the first year from August 2015 onwards no CA will be carried out for mutual recognition applications or for products intended for non-professional use. After a year this approach will be evaluated.

A draft guidance on comparative assessment is available. The guidance document describes stepwise the approach followed to come to the decision if a candidate will be replaced by an alternative.

- Step 1 – identification of candidates in the product and consideration of further optional assessment in steps I-IV (Article 50(2)).
- Step 2 – mandatory assessment (Article 50(1)- starting with agronomic aspects (EPPO standard PP 1/271 Guidance on comparative assessment)
- Step 3 - first step of assessment for health and the environment will be done on the criteria on which the active substance is a CfS between the alternative and the CfS product. Since this part of the comparative assessment is country specific, the toxicological and environmental risk assessment for the NL is described in the General introduction NL-part.
- Step 4 – second step of assessment for health and the environment for the other aspects between the alternative and the CfS product. Since this part of the comparative assessment is country specific, the toxicological and environmental risk assessment for the NL is described in the General introduction NL-part.

Finally the Board for the Authorisation of Plant Protection Products and Biocides will decide if a particular use product with a candidate for substation will be replaced by an alternative based on the comparative assessment.

## 5. LOW RISK ACTIVE SUBSTANCES

Under Regulation (EC) No 1107/2009 is stated that low-risk active substances shall be listed separately in the Regulation. Article 47 of the Regulation gives information regarding the placing on the market of low-risk plant protection products. Point 5 of Annex II of Regulation

(EC) No 1107/2009 gives additional information on the criteria for substances to be considered low risk. August 2017 the regulation on low risk substances was amended.

Low-risk substances are active substances which have been evaluated as low-risk. For the approval of these active substances, the standard active substance assessment procedure applies. The active substance assessment process determines whether an active substance has a low-risk profile. Active substances approved as low risk active substances are included in the EU database.

Currently, the criteria for low risk substances described in Regulation (EC) 1107/2009 are fairly general. In 2012, the Expert Group Low Risk Substances was formed which aims to expend on the criteria listed in Regulation (EC) No 1107/2009 and to deliver a guidance document on the application of these criteria to harmonize the decision-making process. At this moment (October 2016) the consultation round is ongoing. The final version is not available yet.

## 6. FORBIDDDEN CO-FORMULANTS

In Article 27 of the Regulation (EC) No 1107/2009 is the unacceptable co-formulants are mentioned and products should not contain these co-formulants. Co-formulants are substances or preparations which are used or intended to be used in a plant protection product or adjuvant, but are neither active substances nor safeners or synergists. These chemicals may be of concern where they have an inherent capacity to cause an adverse effect on humans, animals or the environment and are present or are produced in a plant protection product in sufficient concentration to present risks of such an effect.

According to Article 27 a co-formulant shall not be accepted for inclusion in a plant protection product where it has been established that:
"(a) its residues, consequent on application consistent with good plant protection practice, and having regard to realistic conditions of use, have a harmful effect on human or animal health or on groundwater or an unacceptable effect on the environment; or
(b) its use, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, has a harmful effect on human or animal health or an unacceptable effect on plants, plant products or the environment."

Such co-formulants should be listed up in Annex III. The Annex III is currently still empty. At this moment (June 2016) member states and Commission are preparing the list forbidden co-formulants.

## 7. LITERATURE REVIEW

Article 8 (5) of Regulation (EC) 1107/2009 requires that scientific peer-reviewed open literature on the active substance and relevant metabolites dealing with side-effects on health, the environment and non-target species published within the last 10 years before submission shall be added to the dossier.

In section 9 of Commission Regulation (EU) 283/2013 and section 11 of Commission Regulation (EU) 284/2013 setting out the data requirements for active substances and plan protection products the following data is required: “A summary of all relevant data from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and plant protection products containing the active substance shall be submitted”.

The applicants are responsible for providing dossiers including full relevant information from the scientific peer reviewed open literature. A summary of the obtained data shall be provided.

An EFSA guidance is available which provides specific instructions on how to identify and select scientific peer-reviewed open literature and how to report them in the dossier.

## 8. GLP

The principles of GLP are described the directive 2004/10/EC. For active substance the Annex 3 of the Commission Regulation (EU) No 283/2013 and products Annex 3 of the Commission Regulation (EU) No 284/2013 requirements about GLP is provided.

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

For residue trials, GLP compliance is obligatory from 31 December 1997. For studies related to bee and non-target arthropods, this is 31 December 1999. For all other studies, GLP is required for studies conducted after 25 July 1993.