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

Category: Plant Protection Products

Changes in the Evaluation Manual

Evaluation manual PPP EU part General Introduction			
Version	**Date**	**Paragraph**	**Changes**
2.1	October 2016		Initial version
2.2	November 2017	1	PBT/vPvB guidances added
		5	Updated link low risk criteria
2.3	July 2018	2	Guidance for the identification of endocrine disruptors in the context of Regulations (EU) (EC) No 1107/2009
2.4	October 2019	4	Date changed to August 2015
2.5	January 2020	General introduction	Sentence included on the administrative EFSA guidance

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.

Notifiers preparing an assessment report for active substances need to comply with the relevant guidance, instructions and format laid down in the EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances

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

Criteria:
The criteria for endocrine disruption for plant protection products have been published, and entered into force on 10 May 2018. They will apply from 10 November 2018 to all new and ongoing applications for plant protection products. Commission Regulation (EU) 2018/605 d.d. 20th of April 2018 describes the new scientific criteria for the determination of endocrine disrupting properties (see also Corrigendum to Commission Regulation (EU) 2018/605).

According to the Endocrine Disruption criteria, a substance shall be considered as having endocrine disrupting properties if it meets all of the following criteria:

a) it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;
c) the adverse effect is a consequence of the endocrine mode of action.

If an active substance, safener or synergist is concluded to be an endocrine disruptor, it falls under the approval criteria In Annex II of Regulation (EC) 1107/2009 section 3.6.5 and can only be approved if the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, and if the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible.

Assessment:
A guidance document for the identification of substances with endocrine disrupting properties in pesticides and biocides is now available (7 June 2018) (https://www.efsa.europa.eu/en/efsajournal/pub/5311) and should be followed for all future active substance dossiers. The Guidance document has been developed by the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA) with the support of the European Commission Joint Research Centre (JRC).

The guidance document was written to provide guidance to applicants and assessors from competent regulatory authorities on how to identify endocrine disruptors in accordance with the ED criteria laid down in Commission Delegated Regulation (EU) No 2017/21003 and Commission Regulation (EU) No 2018/6054 for biocidal products (BP) and plant protection products (PPP), respectively. The guidance document describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence (WoE) approach, in order to establish whether the ED criteria are fulfilled.

All relevant information on endocrine disruption should be reported. Such information can come from regulatory guideline studies, non-guideline studies, public literature, *in silico* models, read-across approaches, databases (see Appendix D of the Guidance), epidemiological data, field studies, monitoring data and population modelling.

In some cases, active substances are registered for both plant protection and biocidal use. In such cases, additional information on potential endocrine disruption may be found in the biocide dossier. Similarly, some information may be found from REACH dossiers where applicable. When using data from other regulatory frameworks, EU data protection rules nevertheless apply.

The EFSA Guidance document on endocrine disruption includes an Excel template which should be used to insure transparency in the data that will be/was used in the assessment and how it was used, and to assist assessors in assembling the appropriate lines of evidence. It is recommended that applicant use this template to gather the relevant information from the available studies. Applicants are asked to submit the completed template in their substance dossier. The Excel template can be found here, under “Supporting Information”.

The conclusions on endocrine disruption should address the two problem formulations identified within the guidance document:

- Is there a biologically plausible link between endocrine activity and observed adverse effect(s) that are relevant for humans?
- Is there a biologically plausible link between endocrine activity and observed adverse effect(s) that are relevant for non-target organisms at population level?

A conclusion should always be drawn for both humans and non-target organisms.

When concluding on ED properties, the following points should be taken into consideration:

(a) It is sufficient that the substance meets the ED criteria for one group of non-target organisms in order to be identified as ED.
(b) Where, based on a sufficient dataset, no ‘EATS-mediated’ adversity was observed or where endocrine activity was found to be negative, it is possible to bypass the MoA analysis and conclude that the criteria are not met.
(c) Where the MoA is based on ‘EATS-mediated’ adversity, the ED criteria are considered met unless an alternative non-endocrine MoA is demonstrated, and in a comparative analysis found to be the most likely explanation for the observed effects.
(d) Where a MoA is based on ‘sensitive to but not diagnostic of EATS’ adversity, and the MoA supports the biological plausibility of the link between the observed adverse effects and endocrine activity for at least one postulated MoA(s), the substance is considered to meet the ED criteria, unless an alternative non-endocrine MoA is demonstrated, and in a comparative analysis found to be the most likely explanation.
(e) Where the available information is sufficient to postulate a non-EATS endocrine MoA, it is possible that the supporting available information would be not sufficient to develop the MoA for fully. In these situations, an analysis of the available testing methodologies should be carried out by the applicant in order to justify that the generation of further scientific information suitable for the identification of a non-’EATS mediated’ endocrine MoA is not feasible based on the available scientific knowledge, that the biological plausibility is highly uncertain, and that a conclusion is therefore not currently possible.
(f) Failure to provide appropriate data for performing the ED assessment according to this Guidance, without the justifications mentioned above in (e) |(e.g. failure to perform the MoA analysis as required, failure to generate the information needed to sufficiently investigate endocrine activity and/or endocrine related adverse (despite the fact that appropriate test methods are available), and failure to provide adequate scientific

justifications for omission of information) will be considered a data gap. The assessors shall clearly indicate which missing information should have been provided by the applicant/notifier when following the in-force Guidance and to what extent this information is critical for concluding on the ED properties of a substance.

The conclusion on the ED criteria must be transparently documented, including any remaining uncertainties.

If the active substance is identified as a potential endocrine disruptor, and the applicant plans to carry out additional studies on the mode of action, it is advised to discuss the type and conditions of the study(ies) with the Rapporteur.

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. However, at the moment no adopted guidance document is available on this issue.

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.