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

version 2.7; February 2022

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
2.6	July 2021	6	Adding info and link of the published Annex III unacceptable co-formulants
2.6	July 2021	General introduction	Sentence included on the EFSA guidance on stereoisomers
2.7	February 2022	General introduction	Information added on Annex ‘Further guidance on performing and presenting the literature search’ (Administrative Guidance Section 3.5)

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.

Notifiers preparing an assessment report for active substances need to comply with the relevant guidance, instructions and format laid down in the EFSA guidance on risk assessments for active substances of plant protection products that have stereoisomers as components or impurities and for transformation products of active substances that may have stereoisomers (for all dossiers submitted from the entry into force date August 1st, 2021 onwards).

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. Please see the following section, 3. Negligible exposure, for more details.

Assessment:

A guidance document for the identification of substances with endocrine disrupting properties in pesticides and biocides is available as of 7 June 2018, including an Annex on the use of the OECD 248 (XETA, published 09 April 2021), and should be followed for all active substance dossiers.

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. It 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.

The conclusions on endocrine disruption 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 will be drawn for both humans and other non-target organisms.

Data requirements for assessment endocrine disruption

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.

The specific studies that are required to consider the dataset adequate to assess the potential for endocrine disruption can be found in the ECHA/EFSA Guidance (2018), and are discussed in the relevant sections for ecotoxicology (Chapter 7, Ecotoxicology; general introduction and over-arching issues) of this Evaluation Manual.

Applicants are encouraged to discuss their testing program for endocrine disruption assessment with the Ctgb. Particularly if the applicant plans to carry out additional studies, for example to elucidate further the possible mode(s) of action, it is advisable to discuss the type and conditions of the study(ies) with the Ctgb.

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.

In addition to specific studies and endpoints mentioned in the Guidance, a specific literature search is also described. The methodology, key words, and exclusion criteria for this search differ from those according to Regulation (EU) 283/2013, and EFSA Journal 2011; 9(2): 2092 and it should be clearly stated that the requirements of the ECHA/EFSA Guidance were also met when discussing the literature search for the dossier, and/or a separate literature search for the ED assessment should be provided.

Formatting

The Ctgb as RMS will present an assessment of the potential of the a.s. for endocrine disruption in Volume 1 of the RAR. The study summaries and evaluations will be shown in Volume 3 CA 6 and 9, as appropriate. The applicant should submit an ED assessment to the Ctgb according to the recommendations of the ECHA/EFSA Guidance (2018).

Specifically, applicants should note that the ECHA/EFSA Guidance includes an Excel template (Appendix E) which should be submitted for all active substance dossiers and should include all relevant toxicology and ecotoxicology studies/endpoints. Applicants should submit a completed template in their active substance dossier. The Excel template can be found here,

under “Supporting Information”. In addition, applicants should provide a summary of the lines of evidence for the ED assessment, according to Table 3 of the ECHA/EFSA Guidance.

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. UNACCEPTABLE CO-FORMULANTS

According to the definition in Regulation (EC) No 1107/2009, 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*'. Article 27 of the PPP-Regulation furthermore refers to a special category of co-formulants that are considered intrinsically hazardous to humans, animals or the environment, and are therefore not accepted for use in plant protection products or adjuvants. According to the article, these particular substances are to be included in a dedicated appendix to (EC) No 1107/2009, the 'Annex III'.
As of March 24th 2021, Regulation (EU) 2021/383 has entered into force, which finally substantiates the Annex III by providing an initial list of 144 substances selected for phaseout.

Substances included in the Annex meet the following criteria:
- they have been assigned a harmonized classification as 'CMR'; carcinogen (1A or 1B), mutagen (1A or 1B), or reprotoxicant (1A or 1B), according to Regulation (EC) No 1272/2008;
- they have been identified as being persistent, bioaccumulative, and toxic ('PBT') or very persistent and very bioaccumulative ('vPvB'), in accordance with Article 57(point d and e) of Regulation (EC) No 1907/2006;
- they are either of very high concern due to their endocrine disrupting properties (see point (f) of Article 57 of Regulation (EC) No 1907/2006) or are recognized as endocrine disruptors under Regulation (EU) No 528/2012;
- they have been established as persistent organic pollutants ('POPs'), as per Regulation (EU) 2019/1021.

As intentionally added (part of a) co-formulant, the substances shall not be present at all in any EU-authorized PPP. Nonetheless, they are limitedly tolerated when present in a co-formulant as (unintentional) impurity; for these cases a default threshold of 0.1 % w/w in the final product applies. Lower thresholds may exist based on CMR properties.
After March 24th 2023, all plant protection products and adjuvants authorized in the EU shall be in compliance with Regulation (EU) 2021/383. Member States have individually aligned their screening systematic with the Regulation to avoid authorization of new products with Annex III issues.

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 Document [1] 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. In an Appendix to this guidance, published by EFSA as supportive document, additional instructions and guidance is provided for both applicants and rapporteur Member States (RMS) on how the literature search should be presented in the (summary) dossier and Assessment Reports. It is based on experience collected since the publication of the guidance document and aims to ensure a transparent and comprehensive reporting of the open literature.

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.

[1] EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092. 49 pp. doi:10.2903/j.efsa.2011.2092