STUDY

Requested by the PEST committee

European Parliament

Guidelines for submission and evaluation of applications for the approval of active substances in pesticides

Policy Department for Economic, Scientific and Quality of Life Policies
Directorate-General for Internal Policies
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Abstract

Active substances are an essential element of pesticides. The approval of active substance occurs at EU level, and guidance documents and guidelines for this procedure exist. They aim to clarify, harmonise and standardise the complex approval process. This study examines the guidance and guidelines which exist for active substance approval, the level of harmonisation among them, the connection to the good laboratory practice (GLP) principles, and provides an overview of the studies which are required for active substance approval.

This document was provided by Policy Department A at the request of the Special Committee on the Union's authorisation procedure for pesticides (PEST Committee).

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LIST OF ABBREVIATIONS

A.S.	Active Substance
DAR	Draft Assessment Report
DG SANTE	DG Health and Food Safety of the European Commission
EC	European Commission
ECHA	European Chemicals Agency
ECPA	European Crop Protection Association
EFSA	European Food Safety Authority
EMA	European Medicienes Agency
EPA	Environmental Protection Agency (USA)
EPPO	European and Mediterrenean Plant Protection Organisation
FAO	Food and Agriculture Organisation of the United Nations
GD	Guidance Document
GLP	Good Laboratory Practice
HSE	Health and Safety Executive (UK)
MAD	Mutual Acceptance of Data System (OECD)
MRL/s	Maximum Residue Level/s
MS/s	Member State/s
NAS	New Active Substance
OECD	Organisation for Economic Cooperation and Development
PAFF	Plants, Animals, Food and Feed
PEST	Special Committee of the European Parliament on the Union's authorisation procedure for pesticides
PPP/s	Plant Protection Product/s

PPR	Panel on Plant Protection Products and their Residues (EFSA)
PSN	Pesticide Steering Network
RMS	Rapporteur Member State
SCoPAFF	Standing Committee on Pesticides, Animals, Food and Feed
TG	Test Guidelines
WG	Working Group
WHO	World Health Organisation

ESSENTIAL GLOSSARY

Active substance
A substance or a micro-organism that has an action on or against harmful organisms.

Good Laboratory Practice System
A quality system dealing with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Guidance (or guidance document)
It translates the requirements of legislation into practical steps, and hence may be seen as sub-requirements of a kind. Guidance can be technical or procedural; and answers more the question "What must be done?".

Note-taking of guidance
Approved/noted guidance has been accepted by/reflect the views of the SCoPAFF and the European Commission. The RMS and EFSA generally adhere to noted guidance to carry out the risk assessment procedure for the approval of an active substance.

Plant Protection Product/Pesticide
The term 'pesticide' is often used interchangeably with 'plant protection product'; however, 'pesticide' is a broader term that also covers non-plant or crop uses, e.g. biocides. A Plant Protection Product is a specific category of pesticides, which is aimed at protecting crops and plants. All Plant Protection Products must contain at least one active substance.

Test Guideline (or test method)
It specifies the test protocols which must be followed for data generation; and hence answer the question "How must tests be done?".

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EXECUTIVE SUMMARY

Introduction

Plant protection products (PPPs) – a subset of pesticides – must contain at least one active substance to be authorised. EU legislation defines an **active substance** as "*a substance or a micro-organism that has an action on or against harmful organisms*".

An applicant who wishes to obtain approval for an active substance must submit a dossier through a selected national contact point. This dossier contains an extensive set of documentation, which provides the data necessary to carry out the risk assessment.

EU legislation sets out **data requirements** to be included in application dossiers for active substance approval. **Guidance** can be technical (scientific) or procedural. **Technical guidance** provides more detail on what must be done in practical terms to check/fulfil these data requirements and hence effectively act as sub-requirements for approval when used. **Procedural guidance** provides further clarifications on the procedure itself, rather than the scientific data. Furthermore, **Test guidelines** (or test methods) are protocols to follow when performing tests as part of studies to fulfil the data requirements set in the EU legislation.

Approval of active substances occurs at EU level; therefore, EU level guidance should be used. The existence of EU-level guidance eventually ensures the harmonisation of the evaluation and risk assessment procedures at the Union level.

Guidance may be used:

- by the rapporteur national authority in the development of the draft assessment report; or
- during the peer review process conclusions which is co-ordinated by EFSA (EFSA is also responsible for drafting the conclusions of this process).

As guidance documents are used during the risk assessment stage, they can be considered to be of relevance for applicants, whose dossiers must successfully navigate this stage on the way to possibly ultimate approval.

The **Communication to Regulation (EC) No 283/2013** serves the role of indicating technical guidance and guidelines relevant for the approval of active substances. Relevant technical guidance and guidelines are indicated by data requirements for the dossier to be submitted for approval. However, the Communication has not been updated since its publication in 2013.

Since then, new applicable technical guidance has emerged. New technical guidance which should be used for active substance approval is indicated on the website of **DG SANTE**. This has generally been developed by **EFSA** and must be noted/approved by SCoPAFF before its publication on the website. In addition to this noted/approved guidance, there are three non-noted technical guidance documents published on the EFSA website. These may be applied for active substance approval in some cases, as may some EFSA scientific opinions, which are originally not intended to serve the role of guidance.

The original list of guidance and guidelines in the Communication was developed through a process driven by the Commission with some consultation of Member States' experts and stakeholders. The ongoing update also includes a phase of consultation from these parties. EFSA guidance, which may be developed either at the request of the Commission or on EFSA's own initiative, is established independently by EFSA with a phase of consultation both with Member States and more broadly with stakeholders on the draft.

There is also procedural guidance for active substance approval (generally drafted by DG SANTE) and this is also listed on the Commission website.

Test guidelines are generally drafted by the **OECD**. They are developed based on regulatory need identified by an OECD member and require unanimity for adoption. These guidelines are periodically updated as issues are identified with old guidelines using the same general process as that for adoption.

As a general rule, **guidelines** are of primary relevance to applicants and **technical guidance** to risk assessors, while the primary relevance of procedural guidance depends on the document itself. However, in practice all guidance documents and guidelines are of relevance to both applicants and risk assessors, given that both parties need to know how tests should be conducted and the method by which they will be assessed/procedures which must be followed.

While guidance and guidelines **are not legally binding**, those listed in the communication or noted/approved by SCoPAFF can be considered *de facto* mandatory. While deviations from noted guidance is theoretically possible with scientific justifications, it creates additional complexities/risks; and is understood to rarely ultimately be accepted.

The status of harmonisation of guidance and test guidelines across the EU

There is generally a high level of harmonisation and limited scope between guidance and guidelines for active substance approval for reasons related to:

- the EU level nature of the active substance approval process;
- the targeting of specific data requirements by guidance and guidelines;
- the majority of guidance being published by the same few bodies; and
- the absence of industry guidance or guidelines.

Harmonisation and coherence is a greater issue among guidance documents and guidelines for final product authorisation.

Nonetheless, two notable cases of incoherence, which also impact harmonisation, were identified. Firstly, some guidance documents include **requirements for which no validated test guidelines exist**; leading to a lack of harmonisation in approaches taken to fulfil requirements, if the applicant considers it possible to fulfil them in the first place. Secondly, there are **data requirements for which there is are no guidance documents or guidelines**. In these instances, a case by case approach is taken. Efforts have and continue to be made to fill these gaps in guidance documents to the extent the necessary science exists, and resources are available.

The GLP System and the studies required for the submission of an application for the approval of active substances

GLP is a quality management tool on the method of conducting studies that guarantees process rather than outcome. The scope of GLP covers all non-clinical safety testing of chemicals, i.e. a wide range of products, including PPPs and actives substances. The core principles of GLP must be applied as a whole. They are supplemented by mutually recognised consensus documents, as well as advisory and guidance documents for which there is a general consensus among OECD members to adhere to.

GLP is regulated in the EU and EEA under Directives 2004/9/EC and 2004/10/EC. There is a fairly high level of harmonisation in the application of GLP across the EU, with laboratories routinely inspected every two to three years.

In the area of active substances, the annex to Regulation (EU) No 283/2013 states that, with a few exceptions, all tests performed to obtain data on the properties or safety with respect to human or animal health or the environment must be conducted under GLP. There is also some relevant guidance on GLP from the previously regulatory framework still listed.

Studies

The studies required for active substance approval are listed in Annex (Part A) of Commission Regulation (EU) No 283/2013. Further indications can be found in the guidance. However, the studies required can vary from case to case and multiple studies may be required to fulfil some data requirements. Available evidence suggests that a dossier for active substance authorisation typically includes between 100 and 500 studies; and comprises between 50 000 to 150 000 pages. The information submitted by applicants in a dossier should be sufficient to evaluate (a) foreseeable risks, (b) potentially harmful effects, (c) potentially unacceptable effects of the active substance on humans, animals and the environment, and to this end, the information may be generated using test methods (guidelines).

Studies may be rejected for a number of reasons. More common reasons include the absence of guidelines for studies which leads to more discussion on the methods used and result, and the submission of old studies during the re-approval process.

1. INTRODUCTION

The Special Committee on the Union's authorisation procedure for pesticides (PEST Committee) of the European Parliament was established in response to concerns raised about the risk posed by the herbicide glyphosate, which had its marketing license renewed by EU member states for five years in November 2017. The remit of the Committee is to assess:

- the authorisation procedure for pesticides in the EU;
- potential failures in how substances are scientifically evaluated and approved;
- the role of the European Commission in renewing the glyphosate licence;
- possible conflicts of interest in the approval procedure;
- the role of EU agencies, and whether they are adequately staffed and financed to fulfil their obligations.

The PEST Committee requested a study on the Guidelines for submission and evaluation of applications for the approval of active substances in pesticides in order to give the MEPs of the Committee a clear idea of the regulatory framework, stakeholders and action taken for the authorisation of pesticides in the EU.

This study covers the following questions set out in the terms of reference:

1. Which guidelines are available for:
   a) the submission of active substance approval applications by industry?
   b) the evaluation of these requests by national authorities?
2. What is the status of harmonisation of guidelines falling into these two areas?
3. Which good laboratory practices exist and what is the role of international (OECD) guidelines?
4. What is the legal status of available guidelines?
5. How are these guidelines established and by whom?
6. What type of studies are required for the submission of an application for the approval of an active substance?
7. What are the requirements and standards that these studies must meet?

2. OVERVIEW OF THE APPROVAL OF ACTIVE SUBSTANCES IN PLANT PROTECTION PRODUCTS

This chapter presents relevant elements of legislation which provide important context to the existence and use of **guidance** and **test guidelines** ("guidelines" from here on) during the approval process for active substances. Most notably this chapter includes:

- the differentiation between active substances and plant protection products (PPPs);
- a presentation of the authorisation procedure for active substances;
- a presentation of provisions for **guidance**, **test guidelines** and **good laboratory practices** (GLP) foreseen in legislation.

It is noted that in the context of approval of active substances, **guidance** and **guidelines** serve different purposes (Box 1).

Box 1: Guidance and Test Guidelines

Guidance translates the requirements of legislation into practical steps, and hence may be seen as sub-requirements of a kind. Guidance can be technical or procedural, and answers more the question "*What must be done*?"

Test Guidelines specify the test protocols which must be followed for data generation, and hence answer the question "*How must tests be done*?" They are also often referred to as ***test methods***.

2.1. Plant Protection Product and Active Substances

The present study focuses specifically on active substances. It is therefore important to define active substances and their relationship to Plant Protection Products (PPPs). Box 2 below provides the EU definition of an active substance.

Box 2: What is an active substance?

In Regulation (EU) No 528/2012, an active substance is defined as "***a substance or a micro-organism that has an action on or against harmful organisms***". Therefore, all PPPs, i.e. a specific category of pesticides*, which are aimed at protecting crops and plants, contain at least one active substance. However, the use of an active substance within a PPP in the EU has to be approved, before Member States can use it (*EC, n.d. B*).

** The term 'pesticide' is often used interchangeably with plant protection product; however, 'pesticide' is a broader term that also covers non-plant or crop uses, e.g. biocides.*

Consequently, there are separate procedures for (a) the approval of active substances and (b) the authorisation of plant protection products. The overall process of the placing on the market of final plant protection products consists of two steps corresponding to these authorisation procedures:

- Assessment and possible *approval* of an *active substance* at EU level.

- Assessment and *authorisation* of the *final PPP* by the Member State[1].

For the first step to be successful, it must be demonstrated that the active substance ultimately be used in a final product somewhere in the EU (see Box 3).

With regard to the second step, the final PPP can only contain approved substances and must be authorised by the EU Member State where it will be used before it can be placed on the market[2].

Box 3: "Representative product" for approval of an active substance

In order for an active substance to be approved, authorisation of at least one final plant protection product containing the active substance in at least one Member State is expected to be possible on the basis of the dossier submitted for active substance approval (Annex II point 2.1 of Regulation (EC) No 1107/2009). The active substance risk assessment needs to be performed against the background that it will ultimately be used in a final product, and this provision facilitates this.

The following sub-section sets out the approval procedure for active substances.

2.2. Approval procedure for active substances

As set out in Figure 1, the approval of active substances in PPPs is performed by the European Commission, with the dossier assessed jointly by the national competent authorities in EU Member States Rapporteur (RMS) and the European Food Safety Authority (EFSA). The legislative framework for the approval and renewal of an authorisation includes Regulation (EC) No 1107/2009[3] as well as Regulation EU 844/2012[4] (see sections 2.2.1 and 2.2.2).

1 It is important to note that in the context of Regulation (EC) No 1107/2009 approval relates to an active substance; authorisation to a PPP. Throughout this study these terms will therefore be used according to this differentiation.

2 For facilitation of PPPs authorisation, ***the EU is divided into three zones***, each of which has similar agricultural, plant health and environmental conditions (***North, Centre, South***). The pesticide has to be assessed in one EU Member State from each zone in which it is intended to be used.

3 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN as well as implementing Regulation (EU) 283/2013 - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0001:0084:EN:PDF and implementing Regulation (EU) 284/2014 - http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0085:0152:EN:PDF

4 Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:252:0026:0032:EN:PDF

Figure 1: Bodies involved in the procedure for the approval of an active substance

Source: Agra CEAS based on Regulation (EC) 1107/2009

2.2.1. New active substance (NAS) applications

Requirements and conditions for the approval of new active substances (NAS) are laid down in Regulation (EC) No 1107/2009. Applicants submit a science-based application dossier through their chosen national contact point[5] in a Member State, which is then appointed as a "rapporteur" (RMS) to carry out an initial risk assessment and to prepare a Draft Assessment Report (DAR)[6], provided that the dossier submitted with the application is retained admissible, i.e. it contains all the elements provided for in Article 8 of Regulation 1109/2009 (see sections a and b below)[7].

Other Member States, as well as EFSA, are notified and provided with the dossier from an early stage of the process, i.e. after an initial completeness check of the application by the RMS. Furthermore, as described in section d, Member States are allowed to send comments to EFSA, which are considered during EFSA's peer review of the dossier; as well as to express their opinion through endorsement (or not) in the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) in the later stage of the procedure. Approval, if granted, is for a maximum of ten years.

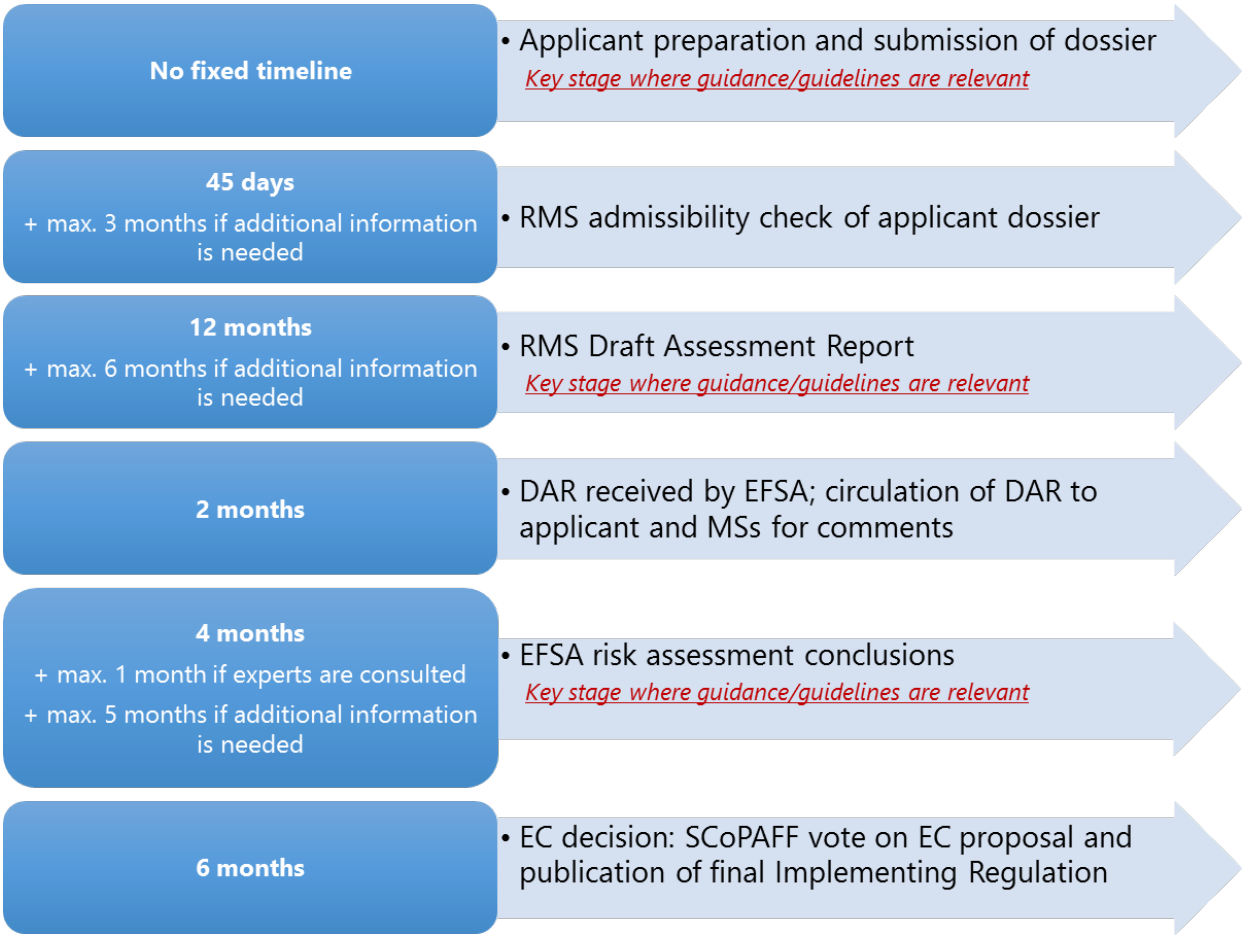
According to the European Commission, under Regulation (EC) No 1107/2009, it takes **2.5 to 3.5 years** from the date of admissibility of the application to the publication of a Regulation approving a new active substance (EC, n.d. A). Detailed steps of the process are set out in Figure 2.

5 Dossiers can be submitted in paper and electronic formats through the CADDY system, as set out in the Commission's guidance documents such as: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_applicants-microbial_en.pdf

6 It should be noted that not all Member States act as RMS; some Member States e.g. Luxembourg do not perform this role.

7 Member States may decline the role of RMS for an application. In this case it is incumbent on the applicant to find another MS who accepts the role.

Figure 2: New active substance (NAS) approval workflow



Note: Key stages where guidance/test guidelines are relevant are indicated above; however, guidance/test guidelines may be also used at other stages.
Source: Agra CEAS based on Regulation (EC) No 1107/2009

Detailed steps of the process are set out below.

a. Submission of the application dossier

As already indicated, to complete an application for the approval of an active substance, a complete dossier must be submitted in accordance with Regulation (EC) No 1107/2009.

The dossier is an extensive set of documentation, which provides the information necessary to carry out the risk assessment (Figure 3). The dossier should be developed in accordance with the format set out by the Organisation for Economic Cooperation and Development (OECD) (see section 3.2). Furthermore, several guidance documents and test guidelines are available for the applicant to better address the data requirements set out in the Annex (Part A) of Commission Regulation (EU) No 283/2013 (see also sections 3 and 6).

Figure 3: General content and scope of the dossier

Content	Scope
• ***Summary dossier***: - General information on the AS uses. - Results of tests/studies. - Steps taken to avoid animal testing. - Checklist to demonstrate that the dossier is complete. - Reasons why submitted tests/studies are necessary for the approval of the AS. - Reasons for not providing certain test/studies. • ***Full dossier***: full text of the test and study reports.	• Permit any residue of concern to be defined. • Predict the residues in food and feed. • Predict, where relevant, the residue level reflecting the effects of processing/mixing. • Permit a MRL to be defined and determined by appropriate methods in general use. • Permit, where relevant, concentration/dilution factors due to processing/mixing to be defined.

Source: Agra CEAS based on Article 8 and Annex II of Regulation (EC) No 1107/2009

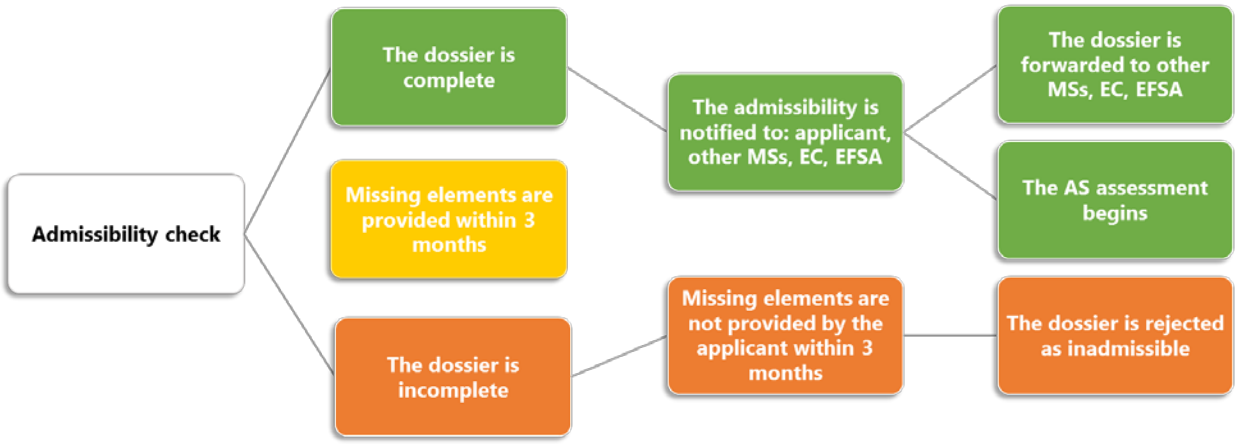
b. The admissibility check procedure

The admissibility check is the first administrative step for the evaluation of an active substance. As illustrated in Figure 4, the RMS (see above) verifies that the application dossier is compliant with the requirements set out in Regulation (EC) No 1107/2009 (see section a). If the dossier contains all the necessary elements to cover each data requirements, the RMS notifies the admissibility to the applicant, other Member States, the European Commission, and EFSA.

In the event that the dossier is not complete, the applicant is allowed three months to provide the missing elements, otherwise its application is rejected as inadmissible.

The complete dossier is then forwarded to other Member States, the Commission and EFSA and the summary report is made publicly available by EFSA.

Figure 4: RMS admissibility check of the application dossier



Source: Agra CEAS based on Article 9 of Regulation (EC) No 1107/2009

c. The Draft Assessment Report (DAR)

In accordance with Regulation (EC) No 1107/2009, the RMS has a period of maximum 12 months[8] from the notification of admissibility (which is outlined in section b), to prepare a Draft Assessment Report (DAR). The DAR assesses the dossier compliance with Article 4 of the Regulation, i.e. whether the active substance under evaluation meets the criteria outlined below:

- it complies with Annex II of the Regulation, which set out procedures and criteria for the approval of active substances;
- it has no harmful effect on human and animal health;
- it does not have unacceptable effects on plants and the environment;
- it does not cause unnecessary suffering and pain to vertebrates to be controlled;
- it is contained in a plant protection product which is sufficiently effective.

Several **guidance documents** exist for this stage to ensure the harmonisation of the evaluation and risk assessment procedures at the EU level, including guidance for the RMS to be used to draft the assessment reports.[9] For example, the structure of the DAR is agreed by the European Commission and the OECD, as summarised below[10]:

- Volume 1 provides the overall conclusion on the active substance.
- Volume 2 lists the tests and studies submitted by the applicant.
- Volume 3 contains a scientific evaluation of all the information submitted by the applicant.
- Volume 4 contains confidential information, e.g. relevant details on any task forces that submitted tests and a study report.

The finalised DAR is submitted to the Pesticides Unit of EFSA by the RMS.

d. EFSA peer-review of the initial risk assessment

EFSA is in charge of peer-reviewing the active substances used in PPPs. The Agency is expected to provide a conclusion on the risk assessment of the active substance, i.e. whether it complies with Regulation (EC) No 1107/2009.

EFSA's risk assessment role and responsibilities are set out in Figure 5.

Figure 5: EFSA risk assessment role and responsibilities

Source: Agra CEAS based on Regulation (EC) No 1107/2009

8 Which may be extended in case the RMS needs additional studies or information from the applicant. In this case an extension can be issued for a maximum period of six months.

9 See **section 3.3**.

10 The detailed structure is provided in Annex II.

As a first step EFSA's Pesticides Unit circulates the DAR to the applicant and all Member States and makes it available for public consultation. Both Member States' competent authorities and stakeholders can therefore submit written comments to the rapporteur Member State (RMS) at this stage.

Later, all comments received are listed in the '*Reported Table*' where the RMS provides an answer to all the observations. The completed table is then forwarded to EFSA, whose experts assess the responses and indicate their proposals for further action (*EC, 2013*).

To resolve some specific issues, EFSA may also organise an expert meeting for one or more of the sections, i.e. physical/chemical properties and analytical methods, toxicology, residues, environmental fate, ecotoxicology (*Belgian FPS Health, Food Chain Safety and Environment, 2016*).

On the basis of experts' observations (which are summarised in a "*discussion table*"), EFSA draft their conclusion document which presents a comprehensive independent summary of the risk assessment[11].

In accordance with the Regulation, EFSA's conclusion is sent to the applicant, all Member States, as well as the European Commission, and it is made publicly available.

e. Commission risk management and final decision on the approval

All active substances are discussed in at least two meetings of the Working group of Pesticides Legislation. These meetings, which are chaired by the Pesticides Unit of DG SANTE of the European Commission, are attended by MSs and EFSA experts (*Belgian FPS Health, Food Chain Safety and Environment, 2016*).

Later, on the basis of the DAR, EFSA conclusions, and the outcome of the Working Group meetings, the European Commission prepares a draft regulation on the approval of the active substance, accompanied by a report (the 'Review Report') which provides more details on the decision. The applicant has the possibility to comment on the report. The draft regulation is then presented to the SCoPAFF, which issues an opinion by qualified majority vote (*EC, n.d. A*).

If the SCoPAFF rejects the draft regulation, the proposal may be referred to an appeal committee, made up of the Member States' Permanent Representations representatives, where further negotiation and discussions take place in view of reaching a compromise (*Belgian FPS Health, Food Chain Safety and Environment, 2016*).

If the SCoPAFF approves the European Commission proposal, the latter adopt and publish in the Official Journal a final Implementing Regulation. The review report is also made publicly available. Furthermore, the European Commission update the database on the current status of active substances in the EU.

Following the approval of the active substance, it can be considered for use in plant protection products in the EU; though the PPP itself must still be authorised first.

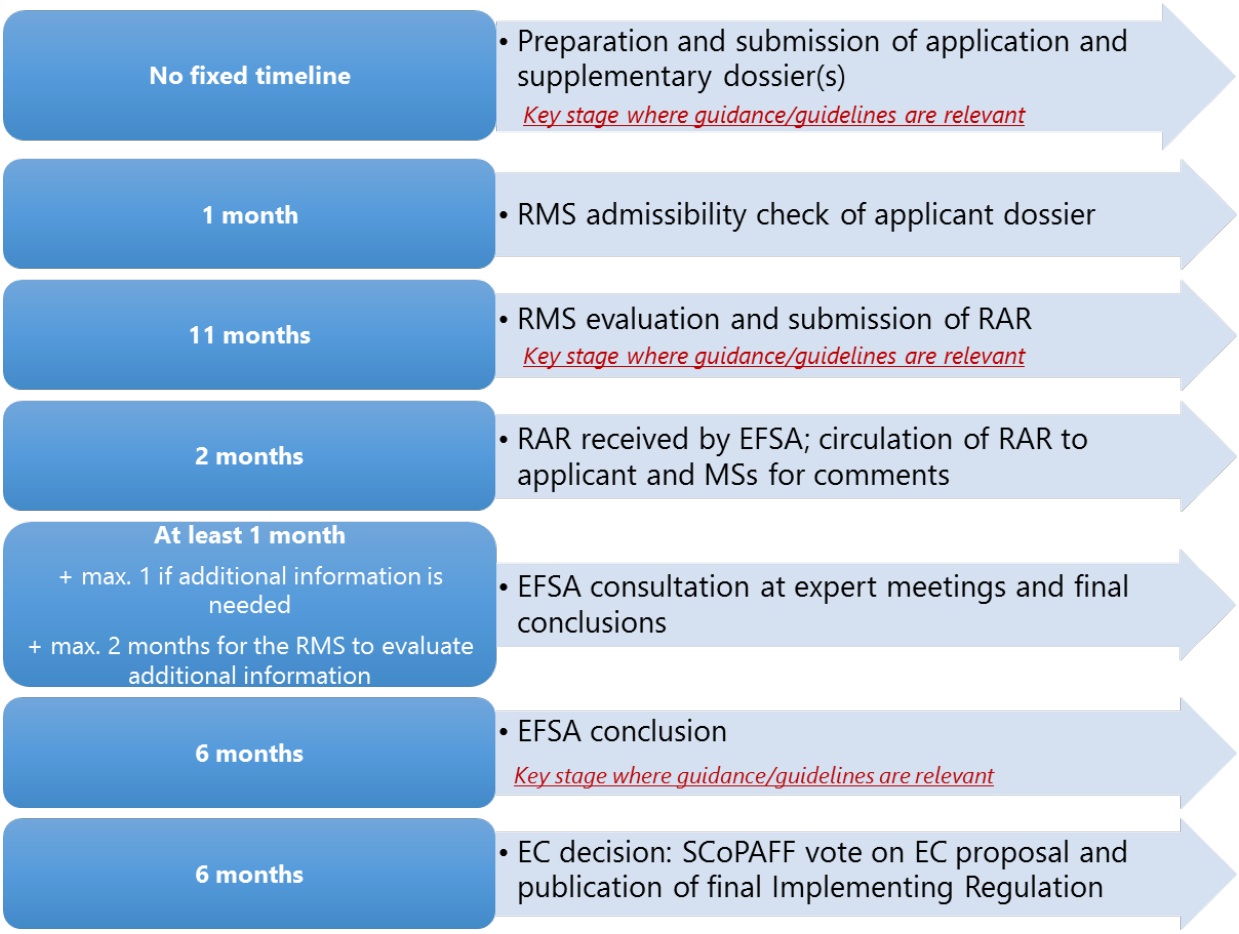
[11] The document is given the following title: "Conclusion on the peer review of the pesticide risk assessment of the active substance […]".

2.2.2. Renewal of approval of active substances

Articles 14 to 20 of Regulation (EC) No 1107/2009 set out the procedure for the renewal of the approval of active substances, once the initial 10-year approval period has expired. The procedure for the renewal is similar to the procedure for the initial approval of the active substance, with the risk assessment responsibilities shared between the RMS (which drafts a Renewal Assessment Report - RAR) and the EFSA (which adopt a conclusion on the renewal procedure). Guidance documents are also available for the renewal process to ensure the harmonisation of studies and tests carried out by the applicants, as well as risk assessment procedures at the RMS and EFSA level[12].

The Commission is later responsible for the presentation of a Review Report and a draft Implementation Regulation to the SCoPAFF, which votes on the decision to renew the approval for a period not exceeding 15 years. If renewal is granted, the Implementing Regulation is adopted by the Commission and published in the Official Journal. The renewal process is thus likely to take well above two years since the RMS receives the application, as set out in Figure 6.

Figure 6: Renewal of active substance approval workflow



Note: Key stages where guidance/guidelines are relevant are indicated above; however, guidance/guidelines may be also used at other stages.

Source: Agra CEAS based on Regulation (EC) No 1107/2009

[12] This issue will be examined in detail in **section** 3 of this report.

Two programmes of renewal are established at the EU level, under Directive 91/414/EEC[13], i.e.:

- the AIR-1 Programme, under Regulation (EC) No 737/2007, and
- the AIR-2 programme, under Regulation (EU) No 1141/2010.

Rules for the renewal of the approval of active substances which are not covered by AIR-1 or AIR-2 are laid down in the Implementing Regulation (EU) No 844/2012 (*EC, n.d. C*).

A link between the process for reauthorisation of a final product and the process for reapproval is created through Article 43 of Regulation (EU) No 1107/2009 (see Box 4).

Box 4: Renewal of authorisation (PPP) and renewal of approval (active substance)

According to Article 43 of Regulation (EU) No 1107/2009, within 3 months from the renewal of the approval of an active substance contained in a plant protection product for which reauthorisation is requested, the applicant shall submit certain new data, if required. This effectively creates a link between the re-approval and reauthorisation process. The level of new data are required varies between active substance; and the extent to which it poses a challenge for applicants is likely to be influenced by whether or not the applicant for reauthorisation was also an applicant for the reapproval of the active substance; and hence has access to the necessary documents. A guidance document has been drafted specifically on this article.

2.3. Provisions for guidance, guidelines and GLP in EU legislation

2.3.1. Provisions in Regulation (EC) No 1107/2009

Various provisions for guidance and guidelines are included in EU legislation. **Regulation (EC) No 1107/2009** provides the foundation for most provisions.

With regards to **guidance**:

Article 11 of this Regulation states that "*the rapporteur Member State shall make an independent, objective and transparent assessment in the light of current scientific and technical knowledge*"; while Article 12 notes that EFSA "*shall adopt a conclusion in the light of current scientific and technical knowledge using guidance documents available at the time of application on whether the active substance can be expected to meet the approval criteria in Article 4*".

According to Article 77, "*the Commission may … adopt or amend technical and other guidance documents such as explanatory notes or guidance documents on the content of the application concerning micro-organisms, pheromones and biological products, for the implementation of this Regulation*". Furthermore, "*the Commission may ask the Authority* (EFSA) *to prepare or to contribute to such guidance documents*".

Annex II sets out the procedure and criteria for the approval of active substances. Point 1.3 notes that, during this process "*Member States and the Authority shall take into consideration any further guidance*

[13] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. This was the previous regulatory framework for the authorisation of PPPs. Regulation 1107/2009 repealed Council Directive 91/414/EEC.

developed in the framework of the Standing Committee on the Food Chain and Animal Health for the purposes of refining, where relevant, the risk assessments".

With regards to **guidelines**, various points of Annex II note that an active substance shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, it is not considered to have certain properties or effects.

2.3.2. Regulation (EU) No 283/2013 and the resulting communication

In order to implement the data requirements for the approval of active substances set out in Annex II of Regulation (EC) No 1107/2009, Regulation (EU) No 283/2013 was subsequently introduced[14]. As well as the comprehensive list of data requirements, the introduction to the Annex of this Regulation specified that the list of test methods and guidance documents relevant to the implementation of this Regulation would be published in the Official Journal of the European Union. This list, which would facilitate harmonisation, was to be regularly updated. Communication 2013/C 95/01 was subsequently published in April 2013 to fulfil this requirement (EC, 2013). The communication has not been updated since initial publication; though work on its updating is in progress (the consultation of Member States and Agencies on a draft update is ongoing at the time of writing).

2.3.3. Good laboratory practices

With regards to good laboratory practices (GLP), **Directive 2004/10/EC[15]** harmonises provisions relating to the application of good laboratory practices and the verification of their applications for tests on chemical substances. The scope of the Directive specifies that the principles of good laboratory practice set out in the Directive should be applied to all non-clinical safety testing and environmental safety studies required by regulation for registering pesticide products (unless otherwise specified); therefore, mandating adherence to GLP practices of studies performed for active substance approval.

In addition to this, Article 60 of Regulation (EC) No 1107/2009 notes that Member States shall prepare a list of the test and study reports necessary for first approval, amendment or renewal of an active substance; and that this list shall include information on whether those test and study reports were certified as compliant with the principles of good laboratory practice or of good experimental practice.

Section 5 sets out the Good Laboratory Practice System in more detail.

[14] Regulation (EU) No 544/2011 was initially introduced for this purpose, but later repealed and replaced by Regulation (EU) No 283/2013 in order to take into account scientific and technical knowledge about chemical substances at that time.

[15] Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.

Key messages

An active substance is defined in EU legislation as "*a substance or a micro-organism that has an action on or against harmful organisms*". Plant protection products (PPPs) – a subset of pesticides - contain at least one active substance.

An applicant who wishes to obtain approval for an active substance must submit a dossier through a selected national contact point. This dossier contains an extensive set of documentation, which provides the information necessary to carry out the risk assessment.

EU legislation sets out **data requirements** to be included in application dossiers for active substance approval. **Guidance** can be technical (scientific) or procedural. **Technical guidance** provides more detail on what must be done in practical terms to check / fulfil these data requirements, and hence effectively act as sub-requirements for approval when used. **Procedural guidance** provides further clarifications on the procedure itself, rather than the scientific data.

Guidelines (or test methods) are protocols to follow when performing test to fulfil the data requirements; and therefore must be employed by applicants when performing studies

At the risk assessment level, guidance documents exist to ensure the harmonisation of the evaluation and risk assessment procedures at EU level. They may be used: (1) by the rapporteur national authority in the development of the draft assessment report; or (2) during the peer review process conclusions which is co-ordinated by EFSA (EFSA is also responsible for drafting the conclusions of this process). As guidance documents are used during the risk assessment stage, they can be considered to be of relevance for applicants, whose dossiers must successfully navigate this stage on the way to possibly ultimate approval.

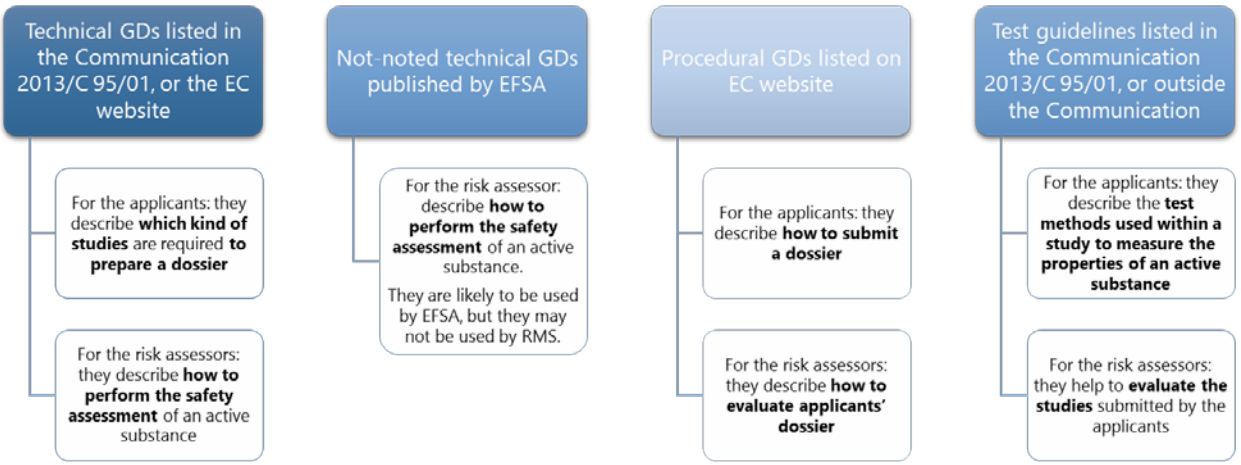
Against the background set out above, the current document will examine the guidance and guidelines that exist for active substances. Data requirements, guidance and guidelines also exist for PPPs; these are summarised at a high level due to the interaction between active substances approval and PPP authorisation. They are not examined in detail in this document, as the focus of the approval process is on the active substance rather than the PPP.

3. AVAILABLE GUIDANCE AND TEST GUIDELINES

Section 2 set out the approval process for active substances and highlighted how **guidance** (which translates requirements of legislation into practical steps) and **guidelines** (test methods to be followed) fit into this process. This section identifies existing guidance and guidelines.

Figure 7 gives a brief overview of all guidance documents and test guidelines currently available for the approval of an active substance, as well as their usefulness for both applicants and risk assessors.

Figure 7: Overview of key guidance documents and test guidelines currently available



Source: Agra CEAS

Relevant guidance and guidelines for active substances are explored in sections 3.1 and 3.2.

3.1. Guidance documents and test guidelines in the Communication

3.1.1. Overview of guidance documents and test guidelines in the Communication

As noted in section 2.3.2, Communication 2013/C 95/01 was published in order to provide guidance and guidelines for fulfilling the data requirements to be included in applications for the approval of active substances. The communication identifies more guidance documents and guidelines than the other sources described in subsequent sections. However, as it dates from 2013 several of the guidance documents listed in the communication may have been superseded by new guidance[16] It remains the most comprehensive source of test guidelines, even if some of the OECD guidelines listed have been subsequently updated (see section 3.3).

The guidance and guidelines in the Communication correspond to the categories of data requirements set out in Regulation (EU) No 283/2013. The Regulation identifies 10 main categories of data requirements; some of these categories have over 50 sub (or sub-sub) categories. However, guidance or guidelines do not exist for all categories and sub (or sub-sub) categories.

Tab**le 3-1** summarises the number of guidance and guidelines available by category and sub categories.

[16] As part of the ongoing update to the Communication, guidance listed in the 2013 Communication that has been superseded by new guidance is being identified

Table 3-1: Summary of guidance and guidelines set out in Communication 2013/C 95/01

Category	Sub categories	Number of sub-sub categories	Guidance	Guidelines
1. Identity of the active substance	11 in total*	3 under sub-category 1.10**	2	0
2. Physical and chemical properties of the active substance	2.1 Melting point and boiling point		0	4
	2.2 Vapour pressure, volatility		0	2
	2.3. Appearance (physical state, colour)		0	0
	2.4. Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity		0	1
	2.5. Solubility in water		0	2
	2.6. Solubility in organic solvents		0	1
	2.7. Partition coefficient n-octanol/water		0	2
	2.8. Dissociation in water		0	1
	2.9. Flammability and self-heating		0	4
	2.10. Flash point		0	2
	2.11. Explosive properties		0	2
	2.12. Surface tension		0	2
	2.13. Oxidising properties		0	5
	2.14. Other studies		0	1
3. Further information on the active substance	***General***		***0***	***1***
	3.1. Use of the active substance		0	0
	3.2. Function		0	0
	3.3. Effects on harmful organisms		0	0
	3.4. Field of use envisaged		0	0
	3.5. Harmful organisms controlled, and crops or products protected or treated		0	0
	3.6. Mode of action		0	0
	3.7. Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies		0	1
	3.8. Methods and precautions concerning handling, storage, transport or fire		0	0
	3.9. Procedures for destruction or decontamination		0	0
	3.10. Emergency measures in case of an accident		0	0
4. Analytical methods	4.1. Methods used for the generation of pre-approval data	2	***4 (for whole category)***	0
	4.2. Methods for post-approval control and monitoring purposes			

Category	Sub categories	Number of sub-sub categories	Guidance	Guidelines
5. Toxicological and metabolism studies	5.1. Studies on absorption, distribution, metabolism and excretion in mammals	2	2	4 (2)***
	5.2. Acute toxicity	7	0	35
	5.3. Short-term toxicity	3	0	14
	5.4. Genotoxicity testing	3	0	18 (17)***
	5.5. Long-term toxicity and carcinogenicity		0	6
	5.6. Reproductive toxicity	2	0	6
	5.7. Neurotoxicity studies	2	0	6
	5.8. Other toxicological studies	3	2	7
	5.9. Medical data	7	0	0
6. Residues in or on treated products, food and feed	***General***		***1***	0
	6.1. Storage stability of residues		0	1
	6.2. Metabolism, distribution and expression of residues	5	0	4 (2)***
	6.3. Magnitude of residue trials in plants		1	1
	6.4. Feeding studies	4	0	3 (1)***
	6.5. Effects of processing	3	1	4 (3)***
	6.6. Residues in rotational crops	2	0	3
	6.7. Proposed residue definitions and maximum residue levels	3	5 (3)***	0
	6.8. Proposed safety intervals		1	0
	6.9. Estimation of the potential and actual exposure through diet and other sources		1	0
	6.10. Other studies	1	0	0
7. Fate and behaviour in the environment	7.1. Fate and behaviour in soil	4 *(20 further categories)*	15 (9)***	11 (7)***
	7.2. Fate and behaviour in water and sediment	3 *(7 further categories under these)*	3	7 (6)***
	7.3. Fate and behaviour in air	3	1	0
	7.4. Definition of the residue	2	0	0
	7.5. Monitoring data		0	0
8. Ecotoxicological studies	***General***		***1***	***0***
	8.1. Effects on birds and other terrestrial vertebrates	5 *(5 further categories under these)*	2	7
	8.2. Effects on aquatic organisms	8 *(11 further categories under these)*	6 (4)***	18 (17)***
	8.3. Effect on arthropods	2 *(8 further categories under these)*	3	10 (6)***
	8.4. Effects on non-target soil meso- and macrofauna	2 *(1 further category under 8.4.2)*	1	3

Category	Sub categories	Number of sub-sub categories	Guidance	Guidelines
	8.5. Effects on soil nitrogen transformation		1	1
	8.6. Effects on terrestrial non-target higher plants	2	1	2
	8.7. Effects on other terrestrial organisms (flora and fauna)		1	0
	8.8. Effects on biological methods for sewage treatment		1	1
	8.9. Monitoring data		0	0
9. Literature data			1	0
10. Classification and labelling			1	0

* These have not been listed in this table as the guidance documents apply to the category as a whole, not to the sub categories.

** Sub-category title: identity and content of additives and impurities.

*** The same guidance/guideline is indicated for more than one sub-category, explaining the two numbers.

Note: in some cases, the same guidance or guideline is indicated for multiple sub categories in the table; meaning that the total number of guidance documents / guidelines is lower than the sum of the individual rows in the table.

Source: Agra CEAS based on Communication 2013/C 95/01

Important observations from this table are:

- The largest number of **guidance** documents relate to Ecotoxicological studies (category 8) and Fate and behaviour in the environment (category 7).
- There are at least some **guidance** documents for all categories except categories 2 (Physical and chemical properties of the active substance) and 3 (Further information on the active substance). That said, there are sub categories under other categories for which no guidance documents are listed.
- The largest number of **guidelines** relate to Toxicological and metabolism studies (category 5) and Ecotoxicological studies (category 8). There are no guidelines for some categories (e.g. 1, 9 and 10) as the nature of these categories do not foresee specific testing. Once again there are sub categories under other categories for which no guidelines are listed.

3.1.2. Parties for whom guidance documents and guidelines in the communication are relevant

While primarily intended for different parties, both guidelines and guidance listed in the communication are ultimately of relevance to both applicants and risk assessors. More concretely:

- **Guidelines**: as set out in Box 1, guidelines are test methods that must be followed when conducting studies, and as such are directly followed by applicants. However, risk assessors must also be aware of the applicable guidelines which should have been followed during their assessment.
- **Guidance**: the guidance listed in the communication indicate what risk assessors should examine in order to ensure the fulfilment of data requirements. However, applicants need to know what risk assessors will check in order to ensure the fulfilment of these requirements.

3.1.3. Bodies that developed guidance documents and guidelines listed in the Communication

As a starting point, the Communication indicates the existing guidance documents which should be used[17]. Against this background, the process of selecting the documents for use in the original communication holds importance. The Communication itself was originally developed and is currently being updated[18] through a process steered by the European Commission. A working group of experts from Member States appointed by SCoPAFF (and chaired by the Commission or a volunteer Member State) is responsible for the first full draft. Consultation on this draft with Member States and stakeholders follows for feedback of a technical nature. After any changes resulting from these consultations, the Commission proceeds with adoption.

The guidance documents and guidelines in the Communication were developed by a variety of bodies. In particular, as set out in Table 3-2, the majority of the guidance and guidelines were established by the OECD and the European Commission. As for the guidelines established by the European Commission, they were laid down in the Annexes of the following Regulations, which are currently in force:

- On physical and chemical properties of the active substance:
  - Regulation (EC) No 440/2008;
  - Regulation (EC) No 1272/2008.
- On toxicological and metabolism studies:
  - Regulation (EC) No 440/2008;
  - Regulation (EC) No 761/2009;
  - Regulation (EC) No 1152/2010.

Table 3-2: Number of test guidelines and guidance documents by establishing bodies

Body	Guidance documents	Guidelines
OECD	11	102
European Commission	19	52
EFSA	5	0
US EPA	0	9
UN RTDG	0	5
EPPO	1	4
Others (scientists, ECHA, CIPAC, FAO/WHO, ISO, SETAC)	5	8

Source: Agra CEAS Consulting

The inclusion of guidelines and guidance by parties other than the European Commission or EFSA is explained/justified by the following reasons:

- **Optimal solution considered to exist**. In some cases, the most commonly accepted best method is considered to already exist, and therefore can be directly adopted. This was reported to often be the case with guidelines given their specific test-based nature.

[17] It should be remembered that the Communication dates from 2013, and hence reflects the full guidance which should have been used at that point in time; however, in some cases, subsequent guidance has emerged and is now applicable, as described in subsequent sections.

[18] As previously noted, the Communication has not thus far been updated since original publication; but is in the process of being updated.

- **Avoiding a waste of resources**. It was noted that in some cases, existing internationally-established guidance is considered to be relevant, and subsequently using this avoided the inefficiency of recreating guidance intended for the same purpose.
- **Participation in the original process**. Building on the two points above, in many cases, the European Commission and/or Member States have often been involved in the original development process for guidance documents or guidelines emitted by other parties (e.g. OECD, EPPO – see boxes below).

3.1.4. Legal status of guidance and guidelines in the communication

The guidance documents and the majority of guidelines themselves are not legally binding as they are not set out in legally binding instruments (e.g. Regulations).[19] However, as noted in section 2.3.2, the Communication itself is a result of Regulation (EU) No 283/2013[20]. While deviation from what is listed in the communication is theoretically possible with explanations, it creates additional complexities/risks and is understood to rarely ultimately be accepted. Guidance documents and guidelines listed in the Communication do practically operate as mandatory, although not legally-binding *per se*.

3.2. Guidance documents outside the communication

3.2.1. Overview of guidance documents and guidelines outside the Communication

Several guidance documents exist and are used for the approval process of active substances beyond those which are listed in the Communication. In broad terms, these fall into one of the following categories:

- Additional technical guidance by EFSA or the Commission that is listed on the website of DG SANTE;
- Procedural guidance listed on the website of DG SANTE;
- Technical guidance by EFSA that is not listed on the Commission website;
- Zonal and national guidance.

These are presented in corresponding sub sections.

a. Additional technical guidance by EFSA or the Commission that is listed on the website of DG SANTE

As previously noted in section 2.3.2, the Communication was introduced in 2013, and has not since been updated (though an update is currently ongoing). Subsequently, new guidance documents from EFSA, the Commission, and OECD have emerged and (in the case of EFSA documents) have been noted by SCoPAFF. Such documents are listed on a dedicated Commission's website page[21], along with those from the Communication.

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19 Some test guidelines listed in the Communication are both described in and mandated by Regulations; most notably through the listing of the method in Regulation (EC) No 440/2008 as a result of Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). These can therefore be considered to be legally binding.

20 Article 6 notes: "For purposes of information and of harmonisation the list of test methods and guidance documents relevant to the implementation of this Regulation shall be published in the Official Journal of the European Union. This list shall be regularly updated."

21 Guidelines on Active Substances and Plant Protection Products:
https://ec.europa.eu/food/plant/pesticides/approval_active_substances/guidance_documents_en

Table 3-3: Additional technical guidance listed on the website of DG SANTE

Title of the guidance	Main Recipient: Applicant (A) or Risk Assessor (RA)	Category (*as defined on the EC website*)	Short description
EC COM Working Document concerning the data requirements for certain chemical active substances and PPPs containing such substances	RA	Dossier	GD proposing on a weight of evidence basis a tiered approach to the data requirements for specific active substances and PPPs containing such active substances.
EC GD on the Data Requirements on Efficacy for the Dossier to be Submitted for the Approval of New Active Substances contained in PPPs	A	Dossier	GD on efficacy requirements for new active substances, e.g. the principal objective of an efficacy assessment at the active substance approval stage.
EC GD on risk assessment for birds and mammals	RA	Ecotoxicological studies	GD on how to conduct a risk assessment for birds and mammals in the context of the review of active substances for inclusion in Annex I of Dir. 91/414/EEC.
EFSA Risk assessment for birds and mammals: Joint working group report on the birds and mammals GD	RA	Ecotoxicological studies	This GD addresses approaches to risk assessment for birds and mammals. In both cases, a tiered approach is used to assess the risk of mortality and reproductive effects.
EC GD for Environmental Risk Assessments of Active Substances Used on Rice	RA	Ecotoxicological studies	GD on data requirements and criteria for environmental risk assessment which address the use of PPPs in rice cultivation.
EFSA GD on Tiered Risk Assessment for PPPs for Aquatic Organisms in Edge-of-Field Surface Waters (a)	RA	Ecotoxicological studies	GD on tiered acute and chronic effect assessment schemes with detailed guidance on tier 1 and higher tier effect assessments for aquatic organisms in edge-of-field surface waters and on proposals regarding how to link effects to exposure estimates.
OECD GD on the Environmental Safety Evaluation of Microbial Biocontrol Agents	A + RA	Fate and behaviour in the environment	GD aimed at providing guidance in the context of applications for the approval of microbial biological control agents (mBCAs), and for the registration of microbial biological control products (mBCPs).
EFSA GD on clustering and ranking of emissions of PPPs and transformation products of these active substances from protected crops (GHGs and crops grown under cover) to relevant environmental compartments	RA	Fate and behaviour in the environment	GD on how to assess the emissions from protected crops when performing risk assessments according to Reg. EC no 1107/2009.
EFSA GD for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of PPPs and transformation products of these active substances in soil	RA	Fate and behaviour in the environment	GD on how to obtain DegT50matrix values to be used in exposure assessment when performing risk assessments according to Reg. EC No 1107/2009.
EC GD on Persistence in Soil	A	Fate and behaviour in the environment	GD on the information which should be submitted in order to allow an evaluation of persistent active substances and with elaborations on how to assess accumulation levels.
EC Working Document on Evidence Needed to Identify POP, PBT and vPvB Properties for pesticides	RA	Fate and behaviour in the environment	GD on the assessment of new/existing active substances against the PBT (and POP/vPvB) criteria.
OECD GD on microbial contaminant limits	A + RA	Physical and chemical properties	GD on current international microbial contaminant criteria on food and drinking water.
EC GD for the Assessment of The Equivalence of Technical Grade Active Ingredients for Identical Microbial Strains or Isolates	RA	Physical and chemical properties	GD for the assessment of technical equivalence of micro-organisms used in PPPs, in these cases: (a) Change of location of manufacturing plant,

Title of the guidance	Main Recipient: Applicant (A) or Risk Assessor (RA)	Category (*as defined on the EC website*)	Short description
			(b) Scale up of fermentation vessel, (c) Change of manufacturing process.
EC GD on significant and non-significant formulation changes of the chemical composition of authorised PPPs	A	Physical and chemical properties	GD for the harmonisation of the approach to significant and nonsignificant changes of the chemical composition of PPPs in the EU, and to provide information on a process and timeframe for such a procedure.
EC GD on the finalisation of the reference specification for technical active substances after the peer review	RA	Physical and chemical properties	GD focusing on three situations in which the specification of the technical material hasn't been harmonised before the respective active substance is listed in Annex I.
EC GD for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414	A	Physical and chemical properties	GD on the requirements for analytical methods supporting all submissions under Directive 91/414/EEC and, for formulated products only, for post-registration control and monitoring purposes.
EC Residues: GD for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Dir. 91/414	A	Residues in/on treated products, food, feed	GD on methods supporting the generation of data for registration, i.e.: method description; method validation; confirmatory techniques; derivatisation; non-specific and common moiety methods, immunological analysis.
EFSA GD on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products	A + RA	Toxicological and metabolism studies	GD on the quantification of potential non-dietary, systemic exposures as part of regulatory risk assessment for PPPs.
EFSA Guidance on dermal absorption - 2017	RA	Toxicological and metabolism studies	GD on critical aspects related to the setting of dermal absorption values to be used in risk assessments of active substances PPPs (based on the 2012 EFSA Scientific Opinion).
EC GD for the Setting of an Acute Reference Dose	RA	Toxicological and metabolism studies	Proposals for acute reference dose levels on the basis of all relevant toxicological information as required in Directive 1/414/EEC.

(a) Replaces the 2002 EU Guidance on Aquatic Toxicology listed in the 2013 EC Communication
Note: Some of these guidance documents are both relevant for the approval of active substances and the authorisation of PPPs. Furthermore, most of these guidance documents may be considered useful for other recipients than the ones indicated above. However, the table reported the recipients as indicated in each of the documents listed in the Table.
*Document author indicated in **bold**.*
Source: Agra CEAS based on DG SANTE website, https://ec.europa.eu/food/plant/pesticides/approval_active_substances_en

The guidance listed does not replace that listed in the Communication; it is additional.

b. Procedural guidance listed on the website of DG SANTE

The Communication only includes technical guidance to respond to the data requirements for active substance approval. It does not include guidance relating to the application process itself. DG SANTE has therefore developed a series of procedural application guidance documents. These are published on DG SANTE's website. A list of procedural guidance is set out in Table 3-4.

Table 3-4: Procedural guidance listed on the website of DG SANTE

Title of the guidance	Recipient: Applicant (A) or Risk Assessor (RA)	General topic
GD for applicants on preparing dossiers for the approval of a microbial active substance	A	Applicant dossier
GD on semiochemicals	A	Applicant dossier
GD on the Interpretation of the Transitional Measures for the Data Requirements for AS and PPPs	RA	Assessment Report
GD on botanicals	A	Applicant dossier

Title of the guidance	Recipient: Applicant (A) or Risk Assessor (RA)	General topic
GD on preparing list of test and study reports	A	Applicant dossier
GD for applicants on preparing dossiers for the approval of a chemical active substance	A	Applicant dossier
GD on Rules for Revision of Assessment Reports	RA	Assessment Report
Working Document on GLP - general requirements - 7017/VI/95	RA	Good Laboratory Practice
Working Document on GLP - detailed requirements for Part A, Annexes II and III - 7109/VI/94	RA	Good Laboratory Practice
GD on the Renewal of Authorisations according to Article 43 of Regulation (EC) No 1107/2009	RA	Renewal of approval
GD on Comparative Assessment and Substitution of PPPs	RA	Candidate for substitution
Working document on emergency authorisations according to Article 53	RA	Post-approval issues
Renewal GD on implementation of Regulation (EU) No 844/2012	A + RA	Renewal of approval
GD on the evaluation of new active substance data post approval	RA	Post-approval issues
GD on zonal evaluation and mutual recognition	A + RA	Post-approval issues
GD on the assessment of new isolates of baculovirus species	RA	Post-approval issues
GD on the assessment of new substances falling into the group of Straight Chain Lepidopteran Pheromones (SCLPs)	RA	Post-approval issues
GD on a Process for Intra & inter-zonal work-sharing to facilitate the registration and re-registration	A + RA	Post-approval issues
GD on the renewal of active substances	A	Renewal of approval
GD on submission and assessment of confirmatory information	A + RA	Post-approval issues
GD on data protection	A + RA	Procedures
GD on the taxonomic level of micro-organisms to be included in Annex I	RA	Procedures
Guidance on presenting and evaluating dossiers as per annex III, Directive 91/414/EEC as (draft) Registration Report	RA	PPP Draft Assessment Report
GDs on the presentation and evaluation of PPP dossiers in the format of a (draft) Registration Report	A + RA	PPP Draft Registration Report
Guidance document on the preparation and submission of dossiers for plant protection products according to the "risk envelope approach"	A	Dossier for PPPs

Note: Categories are defined by the European Commission.
Source: Agra CEAS based on DG SANTE website, https://ec.europa.eu/food/plant/pesticides/approval_active_substances_en

c. Technical guidance by EFSA that is not listed on the Commission website; EFSA opinions

All **guidance documents** established by EFSA are presented to the SCoPAFF for approval through note taking (see section 3.2.2). However, the procedure of note taking (which equates to a general agreement to use the guidance and leads to publishing the guidance document on the Commission website) might be delayed due to difficulties for Member States to agree on all elements of the guidance document. Such "not-noted" guidance will continue to appear on the EFSA website[22].

Despite the lack of overall acceptance EFSA may adhere to elements of not-noted guidance during the peer review phase; as may some Member States either during initial risk assessment (DAR), or for comments during the peer review phase. Therefore, applicants may also need to follow not-noted EFSA technical guidance in order to avoid problems with the application.

The titles of the three current EFSA guidance documents which have not been noted are set out below:

- **Toxicological and metabolism studies (2 documents)**:

[22] In the cases that the parts causing disagreement are limited in scope, guidance documents may be noted with exceptions for unresolved issues. This is described in section 3.2.2.

(a) Risk assessment of PPPs on bees (Apis mellifera, Bombus spp. and solitary bees);
(b) Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticides;

- **Ecotoxicological study**: Default Q10 value to describe the temperature effect on transformation rates of pesticides in soil.

Table 3-5 summarises the extent to which non-noted guidance is used by EU Member States and EEA countries for active substance approval. This varies among RMS. As highlighted above, it should be remembered that EFSA may also apply the guidance during peer review. Interviews reported that this occurs to different extents; some perceived EFSA to systematically apply such guidance during peer review, while others stated it is applied on a case by case basis. Public health or environmental concerns were cited by one interviewee as the main reasons for which non-noted guidance may be used during the peer review stage.

Table 3-5: EFSA non-noted guidance documents recommended/used by EU/EEA countries

EU/EEA country	*Do you recommend or require the use of guidance documents from EFSA which have not been noted by the SCoPAFF and the European Commission?*				*For which reasons?*
	Yes, always	Yes, often/ sometimes	Not frequently / generally not	Never	
BE		X **GD:** The Bee guidance			Recommended/required to address **lack of guidance** with endpoints from new data requirements.
DE			X		Non-noted GDs **may lead to** inconsistencies in the assessments and to **less harmonisation**.
EE			X		**In general, there is no need** for GDs which have not been noted. The need for such a guidance may arise when higher tier risk assessment needs to be carried out and evaluated.
ES			X		Only **when there is a GD from EFSA which has not been adopted**, for a given topic and there are **no guidelines** in this respect **in the regulation** we use EFSA non-noted GDs.
FI				X	No reasons provided.
IT			X		GDs are recommended/used only in the cases where proposed and agreed by the applicant or expressly suggested by the Commission and **agreed by MSs** during the discussion **at the SCPAFF**.
LT	X **GD:** The Bee guidance				It was agreed at the Pesticides Peer Review Expert Meeting that it should be used and now it is necessary to provide **chronic adult and larvae data** according to regulation 283/2013 and there are **no alternative** risk assessment schemes **to address these points**.
NL				X	No reasons provided.
PL			X		1. Non-noted draft GD covers stricter scenario (worst case scenario), comparing to the GD noted/ adopted and binding. 2. Information/ recommendations of the noted guidance are not sufficient to perform and finalise the risk assessment (e.g. in case when sophisticated refinements are required). 3. When not noted guidance describes test methods for which OECD guidelines are not available.
PT				X	Documents have not received consensus from a technical or formal point of view by all MS thus use or recommendation for use **may cause un-harmonised approach** by MS experts during evaluation and Risk Assessment.
SE			X		No reasons provided.

EU/EEA country	*Do you recommend or require the use of guidance documents from EFSA which have not been noted by the SCoPAFF and the European Commission?*				*For which reasons?*
	Yes, always	Yes, often/ sometimes	Not frequently / generally not	Never	
SI		X			With regards to the GD on RDDRA: Because it was assumed by the applicant and us /RMS that **EFSA will ask for the evaluation** of residues **according to this guidance** during the peer review. **GDs:** 1. For the identification of endocrine disruptors (which enters into force from November 2018). 2. On the establishment of the residue definition for dietary risk assessment (RDDRA).
SK		X			No reasons provided. **GD:** The Bee guidance
NO		X			No reasons provided. **GD:** The Bee guidance

Note: only contains Member States who replied to the survey; with the exception of Luxembourg and Iceland which reported that they do not act as RMS, therefore questions were not applicable to their case.
Source: Agra CEAS based on the EU/EEA CAs survey

As well as guidance, EFSA may produce relevant **scientific opinions**. These are assessments of scientific information available, rather than guidance for the regulatory context (indeed they generally are not intended to contain sufficient information for risk assessment). Despite this there was acknowledgement from different stakeholders (both industry and regulatory) that there are some scientific opinions which may be used in some cases for risk assessment. The extent to which this was acknowledged as occurring differed between stakeholders. Scientific opinion documents identified as possibly having been used as guidance for risk assessment to some extent are:

- Scientific Opinion on good modelling practice in the context of mechanistic effect models for risk assessment of plant protection products;
- Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms;
- Scientific Opinion on the state of the science on pesticide risk assessment for amphibians and reptiles;
- Scientific Opinion on the Science behind the Revision of the Guidance Document on Dermal Absorption (*prior to the publishing of the new guidance document*).

Finally, if there are repeated questions on a specific issue across different dossiers, EFSA may call an expert meeting to discuss how to address the issue in question. This may ultimately lead to an EFSA publication (**technical report**) which can be used as a kind of guidance, at least in the short term. These documents are not subject to the noting or approval; and may not be known to Competent Authorities if they were not present at the meeting.

Competent authorities answering to the survey reported some examples of reports drafted in occasion of experts' meetings. These are listed below:

- Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology;
- Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology (2015);
- Pesticides Peer Review Expert Meeting 133 (2015);
- The pesticides peer review meeting on the OECD 106 evaluators checklist.

Box 5: recent and ongoing work by EFSA

EFSA has recently worked on a number of scientific opinions and guidance documents of relevance to active substance approval and/or PPP authorisation, as well as some statements and other reports. Many of these, such as the guidance document on dermal absorption and the scientific opinion on risk assessment of PPPs for in-soil organisms have already been published (and noted in the case of the former). Work remains ongoing with an estimated seven guidance documents or scientific opinions expected for completion during the next year or so. Some work on scientific opinions is being completed as a precursor to possible future guidance documents.

d. Zonal and national guidance

The process of active substance approval, unlike that of final product authorisation, is an EU level process. Consequently, only EU level guidance should theoretically be used. Interviewees noted that there have been some cases of Member States using guidance other than EU level guidance in areas for which no harmonised guidance exists. Historically, the area of operator exposure is an example, though there is now harmonised EU level guidance on this[23]. Only one Member State was identified as currently using guidance for active substance approval at EU level (see below).

Table 3-6: National guidance used by EU MS

Non-noted GD which are recommended/ used	Type	Country where it is recommended/ required	For whom it is intended	Author	How it was established
De Jong (2010) - Guidance for summarising and evaluating field studies with non-target arthropods	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands (RIVM)	*Not available*
"Bird Bible" Birds and farming: information for risk assessment	Test guidelines	PL	Applicant & Risk Assessor	PSD/HSE UK: CSL Project No. M37	*Not available*
"Mammal Bible" Mammal and farming: information for risk assessment	Test guidelines	PL	Applicant & Risk Assessor	PSD/HSE UK: CSL Project No. M37	*Not available*
Guidance for summarising earthworm field studies (de Jong et al., 2006)	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands	The guidance was developed on request of the CTGB to standardise methods for evaluation of field studies with earthworms
Monitoring data in pesticide registration, RIVM report 601450015/2003	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands (RIVM)	*Not available*

Source: Agra CEAS based on the EU/EEA CAs survey

[23] Indeed, the introduction (page 6) of the guidance document on *the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment* specifically acknowledges the historical use of different approaches by different Member States.

Though not of direct relevance to active substance approval, zonal and national level guidance does exist for the national level authorisation procedure for PPPs. A brief overview is provided in Box 6. Some interviewees indicated that some Member States may apply this zonal and national guidance to ensure the possibility to authorise a representative product containing the active substance for approval, though the findings of the Member State survey and interviews with regulatory bodies did not confirm this.

Box 6: Zonal and national guidance for final products

As already noted in section 2, to facilitate the process of authorisation of plant protection products, the EU is divided into three zones, each of which has similar agricultural, plant health and environmental conditions (North, Centre, South). The final plant protection product has to be assessed in one EU Member State from each zone it is intended to be used in.

The three zones are described in Annex I of Regulation (EC) No 1107/2009, as set out below:

- **Zone A - North**: Denmark, Estonia, Latvia, Lithuania, Finland, Sweden.
- **Zone B - Centre**: Belgium, Czech Republic, Germany, Ireland, Luxembourg, Hungary, Netherlands, Austria, Poland, Romania, Slovenia, Slovakia, United Kingdom.
- **Zone C - South**: Bulgaria, Greece, Spain, France, Italy, Cyprus, Malta, Portugal.

Each zone has its own guidance document for the assessment of PPPs. Member States may also have their own guidance for authorisation.

3.2.2. Method of development of guidance documents outside the Communication

Technical guidance which is not included in the European Commission Communication can be either developed by (1) EFSA or (2) other bodies.

a. Development of guidance by EFSA

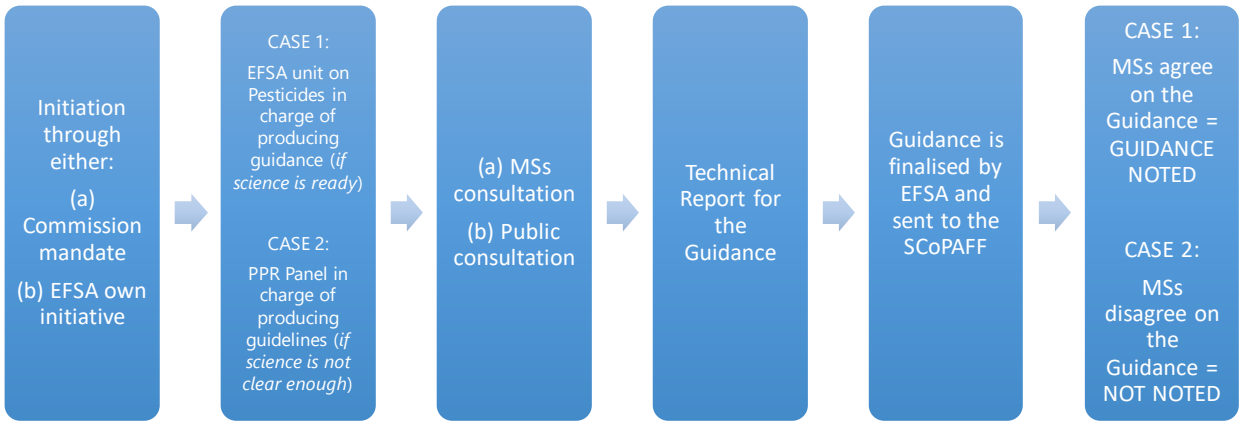
The process of development of guidance by EFSA generally takes between 18 months and 5 years.

Initiation

There are two mechanisms through which the development of guidance by EFSA can be initiated:

- EFSA establishes guidance at the request of the European Commission (e.g. in case of gaps or updates identified by the latter), often following a consultation with the Member States through the Pesticide Steering Network (PSN).
- EFSA takes the initiative to develop guidance documents for issues which are internally considered a priority.

Figure 8: EFSA procedure to develop Guidance Documents



Source: Agra CEAS

Development

Regardless of the mechanism through which work on guidance is initiated, the procedure to establish guidance documents at EFSA level varies depending on whether or not the science for developing the guidance is ready (see Figure 8 above):

- **Scientific panel**[24]: If it is considered that the ***science for establishing guidance is not clear enough***, EFSA will ask a scientific panel, i.e. the Panel on Plant Protection Products and their Residues (PPR), to develop a guidance document. For that purpose, EFSA selects a working group (WG) from the PPR members and external experts. The working group then presents its findings to the scientific panel, which can adopt the guidance if satisfied.
- **Regulatory panel**: if the science is considered ready, then EFSA guidance can be produced directly by the EFSA unit on Pesticides and biocides itself or a working group which reports to the Unit, without the involvement of the PPR.

Consultation

As reported in Figure 8, EFSA has been using a standard procedure for consultation in recent years. This consists of:

- a consultation phase with Member States through the PSN.
- a public consultation on the draft guidance.

Additional consultations of Member States may occur if deemed necessary.

The outcome of all consultations is included in a technical report for the guidance. The working group which drafted guidance examines each comment and indicates in the technical report if each comment was either (1) accepted or (2) not supported / deemed not relevant; and how each accepted comment was taken into account.

[24] The EFSA Scientific Committee and panels are composed of independent scientific experts with a three-year mandate.

Note-taking

Once the guidance document is finalised by EFSA, it is sent to SCoPAFF for a process referred to as "taking note" (Figure 8). This is essentially agreement and approval from Member States on the guidance document and its use. The note taking process can be complicated if Member States do not agree on the guidance document. This may happen for various reasons including most commonly: differences of opinion; and the absence of guidelines to enable tests required under the guidance (see also section 4.1). EFSA does not change guidance documents solely due to difficulties in the note-taking process arising from comments related to risk management. In the case that disagreements occur on a limited number of issues, the guidance document may be taken note of with exceptions for certain unresolved issues. These will be listed in the implementation schedule at the beginning of the guidance document, along with the date from which the guidance document should be applied.

Box 7: Can external stakeholders influence the development of EFSA guidance?

In procedural terms, external stakeholders cannot directly influence the development of guidance. The guidance is drafted without direct stakeholder input. While there is a review of the draft guidance following a public consultation, EFSA will review the outcomes of this and if/how to take points into account independently. Once EFSA guidance is published it is only reviewed if EFSA independently believes it can be improved – not due to comments from external stakeholders, whether Member States during the noting stage, industry or NGOs.

External stakeholders can make efforts to indirectly influence the content of guidance. In addition to the public consultation on draft guidance, stakeholders may publish scientific papers, make presentations at scientific conferences or similar in an effort to bring new efforts to the attention of EFSA for consideration.

The "closed door" approach to developing guidance has been criticised by some stakeholders. For example, in 2015 one stakeholder officially proposed a new procedure to develop guidance documents. This consisted of a working group made of external end-users (i.e. national risk assessors and risk managers) working in conjunction with EFSA; the rationale given was that it would ensure guidance documents are 'fit for purpose' for efficient risk assessment evaluations and decision-making procedures*.

Perceived bias in the composition of the EFSA board remains a topic of broader debate and is an issue beyond the mandate of the current study**.

* ECPA: Letter of 3rd March 2015 to DG SANTE on Development of scientific guidance documents

** e.g. PAN Europe, 2018: Industry writing its own rules.

b. Development of guidance by other bodies

In the case that other bodies develop guidance, this is done independently of the Commission (i.e. the development of guidance is not requested or mandated by the Commission) on the initiative and following the procedure of the drafting body. If deemed useful / suitable, the guidance may be adopted by the SCoPAFF. The clearest example of such guidance is the document on *the assessment of exposure of operators, workers, residents and bystanders,* originally drafted by the Health and Safety Executive (HSE) of the UK in September 2015 and adopted by SCoPAFF in January 2017.

3.2.3. Legal status of guidance documents outside the Communication

Box 8: A reminder on noted and not-noted guidance documents developed by EFSA

EFSA Guidance Documents may be:

- **Noted**, i.e. **approved** by the SCoPAFF and the European Commission. Noted guidance has been accepted by / reflect the views of these parties. The RMS and EFSA generally adhere to noted guidance to carry out the risk assessment procedure for the approval of an active substance.
- **Not-noted**, i.e. **not approved** by the SCoPAFF and the EC, since the guidance has not been accepted by / does not reflect the views of all Members. However, EFSA usually adheres to not-noted guidance to carry out a risk assessment procedure and some Member States may choose to adhere to this guidance as well.

Similar to guidance documents published in the Official Journal of the EU, the guidance documents outside the Communication are not legally binding. As reported by interviewees, diverging from a guidance document is therefore theoretically possible with proper scientific justification, although assessors tend to rely on the text of the noted guidance. New guidance documents on the Commission website which have been noted (EFSA) or approved (other authors) are *de facto* mandatory following this noting/approval, and are expected to be included in the update to the Communication which was initially developed in accordance with Regulation (EU) No 283/2013 (see section 3.1.4).

3.2.4. Industry own guidance

There is no broadly-used technical guidance developed by the industry. Individual companies develop internal procedures for how they think that the most meaningful risk assessment is performed, based on their experience and interpretation. These procedures, based on accumulated knowhow, are specific to each company and are not public. These are neither a replacement for guidance nor guidelines.

There are some recommendations developed by industry association ECPA (European Crop Protection Association) for assisting with the procedural aspects of submission. Officially these are not guidance, but may be considered to perform a role similar to that of procedural guidance. These can be found at: http://www.ecpa.eu/pre-market-resources-for-industry/technical-guidance-papers-common-standards-product-dossier-submissions.

There is also a Vademecum on Regulation (EC) No 1107/2009 published by Pappas and Associates. This is intended to assist the industry with all aspects of the Regulation, and includes an up to date list of guidance documents and guidelines with some clarifications. The Vademecum in itself does not constitute a guidance document for active substance approval.

3.3. Guidelines outside the communication

As indicated in section 3.1.3, the guidelines laid down in the Annexes of European Commission's Regulations are still in place and there have been no revisions to them since the publication of the 2013 Commission Communication. Nonetheless, the guidelines listed in the Communication (OECD ones in particular) have in some cases been revised. For example, in June 2018, the OECD adopted two new test guidelines and updated other existing ones, as set out below.

New OECD guidelines:

- Test No. 319A: Determination of in vitro intrinsic clearance using cryopreserved rainbow trout hepatocytes (RT-HEP);
- Test No. 319B: Determination of in vitro intrinsic clearance using rainbow trout liver S9 sub-cellular fraction (RT-S9).

Up-to-date guidelines, e.g.:

- Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents;
- Test No. 414: Prenatal Development Toxicity Study;
- Test No. 438: Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage;
- Test No. 442B: Skin Sensitization;
- Test No. 442D: In Vitro Skin Sensitisation;
- Test No. 492: Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage (OECD, n.d.).[25]

Similarly, some new or revised internationally established guidelines have been published, e.g. EPPO Standards for the efficacy evaluation of plant protection products (PP1) were revised in January 2018 (EPPO, n.d.).[26]

A complete list of revised guidelines is expected to be included in the forthcoming update to the original 2013 Commission Communication.

[25] The list is not exhaustive. A comprehensive list of updated guidelines can be retrieved at: http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm

[26] Most of the updated guidelines published by other bodies than the EC, EFSA, and EPPO can be retrieved at the following links:
CIPAC http://www.cipac.org/
ASTM http://www.astm.org/Standard/index.shtml
ISO http://www.iso.org/iso/home/store/catalogue_ics.htm
US EPA OCSPP http://www.epa.gov/ocspp/pubs/frs/home/testmeth.html

Key messages

Approval of active substances occurs at EU level; therefore, EU level guidance should be used. The Communication to Regulation (EC) No 283/2013 serves the role of indicating technical **guidance** and **guidelines** relevant for the approval of active substances. Relevant technical guidance and guidelines are indicated by data requirements for the dossier to be submitted for approval.

However, the Communication has not been updated since its first publication in 2013. In the interim, new applicable **technical guidance** has emerged. New technical guidance which should be used for active substance approval is indicated on the website of DG SANTE. This has generally been developed by EFSA and must be noted/approved by SCoPAFF before its publication on the website. In addition to this noted/approved guidance, there are three non-noted technical guidance documents published on the EFSA website. These may be applied for active substance approval in some cases, as may some EFSA scientific opinions, which are originally not intended to serve the role of guidance.

There is also **procedural guidance** for active substance approval (generally drafted by DG SANTE); and this is also listed on the Commission website.

Test **guidelines** are generally drafted by the OECD. They are developed based on regulatory need identified by an OECD member, and require unanimity for adoption. These guidelines are periodically updated as issues are identified with old guidelines using the same general process as that for adoption.

As a general rule, **guidelines** are of primary relevance to applicants and **technical guidance** to risk assessors, while the primary relevance of procedural guidance depends on the document itself. However, in practice all guidance documents and guidelines are of relevance to both applicants and risk assessors, given that both parties need to know how tests should be conducted and the method by which they will be assessed / procedures which must be followed.

While **guidance** and **guidelines** are not legally binding, those listed in the communication or noted/approved by SCoPAFF can be considered *de facto* mandatory.

The original list of guidance and guidelines in the Communication was developed through a process driven by the Commission with some consultation of Member States and stakeholders. The ongoing update also includes a phase of consultation from these parties. EFSA guidance, which may be developed either on the mandate of the Commission or on EFSA's own initiative, is developed independently by EFSA with a phase of consultation both with Member States and more broadly with stakeholders on the draft.

4. STATUS OF HARMONISATION OF GUIDANCE AND TEST GUIDELINES

The previous section showed that:

- Technical guidance documents and guidelines relate to specific data requirements for the dossier.
- Technical guidance documents in the communication have not been replaced by new guidance published on the Commission website; subsequently published guidance tends to cover different areas.
- The majority of technical guidance is published by EFSA and the Commission; the majority of guidelines by the OECD. The Commission drafts procedural guidance.
- The industry does not publish guidance or guidelines.
- Approval of active substances is an EU level issue, and subsequently only EU level guidance should apply.

These findings already ensure a certain level of harmonisation / greatly limit the scope for incoherence among guidance and guidelines for active substance approval. More specifically:

- There is limited scope for incoherence between guidance documents and guidelines applying to different data requirements[27].
- The bodies drafting the majority of guidance or guidelines can ensure coherence with existing guidance and guidelines. For example, when updating one test guideline, the OECD performs a coherence check with other test guidelines; and subsequently several other guidelines may also be updated as a result.
- As the industry does not publish guidance or guidelines, there is no scope for incoherence with the official guidance and guidelines.
- The application of EU level guidance should ensure harmonisation of guidance and guidelines across the EU (even if the guidance may still leave room for differences in interpretation).

Indeed, guidelines and guidance were found, in general terms to be harmonised and coherent. Nonetheless, certain specific issues with coherence were identified. These are:

- Guidance for which guidelines do not exist
- Gaps in available guidance and guidelines

These are detailed in the following corresponding sub-sections.

Finally, interviewees noted that there are substantial issues of coherence among different guidance documents for final product authorisation. This issue, which is fundamentally outside the scope of the present study, is summarised in Box 9.

[27] Nonetheless, it was noted by one interviewee that guidance documents for different data requirements sometimes use different assumptions for the same variable for reasons of conservatism; and this may be considered a conflict of sorts.

Box 9: A summary and examples of incoherence among guidance documents for final product authorisation

Incoherence among guidance documents for final product authorisation may at least partly be considered a consequence of the authorisation system for PPPs itself. As authorisation is national and the EU is divided into three zones – effectively removing harmonisation - there is the scope for incoherence at multiple levels: between different zonal guidance; between different national guidance; and between EU guidance/data requirements, zonal guidance and national guidance. Examples include: Operator Exposure assessment, for which EU data requirements foreseen certain higher tier studies but the Nordic zone guidance rejects; and aquatic risk assessment, for which the central zone guidance has some stricter requirements than EFSA guidance, and central zone Member States may ultimately differ in which guidance they follow.

4.1. Guidance for which guidelines do not exist

There are some cases in which technical guidance includes requirements for which validated guidelines for the test to fulfil these requirements do not exist. In such cases, examples of test methods which could be used may be provided in the annexe to the guidance. Nonetheless, this lack of guidences can result in challenges to fulfil data requirements, and ultimately either the use of different test methods by different applicants or a lack of fulfilment of the data requirement (due to the challenges), as subsequently highlighted in the DAR or peer review report.

The not-noted guidance on risk assessment of PPPs on bees is an example of guidance with some requirements for which validated guidelines do not exist. These are set out in Table 4-1. Another example is endocrine disruption, for which validated methodologies to perform tests for all the listed modes of action do not exist.

Table 4-1: Requirements in guidance on risk assessment of PPPs on bees for which validated test methods do not exist

Test required	Honey bees	Bumble bees	Solitary bees
8.3.1.1.1. Acute oral toxicity	OECD 213	OECD 247	ICPPR ring test
8.3.1.1.2. Acute contact toxicity	OECD 214	OECD 246	ICPPR ring test
8.3.1.2. Chronic toxicity to bees	OECD 245	No validated methods	No validated methods
8.3.1.3. Effects on bee development and other bee life stages	OECD 237; Guidance doc 239	No validated methods; and issues around technical feasibility	No validated methods; and issues around technical feasibility
8.3.1.4. Sub-lethal effects	No validated methods for Hypophryngeal glands	*N/A*	*N/A*
Higher tier (cage, tunnel, field)	EPPO 170 OECD 75; Oomen et.al.	No validated methods	No validated methods

In this context it should be highlighted that the absence of validated methodologies to fulfil guidelines is one of the issues identified as contributing to difficulties in the noting of guidance (see section 3.2.2).

4.2. Gaps in available guidance and guidelines

As was seen in Table 3-1, the Communication does not list guidance for every data requirement. While new guidance has subsequently been published on the website of the Commission and this fills some of the gaps, there are still data requirements for which there is no guidance. The reasons identified for this are:

- Insufficient scientific knowledge / clarity for guidance to be developed, particularly for fields which can be considered newer.
- A lack of internationally harmonised guidelines which facilitate both the development and workability of guidance.
- Limited resources from EFSA which restricts the number of new guidance document which can be drafted each year.

This can cause problems of harmonisation and, as in the absence of guidance, a case by case approach must be taken. In the case of active substances, the Commission may allow a data requirement to remain an open point if there are no guidelines or guidance and the provided scientific information is not considered sufficient. In such cases, a sentence to the effect of "*The Member States concerned shall ensure that the applicant submits to the Commission the relevant information at latest two years after the adoption of a specific guidance document*" will be placed in the regulation authorising the active substance[28]. Some interviewees indicated that the absence of guidance may pose greater issues during the final product authorisation than during the active substance approval process.

In this context, it should be noted that Member States can indicate areas where the absence of guidance is particularly troublesome, and following discussion among Member States, the Commission can take a decision on whether to mandate EFSA to develop guidance for this area. EFSA may also develop scientific opinions in an effort to gather the scientific information available, and this may ultimately facilitate the development of guidance at a later date in areas where scientific knowledge was previously considered insufficient.

[28] E.g. see various active substance approvals/reapprovals listed in Commission Implementing Regulation (EU) No 540/2011.

Key messages

There is generally a high level of harmonisation and limited scope between guidance and guidelines for active substance approval for reasons related to: the EU level nature of the active substance approval process; the targeting of specific data requirements by guidance and guidelines; the majority of guidance being published by the same few bodies; and the absence of industry guidance or guidelines. Harmonisation and coherence is a greater issue among guidance documents and guidelines for final product authorisation.

Two notable case of incoherence, which also impact harmonisation, were identified. Firstly, some guidance documents include requirements for which no validated test guidelines exist, leading to a lack of harmonisation in approaches taken to fulfil requirements, if the applicant considers it possible to fulfil them in the first place. Secondly, there are data requirements for which there is are no guidance documents or guidelines. In these instances, either a case by case approach is taken or a clause requesting data after the development of guidance at a future date is placed in the authorising regulation. Efforts have and continue to be made to fill these gaps in guidance documents to the extent the necessary science exists and resources are available.

5. GOOD LABORATORY PRACTICE AND THE ROLE OF INTERNATIONAL GUIDANCE

Box 10: What is the Good Laboratory Practice (GLP) system?

According the **OECD** (1998) **definition** the **Good Laboratory Practice** (GLP) is "*a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported*".

5.1. An overview of GLP

GLP is a quality system and a management tool concerned with how safety studies are organised, planned, performed, reported, reviewed and archived, allowing the reconstruction and reproducibility of the study to test data integrity. The scope of GLP covers all non-clinical safety testing of chemicals; and therefore, a wide range of products including pesticides, PPPs and active substances. While a quality management tool on the method of conducting studies, GLP does not concern the scientific quality of the study itself. In other words, it effectively guarantees process rather than outcome.

Box 11: History of GLP and OECD/MAD

The OECD started its work in harmonised quality standards through its expert group on good laboratory practice in 1978, in order to alleviate the labour intensive and expensive process of testing chemicals and reduce the possibility for fraud through standardisation. The OECD Council consequently adopted a Council Decision in 1981 – on Mutual Acceptance of Data (MAD). This stated that test data generated in any member country in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) shall be accepted in other member countries for assessment purposes and other uses relating to the protection of human health and the environment. Further OECD council acts have subsequently been adopted to arrive at the current MAD system. MAD requires that testing is conducted using OECD test guidelines in conjunction with GLP.

The principles of Good Laboratory Practice are set out in detail in the first publication of the "OECD Series on Principles of GLP and Compliance Monitoring", i.e. the– *OECD Principles on Good Laboratory Practice*. These Principles cover all types of test, including those not envisioned when the Principles were first established; and as a result, an update of the principles have not been required since they were last revised in 1997. Furthermore, numerous consensus, guidance and advisory documents, which were also published within the above-mentioned OECD Series on Principles of GLP and Compliance Monitoring, are available to ensure the compliance of test facilities with the OECD GLP principles. Consensus documents, which have effectively been mutually recognised by Members and generally date from 1999, include:

- Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice;
- Revised Guidance for the Conduct of Laboratory Inspections and Study Audits;
- Quality Assurance and GLP;
- Compliance of Laboratory Suppliers with GLP Principles;
- The Application of the GLP Principles to Field Studies;

- The Application of the GLP Principles to Short-term Studies;
- The Role and Responsibilities of the Study Director in GLP Studies;
- Guidance for the Preparation of GLP Inspection Reports;
- The Application of the Principles of GLP to Computerised Systems;
- The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP.

Guidance and advisory documents are more dynamic, and often provide additional guidance or clarity concerning the application of GLP to new testing approaches. The most recent document, *Advisory Document of the Working Group on Good Laboratory Practice on the Management, Characterisation and Use of Test Items*, dates from April 2018. Interviewees indicated that there is a general consensus between OECD members that new guidelines are respected; a fact that is assisted by suitable consultation both of OECD members and more widely during the document development process.

5.2. GLP in the EU

In the EU, Iceland, Liechtenstein and Norway, the Good Laboratory Practice System is regulated under Directives 2004/9/EC and 2004/10/EC. As reported by the European Commission (n.d. D), the **EU has transposed the OECD principles on Good Laboratory Practice and the revised OECD Guides for Compliance Monitoring Procedures for GLP**, which are reported in the annexes of the GLP Directives.

Directive 2004/9/EC lays down the obligation of EU Member States to identify national authorities responsible for GLP inspections.[29] Under the Directive, Member States should apply the OECD Principles of GLP and Compliance Monitoring, during laboratory inspections and study audits. Directive 2004/10/EC sets out the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of GLP practice and the verification of their applications for tests on chemical substance. All EU countries are required to take all measures necessary to ensure that test facilities carrying out safety studies on chemical products comply with the OECD GLP Principles. In recent years the European Commission (2015) has reported that all EU countries have transposed the GLP Directives and have established functioning national GLP compliance monitoring programmes. Overall there is a fairly high level of harmonisation in the transposition of the Directives in order to avoid differences in implementation and interpretation, the Commission has established an EU GLP Working group. This comprises the GLP monitoring authorities in the Member States with ECHA, EFSA, EMA, OECD and the monitoring authorities from some EFTA and EU candidate countries as observers. The working group aims to stimulate a common understanding of the GLP principles and monitoring procedures and facilitating the exchange of information between monitoring authorities and receiving authorities.

Table 5-1 illustrates the high level of harmonisation of GLP in general terms, as well as an example of the slights differences in the transposition of the GLP Directives at the Member State level. For example, while inspections take place each 2-3 years in Belgium, they are more frequent in Italy (given that the GLP conformity certificate has a shorter validity period in the latter country). Furthermore, while in Belgium pre-inspections and re-inspections are mandatory, respectively in case of test facilities inspected for the first time and major deviations from the GLP Directives, in Italy they are not required.

[29] The list of national authorities is published on the European Commission website, at: https://ec.europa.eu/docsroom/documents/26123/attachments/1/translations/en/renditions/native

Table 5-1: The transposition and application of the EU GLP Directives in Belgium and Italy

	GLP application in Belgium	GLP application in Italy
EU GLP legislation transposed in:	Royal Decree of 6 March 2002	Decree of 5 August 1999
GLP Monitoring Authority for GLP compliance Assessment	Sciensano – National public health institute	Organismo Nazionale di Controllo (ONC) – National Inspection Body
How long it takes to issue a GLP compliance certificate		6 months
Inspections frequency	Every 2-3 years	At least every 2 years
Types of inspections carried out	**- Mandatory pre-inspection** (test facility inspected for the first time): documentation, organisation, completed and on-going studies are verified; - **Inspection/study audit** which leads to a decision i.e. major deviation (C), minor deviation (B), no deviation (A). - **Mandatory re-inspection**, in case of major deviation. Can be by documentation or at the test site.	- **Not mandatory preliminary information visit** (test facility inspected for the first time) aimed at collecting information. - **Inspection/study audit** which leads to a decision i.e. major deviation, minor deviation, no deviation. - **Not mandatory re-inspection**, in case of minor deviation, to verify the implementation of "corrective measures".
Validity of GLP conformity certificate	3 years	2 years

Source: Agra CEAS based on Ministero della Salute (2018) and ISP WIV (2009).

Box 12: How is GLP assured?

The Member States are responsible for the checking of facilities on their territory. As set out above, the foreseen frequency of routine inspection is every 2-3 years (with precise frequency depending on the transposition of the Directive)*. Inspections may also be carried out more frequently if deemed necessary by the responsible authority. Inspections include checks on the facility; and on both completed studies (documentation) and on-going studies. Nonetheless, main criticisms levelled by some at the inspection system are that laboratories receive a pre-warning before inspections and that reliability and quality of GLP studies are not full assessed**.

In recent years, EFSA has requested that the GLP status of some studies be checked for all regulatory products for which EFSA has a risk assessment role. This selection is done based both on (1) a random selection and (2) also the targeting of selected studies with which EFSA has some concerns. The OECD Member Country where the study was conducted is sent the request to check. It was reported that countries have so far responded positively to OECD requests.

Studies should also be audited by the laboratory's quality assurance unit, which should act independently of the operational unit.

* The 2015 Commission document "Archives - Implementation of the GLP Directives in the European states" lists an overview of the status of transposition by Member State, including the frequency of checks.

** e.g. PAN Europe: GLP –does it create reliable and high quality studies?

5.3. GLP specifically in the area of pesticides

As noted above, the scope of GLP covers all non-clinical safety testing of chemicals. GLP must be applied as a whole with all principles applicable to all products falling under GLP (i.e. it is not a menu of principles which varies by product). That said, GLP data requirements (i.e. which studies must be conducted under GLP) are not contained in the GLP Directives but in product-specific legislation.

In the case of PPPs and A.S., there is one key legislative reference and one guidance document:

Legislative reference: Section 3 of the annex of Regulation (EU) No 283/2013 states that *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 (4) where testing is done to obtain data on the properties or safety with respect to human or animal health or the environment*. In a nutshell, certain derogations are provided:

- for certain cases of active substances consisting of micro-organisms or viruses for non-human health safety tests;
- for some tests to obtain data for minor crops; and,
- for some studies conducted before the application Regulation (EU) No 283/2013 for animal tests.

Guidance document on the applicability of GLP to data requirements according to the annexes of directive 91/414/EEC. This guidance document drafted in 1995 under the previous regulatory framework, sets out the GLP requirement for studies by data requirement under the previous directive[30]. It has theoretically been superseded by the legislative requirement above, though the document is still published on the Commission website guidance list, along with a more general guidance document on GLP drafted in 1996.

In addition to this, as indicated in section 2.3.3, under article 60 of Regulation (EC) No 1107/2009 Member States are required to prepare a list of the test and study reports necessary for first approval, amendment or renewal of an active substance. This list shall include information on whether those test and study reports were certified as compliant with the principles of good laboratory practice or of good experimental practice.

[30] These data requirements do not map precisely to those under the current legislative framework.

Key messages

GLP is a quality management tool on the method of conducting studies. It does not concern the scientific quality of the study itself. Therefore, it effectively guarantees process rather than outcome. The scope of GLP covers all non-clinical safety testing of chemicals, i.e. a wide range of products. This includes PPPs/actives substances.

The core principles of GLP cover all types of test, including those not envisaged when the Principles were first established. These core principles must be applied as a whole. Their relevance does not fundamentally vary depending on the nature of the product. The principles are supplemented by mutually recognised consensus documents, as well as advisory and guidance documents for which there is a general consensus among OECD members to adhere to.

GLP is regulated in the EU and EEA under Directives 2004/9/EC and 2004/10/EC. There is a fairly high level of harmonisation in the application of GLP across the EU. The EU GLP working group assists in maintaining this continued harmonisation. Laboratories are routinely monitored every 2-3 years depending on the country.

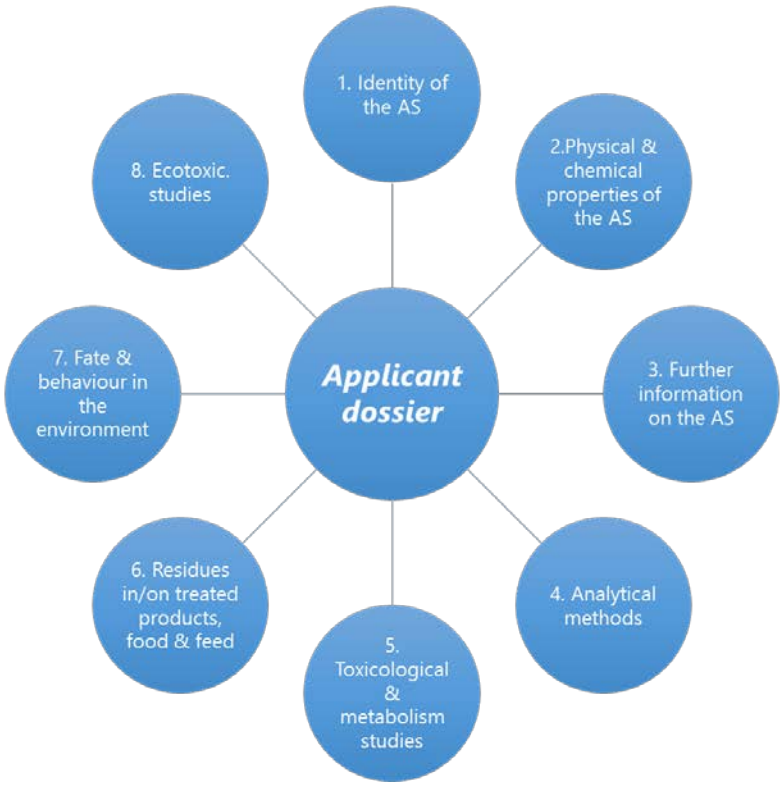
In the area of active substances, the annex to Regulation (EU) No 283/2013 stipulates that more or less all tests performed to obtain data on the properties or safety with respect to human or animal health or the environment must be conducted under GLP. There is also some guidance from the previously regulatory framework on GLP for PPPs / active substances which is included on the Commission guidance document website.

6. STUDIES REQUIRED FOR THE SUBMISSION OF AN APPLICATION

6.1. Type of studies required

As already indicated in section 2.2.1.a, the applicant's dossier for the approval of an active substance shall include information regarding the producer and the active substance itself. In particular, the dossier contains 8 major sections (Figure 9), together with two sections about literature data[31], and classification and labelling information, as set out in the Annex (Part A) of Commission Regulation (EU) No 283/2013.

Figure 9: Applicant dossier main sections



Source: Agra CEAS

A comprehensive list of the essential studies and tests to apply for the approval of a new active substance is set out in set out in Annex I of this study, based on Annex (Part A) of Commission Regulation (EU) No 283/2013. All studies potentially required are set out in this annex, though the annex cannot be considered a straight checklist of studies required for various reasons (see Box 13).

[31] According to the literature data requirement, 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. (Section 9, Part A, Annex to Regulation (EU) No 283/2013).

Box 13: How many studies are submitted in a dossier for A.S. approval?

There is no single answer for the number of studies which are required for A.S. approval. While the list in the Annex (Part A) of Commission Regulation (EU) No 283/2013 provides a starting point, multiple studies may be required to fulfil some data requirements. Interviewees indicated that the number of studies tends to be in the range of 100 to 500. The number of studies for reapproval dossiers may be higher. According to the March 2018 version of the Vademecum of Regulation 1107/2009 published by Pappas and Associates, the dossier for new active substance approval – which includes the study reports as well as summary dossiers and supporting information – comprises in the ranges of 50 000 to 150 000 pages.

6.2. Requirements and standards that studies must meet

In accordance with the Annex of Commission Regulation (EU) No 283/2013, the information submitted by applicants, when applying for the approval of an active substance, shall be sufficient to evaluate the (a) **foreseeable risks**, (b) **potentially harmful effects** and (c) **potentially unacceptable effects** of the active substance on humans, animals and the environment. To this end, the information may be generated using **test methods**. In the absence of suitable internationally or nationally validated test guidelines, test guidelines accepted by the European Commission shall be used. Deviations are possible but need proper scientific justifications.

As set out in detail in Annex IV, among other things, the information on the active substance shall be sufficient to:

- Permit an assessment of the risks for human and animal health (arising from the use of the active substances and its residues in water, air, food and feed);
- Predict the distribution, fate and behaviour in the environment;
- Permit an assessment of the impact on non-target species (flora and fauna), which result from exposure to the active substance;
- Evaluate the overall impact on biodiversity and the ecosystem;
- Specify the symbols or statements to be used for labelling purposes;
- Establish, where relevant, an acceptable daily intake (ADI) level for humans;
- Establish acceptable operator exposure levels (AOEL);
- Establish, where relevant, an acute reference dose, (ARfD) for humans;
- Establish maximum residue levels and concentration/dilution factors;
- Specify conditions or restrictions to be associated with any approval.

Studies which do not fulfil requirements may be rejected (see Box 14 for common reasons).

Box 14: What are common reasons for the rejection of studies

While studies may be rejected for a number of reasons, particularly common ones are:

- The absence of guidelines for higher tier studies, which can lead to more discussion on the suitability of the method used and the result.
- The submission of old studies used in the initial approval of an active substance during the re-approval process. The emergence of new guidelines and guidance based on new science may mean that such studies, even if well done, do not fulfil these new guidelines and guidance. There is a provision for exceptions in certain cases where a study was not performed under GLP in the legislation (see section 5.3).

Studies may also be rejected if the methods of evaluation set out in new guidance published since the study was conducted are not met. The programmed delay in the application of new noted guidance is intended to reduce such cases.

Finally, while not a reason for rejection of a study *per se*, the number of steps of studies which were completed for a data requirement may have an impact during the risk assessment stage. Risk assessors may, based on their interpretation, believe that an insufficient number of steps were completed by the applicant and hence that the studies performed still leave data gaps.

Key messages

Annex (Part A) of Commission Regulation (EU) No 283/2013 lists the studies required, and further indications can be found in the guidance. However, this annex cannot be considered a straight checklist of studies required as these vary from case to case. Multiple studies may be required to fulfil some data requirements. Available evidence suggests that a dossier for active substance authorisation typically includes between 100 and 500 studies; and comprises 50 000 to 150 000 pages. The information submitted by applicants in a dossier should be sufficient to evaluate (a) foreseeable risks, (b) potentially harmful effects, (c) potentially unacceptable effects of the active substance on humans, animals and the environment. To this end, the information may be generated using test methods (guidelines).

Studies may be rejected for a number of reasons. More common reasons include the absence of guidelines for studies which leads to more discussion on the methods used and results, and the submission of old studies during the re-approval process.

7. CONCLUSIONS

EU legislation sets out data requirements to be included in application dossiers for active substance approval. Guidance documents, which are now primarily published by EFSA, may provide more detail on these data requirements. In order to fulfil data requirements, it is necessary to produce one or more studies, generally under GLP. Guidelines describe how these studies should be conducted. The majority of these are published by the OECD. Guidance documents should then facilitate/harmonise the interpretation of the results.

Approval of active substances occurs at EU level, and for this reason, guidance used should also be at EU level. Evidence suggests that, with a few exceptions, this is now generally the case. The EU-level guidance for active substance approval is aimed at ensuring the harmonisation of the evaluation and risk assessment procedures at EU level.

The findings of the study show that there is **generally a good level of harmonisation and coherence among** guidance and guidelines for active substance approval. Some cases of incoherence were identified, which in turn impact harmonisation, as different approaches are adopted across the EU. This is the case of some guidance for which guidelines do not exist. Furthermore, a few gaps in available guidance and guidelines were observed. However, efforts have and continue to be made to fill these gaps in guidance documents to the extent the necessary science exists, and resources are available. Guidance and guidelines for PPP authorisation – a topic outside the scope of this study, and which is based on a national/zonal authorization system – appear to face more challenges in terms of harmonisation and coherence.

Under the OECD MAD (mutual acceptance of data agreement), studies conducted using OECD test guidelines and under GLP are accepted across the OECD for assessment purposes. Consequently, EU legislative requirements on the use of GLP and OECD guidelines aside, it is in the interest of applicants to ensure studies are conducted under GLP and using OECD guidelines.

With regards to the GLP system, there is a fairly high level of harmonisation in the application of GLP across the EU. The EU GLP working group assists in maintaining this continued harmonisation.

Although the scope for incoherence among guidance and guidelines for active substance approval may seem limited, the current **complex system poses some challenges**. Sources of guidance are various: Communication 2013/C 91/01, the website of DG SANTE, and EFSA website, amongst others. Although the Communication has not been updated since 2013, it remains one of the most important sources of test guidelines, even though some of these may have been updated. The DG SANTE website is the only source of noted/approved guidance which is constantly updated. EFSA may develop guidance which is finally not noted/approved, or whose note-taking is delayed due to Member States' disagreement. The latter may be used either by the RMS or later during the peer-review procedure and is usually merely reported on the EFSA website. Furthermore, elements of scientific opinions and technical reports may be used as guidance on a case by case or temporary basis. In this context it should be noted that the Communication is in the process of being updated, which would go some way to removing some of the complexity. Nonetheless, the number of documents to take into account has increased over time and appears likely to continue to do so in the future.

As a result of the system, the applicant may have to deal with **some level of uncertainty** inherent to the system. While noted/approved EU guidance should and generally is adhered to, other guidance may be used in some cases. The emergence of new guidance may pose some challenges if it emerges close to the time of submission of an application; though to address this, a delay of 3-6 months is generally applied before noted guidance should be used.

In conclusion, it appears that both applicants and RMS have to constantly monitor the development of new guidance from multiple sources and are currently not provided with up-to-date instruments to navigate this complex system. Member States may still have differences in opinions despite the existence of guidance.

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- Commission Regulation (EC) No 737/2007 of 27 June 2007 on laying down the procedure for the renewal of the inclusion of a first group of active substances in Annex I to Council Directive 91/414/EEC and establishing the list of those substances.
- Commission Regulation (EC) No 761/2009 of 23 July 2009 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
- Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.
- Commission Regulation (EU) No 1141/2010 of 7 December 2010 laying down the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC and establishing the list of those substances.
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- Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

INTERVIEWEES

Note: a number of interview targets declined the opportunity to participate in an interview. These are not included in this list.

- Unit E4 (Pesticides and Biocides), DG SANTE, European Commission
- Unit D2 (Chemicals), DG GROW, European Commission
- Pesticides Unit, EFSA
- Pesticide unit, KEMI (Swedish Chemical Agency)
- EPPO
- OECD
- ECPA
- ECCA
- PAN Europe

ANNEXES

ANNEX I: Content of the applicant dossier

Table 7-1: The applicant dossier template

SECTION 1. Identity of the active substance
Applicant
Producer
Common name proposed or ISO-accepted and synonyms
Chemical name (IUPAC and CA nomenclature)
Producer's development code numbers
CAS, EC and CIPAC numbers
Molecular and structural formula, molar mass
Method of manufacture (synthesis pathway) of the active substance
Specification of purity of the active substance in g/kg
Identity and content of additives (such as stabilisers) and impurities: • Additives • Significant impurities • Relevant impurities
Analytical profile of batches
SECTION 2. Physical and chemical properties of the active substance
Melting point and boiling point
Vapour pressure, volatility
Appearance (physical state, colour)
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity
Solubility in water
Solubility in organic solvents
Partition coefficient n-octanol/water
Dissociation in water
Flammability and self-heating
Flash point
Explosive properties
Surface tension
Oxidising properties
Other studies
SECTION 3. Further information on the active substance
Use of the active substance
Function
Effects on harmful organisms
Field of use envisaged
Harmful organisms controlled and crops or products protected or treated
Mode of action
Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies
Methods and precautions concerning handling, storage, transport or fire

Procedures for destruction or decontamination
Emergency measures in case of an accident
SECTION 4. Analytical methods
Methods used for the generation of pre-approval data: • Methods for the analysis of the active substance as manufactured • Methods for risk assessment
Methods for post-approval control and monitoring purposes
SECTION 5. Toxicological and metabolism studies
Studies on absorption, distribution, metabolism and excretion in mammals • Absorption, distribution, metabolism and excretion after exposure by oral route • Absorption, distribution, metabolism and excretion after exposure by other routes
Acute toxicity • Oral • Dermal • Inhalation • Skin irritation • Eye irritation • Skin sensitisation • Phototoxicity
Short-term toxicity • Oral 28-day study • Oral 90-day study • Other routes
Genotoxicity testing • In vitro studies • In vivo studies in somatic cells • In vivo studies in germ cells
Long-term toxicity and carcinogenicity
Reproductive toxicity • Generational studies • Developmental toxicity studies
Neurotoxicity studies • Neurotoxicity studies in rodents • Delayed polyneuropathy studies
Other toxicological studies • Toxicity studies of metabolites • Supplementary studies on the active substance • Endocrine disrupting properties
Medical data • Medical surveillance on manufacturing plant personnel and monitoring studies • Data collected on humans • Direct observations • Epidemiological studies • Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests • Proposed treatment: first aid measures, antidotes, medical treatment • Expected effects of poisoning

SECTION 6. Residues in or on treated products, food and feed
Storage stability of residues
Metabolism, distribution and expression of residues • Plants • Poultry • Lactating ruminants • Pigs • Fish
Magnitude of residue trials in plants
Feeding studies • Poultry • Ruminants • Pigs • Fish
Effects of processing • Nature of the residue • Distribution of the residue in inedible peel and pulp • Magnitude of residues in processed commodities
Residues in rotational crops • Metabolism in rotational crops • Magnitude of residues in rotational crops
Proposed residue definitions and maximum residue levels • Proposed residue definitions • Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed • Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)
Proposed safety intervals
Estimation of the potential and actual exposure through diet and other sources
Other studies • Residue level in pollen and bee products
SECTION 7. Fate and behaviour in the environment

Fate and behaviour in soil
• Route of degradation in soil
  • Aerobic degradation
  • Anaerobic degradation
  • Soil photolysis
• Rate of degradation in soil
  • Laboratory studies
  – Aerobic degradation of the active substance
  – Aerobic degradation of metabolites, breakdown and reaction products
  – Anaerobic degradation of the active substance
  – Anaerobic degradation of metabolites, breakdown and reaction products
  • Field studies
  – Soil dissipation studies
  – Soil accumulation studies
• Adsorption and desorption in soil
  • Adsorption and desorption

- Adsorption and desorption of the active substance
- Adsorption and desorption of metabolites, breakdown and reaction products
- Aged sorption

- Mobility in soil
  - Column leaching studies
    - Column leaching of the active substance
    - Column leaching of metabolites, breakdown and reaction products
  - Lysimeter studies
  - Field leaching studies

Fate and behaviour in water and sediment

- Route and rate of degradation in aquatic systems (chemical and photochemical degradation)
  - Hydrolytic degradation
  - Direct photochemical degradation
  - Indirect photochemical degradation
- Route and rate of biological degradation in aquatic systems
  - Ready biodegradability'
  - Aerobic mineralisation in surface water
  - Water/sediment study
  - Irradiated water/sediment study
- Degradation in the saturated zone

Fate and behaviour in air

- Route and rate of degradation in air
- Transport via air
- Local and global effects

Definition of the residue

- Definition of the residue for risk assessment
- Definition of the residue for monitoring

Monitoring data

SECTION 8. Ecotoxicological studies

Effects on birds and other terrestrial vertebrates

- Effects on birds
  - Acute oral toxicity to birds
  - Short-term dietary toxicity to birds
  - Sub-chronic and reproductive toxicity to birds
- Effects on terrestrial vertebrates other than birds
  - Acute oral toxicity to mammals
  - Long-term and reproductive toxicity to mammals
- Active substance bioconcentration in prey of birds and mammals
- Effects on terrestrial vertebrate wildlife (birds, mammals, reptiles and amphibians)
- Endocrine disrupting properties

Effects on aquatic organisms

- Acute toxicity to fish
- Long-term and chronic toxicity to fish
  - Fish early life stage toxicity test
  - Fish full life cycle test
  - Bioconcentration in fish
- Endocrine disrupting properties
- Acute toxicity to aquatic invertebrates
  - Acute toxicity to Daphnia magna
  - Acute toxicity to an additional aquatic invertebrate species

• Long-term and chronic toxicity to aquatic invertebrates
  • Reproductive and development toxicity to Daphnia magna
  • Reproductive and development toxicity to an additional aquatic invertebrate species
  • Development and emergence in Chironomus riparius
  • Sediment dwelling organisms
• Effects on algal growth
  • Effects on growth of green algae
  • Effects on growth of an additional algal species
• Effects on aquatic macrophytes
• Further testing on aquatic organisms

Effect on arthropods
• Effects on bees
  • Acute toxicity to bees
  • Acute oral toxicity
  – Acute contact toxicity
  • Chronic toxicity to bees
  • Effects on honeybee development and other honeybee life stages
  • Sub-lethal effects
• Effects on non-target arthropods other than bees
  • Effects on Aphidius rhopalosiphi
  • Effects on Typhlodromus pyri

Effects on non-target soil meso- and macrofaunal • Earthworm — sub-lethal effects • Effects on non-target soil meso- and macrofauna (other than earthworms)   • Species level testing
Effects on soil nitrogen transformation
Effects on terrestrial non-target higher plants • Summary of screening data • Testing on non-target plants
Effects on other terrestrial organisms (flora and fauna) Effects on biological methods for sewage treatment
Monitoring data
SECTION 9. Literature data
SECTION 10. Classification and labelling

Source: Agra CEAS based on Annex (Part A) of Commission Regulation (EU) No 283/2013.

ANNEX II: Content of the Draft Assessment Report (DRA)

Table 7-2: DRA Template

Volume 1
Level 1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION: • Context in which the DRA was prepared • Applicant information • Identity of the active substance • Information on the plant protection product • Detailed uses of the plant protection product
Level 2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

- Identity
- Physical and chemical properties
- Data on application and efficacy
- Further information
- Methods of analysis
- Effects on human and animal health
- Residue
- Fate and behaviour in the environment
- Effects on non-target species
- Proposed harmonised classification and labelling according to the CLP criteria
- Relevance of metabolites in groundwater
- Consideration of isomeric composition in the risk assessment
- Residue definitions

Level 3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION:

- Background to the proposed decision
- Proposed decision
- Rational for the conditions and restrictions to be associated with the approval or authorisation(s), as appropriate

APPENDICES

REFERENCE LIST

Volume 2

LIST OF THE TESTS, STUDIES AND INFORMATION SUBMITTED

- Identity
- Physical and chemical properties
- Data on application and efficacy
- Further information
- Methods of analysis
- Toxicology and metabolism data
- Residue data
- Environmental fate and behaviour
- Ecotoxicology data

Volume 3 - B.1

IDENTITY

- Identity of the active substance
- References relied on

Volume 3 - B.2

PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

- Melting point and boiling point
- Vapour pressure, volatility
- Appearance (physical state, colour)
- Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelenghts, optical purity
- Solubility in water
- Solubility in organic solvents
- Partition coefficient n-octanol/water
- Dissociation in water
- Flamability and shelf-heating
- Flash point
- Explosive properties
- Surface tension
- Oxidising properties
- Other studies

- References relied on

Volume 3 - B.3

DATA ON APPLICATION

- Use of the active substance
- Function
- Effects on harmful organisms
- Field of use envisaged
- Harmful organisms controlled and crops or products protected or treated
- Mode of action
- Information on the occurrence or possible of the development of resistance and appropriate management strategies
- References relied on

Volume 3 – B.4

FURTHER INFORMATION

- Methods and precautions concerning handling, storage, transport or fire
- Procedures for destruction or decontamination
- Emergency measures in case of an accident
- References relied on

Volume 3 – B.5

METHODS OF ANALYSIS

- Methods used for the generation of pre-authorisation data
- Methods for the analysis of the active substance as manufactured
- Methods for risk assessment
- Methods for post-approval control and monitoring purposes
- References relied on

Volume 3 – B.6

TOXICOLOGY AND METABOLISM DATA

- Absorption, distribution, metabolism and excretion in mammals
- Acute toxicity
- Short-term toxicity
- Genotoxicity
- Long-term toxicity and carcinogenesis
- Reproductive toxicity
- Neurotixicty
- Other toxicological studies
- Medical data and information
- References relied on

Volume 3 – B.7

RESIDUE DATA

- Storage stability of residues
- Metabolism, distribution and expression of residues
- Magnitude of residue trials in plants
- Feeding studies
- Effects of processing
- Residues in succeeding or rotational crops
- Other studies
- References relied on

Volume 3 – B.8

ENVIRONMENTAL FATE AND BEHAVIOUR

• Fate and behaviour in soil • Fate and behaviour in water and sediment • Fate and behaviour in air • Monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products • References relied on
Volume 3 – B.9
ECOTOXICOLOGY DATA • Effects on birds and other terrestrial vertebrates • Effect on aquatic organisms • Effects on arthropods • Effects on non target soil meso- and macrofauna • Effects on soil nitrogen transformation • Effects on terrestrial non-target higher plants • Effects on other terrestrial organisms (flora and fauna) • Effects on biological methods for sewage treatment • Monitoring data • Biological activity of metabolites potentially occurring in groundwater • References relied on
Volume 4
CONFIDENTIAL INFORMATION AND, WHERE RELEVANT, DETAILS OF ANY TASK FORCE FORMED FOR THE PURPOSES OF GENERATING TESTS AND STUDIES SUBMITTED • Confidential information • Summary of information relating to any task forces that submitted tests and study report • Summary of information relating to avoidance of duplicative testing and sharing of tests and studies involving vertebrate animals • Reference relied on

Source: Agra CEAS based on COM Templates to be used for Assessment Reports and Proposals for Classification, March 2018, online: https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_doss_temp-assess-report_201211.pdf

ANNEX III: Lists of Available guidance/guidelines for the approval of an Active Substance and the authorisation of PPPs

Table 7-3: List of Guidance Documents available for the approval of an active substances and the authorisation of PPPs

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
Submission of scientific peer-reviewed open literature for the approval of pesticide active substances	Applicant dossier		x	x		2013 EC Communication	EFSA
GD for applicants on preparing dossiers for the approval of a microbial active substance	Applicant dossier		x	x		EC website	EC DG SANTE
GD on semiochemicals	Applicant dossier		x	x		EC website	EC DG SANTE
GD on botanicals	Applicant dossier		x	x		EC website	EC DG SANTE
GD on preparing list of test and study reports	Applicant dossier		x	x		EC website	EC DG SANTE
GD for applicants on preparing dossiers for the approval of a chemical active substance	Applicant dossier		x	x		EC website	EC DG SANTE
GD on the Interpretation of the Transitional Measures for the Data Requirements for AS and PPPs	Assessment Report		x		x	EC website	EC DG SANTE
GD on Rules for Revision of Assessment Reports	Assessment Report		x		x	EC website	EC DG SANTE
GD on Comparative Assessment and Substitution of PPPs	Candidate for substitution		x		x	EC website	EC DG SANTE
Guidance on the application of the CLP criteria	Classification and labelling	x			x	2013 EC Communication	EFSA
GD on data protection	Data protection		x	x	x	EC website	EC DG SANTE
Guidance document on the preparation and submission of dossiers for plant protection products according to the "risk envelope approach"	Dossier for PPPs		x		x	EC website	EC DG SANTE
GD on risk assessment for birds and mammals	Ecotoxicological studies	x			x	EC website	EFSA
Risk assessment for birds and mammals: Joint working group report on the birds and mammals GD	Ecotoxicological studies	x			x	EC website	EFSA
GD on Tiered Risk Assessment for PPPs for Aquatic Organisms in Edge-of-Field Surface Waters	Ecotoxicological studies	x			x	EC website	EFSA

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
GD on Terrestrial Ecotoxicology	Ecotoxicological studies	x		x	x	EC website; 2013 EC Communication	EC DG SANTE
GD on risk assessment for birds and mammals	Ecotoxicological studies	x			x	EC website	EC DG SANTE
GD on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods	Ecotoxicological studies	x		x	x	2013 EC Communication	Candolfi et al (ESCORT II workshop)
Default Q10 value to describe the temperature effect on transformation rates of pesticides in soil	Ecotoxicological studies	x		x	x	EFSA website	EFSA
Scientific Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil	Ecotoxicological study	x		x	x	2013 EC Communication	EFSA
GD on the Data Requirements on Efficacy for the Dossier to be Submitted for the Approval of New Active Substances contained in PPPs	Dossier	x		x		EC website	EC DG SANTE
GD On the Efficacy Composition of Core Dossier and National Addenda Submitted to Support the Authorization of Plant Protection Products	Dossier	x			x	EC website	EC DG SANTE
GD on clustering and ranking of emissions of PPPs and transformation products of these active substances from protected crops (GHGs and crops grown under cover) to relevant environmental compartments	Fate and behaviour in the environment	x			x	EC website	EFSA
GD for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of PPPs and transformation products of these active substances in soil	Fate and behaviour in the environment	x			x	EC website; 2013 EC Communication	EFSA
GD on the Environmental Safety Evaluation of Microbial Biocontrol Agents	Fate and behaviour in the environment	x			x	EC website	OECD
GD on the Assessment of the relevance of metabolites in groundwater	Fate and behaviour in the environment	x			x	EC website; 2013 EC Communication	EC DG SANTE
GD on Persistence in Soil	Fate and behaviour in the environment	x		x		EC website	EC DG SANTE
EC Working Document on Evidence Needed to Identify POP, PBT and vPvB Properties for pesticides	Fate and behaviour in the environment	x			x	EC website	EC DG SANTE

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
GD for Environmental Risk Assessments of Active Substances Used on Rice	Fate and behaviour in the environment	x			x	EC website	EC DG SANTE
Procedures for assessing the environmental fate and ecotoxicity of pesticides	Fate and behaviour in the environment	x			x	2013 EC Communication	SETAC
FOCUS Working Group: Ground Water Assessments	Fate and behaviour in the environment	x		x		EC website; 2013 EC Communication	EC DG SANTE
FOCUS Working Group: GD on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration	Fate and behaviour in the environment	x		x		EC website; 2013 EC Communication	EC DG SANTE
FOCUS Working Group: Soil persistence models and EU registration	Fate and behaviour in the environment	x		x		EC website; 2013 EC Communication	EC DG SANTE
Regulatory Directive DIR2006-01: Harmonization of Guidance for Terrestrial Field Studies of Pesticide Dissipation under the NAFTA	Fate and behaviour in the environment	x		x		2013 EC Communication	Government of Canada
Opinion of the Scientific Committee on Plants on methods for the determination of the organic carbon adsorption coefficient (K0c) for a PPP AS	Fate and behaviour in the environment	x		x		2013 EC Communication	EC DG SANTE
ECHA Guidance on information requirements and chemical safety assessment Chapter R 11: PBT Assessment	Fate and behaviour in the environment	x			x	2013 EC Communication	ECHA
FOCUS Working Group: Pesticides in air - considerations for exposure assessment	Fate and behaviour in the environment	x			x	EC website; 2013 EC Communication	EC DG SANTE
Current approaches in the statistical analysis of ecotoxicity data: a guidance to application	Fate and behaviour in the environment	x		x		2013 EC Communication	OECD
Workshop report on OECD countries activities regarding testing, assessment and management of endocrine disrupters	Fate and behaviour in the environment	x		x	x	2013 EC Communication	OECD
GD on aquatic toxicity testing of difficult substances and mixtures	Fate and behaviour in the environment	x		x	x	2013 EC Communication	OECD
Short guidance on the threshold approach for acute fish toxicity	Fate and behaviour in the environment	x		x		2013 EC Communication	OECD
EPPO Standard PP 3/10 (3) Environmental risk assessment scheme for plant protection products. Chapter 10: honeybees	Fate and behaviour in the environment	x			x	2013 EC Communication	EPPO
Working Document on GLP - general requirements - 7017/VI/95	Good Laboratory Practice		x		x	EC website	EC DG SANTE
Working Document on GLP - detailed requirements for Part A, Annexes II and III - 7109/VI/94	Good Laboratory Practice		x		x	EC website	EC DG SANTE

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
Manual on development and use of FAO and WHO specifications for pesticides	Identity of the AS	x		x		2013 EC Communication	WHO / FAO
GD for the Assessment of The Equivalence of Technical Grade Active Ingredients for Identical Microbial Strains or Isolates	Physical and chemical properties	x			x	EC website	EC DG SANTE
GD on significant and non-significant formulation changes of the chemical composition of authorised PPPs	Physical and chemical properties	x		x		EC website	EC DG SANTE
The Working Document on microbial contaminant limits	Physical and chemical properties	x			x	EC website	OECD
GD on the assessment of the Equivalence of Technical Materials of Substances Regulated under Reg. (EC) 1107/2009	Physical and chemical properties	x		x		EC website; 2013 EC Communication	EC DG SANTE
GD on the finalisation of the reference specification for technical active substances after the peer review	Physical and chemical properties	x			x	EC website	EC DG SANTE
EC Working Document concerning the data requirements for certain chemical active substances and PPPs containing such substances	Physical and chemical properties	x			x	EC website	EC DG SANTE
GD for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414	Physical and chemical properties	x		x		EC website; 2013 EC Communication	EC DG SANTE
Working document on emergency authorisations according to Article 53	Post-approval issues		x		x	EC website	EC DG SANTE
GD on the evaluation of new active substance data post approval	Post-approval issues		x		x	EC website	EC DG SANTE
GD on zonal evaluation and mutual recognition	Post-approval issues		x	x	x	EC website	EC DG SANTE
GD on the assessment of new isolates of baculovirus species	Post-approval issues		x		x	EC website	EC DG SANTE
GD on the assessment of new substances falling into the group of Straight Chain Lepidopteran Pheromones (SCLPs)	Post-approval issues		x		x	EC website	EC DG SANTE
Authorisation of plant protection products following inclusion of an existing active substance	Post-approval issues		x		x	EC website	EC DG SANTE
GD on a Process for Intra & inter-zonal work-sharing to facilitate the registration and re-registration	Post-approval issues		x	x	x		EC DG SANTE

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
GD concerning the parallel trade of PPPs	Post-approval issues		x		x	EC website	EC DG SANTE
GD on submission and assessment of confirmatory information	Post-approval issues		x	x	x	EC website	EC DG SANTE
Guidance on presenting and evaluating dossiers as per annex III, Directive 91/414/EEC as (draft) Registration Report	PPP Draft Assessment Report		x		x	EC website	EC DG SANTE
GDs on the presentation and evaluation of PPP dossiers in the format of a (draft) Registration Report	PPP Draft Registration Report		x		x	EC website	EC DG SANTE
GD on the Renewal of Authorisations according to Article 43 of Regulation (EC) No 1107/2009	Renewal of approval		x		x	EC website	EC DG SANTE
Renewal GD on implementation of Regulation (EU) No 844/2012	Renewal of approval		x	x	x	EC website	EC DG SANTE
GD on the renewal of active substances	Renewal of approval		x	x		EC website	EC DG SANTE
GD on pesticide residue analytical methods	Residues in/on treated products, food, feed	x		x		EC website; 2013 EC Communication	EC DG SANTE
Residues: GD for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Dir. 91/414	Residues in/on treated products, food, feed	x		x		EC website; 2013 EC Communication	EC DG SANTE
GD on Pesticide Residue Analytical Methods	Residues in/on treated products, food, feed	x		x	x	2013 EC Communication	OECD
GD on Overview of Residue Chemistry Studies	Residues in/on treated products, food, feed	x		x		2013 EC Communication	OECD
GD on Crop Field Trials	Residues in/on treated products, food, feed	x			x	2013 EC Communication	OECD
GD on magnitude of pesticide residues in processed commodities	Residues in/on treated products, food, feed	x		x		2013 EC Communication	OECD
GD on the Definition of Residues	Residues in/on treated products, food, feed	x		x	x	2013 EC Communication	OECD
GD on comparability, extrapolation, group tolerances and data requirements for setting MRLs	Residues in/on treated products, food, feed	x		x		2013 EC Communication	EC DG SANTE

Title of the document	Topics covered	Technical guidance	Procedural guidance	Guidance for industry (submission)	Guidance for RMS and EFSA (evaluation)	Source	Author
OECD MRL calculator	Residues in/on treated products, food, feed	x		x		2013 EC Communication	OECD
GD on calculation of Maximum Residue Levels and Safety Intervals	Residues in/on treated products, food, feed	x		x		2013 EC Communication	EC DG SANTE
Calculation model Pesticide Residue Intake Model "PRIMo" - revision 2	Residues in/on treated products, food, feed	x		x		2013 EC Communication	EFSA
GD on the taxonomic level of micro-organisms to be included in Annex I	Taxonomic level		x		x	EC website	EC DG SANTE
GD on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products	Toxicological and metabolism studies	x		x	x	EC website	EFSA
Draft GD for the Setting and Application of Acceptable Operator Exposure Levels	Toxicological and metabolism studies	x		x	x	EC website; 2013 EC Communication	EC DG SANTE
Scientific Opinion on dermal absorption - 2012	Toxicological and metabolism studies	x			x	EC website	EFSA
Guidance on dermal absorption - 2017	Toxicological and metabolism studies	x			x	EC website	EFSA
GD for the Setting of an Acute Reference Dose	Toxicological and metabolism studies	x		x	x	EC website; 2013 EC Communication	EC DG SANTE
GC for conducting a single exposure toxicity study	Toxicological and metabolism studies	x		x		2013 EC Communication	OECD
GD for the Derivation of an Acute Reference Dose	Toxicological and metabolism studies			x		2013 EC Communication	OECD
Risk assessment of PPPs on bees (Apis mellifera, Bombus spp. and solitary bees)	Toxicological and metabolism studies	x		x	x	EFSA website	EFSA
Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticides	Toxicological and metabolism studies	x		x	x	EFSA website	EFSA

Source: Agra CEAS based on EC (2016a), and Commission Communication (2013).

Table 7-4: List of further documents available for the approval of active substances and the authorisation of PPPs

Title of other documents	Type	For producers (submission)	For RMS and EFSA (evaluation)
CIPAC code numbers	Codes	x	
Templates for Assessment Reports and Proposals for Classification	Template		x

Title of other documents	Type	For producers (submission)	For RMS and EFSA (evaluation)
Templates draft Registration Report for micro-organisms	Template		x
Template for assessment reports	Template		x
Comparison list for dossier submission in CADDY-Format (chemicals) - Annex II and Annex III points (OECD vs. former EC system)	Comparative table	x	
Comparison list for dossier submission in CADDY-Format (microbials) - Annex II and Annex III points (OECD vs. former EC system)	Comparative table	x	
Template for Notification art.44	Template	x	
Template for notification according to Art. 36(3) of Regulation (EC) No 1107/2009	Template		x
Template to notify intended zonal applications under Article 33 of Regulation (EC) No 1107/2009 (SANCO/12544/2014) rev 2	Template	x	
Template for data matching checks	Template		x

Source: Agra CEAS based on EC (2016a), and Commission Communication (2013).

Table 7-5: List of Test Guidelines available for the approval of active substances in pesticides

Title of the test guideline	Topics covered	Source
Method A.1 Melting/Freezing temperature	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
TG 102: Melting Point/ Melting Range	Physical and chemical properties	OECD
Method A.2 Boiling temperature	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
TG 103: Boiling point	Physical and chemical properties	OECD
Method A.4 Vapour pressure	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
TG 104: Vapour Pressure	Physical and chemical properties	OECD
Method A.6 Water solubility	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
OECD TG 105: Water Solubility	Physical and chemical properties	OECD
Method MT 181: Solubility in organic solvents	Physical and chemical properties	CIPAC
Method A.8 Partition coefficient	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
TG 107: Partition coefficient, shake-flask method	Physical and chemical properties	OECD

Title of the test guideline	Topics covered	Source
OECD Test Guideline 112: Dissociation Constants in Water.	Physical and chemical properties	OECD
Methods A.10 Flammability (solids), A.11 Flammability (gases), A.12 Flammability (contact with water);	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
Test N.1: test method for readily combustible solids	Physical and chemical properties	UN RTDG
Methods A.15 Auto-ignition temperature (liquids and gases), A16 Relative self-ignition temperature for solids	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
Test N.4: test method for self-heating substances	Physical and chemical properties	UN RTDG
Method A.9 Flash-point	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
Test methods according to table 2.6.3 of Annex I, Part 2 of Regulation (EC) No 1272/2008 (liquids)	Physical and chemical properties	Regulation (EC) No 1272/2008
Method A.14 Explosive properties	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
United Nations Recommendations on the Transport of Dangerous Goods	Physical and chemical properties	UN RTDG
Method A.5 Surface tension	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
TG 115: Surface tension of aqueous solutions	Physical and chemical properties	OECD
Solids: Method A.17 Oxidising properties (solids)	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
Liquids: Method A.21 Oxidising properties (liquids) (Annex to Regulation (EC) No 440/2008)	Physical and chemical properties	Annex to Regulation (EC) No 440/2008
Test O.1: Test for oxidizing solids	Physical and chemical properties	UN RTDG
Test O.2: Test for oxidizing liquids	Physical and chemical properties	UN RTDG
Test methods reported in Annex I, Part II to Regulation (EC) No 1272/2008	Physical and chemical properties	Regulation (EC) No 1272/2008
Standard series PP1: Efficacy evaluation of plant protection products	Further information on the AS	EPPO
Standard PP 1/213: Resistance risk analysis	Further information on the AS	EPPO
Method B.36 Toxicokinetics	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 417: Toxicokinetics	Toxicological and metabolism studies	OECD
Method B.1 bis Acute oral toxicity - fixed dose procedure	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.1 tris Acute oral toxicity - Acute toxic class method	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008

Title of the test guideline	Topics covered	Source
TG 420: Acute oral toxicity: fixed dose procedure	Toxicological and metabolism studies	OECD
TG 423: Acute oral toxicity: acute toxic class method	Toxicological and metabolism studies	OECD
TG 425: Acute oral toxicity: up-and-down procedure	Toxicological and metabolism studies	OECD
TG 401: Acute oral toxicity	Toxicological and metabolism studies	OECD
Method B.3 Acute toxicity (dermal)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 402: Acute Dermal Toxicity	Toxicological and metabolism studies	OECD
Method B.2 Acute toxicity (inhalation)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 403: Acute Inhalation Toxicity	Toxicological and metabolism studies	OECD
TG 436: Acute Inhalation Toxicity – Acute Toxic Class Method	Toxicological and metabolism studies	OECD
Method B.4 Acute toxicity: dermal irritation/corrosion	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.40 In vitro skin corrosion: transcutaneous electrical resistance test (TER)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.40 bis In vitro skin corrosion: human skin model test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 404: Acute Dermal Irritation/Corrosion	Toxicological and metabolism studies	OECD
TG 431: In vitro Skin Corrosion: Human Skin Model Test	Toxicological and metabolism studies	OECD
TG 430: In vitro Skin Corrosion: Transcutaneous Electrical Resistance Test	Toxicological and metabolism studies	OECD
TG 435: In vitro Membrane Barrier Test Method for Skin Corrosion	Toxicological and metabolism studies	OECD
TG 439: In vitro Skin Irritation: Reconstructed Human Epidermis Test Method	Toxicological and metabolism studies	OECD
Method B.46 In vitro skin irritation: reconstructed human epidermis model test.	Toxicological and metabolism studies	Annex III of Regulation (EC) No 761/2009
Method B.5 Acute toxicity: eye irritation/corrosion	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 405: Acute eye irritation/corrosion	Toxicological and metabolism studies	OECD
TG 437: Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants	Toxicological and metabolism studies	OECD
TG 438: Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants	Toxicological and metabolism studies	OECD
Method B.47 Bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants	Toxicological and metabolism studies	Annex of Regulation (EC) No 1152/2010
Method B.48 Isolated chicken eye test method for identifying ocular corrosives and severe irritants	Toxicological and metabolism studies	Annex of Regulation (EC) No 1152/2010

Title of the test guideline	Topics covered	Source
Method B.42 Skin sensitisation: Local lymph node assay	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.6 Skin sensitisation	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 429: Skin Sensitisation – Local Lymph Node Assay	Toxicological and metabolism studies	OECD
TG 406: Skin sensitisation	Toxicological and metabolism studies	OECD
TG 442A: Skin Sensitisation – Local Lymph Node Assay: DA	Toxicological and metabolism studies	OECD
TG 442B: Skin Sensitisation – Local Lymph Node Assay: BrdU-ELISA	Toxicological and metabolism studies	OECD
Method B.41 In vitro 3T3 NRU phototoxicity test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 432: In vitro 3T3 NRU Phototoxicity Test	Toxicological and metabolism studies	OECD
TG 101: UV-VIS Absorption Spectra	Toxicological and metabolism studies	OECD
Method B.7 Repeated dose (28 days) toxicity (oral)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 407: Repeated dose 28-day oral toxicity study in rodents	Toxicological and metabolism studies	OECD
Method B.26 Sub-chronic oral toxicity test. Repeated dose 90-day oral toxicity study in rodents	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.27 Sub-chronic oral toxicity test. Repeated dose 90-day oral toxicity study in non-rodents	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
OECD Test Guideline 408: Repeated dose 90-day oral toxicity study in rodents	Toxicological and metabolism studies	OECD
OECD Test Guideline 409: Repeated dose 90-day oral toxicity study in non-rodents	Toxicological and metabolism studies	OECD
Method B8 Repeated dose (28 days) toxicity (inhalation)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.9 Repeated dose (28 days) toxicity (dermal)	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.28 Sub-chronic dermal toxicity test: 90-day repeated dermal dose study using rodent species	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.29 Sub-chronic inhalation toxicity study 90-day repeated inhalation dose study using rodent species	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 410: Repeated dose dermal toxicity: 21/28-day study.	Toxicological and metabolism studies	OECD
TG 411: Subchronic dermal toxicity: 90-day study.	Toxicological and metabolism studies	OECD
TG 412: Subacute inhalation toxicity: 28-day study.	Toxicological and metabolism studies	OECD
TG 413: Subchronic inhalation toxicity: 90-day study.	Toxicological and metabolism studies	OECD

Title of the test guideline	Topics covered	Source
Method B.13/14 Mutagenicity - reverse mutation test using bacteria	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.10 Mutagenicity - In vitro mammalian chromosome aberration test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.17 – Mutagenicity – In vitro mammalian cell gene mutation test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 471: Bacterial Reverse Mutation Test	Toxicological and metabolism studies	OECD
TG 473: In vitro Mammalian Chromosome Aberration Test	Toxicological and metabolism studies	OECD
TG 476: In vitro Mammalian Cell Gene Mutation Test - For this test mouse lymphoma assay is recommended.	Toxicological and metabolism studies	OECD
TG 487. In vitro Mammalian Cell Micronucleus Test.	Toxicological and metabolism studies	OECD
Method B.12 - Mutagenicity - In vivo mammalian erythrocyte micronucleus test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.11 - Mutagenicity – In vivo mammalian bone-marrow chromosome aberration test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 474: Mammalian Erythrocyte Micronucleus Test	Toxicological and metabolism studies	OECD
TG 475: Mammalian Bone Marrow Chromosome Aberration Test	Toxicological and metabolism studies	OECD
TG 486: Unscheduled DNA synthesis (UDS) - Test with mammalian liver cells in vivo.	Toxicological and metabolism studies	OECD
TG 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays	Toxicological and metabolism studies	OECD
Method B.39 Unscheduled DNA synthesis (UDS) - Test with mammalian liver cells in vivo	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Minimum Criteria for the acceptance of in vivoalkaline Comet Assay Reports	Toxicological and metabolism studies	EFSA
Method B.23 Mammalian spermatogonial chromosome aberration test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 483: Mammalian Spermatogonial Chromosome Aberration Test.	Toxicological and metabolism studies	OECD
Method B.30 Chronic toxicity test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.32 Carcinogenicity test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.33 Combined chronic toxicity/carcinogenicity test	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 451: Carcinogenicity Studies.	Toxicological and metabolism studies	OECD
TG 452: Chronic Toxicity Studies.	Toxicological and metabolism studies	OECD

Title of the test guideline	Topics covered	Source
TG 453: Combined Chronic Toxicity/Carcinogenicity Studies.	Toxicological and metabolism studies	OECD
Method B.35 Two-generation reproduction toxicity study	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 416: Two-Generation Reproduction Toxicity.	Toxicological and metabolism studies	OECD
TG 443: Extended One-generation Reproduction Toxicity.	Toxicological and metabolism studies	OECD
Method B.31 Prenatal developmental toxicity study.	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 414: Prenatal developmental toxicity study.	Toxicological and metabolism studies	OECD
TG 426: Developmental neurotoxicity study.	Toxicological and metabolism studies	OECD
Method B.43 Neurotoxicity study in rodents	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 424: Neurotoxicity study in rodents.	Toxicological and metabolism studies	OECD
Method B.37 Delayed neurotoxicity of organophosphorus substances after acute exposure	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
Method B.38 Delayed neurotoxicity of organophosphorus substances 28-day repeated dose study	Toxicological and metabolism studies	Annex to Regulation (EC) No 440/2008
TG 418: Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure.	Toxicological and metabolism studies	OECD
TG 419: Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study.	Toxicological and metabolism studies	OECD
TG 456: H295R Steroidogenesis Assay	Toxicological and metabolism studies	OECD
TG 441: Hershberger Bioassay in Rats, A Short-term Screening Assay for (Anti)Androgenic Properties	Toxicological and metabolism studies	OECD
TG 455: Stably Transfected Human Estrogen Receptor-alpha Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals	Toxicological and metabolism studies	OECD
TG 440: Uterotrophic Bioassay in Rodents A short-term screening test for oestrogenic properties	Toxicological and metabolism studies	OECD
Guideline 890.1500: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Male Rats Assay	Toxicological and metabolism studies	US EPA
Guideline 890.1450: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Female Rats Assay	Toxicological and metabolism studies	US EPA
15-Day Intact Adult Male Rat Assay	Toxicological and metabolism studies	US EPA
TG 506: Stability of pesticide residues in stored commodities	Residues in/on treated products, food, feed	OECD
TG 501: Metabolism in crops	Residues in/on treated products, food, feed	OECD

Title of the test guideline	Topics covered	Source
TG 503: Metabolism in livestock	Residues in/on treated products, food, feed	OECD
TG 509: Crop field trials	Residues in/on treated products, food, feed	OECD
TG 505: Residues in livestock.	Residues in/on treated products, food, feed	OECD
TG 507: Nature of the pesticide residues in processed commodities – High temperature hydrolysis.	Residues in/on treated products, food, feed	OECD
TG 508: Magnitude of the pesticide residues in processed commodities.	Residues in/on treated products, food, feed	OECD
TG 502: Metabolism in rotational crops.	Residues in/on treated products, food, feed	OECD
TG 307: Aerobic and anaerobic transformation in soil.	Residues in/on treated products, food, feed	OECD
ISO 10381-6:2009 Soil quality. Sampling. Guidance on the collection, handling and storage of soil under aerobic conditions for the assessment of microbiological processes, biomass and diversity in the laboratory	Residues in/on treated products, food, feed	ISO
OCSPP 835.6100: Terrestrial field dissipation	Residues in/on treated products, food, feed	US EPA
TG 106: Adsorption - Desorption Using a Batch Equilibrium Method	Residues in/on treated products, food, feed	OECD
TG 121: Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)	Residues in/on treated products, food, feed	OECD
TG 312: Leaching in Soil Columns	Residues in/on treated products, food, feed	OECD
TG 22: Guidance Document for the Performance of Out-door Monolith Lysimeter Studies	Residues in/on treated products, food, feed	OECD
TG 111: Hydrolysis as a Function of pH	Residues in/on treated products, food, feed	OECD
TG 316: Phototransformation of Chemicals in Water - Direct Photolysis	Residues in/on treated products, food, feed	OECD
Method C.4 Determination of "ready" biodegradability	Residues in/on treated products, food, feed	Annex to Regulation (EC) No 440/2008
GT301: Ready Biodegradability (301 A - F)	Residues in/on treated products, food, feed	OECD

Title of the test guideline	Topics covered	Source
TG 309: Aerobic Mineralisation in Surface Water - Simulation Biodegradation Test	Residues in/on treated products, food, feed	OECD
TG 308: Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	Residues in/on treated products, food, feed	OECD
TG 223: Avian acute oral toxicity study	Ecotoxicological studies	OECD
OCSPP 850.2100: Avian oral toxicity test	Ecotoxicological studies	US EPA
TG 205: Avian Dietary Toxicity Test	Ecotoxicological studies	OECD
OCSPP 850.2200: Avian dietary toxicity test.	Ecotoxicological studies	US EPA
TG 206: Avian Reproduction Test	Ecotoxicological studies	OECD
OCSPP 850.2300: Avian Reproduction Test	Ecotoxicological studies	US EPA
TG 203: Fish, Acute Toxicity Test	Ecotoxicological studies	OECD
OCSPP 850.1500 Fish life cycle toxicity.	Ecotoxicological studies	US EPA
TG 229: Fish Short Term Reproduction Assay	Ecotoxicological studies	OECD
TG 230: 21-day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition	Ecotoxicological studies	OECD
TG 231: Amphibian Metamorphosis Assay	Ecotoxicological studies	OECD
TG 234 Fish Sexual Development Test	Ecotoxicological studies	OECD
TG 202: Daphnia sp. Acute Immobilisation Test	Ecotoxicological studies	OECD
850.1035 Mysid Acute Toxicity Test	Ecotoxicological studies	US EPA
TG 211: Daphnia magna Reproduction Test	Ecotoxicological studies	OECD
OCSPP 850.1350 Mysid Chronic Toxicity Test	Ecotoxicological studies	US EPA
TG 219: Sediment-Water Chironomid Toxicity Using Spiked Water	Ecotoxicological studies	OECD
TG 218: Sediment-Water Chironomid Toxicity Using Spiked Sediment	Ecotoxicological studies	OECD
TG 201: Algae growth inhibition test	Ecotoxicological studies	OECD
TG 221: Lemna sp. Growth Inhibition Test	Ecotoxicological studies	OECD
ASTM E1913-04: Standard Guide for Conducting Static, Axenic, 14-Day Phytotoxicity Tests in Test Tubes with the Submersed Aquatic Macrophyte, Myriophyllum sibiricum Komarov	Ecotoxicological studies	ASTM
Development of a proposed test method for the rooted aquatic macrophyte	Ecotoxicological studies	Maltby et al (SETAC Press)
TG 213: Honeybees, Acute Oral Toxicity Test	Ecotoxicological studies	OECD
Standard PP1/170 (4): Test methods for evaluating the side-effects of plant protection products on honeybees.	Ecotoxicological studies	EPPO
TG 214: Honeybees, Acute Contact Toxicity Test	Ecotoxicological studies	OECD

Title of the test guideline	Topics covered	Source
A new larval in vitro rearing method to test effects of pesticides on honey bee brood	Ecotoxicological studies	Aupin et al
Method for honeybee brood feeding tests with insect growth - regulating insecticides	Ecotoxicological studies	Oomen et al (Bulletin EPPO)
Guidelines to evaluate side-effects of plant protection products to non-target arthropods	Ecotoxicological studies	Candolfi et al (IOBC, BART, EPPO Joint Initiative)
TG 232: Collembolan Reproduction Test in Soil	Ecotoxicological studies	OECD
TG 226: Predatory mite (Hypoaspis (Geolaelaps) aculeifer) reproduction test in soil	Ecotoxicological studies	OECD
TG 216: Soil Microorganisms: Nitrogen Transformation Test	Ecotoxicological studies	OECD
TG 208: Terrestrial Plant Test: Seedling Emergence and Seedling Growth Test	Ecotoxicological studies	OECD
TG 227: Terrestrial Plant Test: Vegetative Vigour Test	Ecotoxicological studies	OECD
TG 209: Activated Sludge, Respiration Inhibition Test	Ecotoxicological studies	OECD

Source: Agra CEAS based on Commission Communication (2013).

ANNEX IV: List of requirements and standards of applicants' studies

Table 7-6: Information to be submitted, its generation and its presentation

Requirements the information shall meet
• The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies submitted by the applicant.
• Any information on potentially harmful effects of the active substance, its metabolites and impurities on human and animal health or on groundwater shall be included.
• Any information on potentially unacceptable effects of the active substance, its metabolites and impurities on the environment, on plants and plant products shall be included.
• The information shall include 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 and dealing with side-effects on health, the environment and non-target species. A summary of this data shall be provided.
• 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: o it is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary; o it is technically not possible to supply. In such a case a justification shall be provided.
• The simultaneous use of the active substance as a biocide or in veterinary medicine shall be reported. If the applicant for the active substance in the plant protection product is identical to the one responsible for the notification of the active substance as a biocide or as a veterinary medicine, a summary of all relevant data submitted for approval of the biocide or the veterinary medicine, shall be submitted. This summary shall include toxicological reference values and MRL proposals, taking into account any possible cumulative exposure due to different uses of the same substance based on scientific methods accepted by the European competent authorities, together with a summary of the residues and toxicology data and information on the use of the product. If the applicant for the active substance in the plant protection product is not identical to the one responsible for the notification of the active substance as a biocide or in veterinary medicine, a summary of all available data shall be submitted.
• Where relevant, the information shall be generated using test methods. In the absence of suitable internationally or nationally validated test guidelines, test guidelines accepted by the European competent authority shall be used. Any deviations shall be described and justified.
• The information shall include a full description of the test methods used.
• The information shall include a list of endpoints for the active substance.
• Where relevant, the information shall be generated in accordance with Directive 2010/63/EU of the European Parliament and of the Council
• The information on the active substance, taken together with the information concerning one or more plant protection products containing the active substance and together, if appropriate, with the information concerning safeners and synergists and other components of the plant protection product, shall be sufficient to: o permit an assessment of the risks for humans, associated with handling and use of plant protection products containing the active substance; o permit an assessment of the risks for human and animal health, arising from residues of the active substance and its metabolites, impurities, breakdown and reaction products remaining in water, air, food and feed.;

- predict the distribution, fate and behaviour in the environment of the active substance and metabolites, breakdown and reaction products, where they are of toxicological or environmental significance, as well as the time courses involved;
- permit an assessment of the impact on non-target species (flora and fauna), including the impact on their behaviour, which are likely to be exposed to the active substance, its metabolites, breakdown and reaction products, where they are of toxicological or environmental significance. Impact can result from single, prolonged or repeated exposure and can be direct or indirect, reversible or irreversible;
- evaluate the impact on biodiversity and the ecosystem;
- identify non-target species and populations for which hazards arise because of potential exposure;
- permit an evaluation of short and long-term risks for non-target species, populations, communities and processes;
- classify the active substance as to hazard in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council;
- specify the pictograms, the signal words, and relevant hazard and precautionary statements for the protection of man, non-target species and the environment, which are to be used for labelling purposes;
- establish, where relevant, an acceptable daily intake (ADI) level for humans;
- establish acceptable operator exposure levels (AOEL);
- establish, where relevant, an acute reference dose, (ARfD) for humans;
- identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of poisoning in humans;
- establish the isomeric composition and the possible metabolic conversion of the isomers, when relevant;
- establish residues definitions appropriate for risk assessment;
- establish residues definitions appropriate for monitoring and enforcement purposes;
- permit a risk assessment of consumer exposure, including, where relevant, a cumulative risk assessment deriving from exposure to more than one active substance;
- permit an estimation of the exposure to operators, workers, residents and bystanders including, where relevant, the cumulative exposure to more than one active substance;
- establish maximum residue levels and concentration/dilution factors in accordance with Regulation (EC) No 396/2005 of the European Parliament and of the Council;
- permit an evaluation to be made as to the nature and extent of the risks for man, animals (species normally fed and kept by humans or food producing animals) and of the risks for other non-target vertebrate species;
- identify measures necessary to minimise contamination of the environment and impact on non-target species;
- decide whether or not the active substance has to be considered as persistent organic pollutant (POP), persistent, bio accumulative and toxic (PBT) or very persistent and very bio accumulative (vPvB) in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;
- decide whether or not the active substance has to be considered as a candidate for substitution in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;
- decide whether or not the active substance has to be considered as a low-risk active substance in accordance with the criteria laid down in Annex II to Regulation (EC) No 1107/2009;
- decide whether, or not, the active substance is to be approved;
- specify conditions or restrictions to be associated with any approval.

- Where relevant, tests shall be designed and data analysed using appropriate statistical methods.
- Exposure calculations shall refer to scientific methods accepted by the European Food Safety Authority, when available. Additional methods, when used, shall be justified.
- For each section of the data requirements, a summary of all data, information and evaluation made shall be submitted. This shall include a detailed and critical assessment according to the provisions of Article 4 of Regulation (EC) No 1107/2009.

Source: Annex of Commission Regulation (EU) No 283/2013.

ANNEX V: List of further guidance which is recommended/used in EU/EEA countries for the approval of active substances/authorisation of PPPs

Non-noted GD which are recommended/ used	Type	Country where it is recommended/ required	For whom it is intended	Who established it	How it was established
EFSA Guidance on the risk assessment of plant protection products on bees	Guidance	BE, LT, SK, NO	Applicant & Risk Assessor	EFSA	Common EFSA procedure
Test No. 239: Water-Sediment Myriophyllum Spicatum Toxicity Test	Test guidelines	DE	Applicant & Risk Assessor	ICPPR/ OECD	Ring Tested
Test No. 245: Honey Bee (Apis Mellifera L.), Chronic Oral Toxicity Test (10-Day Feeding)	Test guidelines	DE	Applicant & Risk Assessor	ICPPR/ OECD	Ring Tested
OECD 75: Honey Bee Brood Test under Semi-field conditions	Test guidelines	DE	Applicant & Risk Assessor	ICPPR/ OECD	Ring Tested
Test No. 246: Bumblebee, Acute Contact Toxicity Test	Test guidelines	DE	Applicant & Risk Assessor	ICPPR/ OECD	Ring Tested
Test No. 247: Bumblebee, Acute Oral Toxicity Test	Test guidelines	DE	Applicant & Risk Assessor	ICPPR/ OECD	Ring Tested
Guidance for the identification of endocrine disruptors	Guidance	DE	Applicant & Risk Assessor	ECHA/EFSA	Developed by ECHA/EFSA with MS
Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data	Guidance	DE	Applicant & Risk Assessor	EFSA	Developed by the Scientific Committee of EFSA
Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC)	Scientific Opinion	DE	Applicant & Risk Assessor	EFSA	Developed by the Scientific Committee of EFSA
Guidance document for WHO monographers and reviewers (2015)	Guidance	PL, SE	Applicant & Risk Assessor	WHO Core Assessment Group	*Not available*
Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology	Technical report	PL	Risk Assessor	EFSA	Recommendations compiled on the basis of the discussions and conclusions achieved at the meeting and further input from the experts of the EFSA Scientific Panel on PPPs.
Guidance on the Biocidal Products Regulation Volume III Human Health - Assessment & Evaluation	Guidance	PL	Risk Assessor	ECHA	*Not available*

Non-noted GD which are recommended/ used	Type	Country where it is recommended/ required	For whom it is intended	Who established it	How it was established
Guidelines for Carcinogen Risk Assessment (1986)	Test guidelines	PL	Risk Assessor	Risk Assessment Forum; U.S. Environmental Protection Agency	*Not available*
IARC Monographs on the Evaluation of Carcinogenic Risk to Humans (2015)	Guidance	PL	Risk Assessor	WHO	*Not available*
Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed (2016)	Guidance	PL	Applicant & Risk Assessor	FAO	*Not available*
Consolidation of bird and mammal PT data for use in risk assessment (Prosser, 2010)	Test guidelines	PL	Risk Assessor	Food and Environment Research Agency	The consolidated PT value for numerous species of birds and mammals in various crops were derived on the basis of the CSL project
ESCORT 3: Linking Non-Target Arthropod Testing and Risk Assessment with Protection Goals	?	PL	Applicant & Risk Assessor	SETAC	*Not available*
De Jong (2010) - Guidance for summarising and evaluating field studies with non-target arthropods	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands (RIVM)	*Not available*
Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology (2015)	Technical Report	PL	Applicant & Risk Assessor	EFSA	Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology (2015)
Pesticides Peer Review Expert Meeting 133 (September, 2015)	?	PL	Applicant & Risk Assessor	EFSA	*Not available*
"Bird Bible" Birds and farming: information for risk assessment	Test guidelines	PL	Applicant & Risk Assessor	PSD/HSE UK: CSL Project No. M37	*Not available*
"Mammal Bible" Mammal and farming: information for risk assessment	Test guidelines	PL	Applicant & Risk Assessor	PSD/HSE UK: CSL Project No. M37	*Not available*
Update: use of the benchmark dose approach in risk assessment	Test guidelines	PL	Applicant & Risk Assessor	EFSA	*Not available*
Guidance for summarising earthworm field studies (de Jong et al., 2006)	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands	The guidance was developed on request of the Ctgb to standardise methods for evaluation of field studies with earthworms
OPPTS 835.7100: Guidance for prospective ground-water monitoring studies. EPA 712-B-10-001, August 25, 2008.	Guidance	PL	Applicant & Risk Assessor	US EPA	*Not available*

Non-noted GD which are recommended/ used	Type	Country where it is recommended/ required	For whom it is intended	Who established it	How it was established
Boesten i in. (2014): Assessing potential for movement of active substances and their metabolites to ground water in the EU. The final report of the Ground Water Work Group of FOCUS. SANCO/13144/2010 version 3, 10 October 2014		PL			*Not available*
Monitoring data in pesticide registration, RIVM report 601450015/2003	Guidance	PL	Applicant & Risk Assessor	National Institute for Public Health and the Environment, The Netherlands (RIVM)	*Not available*
The pesticides peer review meeting on the OECD 106 evaluators checklist (EFSA Supporting publication 2017:EN-1326)	?	SE	Applicant & Risk Assessor	EFSA	Proposal from Member State and discussions at peer review expert meetings organised by EFSA.
OECD Guidance on grouping of chemicals, No. 194	Guidance	SI	Applicant & Risk Assessor	OECD	*Not available*
Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters	Guidance	SI	Applicant & Risk Assessor	EFSA	Mandated by the EC
Alix, A. & Lewis, G. (2010): Guidance for the assessment of risks to bees from the use of plant protection products	Guidance	SI	Applicant & Risk Assessor	EPPO	*Not available*
Practical al guide How to use and report (Q)SAR s	Guidance	NO	Applicant & Risk Assessor	ECHA	*Not available*

Note: This list does not include: (a) guidance listed on the Commission website, and (b) guidance and test guidelines listed in the Communication 2013/C 95/01. It does include some guidance documents of primary relevance to PPPs.

Source: Agra CEAS based on EU/EEA CAs survey

Active substances are an essential element of pesticides. The approval of active substance occurs at EU level, and guidance documents and guidelines for this procedure exist. They aim to clarify, harmonise and standardise the complex approval process. This study examines the guidance and guidelines which exist for active substance approval, the level of harmonisation among them, the connection to the good laboratory practice (GLP) principles, and provides an overview of the studies which are required for active substance approval.

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