Bulletin OEPP/Bulletin OEPP/EPPO Bulletin (2012) **42** (3), 398–402 ISSN 0250-8052. DOI: 10.1111/epp.2585

European and Mediterranean Plant Protection Organization
Organisation Européenne et Méditerranéenne pour la Protection des Plantes

PP 1/223(2)

Efficacy evaluation of plant protection products
Evaluation biologique des produits phytosanitaires

Introduction to the efficacy evaluation of plant protection products

Specific scope

This Standard describes the overall process of efficacy evaluation of plant protection products in the registration procedure.

Specific approval and amendment

First approved in 2003-09.

Revision mainly to reflect zonal assessment approved in 2012-09.

Introduction

Overview

In most EPPO countries, an evaluation of efficacy is required before a plant protection product can be marketed. The objective of this document is to give national registration authorities ('the Authority') information on the evaluation of efficacy data that is submitted in support of registration of a plant protection product. Applicants for registration ('the Applicant') should subject their own efficacy information to the same evaluation process when developing the proposed recommendations for use. Further guidance on efficacy evaluation is available in several other documents, namely:

- EPPO Standard PP 1/214 *Principles of acceptable efficacy*
- EPPO Standard PP 1/152 *Design and analysis of efficacy evaluation trials*
- EPPO Standard PP 1/213 *Resistance risk analysis*.

For the countries of the European Union, EC Regulation 1107/2009 concerning the placing of plant protection products on the market, as subsequently amended by Commission Regulation 545/2011 and Commission Regulation 546/2011 (*Uniform principles for evaluation and authorization of plant protection products*), constitutes the framework for efficacy evaluation.

Where registration across several countries is being considered, guidance is provided in PP 1/278 *Principles of zonal data production and evaluation*.

Requirements also exist for provision of information on a range of other aspects, including: identity of the active substance, its chemical and physical properties and methods of analysis; toxicology and metabolism; residues in or on treated products, food and feed; fate and behaviour in the environment; ecotoxicology. These requirements also form part of the registration decision process but are beyond the scope of this document.

Scope of efficacy

Efficacy can be defined by an equation in which the positive effects of the treatment in performing the desired plant protection activity (e.g. controlling the target pest or modifying crop growth) and any other useful effect, such as controlling other non-target pests, are balanced against the negative effects, such as direct damage to the crop (phytotoxicity) or effects on pollinators and natural enemies, or development of resistance.

Based on EU criteria, the efficacy parameters which should be addressed for registration purposes, and which are used as the basis of this guideline, are:

- direct efficacy (effectiveness);
- resistance risk;
- absence of unacceptable effects on plants or plant products
  - –phytotoxicity
  - –yield
  - –quality (including transformation processes)
  - –plants or plant parts used for propagation
  - –succeeding crops including substitute crops
  - –adjacent crops
  - –subsequently treated crops (effectiveness of tank cleaning)
- absence of unacceptable effects on production and production systems, in particular on pollinators and natural enemies.

Reporting of efficacy evaluation

Applicants

All relevant information from the efficacy evaluation programme for a given product use should be submitted to the Authority in the form of a Biological Dossier, including data from actual trials and other submitted supporting evidence, such as published papers and reports relating to the product, and cases for extrapolation of evidence from other relevant data. Provision of such a document should enable the Authority to evaluate an application for registration without the need to refer back to the Applicant except for occasional clarification or further information, thus improving the efficiency and cost-effectiveness of the registration process.

Further guidance on the content and format of a Biological Dossier is available to applicants in:

- EPPO Standard PP 1/181 *Conduct and reporting of efficacy evaluation trials, including good experimental practice*;
- Guidance document on the efficacy composition of Core Dossier and National Addenda submitted to support the authorization of plant protection products (unpublished SANCO data: pers. comm. S. Mattock)
- Guidance document on zonal evaluation and mutual recognition (SANCO, 2010); EPPO Standard PP 1/278 *Principles of zonal data production and evaluation*
- OECD *Dossier Guidance for Industry Data Submission* (Revision 2, May 2005);
- OECD *Monograph Guidance for Country Data Review* (Revision 3, April 2008).

Authority

The competent Authority should examine the Biological Dossier submitted and then produce a clear and concise report of its evaluation of the efficacy evidence and of the regulatory decisions. The report should include the expert assessment of all submitted evidence. In particular, the report should include statements on:

- the acceptability of the trials' organization, test methods and location of testing;
- the extent, quality and consistency of the data
- the acceptability of any uses supported by evidence other than trials data
  - uses recommended for authorization
  - uses not recommended for authorization
- any restrictions on use
- any particular comments on the conditions relevant to, or limitations on, the use of the product in the region for which use is sought.

For ease of reference, it is recommended that a standard format should be adopted. The requirements of Table 1 should form the basis of any standardized format. The listed requirements should be addressed only if relevant for the intended uses.

Table 1 Basis for a standardized format to be used in the report of the Authority on the biological dossier

Conduct of efficacy evaluation trials
Testing organizations
Test conditions and guidelines
Location
Efficacy
Effectiveness (direct efficacy)
Resistance
Absence of unacceptable effects
Phytotoxicity
Yield
Quality (including transformation processes)
Plants or plant parts used for propagation
Succeeding crops
Adjacent crops
Pollinators and natural enemies
Subsequently treated crops (effectiveness of tank cleaning)
Summary of decision-making
Uses recommended/not recommended for registration
Restrictions on use required, if any

Conduct of efficacy evaluation trials

Testing organizations

All trials should be conducted according to the principles of good experimental practice (GEP). EPPO Standard PP 1/181 *Conduct and reporting of efficacy evaluation trials including good experimental practice* provides information on GEP. In EU countries, these arrangements have been formalized by the requirement that trials should be conducted by official, or officially recognized, testing organizations.

Trials conducted in other countries that comply with the principles of good experimental practice can be accepted for evaluation purposes. Where the Authority can identify from the details provided that the testing organization fails to comply with the requirements of good experimental practice, trials submitted by that testing organization may be discounted for evaluation purposes. Similarly, where the organization conducting the test is within the EU and is not official, or has not been officially recognized, the trials may be discounted for evaluation purposes.

Test conditions and standards

Trials should have been carried out in accordance with specific EPPO Standards, where available, or with national guidelines satisfying at least the requirements of the corresponding EPPO Standard. In cases where no test guideline was available and other experimental methods have been used, or where deviations had been made from accepted test guidelines, the Applicant should explain, and the Authority should evaluate, the suitability of the experimental methods used. If the experimental methods are considered to be suitable for the intended purpose, they may be

accepted for evaluation; otherwise they should be rejected. Further guidance is available in the outline of requirements of EPPO Standards PP 1 Efficacy evaluation of plant protection products.

Location

Trials should have been conducted in locations that represent the range of agricultural, plant health and environmental conditions (including climatic conditions) likely to be encountered in practice in the area of proposed use. Often trials have been conducted within (the) country/ies or agroclimatic zone(s) in which registration is sought. However, trials conducted in other countries or agroclimatic zone(s) may be accepted for evaluation purposes provided conditions have been shown to be comparable. On occasions, trials may be accepted from non-comparable conditions where, for example, the conditions are deemed to represent a more severe test of a product. With the exception of conditions that provide a more severe test of a product, only tests conducted in conditions comparable with intended use can be accepted for evaluation.

General principles for the evaluation of efficacy information

The efficacy evaluation should establish that there is an overall benefit from the use of a product, and should confirm the proposed recommendations for use of the product. The latter are usually presented in the form of draft label recommendations. Data should be provided to support the claims made on the draft label. Evidence should be sufficient to confirm that performance, and absence of any unacceptable effects, are consistent over the range of conditions for which use is recommended, and that the proposed use recommendations present a sound case with respect to resistance management.

The minimum number of trials required to establish acceptable efficacy depends on many factors, including: extent of knowledge of the active substance, extent of variability in the proposed area of use (e.g. plant health conditions, climatic differences, range of agricultural practices, uniformity of crops, importance of crop and target pest). Normally, trials on effectiveness and phytotoxicity (including, where relevant, measurement of yield) should be conducted over at least two growing seasons, unless results from a single season are considered to provide adequate confirmation of the validity of the proposed claims. Where accepted minimum criteria exist, the Authority should ensure that they have been satisfied. Otherwise, expert judgement should be used. See EPPO Standard PP 1/226 *Number of efficacy trials.* For minor uses, see EPPO Standard PP 1/224 *Principles for the efficacy evaluation of minor uses.*

The level of acceptable performance and the level of any adverse effect considered to be acceptable also depend on many factors. For example, acceptable performance depends on the level of control required to achieve a well defined benefit. The first criterion of acceptable performance is that the product should show results that are significantly superior to those recorded in the untreated control. In essence, the product should be able to reduce the pest level or its damage below an economic or phytosanitary threshold. In practice, satisfactory levels of performance are generally met when the performance of the test product is comparable with that of the reference product. For some particularly harmful pests, accepted minimum levels of control exist, and the Authority should then ensure that they have been achieved. On the other hand, the satisfactory level of performance should be achieved by the minimum effective dose (see below). Comparison with untreated controls and with reference products should also form the basis of decision-making on the acceptability of any adverse effects. Where no assessment criteria exist, the decision-making process should rely on expert judgement.

In addition to data from typical small-plot trials, the evidence submitted often includes supporting information, such as published papers and reports relating to the product, data from commercial development trials, and cases for extrapolation of evidence from other relevant data. In some cases, the extent of knowledge in the possession of the Applicant can preclude the need for specific trials data to support a proposed use.

Specific requirements for the evaluation of efficacy information

Direct efficacy (effectiveness)

The evidence submitted should be sufficient to permit an evaluation to be made of the level, duration and consistency of control or desired effect and, where relevant, of the yield response. The intended effects (e.g. protection against a pest, regulation of plant growth) should be considered to be beneficial. For example, the target organism against which use is proposed should be accepted as being a pest.

The level, consistency and duration of control (or other intended effect) should have been shown to give a defined benefit under the range of conditions (including agricultural, climatic, plant health and environmental) likely to be encountered in practical use. Where performance does not hold for all conditions, the proposed label could specify that the product is intended for use in certain specified circumstances (e.g. light pest infestations, particular soil types or particular growing conditions).

The trials should establish that the proposed recommendations for use are justified. These include:

- the amount (i.e. dose) of the plant protection product used;
- if required on the label, the amount of adjuvant added;
- the number, frequency and timing of the applications;
- the method of application.

In addition to justifying that the dose is appropriate for the desired effect, the evidence should demonstrate that the dose is also the minimum necessary for the desired effect. Data should therefore be included from efficacy trials in which at least one dose lower than that recommended is evaluated. Further guidance is available in EPPO Standard PP 1/225 *Minimum effective dose*.

Where relevant, the yield response or reduction of loss in storage should be beneficial. Often, this is achieved when the yield response of the test product is similar to that of the reference product. Where the proposed recommendations on the label include use of the plant protection product in a mixture with other plant protection products and/or adjuvants, an evaluation should be made for each proposed mixture.

Resistance risk

The evidence submitted should be sufficient to permit evaluation of the risk of resistance and of the likely success of any resistance management strategy proposed by the Applicant. The exact information required depends on the pest/active substance combination. The Applicant should provide a summary of the information on which the assessment of resistance risk has been based. This is likely to include information, either from the laboratory or the field, on the target pest (e.g. life cycle, geographic distribution, need for high numbers of applications for control, past history of any resistance problems, etc.), and on the active substance (e.g. persistence of activity, mode of action, mutation/selection potential, fitness of any mutant strains, etc.). Where a relevant risk of resistance exists, evidence should be submitted on the sensitivity of natural field populations of the pest. Such information is likely to include details of the sensitivity and of the test method used. A resistance management strategy should be proposed. Further guidance is available in EPPO Standard PP 1/213 *Resistance risk analysis*.

The Authority should satisfy itself that the proposed recommendations for use have taken due account of the perceived resistance risk. In other words, the proposed recommendations for use should be considered to minimize the likelihood of resistance or cross-resistance developing.

Absence of unacceptable effects

Phytotoxicity

The evidence submitted should be sufficient to permit evaluation of the possible occurrence of phytotoxicity after treatment with the plant protection product. The exact information required depends on the type of plant protection product (e.g. herbicide, fungicide, insecticide or plant growth regulator) and on the treated crop. Further guidance is available in EPPO Standard PP 1/135 *Phytotoxicity assessment*. For herbicides, and for other plant protection products where adverse phytotoxic effects are seen, the evaluation should establish the margin of selectivity by use of data from specially designated crop-safety trials. Where necessary, the evaluation should establish that phytotoxicity does not affect yield adversely (see below).

There should be no unacceptable adverse phytotoxic effects unless it is possible to impose appropriate limitations of use that avoid or ameliorate the effect to acceptable levels (e.g. use of the product could be restricted to certain crop growth stages or to avoid certain defined weather conditions). Where the proposed recommendations on the label include use of the plant protection product in a mixture with other plant protection products and/or adjuvants, an evaluation should be made of the acceptability of the proposed mixture(s).

Yield

The evidence submitted should be sufficient to permit an evaluation to be made of the possible occurrence of yield reduction after treatment with the plant protection product. The exact information required depends on the type of plant protection product (e.g. herbicide, plant growth regulator, fungicide or insecticide) and on the treated crop. Some guidance is available in EPPO Standard PP 1/135 *Phytotoxicity assessment*. For all herbicides, and for other plant protection products where adverse phytotoxic effects are seen, an evaluation should be made of the significance on yield of any adverse effects. This should be assessed at sites with low or zero levels of pests to ensure yield responses resulting from pest control do not mask any negative yield effects from phytotoxicity. For other plant protection products, an evaluation that treatment causes no detrimental effect on yield can usually be obtained from direct efficacy trials.

There should be no reduction of yield at harvest due to phytotoxic effects below that which could have been obtained without use of the plant protection product, unless it is possible to impose appropriate limitations of use that avoid or ameliorate the effect to acceptable levels (e.g. use of the product could be restricted to certain crop growth stages); or unless the reduction is compensated for by an enhancement of quality.

Quality (including transformation processes)

The evidence submitted should be sufficient to permit an evaluation to be made of the effect of the plant protection product on the quality of the treated crop (including possible occurrence of taint or off-flavour). The exact information required depends on the treated crop. Some guidance is available in EPPO Standards PP 1/135 *Phytotoxicity assessment*; PP 1/242 *Taint tests*; and PP 1/243 *Effects of plant protection products on transformation processes*.

There should be no unacceptable adverse effects on quality unless it is possible to impose appropriate limitations of use which avoid or ameliorate the effect to acceptable levels (e.g. use could be excluded from crops intended for processing where adverse effects on processing have been observed).

Plants or plant parts used for propagation
The evidence submitted should be sufficient to permit an evaluation to be made of the effect of the plant protection product on plants or plant parts used for propagation. The exact information required depends on the treated crop. Some guidance is available in EPPO Standard PP 1/135 *Phytotoxicity assessment*.

There should be no unacceptable adverse effect on treated plants or plant parts used for propagation/reproduction unless it is possible to impose appropriate limitations of use that avoid or ameliorate the effect to acceptable levels (e.g. the proposed label could carry a restriction not to use the product on crops to be used for propagation or reproduction).

Succeeding crops (including substitute crops)
The evidence submitted should be sufficient to permit an evaluation to be made of the possible adverse effect of treatment with the plant protection product on succeeding crops. The exact information required depends mainly on the fate and behaviour of the active substance in soil, and on the biological activity of its residues or metabolites on succeeding crops. The issue is of most significance for herbicides. Guidance is available in EPPO Standard PP 1/207 *Effects on succeeding crops*.

There should be no unacceptable adverse effects on succeeding crops unless it is possible to impose appropriate limitations of use that avoid or ameliorate the effect to acceptable levels (e.g. specification that sensitive crops should not be grown following the treated crop). For substitute crops, the evidence submitted should be sufficient to permit an evaluation to be made of the effect of the plant protection product on crops sown or planted after failure of the first sown or planted crop (within 1 year) The exact information required depends on the substitute crop. Herbicide applications on the first crop are of special interest.

Adjacent crops
The evidence submitted should be sufficient to permit an evaluation to be made of the possible adverse effect of treatment with the plant protection product on adjacent crops. The exact information required depends mainly on the volatility of the active substance and on its biological activity on adjacent crops. The issue is of most significance for herbicides.

There should be no unacceptable adverse effects on adjacent crops unless it is possible to impose appropriate limitations of use that avoid or ameliorate the effect to acceptable levels (e.g. specification that treatment should not be performed when sensitive adjacent crops are present). Guidance is available in EPPO Standard PP 1/256 *Effects on adjacent crops*.

Tank cleaning
Consideration should also be given to tank-cleaning procedures to address the risk of damage to crops subsequently treated. This issue is of most significance for herbicides.

Non-target organisms
During efficacy evaluation, evidence of safety to pollinators[1] and natural enemies need be evaluated only where claims of selectivity are made and use in integrated pest management systems is sought. Safety to other non-target organisms[2] is evaluated as part of the ecotoxicology risk assessment, which may recommend that appropriate risk management practices are indicated on the label. The exact information required depends mainly on the treated crop and on the biological activity of the active substance on non-target organisms.

Where compatibility with integrated pest management is claimed on the label, there should be no unacceptable adverse effects on natural enemies unless it is possible to impose appropriate limitations of use that avoid or reduce the effect to acceptable levels (e.g. specification of a minimum interval between treatment and introduction of natural enemies).

References

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SANCO (2010) *Guidance Document on Zonal Evaluation and Mutual Recognition Under Regulation (EC) No 1107/2009*. European Commission, SANCO/13169/2010 rev.5, Brussels.

[1]Some countries make additional requirements for pollinators.
[2]In general, any effects on non-target organisms observed during efficacy trials should be recorded, including effects on non-target pests, for possible consideration in the appropriate part of the registration dossier.