International Code of Conduct on the Distribution and Use of Pesticides

Guidelines on Efficacy Evaluation for the Registration of Plant Protection Products

FOOD AND AGRICULTURE ORGANIZATION
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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The participating organisations are FAO, ILO, OECD, UNEP, UNIDO, UNITAR and WHO. The World Bank and UNDP are observers. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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Abbreviations

CILSS	Comité Permanent Inter Etats de Lutte contre la Sécheresse au Sahel (Permanent Interstate Committee for Drought Control in the Sahel)
EPPO	European and Mediterranean Plant Protection Organization
EU European	Union
FAO	Food and Agriculture Organization of the United Nations
GEP	Good Experimental Practice
GLP	Good Laboratory Practice
IPM	Integrated Pest Management
IPPC	International Plant Protection Convention
N	Recommended dose (of the plant protection product)
NAFTA	North American Free Trade Agreement
OECD	Organization for Economic Co-Operation and Development
OIRSA	Organismo Internacional Regional de Sanidad Agropecuaria
SOP	Standard Operating Procedure
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

Definitions

For the purpose of these guidelines, the following definitions of terms apply.

Active ingredient means the biologically active part of the pesticide[1]. It is also referred to as the active substance.

Biological dossier means the part of the data set that is submitted in support of a request for registration of a plant protection product which provides all necessary information to allow a reliable assessment of the efficacy of that product (also referred to as biological assessment dossier or efficacy dossier).

Biological control agent means a natural enemy, antagonist or competitor, and other self-replicating biotic entity used for pest control[2]

Crop tolerance evaluation means the assessment of (potential) adverse effects of the plant protection product on the crop that is to be treated, such as phytotoxicity, adverse effects on crop yield and quality, and effects on plants or plant parts used for propagation.

Efficacy evaluation means the assessment of the effectiveness of a plant protection product, against the target pest, which may include an assessment of its agronomic sustainability and economic benefits.

Formulation means the combination of various ingredients designed to render the product useful and effective for the purpose claimed; the form of the pesticide as purchased by users.[1]

Good Experimental Practice (GEP) means the measures taken and practices followed with respect to organization, design, conduct, monitoring, recording and reporting of efficacy trials of plant protection products, with the aim to ensure that the trial and its results are reliable, comparable and transparent.[3]

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.[4]

Integrated Pest Management (IPM) means the careful consideration of all available pest control techniques and subsequent integration of appropriate measures that discourage the development of pest populations and keep pesticides and other interventions to levels that are economically justified and reduce or minimize risks to human health and the environment.
IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms.[1]

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[1] Definition as provided in the International Code of Conduct on the Distribution and Use of Pesticides [2].
[2] Definition as provided in the Glossary of Phytosanitary Terms of the International Plant Protection Convention (IPPC) [75]
[3] Definition based on the EPPO Standard on Conduct and Reporting of Efficacy Evaluation Trials, including Good Experimental Practice [20]
[4] Definition as provided in the OECD Principles on Good Laboratory Practice [50].

Minimum effective dose is the dose of a plant protection product that is the minimum necessary to achieve sufficient efficacy against the target pest across the broad range of situations in which the product will be applied (also referred to as lowest effective rate).[5]

Minor uses are those uses of plant protection products in which either the crop is considered to be of low economic importance at national level (minor crop), or the pest is not important on a major crop (minor pest)[6]

Pest means any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products.[7]

Pesticide means any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.[1]

Phytotoxicity means the capacity of a plant protection product to cause temporary or long-lasting damage to plants.[8]

Plant protection product means a pesticide product intended for preventing, destroying or controlling any pest causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products. The term includes products intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

Product (or **pesticide product**) means the pesticide active ingredient(s) and other components, in the form in which it is packaged and sold.[1]

Registration means the process whereby the responsible national government or regional authority approves the sale and use of a pesticide following the evaluation of comprehensive scientific data demonstrating that the product is effective for the intended purposes and does not pose an unacceptable risk to human or animal health or the environment.[1]

Resistance means the naturally occurring, inheritable adjustment in the ability of individuals in a (pest) population to survive a treatment with plant protection product that would normally give effective control.[9]

Semiochemical means a chemical that affects the behaviour of an organism. Such chemicals include pheromones, which are used for communication between members of the same species, and allelochemicals, which act as chemical signals between members of different species.

Standard Operating Procedure (SOP) means a documented procedure which describes how to perform tests or activities normally not specified in detail in study plans or test guidelines.[4]

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[5] Definition as provided in the EPPO Standard on Minimum Effective Dose [23].
[6] Definition as provided in the EPPO Standard on Principles of Efficacy Evaluation for Minor Uses [18]
[7] Definition as provided in the International Plant Protection Convention (IPPC) [51]
[8] Definition as provided in the EPPO Standard on Phytotoxicity Assessment [38]
[9] Definition as provided in the EPPO Standard on Resistance Risk Analysis [39]

Use pattern means the combination of all factors involved in the use of a pesticide, including the concentration of active ingredient in the preparation being applied, rate of application, time of treatment, number of treatments, use of adjuvants and methods and sites of application which determine the quantity applied, timing of treatment and interval before harvest.[1]

Guidelines on Efficacy Evaluation for the Registration of Plant Protection Products

1. Introduction

In 1985, FAO first published its *Guidelines on efficacy data for the registration of pesticides for plant protection* [1]. The objective of these guidelines was to provide advice to registration authorities and pesticide industry on efficacy testing of plant protection products. The document subsequently became part of the technical guidelines supporting the *International Code of Conduct on the Distribution and Use of Pesticides* [2] (further referred to as the Code of Conduct).

Since then, many developments have taken place in pesticide management and regulation, and more particularly in efficacy evaluation. The FAO Code of Conduct has seen a major revision in 2002, providing an updated framework for sound pesticide management. At the national level, many countries have further researched and developed the principles and execution of efficacy evaluation of pesticides. The increased use of biological control agents, behaviour modifying chemicals and plant extracts also poses specific requirements on efficacy evaluation.

Other important developments have been regional and international efforts on the harmonization of efficacy testing methods and evaluation approaches in various parts of the world [3, 4, 5, 6, 7, 8] (Annex 1). Harmonization has occurred at different levels, including the adoption of common experimental protocols by a group of countries, the mutual acceptance of efficacy trial results and the joint evaluation of efficacy data.

The Code of Conduct, in its Article 4 (Testing of pesticides), contains a number of provisions with specific relevance for efficacy testing:

4.1 Pesticide industry should:

4.1.1 ensure that each pesticide and pesticide product is adequately and effectively tested by recognized procedures and test methods so as to fully evaluate its ***efficacy****, behaviour, fate, hazard and risk with regard to the various anticipated conditions in regions or countries of use;*

4.1.2 ensure that such tests are conducted in accordance with sound scientific procedures …;

…

4.1.4 ensure that the proposed use pattern, label claims and directions, packages, technical literature and advertising truly reflect the outcome of the scientific tests and assessments;

…

4.4 Exporting governments and international organizations should play an active role in assisting developing countries in training personnel on trial design and conduct, the interpretation and evaluation of test data, and risk/benefit analysis. …

The present guidelines were developed to provide guidance for both the pesticide industry and for governments on the design, conduct and evaluation of pesticide efficacy trials, as stipulated by the Code of Conduct. The guidelines are limited to pesticides intended for plant protection, including the protection of stored products, and plant growth regulators, desiccants or defoliants. In the rest of the guidelines these will be referred to as *plant protection products*.

The guidelines do not address efficacy testing of veterinary pesticides, domestic pesticides or pesticides applied in vector control and for other public health uses. International guidance on testing of vector control pesticides is provided by the World Health Organization Pesticide Evaluation Scheme (WHOPES) [9]. The Organization for Economic Co-operation and Development (OECD) has initiated the harmonization of efficacy testing for certain antimicrobial pesticides used in public health [10].

These guidelines also do not cover "efficacy testing" of transgenic plants that have been modified to express pest control activity, even though some of the general aspects which are discussed here are also relevant for such testing.

The guidelines discuss the general principles of the efficacy testing and evaluation of plant protection products for registration purposes. The following aspects are addressed:

- scope of efficacy evaluation (Chapter 2);
- data sources and quality (Chapter 3);
- general principles for the design of efficacy testing (Chapter 4);
- design, conduct and analysis of direct efficacy trials (Chapter 5);
- testing for crop tolerance (Chapter 6);
- evaluation of agronomic sustainability (Chapter 7);
- reporting and record keeping (Chapter 8);
- principles for assessing acceptability of the results of efficacy trials (Chapter 9);
- various special issues, such as minor uses, biological control agents, protection of stored products and rodenticides (Chapter 10).

A number of excellent guidelines and protocols for efficacy evaluation have been developed over the last two decades, both by national and international organizations, and this document largely builds upon those experiences [e.g. 3, 4, 5, 6, 11, 12, 13, 14, 15]. Reference is made to relevant national and international guidelines where appropriate, and Internet links are provided whenever available.

2. Scope of efficacy evaluation

2.1 Objectives of efficacy evaluation

The main objective of efficacy evaluation is to assess the benefits that accrue from the use of a plant protection product at its recommended minimum effective dose and to define the product's conditions of use. In other words, the aim of efficacy evaluation is to ensure that the proposed claims and use recommendations on the product label are supported by trial data and reflect the actual performance of the product while providing a clear benefit to the user.

The efficacy of a plant protection product can be defined as the net outcome of an equation that balances the positive effects of the treatment in performing the desired crop protection activity against any negative effects on the crop itself or the production system in a wider sense.

Positive effects of the plant protection product can be expressed in terms of a reduction of a pest insect or weed population occurring in a crop, the reduced development of a disease, a reduction of crop damage, the protection or increase of crop yields, the protection or improvement of crop quality, the protection of stored commodities, etc.

Negative effects of a plant protection product on a crop or the production system may include phytotoxicity to the target or adjacent crops, yield reduction, negative effects on succeeding crops, adverse effects on pollinators or natural enemies of crop pests, an increase in the risk of resistance development, or other effects that may reduce the sustainability of the production system.

2.2 Efficacy evaluation as part of the registration process

In many countries, the evaluation of the biological efficacy of a plant protection product is part of the registration or authorization procedure. Companies submitting a product for registration must supply data on its efficacy on the crops or for the uses involved. The justification for requesting efficacy data is that the registration authority should prevent inefficacious plant protection products or products that are harmful to plants or plant products from being brought onto the market. When products have insufficient efficacy, there is a risk that the user may increase the dose or application frequency, thus augmenting the exposure of humans and the environment to potentially hazardous compounds.

Certain countries do not require biological efficacy data to be submitted as part of the registration dossier, and the evaluation of the effectiveness of the product is left to the user or advisor. This approach is based on the assumption that products will not be purchased or recommended when it becomes known that they are not, or not sufficiently, effective. Users may also have the possibility to start legal procedures against a manufacturer or distributor if the product does not perform well when used as recommended on the label. In such cases it is expected that "the market will regulate itself".

FAO recommends that efficacy evaluation should be an integral part of the registration or authorization process, to prevent inefficacious or harmful plant protection products from being brought onto the market. This is particularly important in countries where pesticide users do not have ready access to independent crop protection advisory or extension services, where self-regulation by pesticide manufacturers and distributors may function in a suboptimal way, where pesticide users have limited possibilities for litigation, or where there are no poison control centres and environmental remediation possibilities are lacking.

The evaluation of biological efficacy should be conducted in the light of the claims and recommendations that are stated (or implied) on the product label. These include the pests and crops on which the product is to be used, the recommended equipment and methods of application, doses, timing and number of applications, use situations, the nature, level and duration of pest control, possible incompatibilities with other products, and benefits and/or adverse effects of product use.

Only authorized uses of the plant protection product should be mentioned on the label, and the efficacy of the product for all these uses should in principle be assessed by the registration authority. The registrant should provide all the data needed for such assessments, as well as with respect to any other claim regarding efficacy that is made on the label.

2.3 Elements of efficacy evaluation

An assessment of the efficacy of a plant protection product will normally include data on its direct efficacy, the sustainability of its application and (sometimes) the economic impact of registering the product [6, 8, 16, 30].

2.3.1 Direct efficacy (effectiveness)

The direct efficacy, or effectiveness, of a plant protection product concerns both the effect of the product on the target pest as well as its possible negative effects on the crop or stored product.

The data provided 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 or effects on quality of the plant product. The various conditions of use, such as the minimum effective dose(s), pest threshold levels (if available) and/or treatment frequency and method of application need to be stated.

Crop tolerance to the plant protection product should also be evaluated. This includes:

- phytotoxicity;
- possible yield reduction or an effect on product quality (including on transformation processes);
- any possible effects on plants or plant parts used for propagation.

2.3.2 Agronomic sustainability

An assessment should ideally also be made of the agronomic sustainability of using the plant protection product. The product should not affect, in an unacceptable manner, the sustainability of the crop production system that is targeted, or any other (succeeding or adjacent) production systems. Examples of undesirable effects on the crop production system(s) are:

- the too rapid development of resistance to the plant protection product;
- effects on succeeding or substitute crops;
- effects on adjacent crops;
- effects on non-target organisms (e.g. impact on pollinators and pollination, effects on natural enemies of the target pests or of secondary pests).

Positive effects of the plant protection product on other pests than the target, if they occur, should also be taken into account in the sustainability assessment.

Of particular concern is the question if registering the plant protection product is compatible with or contributes to sustainable production practices or existing integrated pest management (IPM), and if it may jeopardize the future development of IPM in the crop. The positive effect it may have on adopting IPM should also be assessed.

A sustainability assessment may require expert input from the sector for which the product is intended about existing pest and disease ecology and pest management approaches, including IPM. Crop profiles and crop timelines, as they are produced for instance in North America, may be a useful tool for sustainability assessments. Crop profiles are descriptions of crop production and pest management practices compiled on a regional or national basis for specific commodities, and crop timelines are descriptions of generalised crop phenology, pest occurrence and human activity for specific crops [61].

2.3.3 Economic benefits

The use of a plant protection product should have a clear positive economic benefit to the grower. The overall efficacy of the product is thus not only determined by its direct biological effectiveness and agronomic sustainability, but also by its economic benefits.

A cost-benefit assessment may clarify if the gains obtained by using the product, such as increased yields or farmer revenues, outweigh the costs of the product to the farmer, both direct and indirect.

A comparison can be made between using the plant protection product and not using it at all. However, where plant protection products have already been used, it will be more appropriate to compare the product with the current standard, already registered, plant protection products. It should also be assessed in comparison with alternative approaches such as cultural or agronomic measures, pest or weed resistant or tolerant crops, or biological control, either individually or as a component of IPM.

In certain countries, an economic or benefits assessment is not part of the efficacy evaluation for the registration of a plant protection product. It is left to the grower or user to assess this. In other countries, it is an explicit component of the registration process [e.g. 8, 16]

3. Data generation for efficacy evaluation

3.1 Data sources

Various sources of information can be used for the biological efficacy evaluation. Depending on the national registration requirements, one or more of these sources may be allowed as part of the biological dossier.

3.1.1 Local trials data

Data that are specific to a given product application in the country tend to be generated through local trials. In many countries, this is a major source of biological efficacy information submitted by the registrant for the registration of a plant protection product.

The advantage of this type of data is that it is directly relevant to the specific product use situation that needs to be registered. The disadvantage is that biological efficacy trials of plant protection products may be relatively expensive and it can take several years and a considerable number of trials before a suitable data set has been compiled. Therefore, it makes sense to use as much of the existing efficacy data as possible, provided that a scientifically valid efficacy evaluation can be made.

Limiting the number and extent of the efficacy trials to the absolutely necessary is not only in the interest of the registrant, but also of other stakeholders:

- The registrant will likely reduce the costs of registration and/or the time it will take to market a product.
- Growers may be able to obtain essential products more rapidly, for instance in the case of new outbreaks of pests or diseases for which no effective products are yet on the market. The registration of so-called minor use products, for which pesticide industry does not develop local efficacy data because it considers them of too low economic importance, may also be facilitated.
- It is in the interest of both growers and the general public when products with a reduced environmental or human health risk can be brought onto the market faster to replace highly hazardous plant protection products.
- Agricultural research institutions, particularly in developing countries, often have limited resources and personnel. Such limited resources are wasted if they are spent on efficacy trials that have already been carried out in a satisfactory manner elsewhere. Research institutions can then dedicate their time to more relevant efficacy tests, pest management studies or research into alternatives to chemical plant protection products.

There are basically two (partly overlapping) approaches to limiting the number of nationally executed efficacy trials required for registration: extrapolation or the use of data from other countries. In addition to reducing the number of trials, these approaches can also be used to narrow down the scientific objectives of the national trials to more specific questions or problems that have not yet been solved by foreign trials, thus increasing the efficiency and value of national studies. However, local trials data will remain an important source of information for efficacy evaluation.

3.1.2 Trials data from other countries

Trials data from other countries can be used as part of the biological dossier. They may be acceptable provided the cropping techniques, pest pressure and biology, and climatic conditions are comparable to the situation encountered in the country where the product is to be authorized. Most often, foreign

data are submitted for the same pest, but they may sometimes also be used to support extrapolation to other pests (see below).

The advantage of foreign trials data is that they may be readily available, thus providing a larger data set for the registration authority to base its efficacy evaluation on. A disadvantage may be that a more in-depth assessment of such data is needed to ensure that the results are relevant to the national situation. Also, foreign trial protocols may be different from the ones required for national registration, thus complicating evaluation of the results.

Many countries accept trials data from other countries as part of the registration dossier, on the condition that the registrant can justify comparability or relevance. Whether the use of foreign data is appropriate needs to be assessed on a case by case basis. Increasingly, however, registration authorities of neighbouring countries are setting up agreements in which trial data from specific pest/crop combinations are accepted for an entire group of countries. One option being investigated is the definition of comparable agro-climatic or cropping zones within which efficacy trials are expected to provide similar results [59, 60].

Such mutual acceptance of data can reduce the costs of field testing and may increase the speed of registration. It will also increase the number of trials that a registration authority can use for its efficacy evaluation, e.g. from a wider range of conditions, which may improve the quality of the evaluations.

3.1.3 Public domain evidence

Suitable efficacy information may have been published in scientific journals, books or other reliable public data sources.

The advantages and disadvantages of using public domain evidence are similar to using foreign trials data. An additional advantage is that publications in peer-reviewed journals or books have generally been submitted to a quality check, reducing the risk that inappropriate methods were used or incorrect conclusions drawn. However, public domain data may be summarized to the extent that it becomes difficult to assess if the conditions of the trial are comparable or relevant to the national situation.

3.1.4 Extrapolation

It may be possible to extrapolate efficacy information from one pest or crop to another (closely related) one, between cropping situations or between closely related formulations of the plant protection product. Extrapolation refers to a situation where a full data set has already been accepted by the registration authority for a specific pest control situation and additional pest control claims are then considered based primarily on scientific rationale and less on additional data.

Various types of extrapolation of efficacy information may be possible, for instance:

- for control of one target (i.e. pest, disease or weed) to another closely related one, either on the same crop or on another crop;
- for control of the same target on one crop to a closely related crop or cropping situation;
- for crop safety (e.g. absence of phytotoxicity) between different crops;
- for control with one type of product formulation to a different one, but containing the same active ingredient(s).

Extrapolation may be used to form either all or part of the data package submitted for a given registration request. Various factors are important when considering if extrapolation is appropriate:

Sound data set

Extrapolation must be carried out from a sound data set, i.e. the efficacy data that are used to extrapolate from should be adequate in quantity and quality. If a product has already been tested rigorously under variable environmental or pest conditions and still performed consistently, extrapolation will be easier than when the data set from which to extrapolate from is variable in itself. Also, if the data set contains more than one use (e.g. where a pest is controlled consistently on two or more different crops, or where crop safety has been demonstrated on a range of crops), then extrapolation is more likely to be acceptable.

Sound biological basis

A sound biological basis for extrapolation is essential. Close taxonomic relationship may not be sufficient justification because taxonomy is not always well correlated with the biology and behaviour of the target organism(s). Therefore, all aspects of pest biology and behaviour, as well as the biology of the crop, should be carefully considered when making and evaluating a case for extrapolation.

For instance, data on seed treatments against non host-specific soil pathogens may be extrapolated from one cereal to another or from one legume to another, provided they are grown in similar field conditions. It may also be possible to extrapolate efficacy data acquired on one species of aphid on wheat to another species, if they show similar biology and only cause sucking damage and are not vectors of a disease.

Choice of use from which to extrapolate

It is advisable to consider carefully which crop/pest combinations are likely to be most suitable as a basis for extrapolation to other crops/pests. It is not necessarily the crop with the largest area in the country that should be subject to the greatest number of trials. It may be better to put emphasis on less widely grown crops, if extrapolation from these crops to other ones is likely to be easier.

For example, it is generally more convincing to extrapolate from worst case pest situations to situations that are less difficult to control, i.e. extrapolate to crops that are less susceptible to the pest or disease (for insecticides/fungicides) or more competitive to weeds (for herbicides). The same is true for crop safety, where an extrapolation to a crop that is less susceptible to damage by the plant protection product will be easier to justify. On the other hand, if the dose is determined by efficacy trials on a susceptible crop, it may be higher than that needed on a crop which is resistant or partially resistant to the pest. Thus, care is needed when a lower dose is suitable in for instance an IPM programme using a resistant cultivar.

Acceptable types of extrapolation

The decision on whether to accept a request for extrapolation will generally have to be taken by the registration authority on a case by case basis. However, to avoid that inappropriate extrapolation requests are submitted, or that unnecessary field trials are carried out, registration authorities should define and publish cases for extrapolation that will, under most circumstances, be acceptable to them, or examples of extrapolation that have been accepted in the past [e.g. 15, 16, 17].

Further guidance on extrapolation is provided elsewhere [17, 18].

3.2 Good experimental practice (GEP)

It is essential that efficacy trials are of high quality so that one can have confidence in the results and the reports can be used by different registration authorities. Field studies on safety and residues of

plant protection products must therefore be conducted according to internationally adopted Good Laboratory Practice (GLP) standards [19]. GLP is very stringent and does not allow for much flexibility in the organization of field studies. This standard may not always be appropriate for biological efficacy trials which tend to be carried out under varying environmental and experimental conditions. A different set of guidelines, often referred to as Good Experimental Practice (GEP), is increasingly being applied to efficacy studies of plant protection products [20, 21].

GEP is concerned with the organization, design, conduct, interpretation and reporting of efficacy trials, so that the results are reliable and comparable. GEP provides guidance on various aspects, such organization and staff qualifications, equipment and facilities, trial protocols and operating procedures, as well as recording and verification of results.

3.2.1 Organization and staff qualifications

The organization carrying out the trials should ensure that they are managed in a structured and transparent manner. The organization should also have sufficient staff, equipment and resources to set up and manage the trials effectively and consistently over a prolonged period. It should be able to ensure that GEP will be applied over the entire period and geographical extent of the trials.

The organization should also have at their disposal appropriate and properly located facilities (e.g. buildings for storage and preparation of pesticides, facilities for storage and calibration of equipment, experimental fields, glasshouses, storage facilities for stored product tests, facilities for harvesting, sampling and yield determination, and data-processing facilities, as required for the studies) to carry out valid and accurate trials.

Scientific and technical staff should have the necessary training, knowledge and experience to perform the tasks assigned to them. These qualifications may have been obtained from formal education in agriculture or a related subject, from professional experience or from continued training. Temporary staff should be adequately trained and supervised.

The organization should clearly define responsibilities and assign tasks to specific staff, such as drawing up protocols, planning the trials, performing the trials and writing reports. It should also ensure that staff has the resources needed for the tasks assigned to them.

Suitable equipment, in sufficient quantities, should be available for the correct execution of the tests and measurements that need to be carried out for the trials. This equipment must be properly maintained and calibrated.

3.2.2 Operation

Trial protocols should be elaborated, before starting the work, which are sufficiently detailed so that third parties can understand the contents of the study and verify its quality. Trial protocols should be acceptable to the registration authorities and they should follow national or regional standards, where available.

The organization should elaborate standard operating procedures (SOPs) or standard modes of operation for testing, measurements, data collection and reporting procedures or other tasks that are carried repetitively, to ensure consistency and repeatability of the activities. SOPs must be defined at least for the following activities: distribution, receipt and handling of pesticides; pesticide application; calibration and use of application equipment, use of weighing apparatus, measuring equipment, sowing, planting and harvesting equipment; maintenance of equipment; sampling of plant protection products (for quality control); recording of results. SOPs and protocols should be made available to all relevant personnel involved in the trials.

Note that SOPs and protocols should not be rigid, dictating a trial without taking the actual pest biology and environment in the field into account. For instance, if sprays are applied on a calendar schedule that may not fit the biology of a pest in a given area, this may result in increased variability of the results. This can be overcome by including pest monitoring in the SOP or protocol, so that the timing of treatments relates to pest biology in a similar way in the various replicate trials.

Experimental permits must be obtained by the organization prior to the start of a trial, if required by national legislation. Information on the trial (at least its location, timing and the identity of the product(s) to be tested) should be made available to the competent authority, whenever requested.

3.2.3 Record keeping and reporting

Records of all original observations, measurements, calculations and derived data, calibration records, as well as the final trial report, should be kept by the company holding the registration for as long as required by the registration authority, but at least as long as the product is registered in the country. This holds for data on paper but also for electronic and audiovisual data.

All studies must be fully documented and reported in sufficient detail so that a third party can validate their results and conclusions in the light the used trial methodology. In principle, the reader should be able to exactly repeat the trial only based on the study report. Any deviations from the protocol or from SOPs, or any other special conditions that may have influenced the results of the trial, should be explicitly noted and reported. Reporting is further discussed in Chapter 8.

3.2.4 Verification and quality control

Persons who are scientifically responsible for the trial within the organization should be able to check and validate the trial throughout its course and ascertain that the protocol and SOPs are being followed.

Organizations should accept at any time inspections that may be organized by the registration authority, or another competent national authority, to verify compliance with GEP and other national (or regional) requirements.

It may be practical to set up a certification system, or some other form of official recognition, of the organizations capable of carrying out biological efficacy trials of plant protection products [e.g. 22]. This will facilitate compliance monitoring of GEP and other national testing requirements.

4. General principles for the design of efficacy trials

This chapter discusses a number of general principles for the design of efficacy trials. They mainly concern trials of the direct efficacy (effectiveness) of plant protection products, but are also relevant for other studies dealing with sustainability aspects of efficacy evaluation.

Following the discussion of some general principles in this chapter, the design and execution of direct efficacy trials is discussed in more detail in Chapter 5. Trials assessing phytotoxicity are dealt with in Chapter 6, and other trials relevant for efficacy evaluation (such as effects on succeeding crops, resistance risk and side-effects on beneficial arthropods) are further discussed in Chapter 7. Guidance on reporting of all these types of trials is provided in Chapter 8.

4.1 Minimum effective dose

4.1.1 Principle

In the interest of avoiding undue negative effects of plant protection products on the health of farmers, farm workers, bystanders or consumers, and reducing exposure of the environment, it is important to ensure that only the minimum dose of a product is applied to achieve the desired effect.

Efficacy testing should therefore have as a key objective to determine the minimum dose of a plant protection product necessary to achieve sufficient efficacy against the target pest across a broad range of situations in which the product will be applied. This is referred to as the "minimum effective dose" or the "lowest effective rate" [14, 23] and should be the one recommended on the product label. The minimum effective dose can be defined in terms of level, duration and consistency of control, or a combination of these. It will be specific to crop/pest combinations and pest management or agronomic practices. In some cases an effective dose range rather than a single dose will need to be determined.

To establish the minimum effective dose, it is necessary to demonstrate that it provides one or more of the following:

- a higher level of effectiveness compared to a lower dose
- a longer persistence of action compared to a lower dose
- a more consistent performance under variable conditions compared to a lower dose

The selection of the recommended minimum effective dose will normally be based on the results of a series of trials combined with expert judgement. In addition to direct effectiveness, issues such as the potential for resistance development, the safety of the product to the crop, and other factors relating to efficacy will need to be taken into account.

4.1.2 Testing procedures

An indication of the likely recommended dose will come from trials carried out during the development of the product under laboratory, glasshouse or (semi-)field situations. Any relevant dose-response curves of the product that may have been developed at this stage can be helpful for evaluation by the registration authority and registrants should provide such information as part of the biological dossier.

In order to establish a minimum effective dose, a series of different application rates should be included in the trial programme, to demonstrate the difference in efficacy between lower doses and the proposed one. At least one lower rate than the recommended one should be included in the trials series. Ideally, the recommended rate and approximately 75% and 50% of this rate should be tested. Inclusion of higher rates is normally not necessary, although such information may increase confidence in the results obtained (note: testing of higher rates than the recommended one may be needed for crop tolerance, however; see Chapter 6). The number of trials in which the lower rate(s) are included should be sufficient to cover the range of situations for which the product is proposed.

It is generally not necessary to generate evidence for the minimum effective dose for all targets. Information should be provided for the main or most important target(s), but a justification should be provided for the dose recommendations for the other minor targets for which a registration is sought (e.g. based on preliminary screening tests or extrapolation).

Further guidance on establishing minimum effective doses is provided elsewhere [23].

4.2 Location of trials

Trials should be conducted in locations which represent the range of agronomic, plant health, environmental and climatic conditions likely to be encountered in practice in the area of proposed use. This should preferably be in the country where registration is sought, but could also be elsewhere if trials conditions are comparable to the conditions of proposed use (see Chapter 3.1.2). Sometimes, trials can be accepted from non-comparable conditions, for example if the trial conditions are considered to represent a more severe test of a product.

If trials are to be conducted in glasshouses or in storage facilities, these should also be representative of the conditions that are expected to be encountered in the proposed use situations.

The crops in the experimental locations may be specifically grown for the trials or be part of crops grown for commercial purposes, but in all cases should be grown according to normal agronomic or commercial practice. Any cultural operations in the fields or glasshouses, apart from the one being tested, should be according to normal practice.

If there is a possibility that soil types may affect the efficacy of a plant protection product, the various trial sites should be chosen to be representative of the range of soil types that can be encountered in the proposed use patterns of the product. Within each trial site, environmental and agronomic conditions should be as uniform as possible.

4.3 Number of trials

4.3.1 Factors influencing the required number of trials for direct efficacy

To demonstrate the efficacy of a plant protection product, a number of trials need to be carried out in different regions with distinct environmental conditions and often in different years and growing seasons. This is referred to as a “trial series”, “multi-site trials” or “multi-year trials”, which is a set of trials on the same subject (e.g. efficacy, crop safety, or a given use pattern), set up following a general experimental protocol at different locations and/or in different years or growing seasons.

The number of trials that is required in a series is not fixed, but depends on factors such as:

- The overall importance of the crop or the pest – in general more trials are needed for crops or pests being more important in a given country or region; fewer trials are generally needed for minor uses.
- The severity of crop loss caused – more trials may be required for pests likely to cause important crop losses.
- Cultivar effects – more trials will generally be needed if different cultivars of a crop are grown in a country, that react in a different manner to the pest and/or the product.
- Impact of soil and climatic factors – the product may need to be tested under a wider range of such conditions (i.e. more sites or seasons if the crop or the pest is much influenced by variations in the environmental conditions); where there is little variation, fewer trials may be required.
- Prior knowledge of the active ingredient or the product in similar uses – if a considerable body of experience has been built up with the same active ingredient or product, for related uses, then (partial) extrapolation may be possible and fewer trials may be required.
- Availability of relevant foreign data – fewer trials may be required if efficacy data on the same pest/crop combination are available from other countries, under similar environmental conditions.
- General consistency of trial results – more trials will be required if the results of the trials in the series are variable.

The number of local trials required will have to be determined by the registration authority and be made available to the registrant in advance to allow the trials to be carried out before the planned submission. A minimum number of trials may be fixed for the most important pest/crop combinations, but the exact number will often have to be determined on a case-by-case basis. The principal criterion for such a decision is that one should be confident that the product will provide acceptable and consistent control of the pest for a given crop, at the minimum effective dose and under most of the conditions encountered in the country.

Further information of factors influencing the number of trials required for efficacy evaluation is provided elsewhere [24].

4.3.2 Basic number of trials for direct efficacy

If a new plant protection product is to be used against a major pest and on a major crop, there should be a high degree of confidence in the efficacy of the product. As a general recommendation, a total of about 8 – 10 fully supportive trials will often be needed over a period of at least 2 growing seasons. These trials should be carried out across the range of climatic conditions likely to be encountered, and can also include trials from other countries. Pest infestation levels during the trials must be sufficiently high to be considered challenging to the crop, or the trial should be done in situations where challenging pest infestations can be expected.

4.3.3 Increased number of trials for direct efficacy

There are various situations in which an increased number of trials is warranted, to ensure a proper efficacy evaluation

Low pest pressure

The results of the trials should be “fully supportive” of the efficacy claim made for the plant protection product, i.e. they should show clear and acceptable direct efficacy in situations where the pest attacks were challenging. Results which are less than fully supportive, e.g. when pest attack is low, may still provide useful information, however, but additional trials will likely be needed.

Variable trial results

Additional trials should be carried out if the results obtained so far are too variable or not consistent (e.g. this may occur when the product is to be used in a wide range of environmental conditions, or if

the timing of treatments does not fit the pest biology properly). Such additional trials should investigate under which circumstances the effectiveness of the product is impaired.

4.3.4 Reduced number of trials for direct efficacy

There are various situations where there may be an opportunity to reduce the number of efficacy trials that is required for registration:

Minor uses

When the target pest of the crop is of minor importance, fewer trials may be required. This is particularly the case once the direct efficacy has been demonstrated against a relevant major pest or against the same pest on a major crop, and extrapolation to the minor use situation is possible. In general, about 3 trials should be sufficient in such cases, if done in different locations and/or years.

More information on minor uses is provided in Chapter 10.1.

Stable environments

Where there is little variation in climatic conditions in the use of a product, for instance in storage facilities or glasshouses, a reduced number of trials may be sufficient to demonstrate effectiveness. As a guide, about 6 trials are required for such protected situations, and data from a single year may be sufficient.

Possibilities for extrapolation

If sufficient experience has been built up with the same active ingredient or product, for related uses, then (partial) extrapolation may be possible and fewer trials may be required. Expert judgement is required when judging the reductions in the number of trials on this basis (see Chapter 3.1.4).

Foreign data

If efficacy data on the same pest/crop combination are available from other countries, then fewer trials may be required, provided that the environmental, cropping and pest conditions are comparable to the situation for which the product must be registered. Expert judgement is also required to assess this type of request for trial reductions (see Chapter 3.1.2).

Formulation changes

When a change of formulation of a product with the same active ingredient is submitted for registration, it may be possible to limit the number of efficacy trials considerably (submission of so-called “bridging data”), and in some cases no new trials are required (e.g. minor changes in formulation components (roughly less than 20%), addition of a dye).

The use of bridging data is only appropriate if a full data set has been submitted previously (and accepted) as a basis for comparison, preferably on a range of crops or pests. Comparative (side-by-side) trials can then be used to demonstrate that product efficacy is equivalent for the original, already registered, product formulation and the new one. Equivalence of formulations only needs to be demonstrated for a number of representative crops and pests. These are preferably the more challenging control situations (e.g. the crops most susceptible to the pest or the pest species most difficult to control). Data from a single year may be sufficient.

More guidance on generating bridging data can be found elsewhere [14, 15].

4.3.5 Number of trials for crop tolerance

Apart from showing that a plant protection product is efficacious against the target pest, field trials should also demonstrate that the product does not have unacceptable effects on the treated crop. Unacceptable effects include symptoms of phytotoxicity, as well as effects on the quantity and quality of harvested produce (Chapter 6).

Herbicides and plant growth regulators

Because of their activity, herbicides and plant growth regulators have the greatest potential for adverse effects on the treated crop.

Specific phytotoxicity trials of herbicides and plant growth regulators are often best conducted independently from the direct efficacy trials. As a guide, approximately 8 trials are required per major crop/weed, to cover the range of soil types, weather conditions, weed composition and other conditions of use likely to be encountered in the proposed use. Generally, both the recommended dose (N) and twice this dose (2N) need to be tested. The number of crop tolerance trials may be reduced when more relevant information is available on the use of the product on various crops.

Insecticides and fungicides

No specific phytotoxicity trials need normally be done for insecticides, fungicides, and other products such as acaricides and molluscicides. Observations on crop tolerance (phytotoxicity and effects on yield) can be made as part of the direct efficacy trials.

When the plant protection product has been shown repeatedly not to cause phytotoxicity or adverse effects on crop yield and quality, on several crops and across and broad range of conditions, further evidence for crop tolerance may be limited to visual inspections only, or waived altogether.

Seed treatments

Normal efficacy trials will often provide information on the phytotoxicity of plant protection products used as seed treatments. However, dedicated trials may provide more accurate data, particularly on the risk of reduced emergence. Initial trials are often done under glass; follow-up field trials may sometimes be required.

5. Design, conduct and analysis of efficacy trials

Individual trials are the basis for the efficacy evaluation of a plant protection product and they should therefore be of good quality. The objective of an efficacy trial is generally to assess if, and to what extent, the experimental product performs better (or equally well) as a reference product. Where possible, at least three experimental treatments are evaluated: the reference product, the untreated control, and one or several test products.

The exact objectives of the trial and the criteria by which they are to be judged (i.e. the hypotheses and statistical comparisons of interest) should be clearly defined in advance.

Below, general guidance for the design, conduct and analysis of direct efficacy trials is given. Various excellent guidelines and books exist which provide further advice on designing this type of trials [25, 26, 27, 28].

5.1 Experimental design

5.1.1 Type of design

Efficacy trials should be designed so that appropriate statistical analysis of the data can be performed to ensure that any effects attributable to the plant protection product can be distinguished from other forms of experimental variability. The principal randomized designs that are likely to be appropriate are a fully randomized design or a randomized block design.

A fully randomized design can be applied only if the trial environment is completely homogeneous. If that is the case, the completely randomized design is statistically the most powerful, i.e. there is maximum chance of detecting a significant difference if one exists. However, if there is significant heterogeneity between different parts of the trial area, it is better to use a design that explicitly accounts for that, such as the randomized block design.

The randomized block design is often the most appropriate for efficacy testing. A block is a group of plots laid out in an area within which the environment is homogeneous. Usually, each treatment appears only once in each block. The layout of the blocks must be such that heterogeneity of the environment or treatment conditions is controlled as much as possible (i.e. that variability among plots within blocks is less than between blocks). Plots within the blocks, or blocks themselves, may be placed side by side but do not have to be.

In some cases, a multifactorial design is needed, e.g. if various doses of the same product are tested. A split-plot design is then often used, where the main plots are subdivided into sub-plots. The size of the sub-plots should be sufficient, however, to allow reliable treatment and evaluation.

In many countries, efficacy evaluations are also carried out in farmers' fields, generally after a recommended dose has been set from trials done at experimental stations. Generally, these are direct, paired, comparisons of the treatment versus current farmer practice. The treatment is then randomized within each pair and replicates are at different farms. The advantage of such trials is the large, operational, scale of product applications and the wider range of conditions that can be assessed.

Non-randomized, systematic designs are hardly ever suitable for efficacy evaluation, although they are sometimes used for product demonstrations.

More information on the type of experimental design and layout of plots and blocks, particularly for efficacy testing of plant protection products, is provided elsewhere [25].

5.1.2 Number of plots and power of the trial

The power of a trial is the probability of detecting a given difference between treatments if such a difference exists. The trial design should have sufficient power to detect, with statistical significance, a "meaningful difference" between treatments. The smaller the difference between treatments that one must detect, the higher the power of the trial needs to be. For instance, if it is required that the new test product should have an efficacy of at least 95% of the efficacy of the reference product, the power of the trial needs to be higher than when the test product should only have 80% of the efficacy of the reference product.

For any given meaningful difference that one has to detect, the power of a trial is higher if residual variation in the results (i.e. the variation not caused by the treatments) is smaller or the number of replicates is larger.

As a rule of the thumb, a trial should include at least four replicates per treatment. The exact number depends on the required power of the trial and the variability in the populations of the target organisms, among other factors.

As was mentioned above, the choice of the experimental design also has an influence on the power of the trial to detect a meaningful difference. It is generally considered that for a useful statistical analysis to be made, the number of residual degrees of freedom in the experimental design should be at least 12.

If efficacy significantly depends on environmental conditions, it is generally better to carry out a series of trials in different locations or seasons. The assessment of efficacy should then be based on the grouped results from the entire trial series, and the minimum number of replicate plots for each trial might be reduced to 3 instead of 4.

More information on the power of efficacy trials and the number of required replicates is provided elsewhere [25, 29].

5.1.3 Plot size and shape

The most suitable plot size depends upon many factors such as the mobility of the target organism (larger plots are generally needed for more mobile organisms), the technique of application (application techniques that deposit the product in a more precise and located manner require smaller plots than less precise techniques such as aerial spraying or mist blowing), the size and type of the crop/plant, and the harvesting technique.

For instance, trials with knapsack sprayers may already be done on fairly small plots, but one has to ensure that there is a reasonably sized guard strip. Hand-held spinning disk sprayers generally need at least 20 m x 20 m. Tractor-sprayed plots require at least the boom width of the sprayer plus a guard strip. Trials using ULV drift spraying will have to be carried out on relatively large plots because a regular deposit of the product is achieved through successive overlaying spray swaths.

Guard or buffer rows/strips are needed to minimize interference between plots (e.g. if drift or spread of the plant protection product is likely to occur or pest movement can be expected). In such cases the plots will need to be larger ("gross plot"), and observations and harvesting must be limited to the central part of the plot ("net plot").

Preferably, plots should be of the same size in one trial and of similar sizes for a given trial series, but this need not necessarily always to be the case. Accuracy increases with plot size, but only up to a

certain degree, because variability in soil and infestation levels may also increase. Long narrow rectangular plots are more suitable for mechanical harvesting; square plots reduce the risk of interference between plots and allow better for variations in wind direction.

5.1.4 Reference product and untreated control

Reference product

A reference product should be included in the trial whenever possible. The reference product serves to compare the test product with a plant protection product with known efficacy in practice, and so check the quality of the trial. Furthermore, the inclusion of a reference product facilitates the comparison between different trials in a series. Generally, the test product is compared against the reference product when assessing if efficacy is acceptable.

The reference product should be a product known to be satisfactory in practice. As far as possible, the reference product should be registered in the country for the same use (crop/pest) as for which the test product is being proposed. A non-registered reference product may be acceptable provided that it is known to be satisfactory in practice.

In cases where no reference product is available (e.g. when the mode of action of product or its use are new), one should assess if a non-chemical method of control might be used as a reference. If this is not possible, the efficacy of the test product will need to be assessed against the untreated control.

In cases where a plant protection product is an integral part of an IPM system, comparisons between single products may not be informative regarding the overall efficacy of the applied pest management system. In such cases, comparisons may need to be made between a "reference IPM system" and a similar system including the tested plant protection product.

Untreated control

An untreated control should be included in the trial, whenever possible. The main purpose of the untreated control is to confirm the presence of an adequate pest infestation and to confirm that there were no natural background reductions in their numbers or levels during the course of the trial. If pest infestation levels are low, efficacy cannot be demonstrated and trial results are meaningless. The untreated control therefore serves as a reference point to determine validity.

Furthermore, untreated controls are often used to calculate efficacy levels, usually in combination with results from the reference product. In the absence of a reference product, the untreated control becomes essential for determining efficacy.

Untreated controls can have other useful roles in efficacy trials. For instance, they can provide information on major overall changes in pest populations (e.g. mass migration) or on the development of the pest (e.g. emergence, spore release). They can also provide comparisons of yield and quality of produce in case no plant protection product is being used. Furthermore, untreated controls make it possible to express results of the trials as efficacy rates rather than mortality or density, which tends to facilitate graphical presentation and comprehension of the results. Caution is asked for, however, when comparing untreated controls with treatments, because natural movement of pest populations among trial plots may (partially) mask the treatment effect.

Untreated control should not receive any of the treatments under study, but they should be subject to all other measures that are applied throughout the trial, in particular cultivation measures and applications against pests not being studied.

More information on the role of reference products and untreated controls in efficacy testing is provided elsewhere [25, 30].

5.2 Target (pest) organism

The target (pest) organism should in principle be present at levels of agronomic importance, or expected to be present at such levels during the treatment. Population, infestation or infection levels should be similar in treated plots and in untreated controls at the start of the trial, and preferably until the first treatment.

The organism must be identified by its full scientific name (whenever possible) and, where relevant, subspecies, variety, isolate, etc. should be stated. Growth stage of the pest, as well as its density, level or frequency of infestation or infection should be noted and be quantified, whenever possible.

A naturally occurring infestation or infection in the plots is preferable, but if artificial inoculation of a pathogen or introduction of a pest is carried out, the applied procedures must be described.

Trial series should include different growth stages of the target organisms where relevant. They should include different strains or races where these are likely to show different degrees of susceptibility to the product.

5.3 Application of plant protection products

The equipment and method of application of the plant protection product should be the same or similar to the one to be recommended on the label. However, especially in small-scale trials hand-held equipment may be used, while the product is later to be applied using vehicle-mounted equipment. Registration authorities should assess if the equipment used in the trials is expected to lead to similar efficacy as equipment that is available in the country. Application rates (both the product dose and, for sprays, the volume application rate) and dilution ratios (as appropriate) should be the same as recommended for use, except if the influence of the dose on efficacy is being evaluated.

Treatments should be timed as to be recommended on the label. Inclusion of earlier and later timings in the trial may provide additional information in certain situations. Where repeated application is recommended, the same application frequency should be tested. Different application frequencies may need to be compared in the trial, to determine the optimum interval between applications.

Application equipment should be properly calibrated to give the intended application rate and droplet spectrum (the latter for sprays only). Details of the sprayer, its operating pressure, nozzle type and position of nozzle(s) relative to crop, forward speed and volume application rate need to be specified as well as dose, spray concentration, and formulation used. Whenever feasible, it is recommended that the actually applied volume application rate is also determined and reported, rather than only the nominal (calculated) rate based on the calibration, to confirm the quality of the treatments.

Further guidance on pesticide application techniques is provided elsewhere [26, 31, 32, 33], as are guidelines for the appropriate expression the dose of the product in field trials [58].

5.4 Environmental conditions

Weather conditions should be measured at the trial site on the day of treatment. Ambient temperature, relative humidity, precipitation, wind speed and direction should be recorded, where relevant, preferably several times just before, during, and just after product application.

Temperature, relative humidity, precipitation and extreme weather conditions may also need to be recorded on a regular basis throughout the trial period. The exact parameters and frequency of recording will depend on the type of crop/pest/product under study.

Basic soil conditions, such as soil type, pH, organic matter content and soil moisture, should be recorded, where relevant. While the results of a soil analysis would be useful, it is usually sufficient to report qualitative information based on observation and local knowledge. Relevant data concerning irrigation should also be recorded.

For trials in glasshouses or storage facilities, temperature and humidity should be recorded throughout the trial period.

5.5 Assessment of biological efficacy

The variables that need to be assessed to determine the efficacy of the plant protection product will strongly depend on the crop and pest being studied. They may include density or incidence of the pest, infestation levels, percentage mortality or control, severity of symptoms or damage to the crop, quantity of yield, quality of the product, etc.

Pre-treatment assessments should be taken, whenever relevant. This is particularly important for trials with insecticides, acaricides and fungicides, where infestation levels can change rapidly over time. Parameters such as population reduction, expressed as percent mortality, should be corrected to account for mortality in untreated control plots to provide values for percentage control.

For many pests and crops, detailed methods on sampling and damage or yield assessments have been developed, though not always specifically for efficacy trials of plant protection products. In certain countries and regions, specific protocols for efficacy testing exist that include methods for the assessment of effectiveness of the product [e.g. crop/pest-specific efficacy testing guidelines published by EPPO, CILSS, and several national registration authorities]. These should be used for the trials, whenever required by the registration authority or otherwise appropriate.

If no specific efficacy trial protocols exist, well researched and peer-reviewed biological assessment methods for a given crop or pest may have been published and these should be used where relevant. In all other cases, general publications on biological or ecological sampling and assessment methods can be consulted for further guidance [e.g. 26, 34, 35, 36].

Regardless of the type of assessment chosen, the sampling or assessment methodology should be described in sufficient detail, so that the reader can repeat the method based on the information provided in the report.

5.6 Other observations

Various other observations can be made during an efficacy trial, such as phytotoxicity, effects on succeeding crops and side-effects on beneficial organisms. They are discussed in the next chapters.

5.7 Analysis of results

Results from a field trial or a trial series should, in principle, always be statistically analysed. The following sequential assessment should be made for trials that include an untreated control, a reference product and one or more test products [25]:

1. Has the trial been realistic, i.e. been able to generate useful data? This will generally only be the case if pest population levels in the untreated control were sufficiently high to provide a challenge to the crop.

2. Are the results of the trial coherent? Does the reference product give the expected result in comparison with the untreated control?

3. If condition 1 and 2 are satisfied, it is then valid to compare the test product(s) with the reference product, and make comparisons between the test products themselves, if several were tested.

   The principal objective of the analysis is to estimate the magnitude of the differences between the various treatments and to provide a measure of variability of those estimates. The treatments should be compared using an appropriate statistical test.

4. If no significant differences are found between a test product and the reference product and/or the untreated control, it is important to assess whether the trial was powerful enough to find a meaningful difference (see Chapter 5.1.2). If it was not powerful enough, the trial should be regarded as inconclusive.

Many methods of statistical analysis may be applied to efficacy trial data. The method to be used will depend to a large extent on the type of variables that have been recorded. If the variable is quantitative, a parametric statistical method should be used, usually based on analysis of variance. If the variable is qualitative, non-parametric methods are appropriate.

The statistical methods used for analysis the data must be reported in sufficient detail, so that they are comprehensive for external reviewers.

It is strongly recommended to consult a statistician before design of the trial, for advice on the design, lay-out and statistical analysis of the efficacy trial. This is especially relevant if new or unusual trial designs are to be applied (e.g. a factorial design to cope with different doses, cultivars, application timing or intervals between treatments). Advice from someone with much experience in the analysis of agricultural or ecological field data is generally to be preferred to that from a purely theoretical statistician.

There are various good publications on the design and statistical analysis of field experiments that can provide further guidance on this topic [27, 28, 29, 37]. Specific advice on the analysis of efficacy trials of plant protection products is also available [25].

6. Crop tolerance

The assessment of crop tolerance is an essential element of the efficacy evaluation of a plant protection product. This includes the occurrence of phytotoxicity, adverse effects on crop yield and quality, and any effects on plants or plant parts used for propagation.

In many cases, observations on crop tolerance are integral part of the trials that evaluate the performance of the product on the target pest. In some situations, dedicated crop tolerance studies are required.

Crop tolerance trials should cover the range of growth stages of the crop that is proposed to be treated, as well as potentially sensitive timings of treatment (e.g. flowering, fruit setting). For all crops, absence of specific varietal sensivity should be demonstrated. This can be done by conducting trials over a range of cultivars, by testing a series of cultivars with limited or not replication, or by a combination of both.

6.1 Phytotoxicity

Phytotoxicity is the capacity of a plant protection product to cause temporary or long-lasting damage to plants [38].

Phytotoxicity is most often a direct effect of the single product on the crop, but it may also arise from interactions between different products. Furthermore, phytotoxicity may occur as an effect of the use of a product on the preceding crop, or it may affect a succeeding one (e.g. a persistent herbicide; see Chapter 7). This should be taken into account when designing the field trials.

Because of their activity, herbicides have the greatest potential for adverse effects on a treated crop. Specific phytotoxicity trials of herbicides should therefore be conducted, independently from the direct efficacy trials. They should be done in the absence of weeds, because weeds compete with the crop and because their presence may reduce the amount of herbicide reaching the crop. For seed treatments a number of specific crop tolerance trials are generally also required (particularly to assess possible reduced emergence).

Both the recommended dose (N) and about twice this level (2N) should be tested, to determine the margin of safety that exists when using the product. If serious adverse effects are observed, intermediate rates may need to be studied as well.

For insecticides, fungicides, and other products such as acaricides, molluscicides, no specific phytotoxicity trials need normally be carried out. Observations on crop tolerance (e.g. phytotoxicity) should be made as part of the direct efficacy trials. If any adverse effects are observed at the recommended dose (N), then the effects of (approximately) the double dose (2N) should also be investigated. In such a case, specific crop tolerance trials are likely to be required.

The effects of phytotoxicity may be observed on the crop at emergence, during growth or at harvest. They may be temporary or lasting. The symptoms may affect the whole plant or only a part of the plant, such as the roots, leaves, flowers or fruits. Some examples of effects of phytotoxicity are:

- loss of whole plants (thinning)
- delays in emergence, growth, flowering or fruit-setting
- discolouration of the plant or parts of it

- necrosis of plant tissue
- wilting
- deformations of the plant or plant parts

In practice, it is unlikely that the most severe effects or symptoms will be observed frequently in efficacy trials, because plant protection products causing such effects would probably not have reached the stage of field testing. Therefore, symptoms of phytotoxicity will often be inconspicuous and observations should be carried out carefully and in a thorough manner.

The number of trials required for phytotoxicity assessment has been discussed in Chapter 4.3.5. Further guidance on phytotoxicity trials can be found elsewhere [38]

6.2 Effects on yield

While the objective of the use of a plant protection product is to protect or to increase the yield of a crop, in some cases such products may adversely affect them. The efficacy evaluation should provide sufficient information to ascertain that yield reduction does not occur. Where treated crops or produce is likely to be stored, the effect on yield after storage, including storage life, should be determined.

For herbicides, and for any other plant protection products where adverse phytotoxic effects are seen, an assessment should be made of the possible occurrence of yield reduction. These observations can often be combined with (some of) the dedicated phytotoxicity trials.

For other plant protection products, an assessment of possible yield reduction can generally be made as part of the direct efficacy trial, and no specific trials need to be set up.

Sites with low pest infestation levels are most useful to assess a possible effect on yield because yield responses resulting from pest control do not mask any adverse yield effects from phytotoxicity.

6.3 Effects on quality and transformation

Similarly, sufficient information should be collected to assess if treatment with the plant protection product causes negative effects on the quality of the crop or produce, such as tainting of leaves or fruits, odour or effects on flavour, or effects on the quality grading of the (processed) produce.

Testing should initially be conducted on the main crops on which the plant protection product is to be used, at about twice the recommended dose (2N). If effects are observed, testing at recommended rate (N) should also be carried out.

In some cases it may be necessary to carry out taste-panel tests (organoleptic tests) to verify that no unacceptable effects occur.

When the treated plants or plant products are to be used in a transformation process such as wine making, brewing or bread-making and significant residues are present at harvest, the possibility of adverse effects should be investigated if there are indications that the plant protection product could have an effect on the transformation process involved.

Further guidance on taint tests and effects transformation processes is provided elsewhere [52, 53].

6.4 Effects on plants or plant parts used for propagation

Plant protection products should not have an unacceptable effect on plants or plant parts used for propagation. The observations that need to be made depend on the type of plant part used for propagation. Examples of relevant parameters are:

- for seeds: viability, germination and vigour;
- for cuttings: rooting and growth rate;
- for runners: establishment and growth rate;
- for tubers: sprouting and growth rate.

Further guidance for seed testing is provided under the International Rules for Seed Testing [36].

7. Agronomic sustainability

Various other assessments can be carried out as part of the efficacy evaluation of a plant protection product. Most of these are done to confirm the absence of unacceptable effects on the crop production system and its agronomic sustainability. Sometimes there will be a need to carry out specific trials or observations; in many other cases risk assessments can be made based on existing data (often available in other parts of the registration dossier) and scientific rationale.

7.1 Resistance risk

Resistance is the naturally occurring, inheritable adjustment in the ability of individuals in a (pest) population to survive a treatment with plant protection product that would normally give effective control [39].

Loss of performance of a plant protection product because of the development of resistance may lead to increased use of the product to achieve control and will thus be costly and/or harmful to the grower, the pesticide manufacturer, the consumer and the environment. In some cases, the product may need to be removed from use entirely, reducing the options for a grower to manage a pest.

Increasingly, a resistance risk analysis is required before registration of a plant protection product. Such an analysis evaluates the potential of the product and the way in which it is proposed to be used on the development of resistance, and proposes strategies to manage and minimize resistance in the field.

The risk of resistance development is a result of a combination of inherent factors and factors related to the conditions of use. The risk which results from the conditions of use (agronomic risk) can be managed to a certain extent by the user of the product by changing or adapting its pattern of use. The inherent risk, on the other hand, is defined by characteristics of both the target pest and the plant protection product, and can generally not be changed by modifying the pattern of use. Therefore, resistance risk analysis should not be based on an evaluation of the inherent risk alone but also include the use conditions as proposed by the registrant.

To enable the registration authority to evaluate the risk of resistance, the following information should normally be provided by the registrant, unless it can be shown to be irrelevant for the risk analysis:

- Mode of action of the active ingredient;
- Evidence of resistance as a result of prior uses;
- Mechanism of resistance in the target pest(s);
- Knowledge of cross resistance to other compounds;
- Susceptibility data (i.e. baseline variability in susceptibility of the target pest to the product);
- Use pattern of the product, in the absence of resistance;
- Resistance management strategy (if there is medium to high risk of the development of resistance.

Detailed guidance on resistance risk assessment, risk factors and data requirements can be found elsewhere [39, 40]. Standardised susceptibility or resistance testing and detection methods are available for a number of pests [41, 42, 43]. International databases on worldwide occurrence of resistance exist for herbicides [44] and insecticides [45].

7.2 Effects on succeeding crops

The active substance of a plant protection product, or its biologically active metabolites, may under certain circumstances pose a risk to crops grown after a crop treated with that product. Such succeeding crops can be grown in the normal rotation that is practiced in a given location or they may be sown as replacement immediately after failure of the original crop. Information should be submitted as part of the biological dossier to allow an assessment of the risk that the product affects succeeding crops.

The extent and type of field trials that are required depend mainly on the fate and behaviour of the active ingredient (or its metabolites) in the soil, and on its biological activity. Studies on fate and behaviour are normally carried out as part of the environmental assessment and such data can be used to do an assessment of the risk for succeeding crops. When crop residues (e.g. straw) are left on the field until sowing of the succeeding crop, or if they are incorporated in the soil, persistence of the active ingredient or its metabolites on these crop residues should also be assessed.

Studies on the possible biological activity of the product on germination and growth of the major rotational crops will often be available from preliminary screening tests. Such data can be used to assess if a risk exists that certain succeeding crops are affected by the levels of pesticide residues that may be encountered when sowing a succeeding crop.

If it can be shown from the above data that persistence is low (i.e. no biologically active levels of residues of the active ingredient or its active metabolites persist until sowing of the succeeding crop), then specific field trials on succeeding crops will generally not be required.

If, however, it is likely that damaging levels of pesticide residues will be present in the soil, or if this cannot be clarified, then specific field trials on succeeding crops should be carried out. A general decision scheme on whether field trials on succeeding crops are necessary is available elsewhere [46].

Trials on succeeding crops can be done following a direct efficacy trial, or they can be set up independently. In the latter case, the target crop is treated as recommended, but no observations need to be carried out in this crop. After harvest of the treated crop, succeeding crops are sown into these plots to examine whether growth is affected. Measurements of the level of the active substance in the soil, or its metabolites, may be useful to assist in interpreting the results. Detailed guidelines on the design and conduct of field trials on succeeding crops are provided elsewhere [46].

7.3 Effects on adjacent crops

Information should be provided to permit an evaluation of the possible adverse effects of treatments with the plant protection product on adjacent crops or other non-target plants that may be exposed to the treatment.

Such data are only required if there are indications that such crops or plants may be affected by the product. Examples of products or situations where there may be an increased risk to adjacent crops are:

- application of herbicides or plant growth regulators;
- application from aircraft or by other methods conducive to drift;
- application of volatile compounds;
- application in or near to waterways.

This information is normally generated in the environmental part of the registration dossier or from observations in direct efficacy trials [76]. Specific field trials are rarely necessary for this aspect of efficacy evaluation.

7.4 Effects on beneficial organisms

Adverse effects on beneficial, non-target organisms are normally evaluated as part of the environmental dossier of the plant protection product [77, 78]. They should only be assessed as part of the biological dossier whenever claims to selectivity of the product are being made, or if it is intended for use in IPM systems. This particularly concerns possible effects on pollinators and on natural enemies of pests.

However, any negative or positive effects on non-target organisms observed during efficacy trials should be recorded, including effects on non-target pests. In particular, any (apparent) increases in the presence of secondary pests should be noted. These are normally observed during the various efficacy trials and generally do not require additional field studies to be carried out (which are covered in the environment dossier).

8. Reporting

8.1 The biological dossier

All relevant information from the efficacy evaluation programme for a given product use is compiled and presented in the "biological dossier". The biological dossier is normally part of the overall registration dossier (containing also the product label, the toxicological studies, environmental studies, etc.) that is submitted by the registrant to support its request for authorization of the plant protection product. It is also referred to as the "biological assessment dossier" or the chapter/section in the overall dossier dealing with "efficacy and crop safety", "product performance", or the "value assessment" of the product.

The biological dossier contains the individual efficacy trial reports or their summaries. These individual reports are generally grouped in a trial series report, which is a set of trials on the same subject (e.g. efficacy, or crop safety, of a given product use), set up following a general experimental protocol at different locations and/or in different years or growing seasons. The biological dossier may contain one or more trial series reports, depending on the number of different product uses that are being submitted for registration. In addition, it will contain other information necessary for a comprehensive efficacy assessment, such as additional data on direct efficacy (preliminary trials, phytotoxicity studies, etc.), agronomic sustainability (resistance studies, observed side-effects, etc.) and economic impact.

A schematic presentation of the composition of the biological dossier is provided in Figure 1. Further guidance on constituting a biological dossier is provided elsewhere [8, 20, 47].

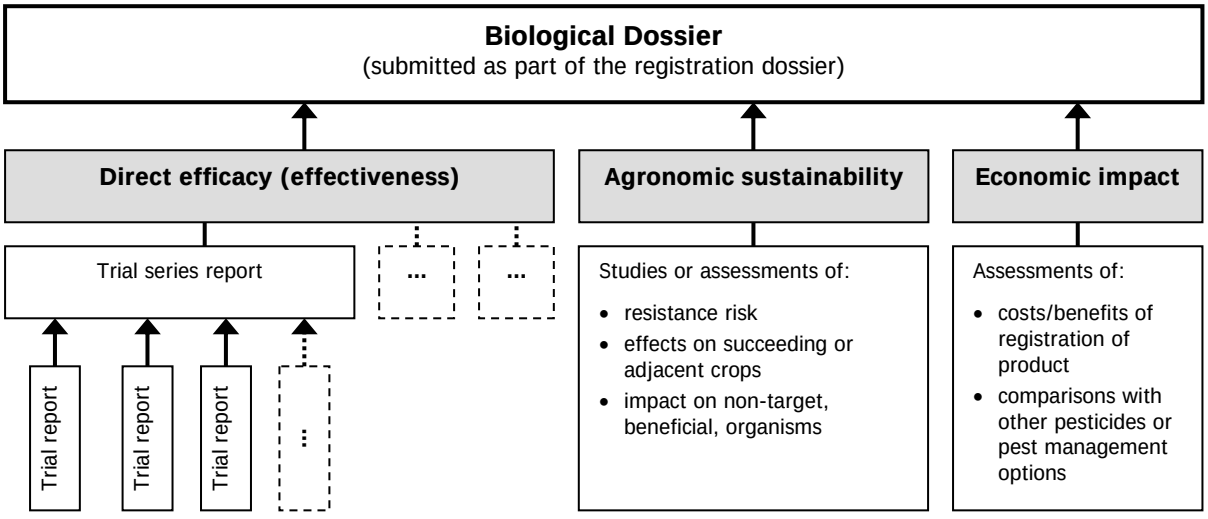

Figure 1 Elements of efficacy evaluation as the basis for the biological dossier

8.2 Record keeping and reporting of individual trials

8.2.1 The field notebook

Record keeping is essential to the success of an efficacy trial. If key observations and activities are not adequately documented, the results of the trial may not be acceptable to the registration authority. A field notebook (or trial notebook) provides a place to record all the information that is necessary to reconstruct and interpret an efficacy trial, such as observations, measurements, equipment readings, outcome of analysis, references to used methods and protocols, personnel involved, etc.

The field notebook can either be a real (hard copy) notebook, a set of pre-printed forms, a computerized recording system, or a combination of any of these. Annex 3 provides some basic guidance on the correct and transparent way of constituting a field notebook.

Specially designed laboratory or field notebooks are commercially available and facilitate proper documentation of the study. Dedicated electronic data recording systems for field trials are also increasingly being developed.

8.2.2 The trial report

The trial report is the basic piece of documentation of the trial on which the registration authorities need to base their evaluation of efficacy of the product. Therefore, the report should be concise but contain all relevant information, and it should be accurate. In principle, the report should contain all the necessary information so that the reader can replicate the trial. It should also contain the results of the trial in sufficient detail for the registration authority to be able to assess any conclusions that are drawn about the efficacy of the product.

The actual format of the trial report will vary, and may follow national or regional standards or regulations. However, in all cases, the following subjects will need to be treated:

Objective of the trial

Introduction specifying the objectives of the trial including, among others, the plant protection product(s) being evaluated, the target pest, the crop and the type of protection intended.

Organizational aspects

Description of a number of basic organizational issues related to the execution of the trial, such as references to protocols and SOPs being followed, any deviations from the protocol or SOPs, the system of quality assurance put in place (where relevant), identification of the site/location of the trials, staff involved in the trial and contact details for the institution carrying out the trial.

Methodology

Description of methods used for the trial, such as the experimental conditions, the design and layout of the trial, the product application, methods of biological assessments, methods for environmental data collection and methods of statistical analysis applied.

Results

Concise but complete description of the results of the trial, such as product application details, environmental conditions during and after the application, results of the biological efficacy assessments, calculations of levels of efficacy (where relevant), observations on adverse effects, results of the statistical analyses.

Discussion and conclusions

The discussion should treat at least three issues. First, the validity of the trial should be evaluated, with particular attention to the results in the untreated control and the reference plots. If the trials can be considered valid, the efficacy of the test product(s) needs to be appraised in relation to the reference product, to the untreated control (where relevant) and to other parameters of the trial (e.g. dose, application time and frequency). Finally, any side-effects should be assessed.

A more detailed outline of the trial report is provided in Annex 4.

8.2.3 The trial series report

In many cases, the results of the various trials carried out with the same product for the same use pattern are compiled in a trial series report. The trials series report includes a critical evaluation of the quality and validity of all the trials. The results of the trials covered by the trial series report can then be combined to facilitate evaluation of the data. Depending on the parameters that are considered relevant for the evaluation, the results can be grouped (e.g. by soil type, species or development stage of the pest, region, or date of product application).

Further guidance on the elaboration of trial series reports is provided elsewhere [8, 20]

9. Principles for assessing acceptability of efficacy

After a biological dossier has been submitted to the registration authority as part of the request for authorization of the plant protection product, an evaluation has to be made as to the acceptability of the product for the proposed use pattern. This assessment is made by the registration authority.

It lies beyond the scope of these guidelines to propose concrete criteria for the acceptability of the efficacy of a plant protection product. Such criteria are normally defined in national legislation or regulations. However, a number of general principles will always need to be addressed when evaluating a biological dossier and deciding on the acceptability of the product [30]. They are briefly discussed in this chapter.

9.1 Direct efficacy

Various parameters should be taken into account when evaluating the acceptability of the direct efficacy or effectiveness of a plant protection product.

9.1.1 Comparison with the untreated control

The product will always have to show results (e.g. level, duration and consistency of control of or protection against a pest) that are significantly superior to those recorded in the untreated control.

It is not possible to set generally applicable levels of control that should be achieved. In some cases, relative low efficacy levels (e.g. 50 – 70%) may already provide benefits to the grower. Lower levels of control may also be acceptable if the product has little or no effects on natural enemies of pests and can therefore be incorporated into an IPM approach. In other cases, a high level of control may be required, for instance in the case of epidemic pests that can produce extensive damage or for pests that cause direct damage to the marketable portion of a crop (e.g. extensive blemishing on fruits).

The principal criterion is that the product must produce a clear and meaningful (commercial) benefit to the grower.

If no comparison with a reference product is available, this will be the only criterion that can be used to assess the acceptability of direct efficacy.

9.1.2 Comparison with a reference product

The efficacy of the product should normally be comparable to or better than that of an appropriate reference product. The reason for this is to prevent products that have a clearly lower efficacy than already available products to come onto the market. Such products are more likely to be overdosed and so increase exposure of humans or the environment.

However, there are various valid reasons for authorizing a product with a lower efficacy for use in a country. This may occur when other characteristics of the product have advantages over the reference product or over other products registered for the same use. This may be justified if the new product:

- can be used over a wider range of growth stages of the crop;
- is efficacious against more pest stages;
- is efficacious against more pest species;
- is less influenced by climatic factors or soil type;
- has greater compatibility with cultural practices or other plant protection measures (e.g. IPM);

- has a lower probability of causing resistance;
- has fewer undesirable side-effects (e.g. on beneficial organisms, other crops).

9.1.3 Comparison with other pest management approaches

Whenever possible, the efficacy of a new plant protection product should also be compared with other pest management approaches than the use of chemical plant protection products. This includes, but is not limited to, the use of resistant varieties (including genetically modified varieties), cultural or agronomic pest management measures, biological control or IPM.

While the comparison of efficacy of a plant protection product with an entirely different pest management technique may not always be straightforward, such assessments should be done whenever feasible, to evaluate the overall benefits of registering a new product [8, 16].

9.1.4 Crop tolerance

The use of the plant protection product should not result in unacceptable phytotoxic effects on the crop itself. It should not result in an unacceptable reduction in the yield of the crop, and definitely not beyond that what would have occurred without use of the plant protection product (note that in cases of quality improvement, a reduction in yield may sometimes be acceptable). Similarly, there should not be an unacceptable adverse effect on the quality of the crop or its produce, nor on treated plants or plant parts used for propagation.

In certain cases, what are originally unacceptable effects can be mitigated by appropriate measures, and thus become acceptable (e.g. by using specific application equipment, avoiding treatment at particular times during crop growth). In such a case, the registration authority should always appraise to what extent the proposed risk mitigation measures can be realistically applied and respected under the national conditions of use. If realistically the measure cannot be implemented, a decision not to register the product may need to be taken.

9.2 Agronomic sustainability

9.2.1 Resistance

The (over)use of one single product, or a combination of products, that has a clear risk of resistance development is generally undesirable. A resistance management scheme should then be formulated by the registrant to effectively delay the development of resistance.

The registration authority should always appraise to what extent the proposed resistance management scheme can be realistically applied and respected under the national conditions of use. If realistically the scheme cannot be fully implemented, a decision not to register the product may need to be taken.

9.2.2 Effects on succeeding crops

Generally, a high risk of adverse effects of the product on succeeding crops, including substitute crops, is not acceptable. In a few cases, label warnings or other mitigation measures may be proposed that can reduce the risk to an acceptable level (e.g. if no alternative plant protection product or pest control measure is available, or if there is only a risk for certain substitute crops that are directly sown after crop failure).

The registration authority should always apprise to what extent the proposed measures to limit the risk to succeeding crops can be realistically applied and respected under the national conditions of use. If

realistically they cannot be fully implemented, a decision not to register the product may need to be taken.

9.2.3 Effects on adjacent crops

The use of the plant protection product should not result in unacceptable effects on adjacent crops unless the risk of such effects can be minimized using appropriate measures (e.g. use of drift reduction measures, leaving unsprayed barriers).

The registration authority should always appraise to what extent the proposed measures to limit the risk to adjacent crops can be realistically applied and respected under the national conditions of use. If realistically they cannot be implemented, a decision not to register the product may need to be taken.

9.2.4 Effects on non-target organisms

The evaluation of the acceptability of any risk to non-target organisms is normally taken as part of the evaluation of the environmental dossier. The possible observations of adverse effects encountered in efficacy trials should be taken into consideration during that evaluation.

Products that have a major effect on natural enemies of the crop pest will arguably not contribute to sustainable crop protection and may not be acceptable from an agronomic point of view. In particular, when specific claims are being made with respect to the use of the product in IPM schemes, the product should not have unacceptable effects on the natural enemies of the pests covered in the IPM scheme. Similarly, if the product is to be used on blooming crops, or otherwise in periods when pollinators may be exposed, it should not have unacceptable adverse effects on these pollinators, unless mitigation measures can be realistically applied.

10. Specific issues

10.1 Minor uses

Minor uses are those uses of plant protection products in which either the crop is considered to be of low economic importance at national level (minor crop) or the pest is not important on a major crop (minor pest) [18]. Certain specialty crops, which are often grown on a limited acreage, may also require the minor use of a plant protection product.

With respect to efficacy evaluation, the minor uses that are of interest are those for which the volume of plant protection products that would be used at a national level are so low that investments that have to be done by a pesticide company to register the product would not be cost-effective. As a result, for certain minor uses no or only a few products may be available for use by growers. If no alternatives exist, or if they are not sufficiently effective, this may cause problems for the protection of such crops. These problems may become even more acute if resistance develops against the few still available plant protection products or if older active substances are removed from registration.

For minor uses, a reduced data package for efficacy may be justified, both because the volume of the product that will be used in the country will be limited and because it may contribute to the (temporary) resolution of acute plant protection problems. The objective is to reduce the number of efficacy trials that have to be carried out by using information from other sources as far as possible.

There are basically three sources of information for efficacy evaluation of minor use products: extrapolation from already registered uses of the same product, foreign data of the same product for the same or a very similar use situation, and data from local efficacy trials. Some guidance on extrapolation and foreign trials data has been given in Chapter 3.

The most widely accepted solution is to facilitate the extension of an existing registration in the country to include a minor use. Experience will generally have been gained with such a product which will facilitate extrapolation to a (new) minor use and may reduce the number of required local trials. If the product has not yet been used in the country, extrapolation from foreign data may still be possible, but more local efficacy trials will often be needed (Chapter 4.3).

In principle, the registration authority should be assured that at least direct efficacy and the absence of phytotoxicity of the product have been sufficiently demonstrated, and that the product will result in a clear benefit for the users, before registering the product for the minor use in question.

It should be noted that what is a minor use in one country may be a major one in another and *vice versa*. The decision to what constitutes a “minor use” therefore rests with the registration authority. The registration authority should prepare procedures for registration of plant protection uses for minor uses, such as guidance on extrapolation and a reference list of minor uses (crop/pest combinations) that would be covered by such procedures.

Further guidance on efficacy evaluation of plant protection products for minor uses can be found elsewhere [17, 18]

10.2 Biological control agents, semiochemicals and plant extracts

The efficacy of biological control agents, semiochemicals and botanical pesticides also needs to be assessed before their registration, just as is the case for chemical pesticides. For the purpose of these guidelines, biological control agents refer to micro-organisms (such as bacteria, algae, fungi, viruses and protozoa), semiochemicals are behaviour modifying chemicals such as pheromones and kairomones, and botanical pesticides generally refer to plant extracts.

The level of efficacy that is required in a trial of such products may be similar to that expected from a synthetic chemical pesticide. In other cases, however, these types of products are used in combination with other pest management approaches in the framework of IPM, and the level of efficacy may need to be assessed in combination with the other measures. Also, biological control agents, semiochemicals and botanical pesticides may be used in organic or biological agriculture and the level of control that is required can be less than what would be the case in conventional cropping systems.

The extent of the efficacy data required for these types products is generally the same as for chemical plant protection products, but consideration should be given to the nature of any particular agent. Issues that may be need special attention are, for instance:

Environmental conditions

Many biological control agents are sensitive to particular environmental conditions. Where these agents are not used in protected environments (such as glasshouses) adequate evidence should be provided of the effects of environmental conditions on the efficacy of the product.

Chemical characteristics

Many pheromones and other semiochemicals are volatile and may disperse over wide area. This will require specific design and layout of trials and may affect the possibilities for plot replication and use of untreated control plots.

Viability

Biological control agents are often living organisms and the viability of the product needs to be assessed before the trial is carried out, to ensure that its quality is sufficient.

Identity

Closely related isolates or varieties of micro-organisms may result in very different efficacy on the target pest. Accurate identification of such products is therefore of great importance for proper evaluation of the trials.

Certain botanically derived plant protection products are complex mixtures of compounds, levels of which may be strongly influenced by the production process and the quality of the primary matter from which they are extracted. Control of the chemical composition of botanically derived products is therefore important for proper evaluation of the trials.

Reference product

Many biological control agents have very specific modes of action, and appropriate reference products may not be registered in the country or may not be available at all. This will change the design of efficacy trials and will increase the importance of appropriate untreated controls.

Specific guidance on field testing of insect pathogens is available elsewhere [54]. General guidelines on the registration of microbial pest control products and semiochemicals have been published by OECD [55, 56] and FAO [48]. Both insect growth regulators and plant growth regulators are

sometimes considered biopesticides as well, but data requirements for efficacy are the same as for chemical plant protection products.

Macro-organisms used for biological control (such as nematodes, mites and predatory insects) require a different approach to efficacy evaluation and registration [49, 57], as is the case for transgenic plants that have been modified to express pesticidal activity. The latter two groups of crop protection agents are not covered by these guidelines.

10.3 Protection of stored plant products

The testing of plant protection products used to protect stored plant products differs from trials on field crops. Specific guidelines for efficacy testing are available for these situations. The principal types of treatments that are generally encountered are:

- fumigation of stored plant products,
- treatment of store rooms, and
- admixture of pesticides with stored plant products

In some cases fumigation or admixture of pesticides to the commodity is done before it is actually stored. The principles for testing of plant protection products are similar to the one described below for stored commodities, although the certain testing parameters may vary.

Fumigants

Fumigants are used for the disinfestations of plant products such as bulk raw cereals, dried fruits, vegetables or spices, and processed foods such as flour. The storage spaces that may be fumigated include silos, store rooms, shipping containers or agricultural products under impermeable sheeting.

Both the choice of commodity for efficacy trials as the type of storage space in which the trials are carried out should reflect as much as possible the intended use of the fumigant. Because many fumigants have high human toxicity, operator safety should receive particular attention, not only during treatments but also after unsheeting or venting the storage area, when sampling has to be carried out.

Basic parameters that will influence efficacy are not only the applied dose (expressed as a quantity of product per unit of volume) but also the exposure time of the commodity to the fumigant and the distribution of the fumigant throughout the stored commodity. Before testing the capacity of the fumigant to penetrate through packaging, gas-proof sheeting or store walls should be established, as well the extent of sorption by the commodity, as this may influence the concentration (dose) of the fumigant. Ambient temperature tends to affect the activity of the fumigant, and it should be measured throughout the trial.

Biological efficacy of the fumigant can be evaluated on natural free-living infestations of the pest or by introduction of recoverable cages with artificially constituted pest populations. In the latter case, the efficacy of the fumigant against different pest species can be tested in one trial.

Detailed guidelines on fumigation and efficacy testing of fumigants are available elsewhere [62, 63, 64]

Products for treatment of store rooms

The treatment of store rooms concerns either space treatments or treatments of the structure or building itself.

Store rooms may be treated empty, after which agricultural products are introduced, or they may be treated with the commodities already in place. Both the choice of commodity for efficacy trials as the type of storage space in which the trials are carried out should reflect as much as possible the intended use of the product.

Both naturally or artificially infested store rooms can in principle be used in these trials. If laboratory-reared insects are introduced into the store, their placement and monitoring will depend much on the type of product and application being tested.

Guidelines on efficacy testing for treatment of store rooms are available elsewhere [65]

Products for admixture

Plant protection products may be added to and mixed with stored plant products to control or protect against insect or mite pests, and sometimes against fungal diseases.

Probably even more so than with other types of efficacy testing, preliminary laboratory testing of plant protection products for admixture will provide valuable information to define recommended doses. This is so because the mode of application and exposure can be simulated quite well in small scale tests.

Field trials should be representative of agricultural practices in the country, and the methods of handling and storing of the agricultural plant products should be described. The plant protection product may be applied during the conveying of the grain. The applied dose will then depend on the calibration of the sprayer/applicator but also on the conveying rate of the grain. Both should therefore be calibrated before treatment is started. Application should ensure as even a distribution as possible throughout the substrate.

Biological efficacy can be assessed in various ways, by:

- treating agricultural produce before an infestation has taken place, and demonstrating that it remains free of infestation whereas the untreated controls do not;
- treating infested agricultural produce and demonstrating the reduction of elimination of the infestation when compared with the control;
- treating uninfested agricultural produce, sampling it at regular intervals and carrying out a bioassay with the pest insect or mite to demonstrate efficacy.

Ambient temperature and relative humidity may affect the efficacy of the product and they should be measured throughout the trial. Bulk grain or other agricultural produce is rarely homogeneous, and this should be taken into account when sampling.

Efficacy testing against mites needs particular attention, because these organisms are very sensitive to humidity and mite infestation will often develop in the surface layers of otherwise dry grain. This will affect treatment and sampling methods that should be applied. Also, mites are vulnerable to mechanical handling, and it is especially important to set up representative controls. Samples should also be examined as soon as possible after sampling. Stored product mites often respond slowly to plant protection products and post-treatment monitoring needs to be carried out over several weeks or months to assess the total effect of the product.

Detailed guidance on efficacy testing of insecticides and acaricides used for admixture with stored plant products is available elsewhere [66, 67], as are specific guidelines for products used to control fungal diseases in stored agricultural commodities [68, 69].

Pre-harvest applications

Pre-harvest applications of plant protection products may be carried out to protect crops, in particular against storage diseases. The testing of such products tends to be a hybrid between efficacy trials in the field (for the application part of the trial) and tests of storage protection products (for the biological evaluation part of the trial). Crop-specific guidelines for efficacy testing of plant protection products used for pre-harvest treatments are available from national or regional organizations such as EPPO.

10.4 Rodenticides

The characteristics of rodents as pests and the toxicological properties of the chemicals used in their control are quite different from what is the case for other classes of plant protection products. Rodent infestations tend to be highly localized, rodenticide applications often must be targeted to maximize exposure of the rodents but minimize risks to users and non-target organisms, and certain groups of rodenticides (antiocoagulants) need to be ingested several times to exert an effect.

Plant protection products against rodents may include ready-made rodenticidal baits, concentrate rodenticides that need to be made up into a bait by the user, dispensers, contact formulations (e.g. rodenticidal dusts) or burrow fumigants.

Data on the oral potency of the active ingredient and the used formulation, and the palatability of the formulation (e.g. baits) should be evaluated through laboratory tests and their results are generally required to set up a proper field trial.

The sites chosen for field efficacy studies of rodenticides should be representative of locations where the rodeniticide is to be used, and should be infested with rodents of the species to be controlled. Rodent infestations should ideally be discrete populations of one target species with little probability of re-invasion and be large enough to allow accurate activity estimates.

The effects of rodenticides on rodent populations caused can be monitored using various types of census techniques, such as baiting, trapping or activity counts. These census methods may be species-specific and expert advice should be sought when setting up rodenticide field trials.

Excellent guidance on efficacy testing of rodenticides is available elsewhere [70, 71, 72, 73, 74].

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Annex 1

Examples of regional / international harmonization of the efficacy evaluation of plant protection products

Organization	Number of countries involved	Type of harmonization of efficacy evaluation	Ref.*
Comité Permanent Inter-Etats de Lutte contre la Sècheresse au Sahel (CILSS)	9	common trial protocols, mutual acceptance of data, joint pesticide registration	[3]
Comunidad Andina	5	harmonized framework protocol for efficacy trials	[4]
Organismo Internacional Regional de Sanidad Agropecuaria (OIRSA)	9	harmonized framework protocol for efficacy trials	[5]
European and Mediterranean Plant Protection Organization (EPPO)	46	general standards and specific trial protocols	[6]
European Union (EU)	25	general standards and specific trial protocols (=EPPO), mutual acceptance of data, common evaluation criteria	[7]
Nordic Council of Ministers	8	harmonization of testing procedures in Nordic/Baltic region	
North American Free Trade Agreement (NAFTA)	3	harmonization of efficacy evaluations (for Canada and Mexico)	
Organisation for Economic Co-operation and Development (OECD)	30	harmonization of format of biological dossier	[8]

* Numbers refer the *References* section of these guidelines.

Annex 2

Format of the biological dossier

Introduction

The biological dossier is the basis for the efficacy evaluation to be done by the registration authority. It consists of the results of the complete trial series, data on crop safety, effects on succeeding crops, resistance risk, effects on beneficial organisms and any additional information that can assist in carrying out the efficacy evaluation correctly.

The format presented below basically follows the recommendations made by the Organisation of Economic Co-operation and Development (OECD) for pesticide industry when they submit a biological dossier for authorisation in one of the OECD member countries [8].

The format is considered to be generally applicable, also outside OECD, but should not be considered as rigid. Depending on the specific needs of a country, national or regional regulatory requirements, the type of product that is submitted and the evaluation methods used by the registration authority, the format of the biological dossier can be modified as required.

Only the outline of the biological dossier is presented here. OECD provides detailed guidance on the contents of the dossier, such as filled out examples of the various sections and several models for summary tables [8].

Contents of the biological dossier

1. Introduction
   [e.g. mode of action of the product, intended use recommendations, expected use limitations, previous experience or information, proposed label text]

2. Efficacy data
   - 2.1 Efficacy trials – laboratory or growth chamber tests (preliminary screening)
   - 2.2 Efficacy trials – small-scale field or greenhouse tests (preliminary screening)
   - 2.3 Efficacy trials – operational large scale,
     - 2.3.1 Testing facility or organization
     - 2.3.2 Sites
     - 2.3.3 Experimental details
     - 2.3.4 Formulations applied and application rates
     - 2.3.5 Application methods
     - 2.3.6 Assessment methods – control
     - 2.3.7 Assessment methods – crop yield
     - 2.3.8 Assessment methods – crop safety
     - 2.3.9 Assessment methods – safety in following crop
     - 2.3.10 Statistical analysis
     - 2.3.11 Summary and evaluation of individual trials results (by crop and/or pest)
     - 2.3.12 Effects of climate
   - 2.4 Effects on yield and quality
     - 2.4.1 Effects on quality of plant or plant products

2.4.2 Effects on transformation processes
2.4.3 Effects on yield of treated plant or plant products

3. Adverse effects
   3.1 Phytotoxicity to target plants
   3.2 Adverse effects on site of application (discoloration, corrosion, etc.)
   3.3 Adverse effects on beneficial and other non-target organisms
   3.4 Adverse effects on parts of plants used for propagating purposes (e.g. seeds, cuttings, runners)
   3.5 Impact on succeeding cops
   3.6 Impact on other plants, including adjacent crops

4. Economics

5. Consideration of benefits
   5.1 Survey of alternative pest control methods (chemical and non-chemical)
   5.2 Compatibility with current management practices, including IPM
   5.3 Contribution to risk reduction
   5.4 Information on the possible occurrence of the development of resistance or cross-resistance

6. Other/special studies

7. Summary and evaluation of data presented

Annex 3

Constituting a field notebook

The field notebook (or trial notebook) is the main record of the efficacy trial. The trial report, or trial series report, is prepared on the basis of the field notebook. In many cases, it may get a legal status. The field notebook should therefore be constituted in an accurate and transparent manner.

The field notebook may be a real paper notebook, pre-printed forms, an electronic data recording system, or a combination of any of these. The guidance below refers particularly to paper-based notebooks and forms.

A new notebook is in principle started for each field trial. The same notebook may used for several field trials, if they are clearly separated and identified. However, the pesticide company (or other registrant) will often, in the contract with the institute carrying out the trial, stipulate that the original notebook is handed over to them. All trials described in a single notebook should then have been ordered by the same company, to avoid compromising confidentiality.

Generally, a field notebook is assigned to one person only, who has full responsibility over its contents. However, if more than one person will write in the notebook, this should be clearly stated on the first page and every subsequent entry must be signed or initialled by the person concerned.

Some general principles of filling out and managing a field notebook are provided below. National legal requirements with respect to data recording may exist and should be followed where required.

Organization of the notebook

- Enter and date all observations and data immediately, using separate headings to differentiate each.
- Record all concepts, results, references and other information in a systematic and orderly manner (e.g. numbering and cross-referencing systems should be maintained consistently throughout).
- Label all figures, tables and calculations.
- Number all pages in the notebook.
- Never, under any circumstances, remove pages from the field notebook.

Data entry into the notebook

- Record entries legibly, accurately and in permanent ink.
- Start entries at the top of the first page, and always make successive, dated entries, working ones way to the bottom of the last page.
- Make sure that the date of each entry is recorded clearly and unambiguously.
- After completing a page, sign it before continuing to the next page.
- Never leave blank spaces. Simply draw lines through any blank spaces at the same time the entry is made.
- Entries may be brief. However, always include enough details for someone else to successfully duplicate the work that has been recorded.

Data correction in the notebook

- Do not erase errors. Just draw a single line through any erroneous entry and then add your initials. Enter the correct entry nearby.

- Cross-referencing to other data sources
- Entries may be supplemented with supporting data or information, such as loose-leaf forms, separate print-outs from computers or data loggers, electronic data files, SOPs. Whenever possible, these must be permanently affixed onto a page in the notebook, in its proper chronological location.
- Occasionally, supporting data or information might be too large or inappropriate to attach directly to the notebook (e.g. in the case of electronic data files). In such a case, they should be cross-referenced clearly in the notebook, using unambiguous numbers/codes.

Some critical items to be recorded / referenced in the notebook (not exhaustive)

- A copy of the protocol and either an index or actual copy of standard operating procedures (SOPs) to be followed.
- A listing of all of the personnel involved in the trial.
- A chain of custody of the field notebook or trial record.
- A compilation of deviations from the protocol, any SOPs, or GEP.
- Communication details of the study director, principal investigator and other relevant trial personnel (telephone, address, fax, e-mail).
- Test substance information (batch number, chain of custody, final disposition).
- Information on the design and conduct of the trial (see Annex 4).
- Results of observations, measurements, readings and sampling (see Annex 4).

Annex 4

Information to be recorded during trials and contents of the trial report

The following information should be collected and recorded during the trial and included in the field notebook. These elements should also appear in the trial report, although this may be in a summarized form. The format is based, to a large extent, on EPPO guidelines [20], where more details can be found.

Objective of the trial

- Scientific name of the pest(s) against which the crop or produce is to be protected.
- Environment of the trial (e.g. field, glasshouse, storage facility).
- Type of protection that is intended (e.g. activity against certain stages or in certain periods of the season).
- Type of trial (e.g. efficacy, selectivity or crop tolerance, effects on succeeding crops).

Organizational aspects

- Staff names and qualifications.
- References to protocols and SOPs that are being followed.
- Any deviations from protocols, SOPs or GEP.

Methodology (and results)

Experimental conditions

Basic information on the trial site

- Address and geographical coordinates of the trial or plot location(s).
- Name of the crop (and cultivar).
- Details on the trial site (e.g. slope, soil type, exposure, agronomic history).

Trial conditions

- Sowing or planting date, density and row spacing of the crop, etc. (annual crops).
- Row spacing or arrangement, rootstock, canopy height, plant age, whether in production, etc. (perennial crops).
- Arrangement within compartments or on benches; substrate (for glasshouse crops).
- Size and type of storage compartment (for storage treatments).
- Preceding crops (where relevant).
- Plant protection products applied in preceding season(s) (where relevant).
- Cultivation measures (tillage, fertilizer and irrigation regimes, etc.).
- Crop condition (growth normal or under stress, presence of other pests, etc.).

Trial design and layout

- Type of experimental design.
- Design and layout of the plots (number size and shape).
- Arrangement of gross and net plots (protection zones between plots).
- Assignment of plots to blocks and treatments.
- Type and arrangement of untreated control.

Application

Test and reference products

- Common name of active ingredient(s) (according to ISO or specified standard).
- Exact name of formulated product(s) (including formulation and concentration codes).
- Batch number.
- Recommended/proposed dose (as formulated product and as active ingredient).
- Diluent and dilution ratio (where applicable).
- Recommended application intervals (where relevant).
- Registration or authorization number (for reference product).

Mode of application

- Application method and equipment used (e.g. sprayer type, nozzle/atomiser type).
- Number of applications and date of each application.
- System for timing applications (e.g. calendar, stage of crop, threshold levels of pest, external warning system).
- Growth stage of the crop at application.
- Development stage of pest or infestation level at application.
- Application details (e.g. actual speed of sprayer, track spacing, flow rate, spray pressure, nozzle/atomiser settings, droplet spectrum).
- Actually surface area(s) sprayed per plot.
- Actual volume applied to the plot
- Actual dose (as kg or g of active ingredient per ha)

Mode of assessment, recording and measurement

Meteorological data

- Location of weather station relative to the trial plot(s) (where relevant).
- Observations at application (relative humidity, temperature, rainfall, wind speed and direction).
- Observations throughout the trial (relative humidity (if relevant), temperature, rainfall (particularly time of first rain after treatment), unusual weather incidents).

Soil and irrigation data

- Soil type.
- Soil conditions (pH, organic matter content, soil humidity).
- Seed bed quality (where relevant).
- Fertilizer regime.
- Irrigation regime.
- Type of (artificial) substrate (e.g. in glasshouses).

Biological efficacy assessments

- Variables assessed.
- Type of assessment (description of sampling/measurement/observation method(s) used).
- Scale of assessment.
- Frequency and date(s) of assessment, including crop growth stage(s).
- Standards or protocols followed (where relevant).

Yield and quality

- Variables assessed.
- Observation/harvesting method used.
- Standards or protocols followed (where relevant).

Crop tolerance

- Symptoms of phytotoxic effects, whenever present.
- Methods used (e.g. scale of assessment).

Effects on non-target organisms

- Observations of mortality or effects on pollinators or natural enemies of pests.
- Observations of effects on adjacent crops.
- Methods used.

Statistical analysis

The methods of statistical analysis should be described. The statistical comparisons made or contrasts analysed should be clearly indicated. Any transformations, if used, should be reported as well as the reasons for using them.

Results

All results obtained from the above observations and measurement should be presented in a clear and systematic manner, with particular attention given to data relevant for the label claims. Tables should be used whenever possible. Unusual results should be reported and explained.

Raw data (i.e. the results of assessments done in individual plots or samples within plots) do not have to be reported, but should be available on request (preferably in electronic format).

Discussion and conclusions

The discussion should treat at least three issues:

- The validity of the trial should be evaluated, with particular attention to the results in the untreated control and the reference plots. Trials having reduced validity (e.g. if pest levels were low) may sometimes still provide useful supporting information.
- If the trials can be considered valid, the efficacy of the test product(s) needs to be appraised in relation to the reference product, to the untreated control (where relevant) and to other parameters of the trial (e.g. dose, application time and frequency). Any data specifically supporting label claims should be discussed.
- Side-effects should be assessed, if any.