Introduction

Pests, diseases and weeds of major food crops are currently controlled in the European Union (EU) mainly with the use of plant protection products (ppps), which offer, in many cases, the only satisfactory method of limiting yield losses. Efficacy in its first simple approach is the ability of a pesticide to fulfill the claims on the proposed label. It is expressed in terms of a) the extent of decrease of a pest population occurring on the crop and b) the protection of the yield, quantity and quality against damage caused directly or indirectly by the pest organism concerned. However, several additional elements were listed for the first time by the Food and Agriculture Organization (FAO) in 1985 and later on, by the European and Mediterranean Plant Protection Organization (EPPO), for consideration of the experimentation and evaluation of efficacy data. Efficacy, as defined by EPPO, is an equation in which the positive effects of treatment in performing the desired plant protection activity (effectiveness) and any other useful effects, are balanced against the negative effects (such as direct damage to the crop/phytotoxicity, or toxicity to beneficial organisms).

Efficacy evaluation, carried out by regulatory authorities, intends to limit unnecessary pesticide exposure of users/bystanders and impact on the environment that might occur due to ineffective pesticides or unnecessarily high rates and application frequencies. The term “efficacy evaluation” is synonymous with the term “biological evaluation.” Efficacy evaluation at the EU level is mainly based on the data produced and submitted by the notifier and presented in the form of a ‘Bio-

Efficacy evaluation of plant protection products at EU level: Data requirements and evaluation principles

Anna E. KALAMARAKIS* and Emilia MARKELLOU

Benaki Phytopathological Institute, Department of Pesticides Control & Phytopharmacy, Laboratory of Efficacy Evaluation of Plant Protection Products, 8 St. Delta Street, GR-145 61 Kifissia, Athens, Greece

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Plant Protection Products (ppps) have been evaluated and authorised in the European Union (EU), in accordance with a harmonised regulatory system (Dir. 91/414/EEC), since 1993. Efficacy evaluation is an integral part of the EU regulatory system of registration of ppps (Dir. 91/414/EEC) and is the main subject of this review paper. The efficacy data requirements and evaluation principles are analyzed and discussed along with an outline presentation of the evaluation systems of the EU. The trials needed for the efficacy evaluation of plant protection products (ppps) across EU have to be conducted according to the principles of Good Experimental Practice by officially recognized testing facilities and in line with the methods specified by the Standards of the European and Mediterranean Plant Protection Organization. For registration purposes, the efficacy parameters which should be considered in the experimentation and evaluation of a ppp, according to EU criteria, are effectiveness (direct efficacy), resistance risk and the absence of undesirable effects on: a) plants or plant products (phytotoxicity, yield, quality), b) succeeding and adjacent crops, c) plants or plant products used for propagation, and d) beneficial arthropods. Efficacy and other desirable effects from the use of ppps have to be weighed against their potential phytotoxicity and/or other undesirable effects during the evaluation process. The evaluation of efficacy data of ppps, provided by the notifiers in the Biological Assessment Dossier, and the decision taken on authorization are performed across Member States on the basis of the “Uniform Principles” of the EU. Experience gained in implementing the provisions of Dir. 91/414/EEC has demonstrated that a number of changes are required. The main changes to this system, which are in progress, and also other systems on efficacy evaluation of ppps outside EU are discussed. © Pesticide Science Society of Japan

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logical Assessment Dossier. The requirements for the generation of efficacy data, the methods of conducting field trials and reporting the experimental results and the criteria for the evaluation of such data, are harmonized through the EU Member States (MSs). The Directives and Guidance Documents that have been issued by the European Commission (EC) along with the general and specific Standards of EPPO, aim to harmonize and facilitate the tasks of both pesticide manufacturers responsible for the generation and reporting of data, and national authorities responsible for the evaluation of data and the authorization of ppp.s.

The aim of this review is to present and analyze the harmonized standards provided by the EU regulatory system concerning the requirements of efficacy experimentation, the criteria for the evaluation of efficacy data for decision making during ppp registration across EU MSs and in addition to provide an outline of the existing EU regulatory system of registration of ppp.s (Dir. 91/414/EEC) and of the amendments which are in progress based on the experience gained after 15 years of implementation of this Directive.

**Authorization of Pesticides in EU: Background Information**

Plant protection products (ppp.s) have to be evaluated and authorized in the EU Member States (MS), in accordance with the Directive 91/414/EEC, since 1993. This Directive forms the framework for a European harmonized regulatory system for the evaluation and authorization of ppp.s, and the active substances they contain. A two-stage registration process has been established through this Directive, with consideration of the assessment and acceptability of active substances at community level and the authorization of specific products (containing these active substances) and uses by the individual MS. The key feature of the Directive is the development of a positive list of authorized active substances (Annex I of the Directive) that are acceptable for their impact on human and animal health and on the environment. Active substances are added to Annex I of the Directive, either as existing active substances (under the European Commission Review Program) or as new ones. Each MS is responsible for the national authorization of ppp.s containing active substances, which are included in Annex I. The European Commission Review Program for evaluating all the existing active substances (which were sold in the EU market before July 1993) involves several steps and stages, and stretches over a period of 15 years. This was formerly co-ordinated by the European Commission and now by the European Food Safety Authority (EFSA), with the assistance of the ECCO-Team (European Community Co-ordination) since 1996 and by the EPCO-Team (EFSA Peer Review Coordination) since 2003. The EPCO-Team provides technical and administrative support to the program for the evaluation of active substances on behalf of EFSA and is responsible for the peer review program in particular. A total of 1001 existing active substances were identified as being on the market in July 1993. At the present time, 462 existing (old) active substances, that are not being supported for commercial as well as for safety reasons, have been withdrawn from the market, and 74 from a total of 125 new ones (on the EU market after July 1993) have been included in Annex I.

Many of these old active substances are contained in products that are widely used on major and minor crops, mainly in South Europe, and this loss has a serious impact on the agriculture of these countries. In order to mitigate the above problems and to give the MS a time period for the development of alternative solutions for certain crop/pest combinations, a provision for derogations for certain “essential uses” has been introduced in Article 15 of the European Commission Regulation 451/2000. Specifically, according to this provision, it is possible to extend the maintenance of an active substance on the market for certain uses for which it has been demonstrated by MS, that there are no alternatives, and at the same time a detailed plan for the development of alternatives has been provided. This derogation is given for a limited time period (i.e. 25 July 2007), to allow alternatives to be developed and is valid only for those MSs that have applied for it.

As mentioned above, active substances are assessed for the acceptability of their risks at community level, while the efficiency of products is evaluated at MS level during the authorization of ppp.s and their placement on the market, according to common EU criteria. Also for a limited number of remaining “old” active substances, the national laws of the MSs are still valid, with non-harmonized efficacy requirements and evaluation criteria for the ppp.s authorization.

**Requirements in Experimentation**

1. **Conducting efficacy trials**

The data provided in the Efficacy Section of the file of a ppp intended to be registered at European Union (EU) level, have to be sufficient for the reliable evaluation of its biological activity. More specifically, they must allow the evaluation of the nature and the extent of the expected benefits from the use of the ppp and define the conditions of use for the achievement of the expected benefits, which will be clearly described on the product label.

For the acceptance of experimental data across EU, tests have to be conducted according to: a) the principles of Good Experimental Practice (GEP) and b) the general and specific (for each crop/pest combination) Standards/Guidelines of the European and Mediterranean Plant Protection Organization (EPPO), which describe the methodology of conducting efficacy trials. Tests and analyses, required under the provisions of the Efficacy Section, should be carried out by officially recognized or certified GEP Units which have: a) sufficient scientific and technical staff with the necessary education, training, technical knowledge and experience for their assigned responsibilities, b) suitable equipment, properly maintained and calibrated, for the correct performance of the tests and measurements, c) appropriate experimental fields and, where nec-
essary, glasshouses, growth chambers or storage rooms and d) standard operating procedures (SOPs) and protocols.

All the above elements guarantee the quality of the services provided by the GEP Units and facilitate the mutual acceptance of efficacy results by EU countries during the evaluation process.

2. Data requirements
The detailed requirements of experimentation for the generation of data necessary for the efficacy evaluation of ppp, according to the Directive 93/71/EEC, are as follows:

2.1. Preliminary tests
Preliminary laboratory, glasshouse and field studies, provide useful information on the spectrum of biological activity of a ppp, justify the dose range of a ppp for further testing in the field and provide evidence of safety for potential succeeding crops (early screening tests).

2.2. Testing effectiveness
The aim of experimentation on direct efficacy (effectiveness) is to provide sufficient data to permit an evaluation of the level, duration and consistency of control or protection or other intended effects of a ppp in comparison to suitable reference products (where they exist). Normally, the trials consist of three components: the test product, reference product and an untreated control. An authorized ppp which has proven effective in practice under specific agricultural, plant health and environmental (including climatic) conditions in the area of proposed use, is defined as the 'reference product.' In general, the formulation type, the effects on harmful organisms, the spectrum of activity and method of application of the reference ppp should be close to those of the tested ppp.

Plant protection products have to be tested in areas where the target harmful organism on an untreated crop, is usually present at a level causing or known to cause adverse effects on yield or on quality or the level of infection/infestation of the host by the harmful organism is satisfactorily high, so that valid evaluation of the outcome is feasible. Data on the activity of ppp against harmful organisms, must clearly indicate the level of control of the species of harmful organism(s) concerned or of species representative of groups for which claims are made. In efficacy trials, the different growth stages of the life cycle of the harmful species and/or the different strains or races likely to show different degrees of susceptibility, must be considered. Dose rates lower than the recommended one must be included in some trials to enable a valid assessment of whether the recommended dose is the minimum necessary to achieve the desired effect (dose response). The duration of the effects of a treatment must be investigated in relation to the level of control of the target organism or the protection of treated plants or plant products. When more than one application is recommended, a number of trials should be carried out and reported in order of a) the duration of the effects of each application (in days), b) the number of applications necessary, and c) the desired intervals between sprays, to be established.

From the trials it must be evidenced that the applied dose, the application method and the time of application provide adequate control/protection, or have the intended effect in a range of conditions likely to be encountered in practical use. If there are clear indications that the performance of a ppp will be significantly affected by environmental factors, such as temperature or rainfall, an investigation of the effects of such factors on the ppp’s performance has to be carried out and reported (i.e., studies on rainfastness).

The number of trials to be conducted and reported is not standardized and is primarily determined by a) the importance of the crop and pest (major or minor), and the possibility of extrapolation between crops and pests, b) prior knowledge of the active substance or product, c) the range of conditions that arise during its use, (i.e., variability in plant health conditions, climatic differences, range of agricultural practices, uniformity of the crops, mode of application, type of harmful organism, and the type of ppp). A major pest is one which would normally be expected to occur each year at levels that cause significant economic damage in the absence of treatment to a large proportion of the crop area. A minor pest is one that does not occur routinely, its incidence would normally be localized and significant damage on high proportion of the crop would not normally be expected. As a general guide, a total of 10 trials against a major pest on a major crop are fully supportive of direct efficacy. A reduced number of trials is accepted where a) there is a large amount of supportive evidence from the use of the product or of similar products with the same a.s. on closely related pests or against the same pests on different crops, b) the target pest is of minor importance, and c) there is a slight variation in environmental conditions in the use of the product (e.g., stores). For the assessment of seasonal variability, sufficient data have to be generated and submitted by the applicant to confirm the performance of a ppp in each agronomically and climatically different region for each particular combination of crop/harmful organism. In general, trials on effectiveness and/or phytotoxicity should be carried out over at least two growing seasons.

Data on effectiveness could be obtained not only from the MS by which there is a request for registration, but also from other MSs of EU with similar climatic, agronomic or phytosanitary conditions (in the same zone). In this case, the comparability of the abovementioned conditions should be proven and fully justified by the applicant. The EU, on the basis of climatic and other conditions, is divided into two geographical zones: Southern (MSs: Cyprus, South France, Greece, Italy, Malta, Portugal, Slovenia, and Spain) and Northern (MSs: Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Latvia, Lithuania, Luxemburg, The Netherlands, Poland, Slovakia, Sweden, and the United Kingdom). Experiments carried out in any MS of a zone should theoretically be accepted by all other MSs in this zone (mutual recognition), when conducted according to the requirements of the Directive 93/71/EC.
Trials should be designed to investigate specified issues, minimize the effects of random variation between different parts of each site and enable statistical analysis to be applied to the obtained results. The design of the trials, the analysis and the reporting of trial results must be carried out in accordance with the general EPPO guidelines 152 and 181.12,13 The final report should also include a detailed and critical assessment of the data. All trials must be carried out in accordance with specific EPPO (where available) or national guidelines (e.g., CEB methods in France). The latter should, at least, comply with the requirements of the corresponding EPPO guidelines.

2.3. Information on the development of resistance

Resistance is the naturally occurring, inheritable adjustment in the ability of individuals in a population to survive a pesticide treatment that would normally give effective control.14 Although resistance is often demonstrated in the laboratory, this does not necessarily mean that pest control in the field is reduced. Thus, ‘practical resistance’ is the term used for the loss of field control due to a shift in the sensitivity of the target pest. Any loss of efficacy of a ppp due to resistance development can be costly to the grower and the environment, and may also remove a useful tool from a range of commercially available ones for the control of plant pests. Hence, this type of trial is necessary for the assessment and management of the potential risk of development of resistance.

Appropriate laboratory and/or field tests have to be conducted aiming to examine the probability of resistance development or cross-resistance to the active substance that a formulation contains, in various populations of the harmful organism. In cases where there is evidence or information to suggest that, in commercial use, the development of resistance is likely to occur (due to the mode of action of the active substance, high risk-target organism), data must be generated and submitted on the sensitivity of the population of the harmful organism concerned with the ppp under study (baseline sensitivity). In such cases, a ‘management strategy’ designed to minimize the likelihood of resistance or cross-resistance development in the target species, has to be provided by the applicant.

2.4. Effects on the quality of treated plants or plant products

Specific tests have to be carried out which will generate sufficient data to permit the evaluation of the possible effects of treatments with ppps on several characteristics of the quality of plants or plant products (i.e., taint, odour and/or other quality aspects). In general, such tests are required under circumstances where the nature of a ppp or its use (i.e., applications close to harvest) is such that a risk of taint or odour or possible adverse influence on other quality characteristics of the plant products is to be expected. Testing should be initially conducted on the main crop(s) on which a ppp is to be used and under the proposed conditions of use.

2.5. Effects on transformation processes

Many crops are processed after harvest and the final product may be totally different in nature from the raw crop (i.e., milling of cereals, freezing, canning or juicing of fruits or vegetables, etc.). Plant protection products applied to crops may remain as residues in the harvested crop or the processed product(s), thus affecting their quality. The effects of a ppp on transformation processes are addressed when treated plants or plant products are normally intended for use in transformation processes (i.e., wine making, brewing or bread making) and significant residue levels occur in the harvested product. On this basis, specific studies on possible adverse effects are required if there are indications that the use of a ppp could have an influence on transformation processes (e.g., fungicide use in wine grapes close to harvest and possible impact on the fermentation of must) and/or on the quality of their products (e.g., taint tests in wine).

2.6. Effects on the yield of treated plants or plant products

This type of test provides sufficient data to allow the evaluation of the possible occurrence of yield reduction or loss during the storage, of treated plants or plant products. Where adverse phytotoxic effects are seen, an assessment should be performed for a possible impact on yield. This kind of information will normally be obtained from phytotoxicity trials or often from effectiveness trials where the pest has failed to develop. It is more reliable for yield data for crop safety purposes to be obtained from trials which remain more or less weed/pest/disease free in order to avoid yield responses resulting from control measures masking any negative yield effects resulting from phytotoxicity.

2.7. Phytotoxicity

The aim of these trials is the generation of sufficient data to permit the evaluation of the capacity of a compound to cause temporary or long-lasting damage to plants. In particular, when testing herbicides or other ppps, if adverse effects are observed during the efficacy trials, even if they are transitory, the margins of selectivity on the target crops must be established by testing the double recommended rate of application. When serious phytotoxic effects are seen, an intermediate application rate must also be tested. The selectivity of a ppp for the main cultivars of the crop(s) on which it is to be recommended must be demonstrated. In addition, factors that may influence the susceptibility of the host to damage or injury such as crop growth stage, vigor etc., must be considered. Selectivity trials may also be routinely performed for fungicides and insecticides intended for direct treatment of soil or seeds, since it is generally difficult to distinguish between effects due to phytotoxicity and those caused by soil- or seed-borne pests. For the extrapolation of trial results from a ‘major’ to a ‘minor’ crop, the extent of the investigation needed depends on the quantity and quality of available data on the major crop(s) and their similarity to the minor crop(s) and also the method of use of the ppp in these crops. In cases where the
proposed label includes recommendations for the use of a ppp with other ppp(s), the possible phytotoxic effects of the mixture should be examined. Observations on phytotoxicity must always be performed during efficacy trials (obligatory). Any phytotoxic effect must be accurately assessed and recorded in accordance with EPPO guideline 135.15)

2.8. Impact on succeeding crops

Sufficient data are required to permit an evaluation of possible adverse effects of a ppp treatment on succeeding crops (new crops following the treated crop). In cases where data generated in other sections of the registration dossier such as those of residues and the fate and behavior of a ppp in soil (persistence and availability of the active substance in soil, degradation time/DT_{50} value), indicate that significant residues of the a.s., its metabolites or degradation products (with biological activity), remain in soil (organic matter) or in plant materials (straw) at high concentrations up to sowing or planting time of possible succeeding crops, observations must be submitted on the effects of this ppp on a wide range of succeeding crops.10) Trials are also needed in cases of phytotoxic effects (e.g., seed germination, growth of plants through soil) in preliminary greenhouse screening tests.

2.9. Impact on other plants, including adjacent crops

Sufficient data have to be generated to permit the evaluation of possible adverse effects of a ppp treatment on other plants, including adjacent (neighbouring) crops. When there are indications that a ppp could affect neighbouring plants via vapors or spray drift (e.g., applications of herbicides, plant growth regulators or defoliants), data must be submitted to cover its possible phytotoxicity on a range of adjacent crops.

2.10. Impact on treated plants or plant products to be used for propagation

Sufficient data are required on the possible adverse effects of a ppp treatment on plants or plant products to be used for propagation. Specifically, the biological parameters examined in different types of propagation materials are the following: a) seed viability, germination and vigor; b) cutting rooting and growth rates; c) runner establishment and growth rate; and d) tuber sprouting and normal growth.

2.11. Effects on beneficial and other non-target organisms

The aim of these experiments is the collection of data, necessary to assess the impact of the use of a ppp on beneficial arthropods (i.e., parasitoids, predators) and other non-harmful organisms (i.e., pollinators), present in the crop at the time of the application of the ppp. Any negative effects on the incidence of non-harmful organisms, observed during the efficacy trials, must be reported. When the compatibility of a ppp with Integrated Pest Management is claimed, specific trials are needed to illustrate that there will be no unacceptable effects on relevant beneficial arthropods caused by the proposed use of the specific ppp.

3. Reporting of efficacy data

All efficacy data generated in the previous sections have to be presented by the applicant to the competent authority, uniformly through the EU, in the form of a Biological Assessment Dossier under the provisions of the Guidance Document 7600/VI/95 Rev. 6 of the European Commission.17) Apart from data obtained from actual trials, other supporting evidence such as published papers and/or related reports, and well-documented argumentation for the extrapolation of evidence from other relevant information, should be included in this dossier. In cases where specific data are not included in the dossier, a scientific justification for not supplying them should be provided.

Evaluation of Efficacy Data and Decision Making for Authorization

1. General criteria for the evaluation of efficacy data

At the beginning of the evaluation procedure, it should be ensured that the efficacy data submitted are acceptable in terms of quantity, quality, consistency and reliability thus sufficient to permit a proper evaluation of the biological dossier. During this procedure, all relevant technical or scientific information on the performance of a ppp or its potential adverse effects should be taken into consideration by the evaluators. The evaluation of the efficacy of a ppp should be ensured and documented that there is an overall benefit from the use of this ppp on a crop. The aim of this procedure is to determine a) the efficacy frame for each use for which authorization is sought, b) the recommended label uses, and c) the possible restrictions in use. The submitted experimental data is evaluated in a uniform way among all EU Member States according to harmonized approaches and criteria established in the “Uniform Principles” of Council Directive 97/57/EEC.18) It should be stressed that although the major criteria for evaluating efficacy are well defined in the existing EU Directives and Documents, expert judgement is an essential element in the final decision.

2. Specific criteria for the evaluation of efficacy data

2.1. Effectiveness

The evaluation of direct efficacy (effectiveness) should be focused on the intended uses and the conditions of use (agricultural, plant health or environmental conditions in the areas of use, etc.) and in particular on the purpose of use, dose, method, and the frequency and timing of applications. Whenever possible, evaluation should take into account the principles of integrated control. Where the proposed use concerns the control of or protection against an organism, evaluators assess the possibility of this organism to be harmful under the agricultural, plant health and environmental (including climatic) conditions in the area of proposed use. The degree of control or the extent of the desired effect is evaluated in relation to the relevant experimental conditions that may have positively or negatively influenced the trial results [i.e., the...
suitability of the crop (cultivar, growth stage), agricultural and environmental conditions, the suitability (strain, life cycle) and density of the harmful organism, the amount of the plant protection product used, the amount of adjuvant added (if recommended on the label), the frequency and timing of applications, and the type of application equipment(s)]. Expert judgement is needed to elucidate if any of the abovementioned factors or others related to the ppp (i.e., mode of action, formulation type and development of resistance), have influenced effectiveness. By studying and understanding these factors, the expert may be able to set conditions and limitations of use that will improve direct efficacy and prevent negative effects.

The use of a ppp in the field should be ‘acceptable,’ meaning that from the use of the product, a satisfactory effect in relation to its aim is shown.\textsuperscript{19} Two major criteria have to be fulfilled during the evaluation process of a ppp: a) “acceptable efficacy” which means that the product shows results that are significantly superior to those recorded in the untreated control or that the use of the product is better than no use, and b) “comparable performance” to that of suitable reference product(s). This is intended to prevent the use of products that have lower efficacy than commercially available conventional products. In addition, for some particularly harmful pests, accepted minimum levels of control exist and the evaluator should then ensure that they have been achieved.

2.2. Resistance risk

For the assessment of risk of practical resistance of the target pest(s), different factors that contribute to this risk \textit{i.e.}, those related to the compound, those inherent in the pest and those which might result from the practical use pattern have to be considered. Specifically, factors which favor the development of resistance are associated with a) the ppp: single-site mode of action, persistence of action, monogenic resistance, ease of metabolism, b) the characteristics of the target pest: short life cycle/many generations, high fecundity, high inherent genetic variability, existence of a mechanism in the pest to metabolize a range of active substances, existence of cross resistance, high fitness of resistant strains \textit{etc.}, and c) the conditions of use of the ppp that affect selection pressure and increase the risk for resistance development. Other factors that might influence the agronomic risk are the crop (characteristics), the geographic area(s) in which the product is applied and the use pattern(s).

In the evaluation process of this section, useful information and guidance are obtained from the relevant EPPO guideline\textsuperscript{14} and the information/recommendations from three European Resistance Action Committees (RACs). These are intercompany organizations affiliated to the Global Crop Protection Federation (GCPF) aiming to prevent and manage resistance development and prolong the effectiveness of ppps. Depending on the subject of interest, they are devided into three organizations, FRAC, IRAC and HRAC, responsible for resistance issues in fungicides, insecticides and herbicides, respectively.\textsuperscript{20–22} During the registration procedure and before the product is released for full commercial use, the evaluator takes into account the perceived resistance risk and the use pattern(s) of similar products already on the market, with known resistance status. When a risk for resistance development is recognized, appropriate risk management strategies are proposed to minimize the likelihood of resistance or cross resistance development.

2.3. Absence of unacceptable effects on plants or plant products and on beneficial arthropods

In this part of the evaluation procedure, efficacy data presented in the biological dossier along with all relevant information on the active substance should be taken into consideration. The evaluation is focused on: a) the nature, frequency, level and duration of observed phytotoxic effects, and b) the effects of the ppp on yield, transformation processes and quality of products, propagation material, succeeding and adjacent crops, and beneficial arthropods.

When compatibility of a ppp with Integrated Pest Management is claimed, no unacceptable effects on natural enemies (beneficial in-crop arthropods) should be found, unless it is possible to impose appropriate limitations of use. The biological compatibility of the product in a mixture is evaluated when the product label includes recommendations for use of this ppp with other ppps, and/or with adjuvant(s) as a tank mix. In addition, the ‘appropriateness’ of the mix and its conditions of use are considered.

3. Decision for registration

The main criteria for granting authorization for a ppp are based on the “Uniform Principles” of the EU.\textsuperscript{18} The criteria related to the efficacy section could be summarized as follows:

\textit{The need for use is well documented in relation to the target pest and is applicable for the conditions under which its use is proposed.}

When the proposed uses include recommendations for the control of or protection against organisms, which are not considered to be harmful on the basis of experience acquired and scientific evidence, no authorization is granted. Conclusions on the performance of the ppp must be valid for all regions of the MS in which it is to be authorized and must hold for all conditions under which its use is proposed, except where the proposed label specifies that the preparation is intended for use under specified conditions (\textit{e.g.}, low level of infestation, particular soil types or growing conditions).

\textit{The efficacy is similar to or better than the reference product(s).}

The level, consistency and duration of control or protection or other intended effects of the ppp under evaluation must be similar to those resulting from the use of suitable reference product(s).

\textit{The proposed dose is the minimum effective one.}

The authorized amounts of a ppp, in terms of dose/rates
and number of applications, should be the minimum necessary to achieve the desired effect. However, the suggested doses combined with the number of applications, should not cause undesirable effects such as the development of resistance.

The absence of side effects from the use of a ppp, or well-defined restrictions of use.

There must be no phytotoxic effects on treated plants or plant products. There are cases where the proposed label indicates appropriate limitations of use (e.g., cultivars, developmental growth stage of the host, etc.). There must be no unacceptable adverse effects on the quality of treated plants or products, except in the case of adverse effects on processing purposes (e.g., restriction of use in wine-grapes). There must be no unacceptable adverse effects on propagation material, except where the proposed label claims specify that the preparation should not be applied to plants or plant products to be used for propagation or reproduction. There must be no unacceptable impact on succeeding crops or alternatively label claims should specify the particular crops that are affected and the appropriate intervals between the use of a ppp and the planting of these crops (this mainly holds for herbicides). There must be no unacceptable impact on adjacent crops. When there are particularly sensitive adjacent crops, they should always be mentioned on the label of the ppp. In addition, the use of ppp should not have any long-term adverse effects on the abundance and diversity of non-target in-crop species.

The benefits of use counterbalance the side or adverse effects.

Authorization is granted only when the advantages of the use of a ppp [i.e., compatibility with organic agriculture, IPM programs and resistance management programs] under the proposed conditions of use, outweigh the possible adverse effects of its use. Any restrictions on the use of the product related to non-compliance with some of the aforementioned requirements must be mentioned on the label.

Discussion

In the majority of the European Union (EU) Member States (MS), evaluation of efficacy is a prerequisite for a plant protection product (PPP) to be authorized and placed on the market. Applicants for registration submit their own efficacy data to a uniform evaluation process whose framework is constituted by the Council Directive 91/414/EEC and its amendments. The requirements for experimentation and the evaluation principles of the data submitted by the applicants have been presented and analysed in the present review article, based on the provisions of Dir 91/414/EEC and its amendments, and on the Uniform Principles. Until the enforcement of the Directive, individual MSs have had their own national systems for the evaluation of efficacy data, which remain valid. In Greece for example, the requirements of the existing National Law (L.721/1977) for the authorization of ppp containing only non-reviewed old active substances are more simplified than the respective EU requirements. In this “old” Law, the evaluation of efficacy is mainly focused on the direct efficacy of the ppp, crop safety and resistance management. For the acceptance of experimental data, trials have to be conducted after the issue of official experimental permission by the competent authority and submission by the inspector, at the end of the trial, of an official certificate of supervision. National registration systems will be valid until all “old” active substances are reviewed by the European Commission’s Review Program (estimated deadline: end of 2008).

The EU regulatory system on the efficacy evaluation of ppp has similarities to and differences from the respective regulations of the United States (US) and Canada where registration of ppp in general, has common elements with the EU.

Specifically, the US Environmental Protection Agency (EPA), which is the competent authority for the regulation of ppp in the US, requires applicants to assure product efficacy through testing. However, the US EPA does not review efficacy data as part of its routine registration process unless a product targets pests that pose a potential risk to human health and safety. Specific performance standards are used to validate efficacy data in public health areas, including disinfectants used to control microorganisms infectious to humans in any area of the inanimate environment and those pesticides used to control vertebrates (such as rodents, birds, bats and skunks) that may directly or indirectly transmit diseases to humans. Consequently, the need for a product and its efficacy is not a criterion for registration of a pesticide in the US and the marketplace will ensure product performance. The California/EPA Department of Pesticide Regulation (DPR) proposed the elimination of the current requirement for evaluating data on the effectiveness of agricultural pesticides. Specifically, the DPR plans to amend its regulations to only require the submission and evaluation of efficacy data for pesticide products containing new active ingredients, or for label claims that are unique. DPR also retains the authority to require an applicant to submit efficacy data for any label claim on a case-by-case basis, either during evaluation (pre-registration) or after registration. The DPR’s proposed regulatory changes aimed to bring California closer in line with federal data requirements for pesticide products.

In Canada, before a pesticide is considered for registration, it must undergo extensive testing to determine the potential risks posed to human health and the environment, and the pesticide’s value. The term value includes assessment of the efficacy of a product by determining whether it does what it claims to do and at what rate it should be applied. The value of a pest control product lies in its contribution to managing pest problems. This contribution can lead to economic, health, and environmental benefits. According to Canada’s Pest Management Regulatory Agency (PMRA), which is the federal agency responsible for the regulation of pest control products
in Canada, PMRA value assessment helps to ensure that only those products that make a positive contribution to pest management are registered.\(^3\) Value assessment helps to minimize the risks associated with pest control products by eliminating unnecessarily high use rates (establishment of the minimum effective rate) and by ensuring that even products of acceptable risk are approved for use only if their contribution to pest management is significant (sustainability assessment). At present, the PMRA is discussing the above differences in procedure with the US EPA agency in the context of ongoing efforts to harmonize their regulatory processes.

In the EU, the experience gained in implementing Directive 91/414/EEC has demonstrated that a number of changes are needed to reflect current requirements and to clarify certain areas in order for better harmonisation of the operation for the regulatory system for ppps, and to result in overall benefits to regulatory authorities, industry and stakeholders.\(^4\) Although Directive 91/414/EEC was enforced in 1993, only recently have applicants in the EU begun to generate data for the biological dossier of a ppp on a Europe-wide basis (one dossier in a zone with information on a wide range of crops/pest combinations, harmonised patterns of use/GAPs, etc.). The larger the geographical area in which the ppp is to be used, the bigger the chances of work-sharing and equal distribution of workload. The aims and objectives of this new concept are the mutual recognition of evaluations/authorizations between Member States of the EU and, at a later stage, zonal evaluation/authorization, which will follow the inclusion of the active substance in Annex I and authorized by another MS, without the submission of further experimental data. The applicant must demonstrate that there is comparability in terms of climate, soil, and cultural methods, and that the MS that has already authorized the product has implemented the provisions of the decision for the inclusion of the active substance in Annex I. Although mutual recognition is a potentially powerful tool, it is currently under-used for reasons related mainly to differences in additional data requirements and evaluation methodologies between MSs and also difficulties in coordination between industry and regulatory authorities.\(^5\)

Zonal evaluation is a future trend in the authorization of ppps at MS level, which is planned to be accomplished through a step by step procedure. The aim of zonal evaluation is a) the mutual acceptance of the work done by an other MS of the same zone, and b) work-sharing in the evaluation of ppps. Until recently, the main focus of the EU has been on the effort needed to take decisions on the inclusion or non-inclusion of an active substance on the positive list of active substances (Annex I of the Directive). During the enforcement of the Directive, the EU realised that consideration also needs to be given to the amount of work now falling to the MSs after Annex I inclusion.\(^6\) In addition, only a limited number of uses are being considered as a basis for the inclusion of an active substance in Annex I, and this means that the consideration of safety (e.g., risk mitigation measures and other restrictions) and efficacy of the uses being supported for the placement of any ppp on the market, is being put back to the MSs at national registration, with substantial workloads envisaged and the possibility of duplication of effort. The Commission initiative is to look at the possibility of increasing the coordination and rationalization of the evaluation/authorization process for ppps, following an Annex I inclusion decision and in this new system, operational details of work-sharing and mutual recognition are planned to be included. MSs will continue to play a central role as rapporteurs not only for evaluating active substances in the EU but also for evaluating ppps at the zonal level. This direction of increased co-operation in work-sharing and confidence in mutual recognition are the key points for an effective regulatory system.

Zonal evaluation of efficacy data of certain ppps is currently assigned, by EU officials, to different Rapporteur Member States (Pilot Project on work sharing). The first registration reports have already been issued by Rapporteurs and are subjected to evaluation by efficacy experts of all the MSs of a zone. In addition, the EU has set several committees/working groups that discuss the principles of collaboration, enforce trust and confidence between MSs and suggest ways of minimizing the workloads involved in this complex process of ppp authorization by EU MSs.

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