European and Mediterranean Plant Protection Organization
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Efficacy evaluation of plant protection products

Resistance risk analysis

Specific scope

This standard describes how the risk of resistance to plant protection products can be assessed and, if appropriate, systems for risk management can be proposed, in the context of official registration of plant protection products.

Specific approval and amendment

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1. Introduction

Resistance is the naturally occurring, inheritable adjustment in the ability of individuals in a population to survive a plant protection product treatment that would normally give effective control. Although resistance can often be demonstrated in the laboratory, this does not necessarily mean that pest control in the field is reduced. 'Practical resistance' is the term used for loss of field control due to a shift in sensitivity (OEPP/EPPO, 1988).

Loss of performance of a plant protection product because of the development of practical resistance in the target organism and the subsequent need for additional product use to achieve control can be costly to the grower, the crop protection company and the environment. Furthermore, the loss of efficacy due to resistance may remove the plant protection product from the range of methods available to combat the large potential losses caused by plant pests. Registration authorities and crop protection companies now recognize that the development of resistance can be minimized (i.e. delayed or kept at a low level) by means of suitable management strategies, and that it is in both their interests to protect the efficacy of plant protection products. The registration procedure, before the product is released for full commercial use, is seen to be the point at which appropriate risk management strategies should be agreed and implemented. For example, the harmonized registration procedure of the countries of the European Union (EU, 1991) requires that applicants provide information on the possible occurrence and development of resistance (including information on related active substances, other pests or other crops that could indicate the likelihood of resistance developing). If there is evidence to suggest that difficulties of control could result from the development of resistance, a management strategy should be proposed that would minimize the likelihood of resistance. These requirements do not provide any specific guidance on the scale and scope of evidence that must be submitted, nor is any guidance given on the evaluation of this data or of the proposed management strategy.

The aim of this standard is therefore to indicate to the registration authorities and to applicants for registration what their obligations are with regard to assessing and managing the risk of practical resistance in the target organism(s). These elements are included in the process of resistance risk analysis (i.e. evaluation of the risk followed, if necessary, by the choice of management options). The standard provides guidance on:

- the concepts of resistance;
- how resistance risk might be assessed;
- how resistance might be managed;
- what data must be supplied to support the conclusion of a resistance risk analysis;
- other data needed on resistance in the registration dossier;
- reaching a registration decision with regard to resistance risk.

The standard covers all types of plant protection products. It does not cover the registration of genetically modified plants that express pesticidal activity, but it does consider their possible influence on the development of resistance in plant pests. Appendix II indicates different approaches for the main types of plant protection products.

2. Concepts of resistance

Effective prevention and management of resistance can best be achieved by an understanding of the factors relating to its origin, development and spread. Fundamental to this understanding is an appreciation of the factors that contribute to the risk of practical resistance developing in any particular situation. The risk of practical resistance is a result of a combination of inherent factors and factors related to the conditions of use of the product. The risk deriving from conditions of use (agronomic risk) can be altered by the user of the product, whereas the inherent risk is due to the

interaction between certain characteristics of the target pest and the plant protection product and cannot be changed by the pattern of use.

When the plant protection product is applied without any limitations on its conditions of use (unrestricted use), the resulting risk of practical resistance can be called the unmodified risk. Unrestricted use is the use for which the applicant could request registration if resistance was not considered to be of relevance, and is the use which would achieve optimum effect or pest control as indicated by efficacy evaluation trials. If the unmodified risk is considered low and acceptable, then no restrictions on product use would be required.

In many circumstances, however, the unmodified risk is recognized to be too high to be acceptable as it could lead to development of resistance, sometimes rapidly. In such cases, experience has shown that the application of a resistance management strategy can lower the risk to an acceptable level. The management strategy attempts to reduce the selection pressure that leads to resistance and will normally include limitations imposed on how and when the plant protection product should be used. These limitations are termed modifiers and the risk of practical resistance in this case can be termed the modified risk.

From the above, it follows that, when it is required to assess the risk of practical resistance in a particular situation, the first stage is to establish the unmodified risk and, if this is too high, to progress to a consideration of how, and which, modifiers could be introduced to lower the risk to an acceptable level. The relationship between the terminology described here can be represented as follows:

• risk of practical resistance = inherent risk combined with agronomic risk;

• unmodified risk = risk of practical resistance with unrestricted use;

• modified risk = risk of practical resistance with modified use (i.e. with a resistance management strategy composed of modifiers).

It is therefore clear that the issue of relevance to decision-making for registration is not an evaluation of the inherent risk alone, but a consideration of the risk of practical resistance when the plant protection product concerned is used as proposed by the applicant – a combination of the inherent risk and the agronomic risk – and whether (or how) the agronomic risk should be modified.

3. Resistance risk analysis

Resistance risk analysis is a two-stage process, composed of resistance risk assessment, in which the probability of development of resistance and its likely impact are evaluated, and resistance risk management where, if necessary, possible strategies for avoiding or delaying the appearance of resistance are considered and suitable modifiers are chosen and implemented. In resistance risk assessment, the inherent risk is first assessed using the characteristics of the pest and the product; the unmodified risk is then evaluated from the inherent risk when the product is applied under unrestricted conditions of use. In resistance risk management, the decision is made whether the unmodified risk is acceptable; if it is, the process can stop. If the unmodified risk is not acceptable, possible modifiers are then analysed to determine whether they can be used to mitigate the risk. If suitable modifiers exist, the conclusion of the resistance risk analysis will be a resistance management strategy (comprising one or more modifiers) that can be applied when the product is used commercially.

A resistance risk analysis procedure is needed for the following reasons:

• for the manufacturer of plant protection products to assess the potential risk of the development of resistance if the product is used commercially

under conditions of unrestricted use;

• for the manufacturer of plant protection products to decide which management options should be applied (i.e. in the proposed use pattern)

if the assessed risk of resistance is considered to be unacceptable;

• for the registration authorities to evaluate any risk assessment submitted by the applicant concerning the development of resistance;

• for registration authorities to evaluate the proposed use pattern (including any management strategy suggested by the applicant).

The overall management of resistance is a continuous process, starting with the initial assessment of resistance risk, which must be made during product development, and continuing with the selection of appropriate measures before the start of sales, and with the implementation of the measures throughout the commercial use of the active substance. This overall process is summarized in Fig. 1 and Appendix I, which show the steps of resistance risk analysis, the continuation to registration, and monitoring of the resistance management strategy during use. Van Gemerden *et al*. (1999) have published an example of a more detailed and prescriptive decision-making scheme.

4. Resistance risk assessment

4.1 *Risk factors*

In order to assess the risk of practical resistance in the target pest(s), it is necessary to evaluate the different factors contributing to the risk, i.e. those inherent in the compound and its effect on the pest and those that might result from a particular use pattern.

Inherent risk

The inherent risk depends on various factors, some of which are associated with the product and others with the pest. These factors do not necessarily operate in isolation and do not apply in all cases. The factors

associated with the plant protection product that may favour the development of resistance can include:

• persistent activity;

• single-site mode of action;

• monogenic resistance;

• ease of metabolism.

Those associated with the characteristics of the target pest that may favour the development of resistance can include:

• short life cycle/many generations;

• high fecundity/widespread distribution of progeny;

• high inherent genetic variability (including potential for spontaneous mutation);

• existence of a mechanism in the pest to metabolize a range of active substances;

• existence of cross resistance;

• high fitness of resistant strains.

Past experience may also provide a guide to resistance risk; higher risk could be indicated in situations where a target pest has already developed resistance to other active substances or where resistance to the active substance has already developed in other target pests.

Agronomic risk

The risk of resistance inherent in the plant protection product and the pest can be increased by certain conditions of use. This agronomic risk affects selection pressure on the development of resistance and is influenced by the particular characteristics of the crop, the geographic area in which the product is applied and the use pattern. The factors influencing the agronomic risk may include:

• widely grown crop with short rotations;

• monocropping or continuous cropping;

• application techniques;

• other cultural practices (e.g. fertilizers, cultivation);

• need for high numbers of applications or long exposure to obtain control, because of the features of the crop environment;

• use of transgenic plants with genes expressing pesticidal activity;

• use of cultivars susceptible to the pest(s);

• geographic isolation of populations preventing the re-entry of sensitive forms;

• environmental conditions favouring more frequent generations or higher population densities of the pest;

• exclusive reliance on a single active substance;

• lack of diversity of available control measures.

4.2 *Components of risk assessment*

It is beyond the scope of this Standard to give detailed guidance on individual pest species/chemical group combinations because of the very wide range of pests (weeds, insects, fungi, etc.) and chemical groups involved. Some important factors that may influence a resistance risk assessment are summarized below.

4.2.1 *Type of compound*

For the re-registration of a known compound, the risk of resistance can be assessed from experience with that compound in the field, which can demonstrate whether practical resistance has occurred, or the success (or failure) of management strategies already being applied. If it is a new compound belonging to an established group, then the resistance risk can be assumed to correspond to that of other compounds in the same group, unless demonstrated to be different. In the case of a completely new type of compound (new chemical group), a risk of resistance development should be assumed, unless demonstrated otherwise by consideration of other risk factors; this is particularly true for insecticides and fungicides. For herbicides, see Appendix II.

4.2.2 *Mode of action/mechanism of resistance*

A knowledge of the mode of action of a compound and, if known, the mechanism of resistance can be informative. For example, a mode of action involving a single biochemical site may indicate a potential higher risk, whereas 'multisite' action may indicate a lower risk. Similarly, any mode of action which involves an existing mechanism to which resistance has already occurred would, in the absence of contrary evidence, be considered to indicate a high risk of resistance.

4.2.3 *Cross-resistance*

The existence of cross resistance between a new compound and other compounds of the same or other chemical classes can have profound consequences on the commercial use of a plant protection product. It means, in effect, that resistance occurs already in the target organism even before the product is used. Bioassay tests are needed to detect the existence of cross resistance by attempting to control, with the new compound, the various populations of the pest that are known to have resistance to other compounds. It may be useful to explore the possibility of negative cross resistance, in which resistance to one compound results in sensitivity to another, as its existence will influence the types of management strategies that might be used.

4.2.4 *Characterization of strains*

An understanding of whether and how resistant strains might develop in populations of the target pest is not essential for risk assessment but may give useful indications of practical resistance. Data can be obtained from different types of laboratory and glasshouse tests. It should be noted that any experiments involving the use of resistant strains that are not already present in the area should not be conducted in the field because of the danger of escape of those strains.

Test methods for sensitivity

Development of a test method to determine the sensitivity of the target pest(s) to the active substance is highly desirable because it provides the means of measuring the original level of sensitivity before the pest is subjected to the active substance (data generally needed for registration), of identifying resistant strains in laboratory studies, and of monitoring any shifts in response following widespread use. The method should be able to give realistic, quantitative, reproducible and readily understandable results. In general, standardization of test methods is important because it enables direct comparisons to be made between results from different studies. However, there may also be occasions when a particular situation requires the use of a test that differs in some respects from the standardized method and, for this reason, it is important that all such test methods be clearly described in the registration application.

Many of the test methods used to determine sensitivity are somewhat difficult to perform and caution should therefore be applied in comparing results from different testing centres. Furthermore, there are many pests for which suitable methods are not yet available.

Artificial selection of resistant strains

Depending on the type of organism (e.g. fungus, insect, weed) and the mode of action, repeated exposure of successive pest generations to sublethal concentrations of active substances may indicate the potential for selection of resistance in the field. With fungal pathogens it is also possible to study the potential for mutation by treating a target pest with mutagenic compounds or ultraviolet light. Pests surviving the exposure are isolated and tested for resistance.

However, laboratory research concerned with induction of resistance is a notoriously unreliable predictor of the probability of resistance occurring in practice. A failure to induce resistance could result from inadequacies in the techniques used and could lead to a false sense of security. Successfully induced resistance could trigger a warning that resistance is possible and may present an opportunity to study its genetic control, but does not indicate unequivocally that it will occur in the field.

Fitness

Artificial selection of resistant strains is not always a reliable indicator of practical resistance because these strains may lose a proportion of their 'fitness' so that, in practice, they would be unable to compete with fully fit, wild strains. For that reason, it can sometimes be useful to compare the fitness of sensitive wild-type strains and resistant strains in laboratory or glasshouse tests.

Dynamics of resistance build-up

Mixtures of wild (sensitive) and resistant strains can be treated with repeated applications of the active substance, and changes in the frequency of strains can be measured. Such experiments can reveal the potential risk and speed of build-up of resistance in relation to the number of applications, the level of initial resistance and the competitive abilities of wild and resistant strains.

Potential for spread

For some types of pest, the appearance of resistant strains in one geographical locality is quickly followed by their spread throughout the whole range of the species, because of the highly mobile nature of the organism. Resistant strains of other species have limited mobility (e.g. certain weed species) and remain localized at their site of origin. In assessing the risk, the mobility of the target pest(s) needs to be taken into account.

Genetics

Classical and molecular analysis of genetics can be used to identify resistance genes and to study their interactions; the results can provide further useful indications for predicting resistance risk and can suggest monitoring tools.

4.2.5 *Influence of unrestricted use on overall risk*

The conditions under which the plant protection product will be used should be considered in order to assess the degree of selection pressure that will result. This will involve an analysis of the cropping system(s) where the product will be used and should consider the use pattern that would be proposed if resistance were not considered to be a risk. In this 'unrestricted use' pattern, there may be several factors (modifiers) already acting that will help to minimize the risk of practical resistance (e.g. rotation, the availability of several other chemical groups). Other factors that could influence selection pressure are listed in section 4.1 as elements of the agronomic risk.

4.2.6 *Magnitude of resistance risk*

The risk of resistance is composed of the probability of the resistance occurring and the possible consequences if it does occur. Since both the probability and the consequences may range from high to medium to low, the overall risk from different product/pest combinations can show different characteristics (e.g. high probability with low consequences, high consequences with low probability, etc.). At the moment, there is no accepted method to quantify the overall risk, apart from the simple categorization into low, medium or high.

Probability

An estimate of the probability of the occurrence of practical resistance can sometimes be gained from a consideration of existing cases of resistance. If resistance to the chemical group to which the new plant protection product belongs or resistance to other plant protection products has been observed in the target species, the relevance of these cases to the situation being assessed should be considered. For example:

• where a product group has been used for many years with only isolated cases of resistance, this may indicate a rather low probability of resistance development, but where resistance is widespread, the probability is higher;

• if resistance has been observed only in species other than the target pest(s), the probability is lower than if resistance has been observed in the target pest(s);

• the cropping system in which resistance has been identified may favour the development of resistance and may be entirely different from the proposed use in which the probability of resistance development is low.

Consequence

The consequence of resistance will be a reduction in the level of effectiveness of the product, which may ultimately limit the usefulness of the product or of its chemical group. The importance of this will depend on the target pest(s) and crop(s), and on the relevance of the product among the available control measures. In addition, the potential consequences are strongly influenced by the level of resistance in the target pest(s) (i.e. the frequency of resistant strains) and, in particular, by the speed at which the resistance develops.

5. Resistance risk management

5.1 *General principles*

Resistance risk management refers to the process whereby, first, the decision is taken whether the risk of resistance is acceptable and then, if necessary, conditions of commercial use that have the specific purpose of minimizing or delaying the appearance of resistance in the field are selected and applied. These specific conditions of use are termed 'modifiers'. If it is accepted that the risk of resistance developing to a plant protection product is proportional to the exposure of the pest to the product, then any modifier which reduces that exposure will reduce the risk of resistance developing.

To have any chance of success, resistance management should be the collective responsibility of manufacturers, regulatory authorities, advisers and growers. Strategies should be reached by agreement, should as far as possible be implemented uniformly for all members of the same type of active substance and should be understandable and acceptable to the growers.

Information on the resistance management strategy can be given to growers/advisers in a number of ways: recommendations and restrictions on use may be included on product labels; advisory literature or use campaigns may also be used.

5.2 *Acceptability of the resistance risk*

Having determined the magnitude of the risk of resistance (see section 4.2.6), it is then necessary to decide whether this risk is 'acceptable' or 'unacceptable' – in other words, to decide whether the use pattern should be modified to avoid or slow the appearance of resistance. An acceptable risk is one where the magnitude of the unmodified risk of resistance is considered to be so low, when using the proposed use pattern, that there is no need to apply a resistance avoidance strategy. On the other hand, if it is considered that the unmodified use of the product will probably lead to undesirable consequences due to the development of resistance, this will be considered to be unacceptable and the product will generally be subject to resistance avoidance measures.

Whether a resistance risk is considered to be unacceptable can have important consequences for all sellers and users of a plant protection product, since this decision determines whether modifiers need to be applied. If the decision about acceptability of risk is wrong, it will lead either to the imposition of unnecessary modifiers or the development of resistance in the target population(s) sooner than could have been hoped.

The acceptability of the risk does not only depend on the magnitude of the risk (the combination of the probability of resistance occurring and the consequences if it does) but should also take account of the benefits to be obtained from the use of the plant protection product. For example, a higher level of resistance risk may be accepted if:

• there is a limited availability of suitable alternative means of control of the target pest(s). (There may be few practical or sufficiently effective products. In any crop, this could make pest control difficult and may mean that there is an insufficient range of alternatives available to manage resistance risks. It is of particular importance for minor crops where, often, fewer plant protection products are registered.)

or

• the plant protection product has advantages over other available products. (The product may have certain particular advantages over other available products, such as lower impact on the environment, lower toxicity to beneficial organisms or ability to overcome resistance problems associated with other target pests in the crop.)

5.3 *Specific strategies*

There is a range of modifiers that can be used in a resistance management strategy. The integrated use of combinations of different modifiers is likely to be most beneficial. The characteristics of the particular pest/product combination that affect resistance development and have been identified in the assessment of resistance risk should be taken into account when deciding on the exact strategy. In addition, the strategy should take account of the overall pest management in the crop concerned.

5.3.1 *Use of good plant protection practice*

By using the general principles of good plant protection practice (OEPP/EPPO, 1993) and the

specific recommendations for individual crops (OEPP/EPPO, 2001), the amount of plant protection product used can be reduced to what is really necessary. Included in good plant protection practice are such measures as the use of resistant crop cultivars, non-chemical control methods and efficient application methods. Agronomic systems such as crop rotations, husbandry systems or tillage systems can also have a large influence on the development of a particular pest, and hence on resistance. Modification of agronomic systems may be used in a resistance strategy but major changes are often difficult for economic reasons.

5.3.2 Measures related to the application of the product

Frequency Limiting the numbers of applications of a plant protection product against a pest in a season will reduce the selection pressure, and so reduce the risk of practical resistance. This strategy relies on the fact that resistant biotypes that are selected by use of the plant protection product can be less fit than the original biotypes and will tend to disappear from the population when the selection pressure is removed. To be most effective, limiting the number of applications (in cases where multiple applications are otherwise thought to be necessary) should be used in combination with other modifiers, such as a programme of alternation or mixture of products (see 5.3.3 and 5.3.4).

Timing Applications should be made at times of the year, crop growth stage or pest stage critical to optimum pest control. Pest warning systems can be used to predict the development of pest populations and hence optimum application timing. In some situations, it may be appropriate to impose a closed season, during which application of the product is prohibited, in order to limit use to the most vulnerable stage of the crop only.

Dose rate Increasing the dose rate has limited value as a modifier (and should not, of course, be considered after the product has been put on the market). When dose rate can be lowered without reducing efficacy (e.g. through optimal timing), it may be of value in trying to avoid target site resistance. But, if lowering the dose rate results in larger surviving pest populations, this may allow the necessary recombination opportunities for polygenic resistances. Increasing the dose rate may appear to be a first practical and effective reaction to emerging metabolic resistance but the effect is likely to be short-lived and may trigger selection for target site resistance.

5.3.3 Mixtures

The active substance can be applied as a mixture with one or more active substances with similar or complementary properties but with different modes of action. The mixing partner may be able to eliminate the resistant forms as they develop. Compounds for which resistance to the target pest is unknown are often selected as partners. The use of mixtures, especially those that act synergistically, may allow doses to be reduced compared with those used alone, but the components should each make a significant contribution to the control of the target pest(s), in both efficacy and, if relevant, pest spectrum.

Mixtures may be used in the form of tank mixes or as formulated products. The strategy of mixtures may sometimes be enforced by the fact that the active substance with a resistance risk is not available to growers other than in a formulated mixture.

5.3.4 Alternations

Alternations are only effective if the alternating partner or partners are known to control the target pest(s) and to be from different cross resistance groups. They work by reducing the exposure and thus reducing the selection pressure. At the same time, they allow any resistant biotypes that may develop to be controlled by the alternating partner. The alternating partner may or may not be a product with risk of resistance. The pattern of alternation can take many forms, with the product in question used at a frequency of 1:2, 1:3 or less. In general, the risk declines as the proportion of applications with the product declines. Where the product is used to control a pest in a crop over a number of seasons, then the application sequence over seasons should be considered to avoid excess exposure.

5.3.5 Negative cross resistance

Negative cross resistance occurs where the presence in a pest of a resistance mechanism to one active substance automatically increases its sensitivity to another. Although uncommon, the phenomenon has occasionally been of practical importance. An example is the control of *Botryotinia fuckeliana* on grapevine, where benzimidazole fungicides and diethofencarb exhibit negative cross resistance. However, in this example, certain strains of *B. fuckeliana* developed double resistance, indicating that the phenomenon of negative cross resistance may only be of value if it applies to all resistant genotypes (a fact that may not be verifiable until after wide-scale use of the product).

5.3.6 Recommendations on the product label

When the risk of development of practical resistance is assessed to be low, but it is nevertheless believed that, in certain rare circumstances, use of the product may still lead to the appearance of an undesirable level of resistance, it may be considered unnecessary to require the implementation of modifiers. In that case, the product label can carry a warning to the user that resistance could occur under certain circumstances and the label could offer general advice, such as that the product should not be used too frequently or should be used in combination with other products.

6. Registration requirements

To enable the registration authority to assess the risk of resistance, the basic information in this section should be submitted by the applicant to meet the registration requirements, and should preferably be presented in the

general order given in this section. In general, information should be provided for all the pests included in the intended use. However, for plant protection products with activity against a wide range of pests, initial studies could be focused on those pests which are considered to be at particular risk of developing resistance (see Appendix II for sources of information on high-risk pest species). The applicant should also consider the impact of the product on non-target pests which may be present in the crop at the time of application and which may be high-risk pests.

Additional information may be requested on the occurrence of resistance in other pests, other crops and related active substances; such information may derive from public domain data, such as published scientific reports.

The specific information required will depend on the individual pest/ product combination and the use pattern. If the applicant for registration does not provide all the information specified here, considering that part or parts are not relevant or practical, the reasons for this opinion should be reported.

6.1 *Mode of action*

The mode of action of the active substance, if known, should be given. If not known, the modes of action that can be excluded should be listed.

6.2 *Mechanism of resistance*

The mechanism(s) of resistance in the target pest(s), if any, should be given, and their relevance to the plant protection product under discussion should be noted. In addition, information on other mechanisms of resistance in other related pests to this group of compounds should be given, with arguments provided to illustrate their relevance to the current application.

6.3 *Evidence of resistance*

The dossier should include relevant evidence of practical resistance, or the absence of such resistance. For established types of substances that have previously been used in practice and whose resistance status is known, the evidence may comprise or include data (published or otherwise, databases, etc.) of past history of the type of active substance and of the pest(s), and could include evidence that efficacy has not changed during commercial use. For new types of active substances, any indications of the occurrence of resistant strains should be provided, with an evaluation of their relevance to practical resistance.

6.4 *Cross-resistance*

Any knowledge of cross resistance to compounds of a known chemical type should be declared. Where no cross resistance is present, applicants should make a positive statement to this effect and name the tests completed. Evidence of cross resistance may indicate the same risk concern as the cross-resistant compound and should be addressed by the applicant.

6.5 *Sensitivity data*

Pests vary in their sensitivity both between and within populations, and this natural variation should be understood before shifts in sensitivity can be assessed. Although not necessary for the performance of resistance risk analysis, field samples of major target pests which have been identified as having a medium or high risk of practical resistance should be tested before the product is used commercially, in order to provide an understanding of the initial variation in sensitivity and to establish the mean sensitivity. This data on sensitivity is critical for use in future monitoring and provides the means to detect any shifts in sensitivity during product use. See Appendix III for more detailed guidance on the presentation and use of sensitivity data.

6.6 *Use pattern*

A use pattern should be suggested for optimum effect or pest control that would be used in the absence of resistance. This could be considered to be the unrestricted use pattern before any management strategy has been applied.

6.7 *Resistance risk assessment of unrestricted use pattern*

Details of the resistance risk assessment performed on the unrestricted use pattern should be provided, with the major steps indicated and the decision points explained.

6.8 *Test methods*

A brief summary of the main studies used to assess the resistance risk and a complete description of the test methods used should be provided.

6.9 *Acceptability of the resistance risk*

The applicant should comment on the resistance risk that has been evaluated (in 6.7) and argue whether this level of risk should be considered to be acceptable or not.

6.10 *Management strategy*

Where there is information to suggest that, in commercial use, there is a risk of the development of resistance and that this risk is considered unacceptable, a management strategy (which may include monitoring; see section 6.12) designed to minimize the likelihood of resistance developing in the target organism should be provided. In proposing the strategy, the applicant should provide a justification based on all the factors considered in its production so

that an understanding of the reasoning and expected results are clear to those with an appreciation of resistance management but who are not experts in the subject.

In situations where established resistance management strategies are already being used, it will be sufficient to refer to these and provide effi- cacy data from published or unpublished sources to illustrate their success in reducing resistance risks to an acceptable level so that product effectiveness is maintained. If other products with the same mode of action or selecting for the same type of resistance are used against the same target pest(s) in the same crop(s), the applicant should provide a justification of any proposed deviation from the established resistance management strategies.

If the applicant becomes aware that substances which could select for the same resistance mechanism are being developed by other potential applicants, it is advisable for them to develop compatible resistance management strategies. The Resistance Action Committees (RACs) of CropLife International (formerly Global Crop Protection Federation) could have a coordinating role in this respect.

6.11 *Implementation of the management strategy*

Resistance management guidelines have little or no impact unless they are effectively communicated to the user, and a plan should be proposed on how this will be achieved. This may include label statements, leaflets or training courses. It is not necessary to give full details of the resistance management strategy on the product label because resistance management options may be related to the individual farm situation, but the applicant should demonstrate how he intends to provide information on resistance management to the user.

If resistance management guidelines are proposed, the applicant should indicate how they will be communicated and promoted. Any relevant guidelines (developed by the RACs or other appropriate bodies) should be promoted.

6.12 *Monitoring, reporting and reaction to changes in performance*

Sensitivity monitoring, i.e. the continuing observation of field performance and/or evaluation of the sensitivity of target organisms, is imperative to the management of resistance. Monitoring before the commercial introduction of an active substance establishes the 'baseline' sensitivity of the target organism. Thereafter, monitoring can be undertaken to check that management strategies are working and/or to investigate complaints from growers of an apparent loss of field performance.

As part of a management strategy for products whose unmodified risk of resistance has been evaluated as being unacceptable, a programme should be designed before release of the product onto the market to monitor the continuing efficacy of the plant protection product on the target pest(s). This programme normally comprises observations of field performance, with reporting to the registration authority of significant changes in efficacy and, depending on the resistance risk and the availability of appropriate test methods, may also include testing of sensitivity by bioassay. The monitoring should be a continuous process, conducted in representative commercial crops with different cultural conditions and in areas of intensive use of the product. A sufficient number of populations should be sampled in order to be able to determine the distribution of practical resistance.

The results of the monitoring should indicate whether the management strategies are effective, or whether resistance is developing and management strategies may need to be introduced or modified. The monitoring programme should also note any possible development of resistance in non-target pests. In particular, attention should be paid to non-target pests with a known high risk of resistance.

Regulatory authorities should be informed at an early stage about all cases of field failure known to be due to resistance.

7. Registration decision

7.1 *Elements needed for a decision*

In order to reach a decision on whether the plant protection product proposed should be registered, the registration authority should satisfy itself that the information on resistance supplied by the applicant is adequate to ensure that appropriate measures can be taken, when the product is released for commercial use, to limit or delay the appearance of resistance. For this purpose, the authority should establish that:

- an assessment of risk of resistance has been performed;
- the method of assessment is appropriate, i.e. that this EPPO Standard or an acceptable equivalent has been followed;
- the data needed for the risk assessment was correctly obtained and adequate;
- the conclusion of the resistance risk assessment is realistic.

If the conclusion of the resistance risk assessment is that the risk of practical resistance is unacceptable with unrestricted use, the authority should establish that:

- sensitivity data is provided (or assurance that a sensitive biotype will be available) so that development of resistance can be assessed in the future;
- a resistance risk management analysis has been performed;
- the method of resistance risk management is appropriate, i.e. that this EPPO Standard or an acceptable equivalent has been followed;
- the management strategy proposed is practical, likely to be effective and will be properly communicated.

Finally, an evaluation should be made to determine whether the proposed or modified use pattern is consistent with that of other commercially available products that could select for the same resistance mechanism. If not consistent, the registration authority, perhaps in consultation with the applicant and/or other registration holders, should consider how best to resolve this issue.

7.2 *In case of disagreement*

Because resistance risk analysis differs from other more established areas of risk analysis in that there are no accepted trigger values or acceptable quality criteria, there may be disagreement between the applicant and the registration authority regarding the conclusions of the analysis. There are three possible areas of disagreement: level of risk, acceptability of risk and suitability of strategy. If such situations arise and it is not possible for applicant and regulator to reach agreement, the following inputs may be useful before a final regulatory decision is reached:

- mutually acceptable expert opinions, such as independent experts or Resistance Action Committees;
- opinions of other regulatory authorities;
- decisions already taken in other countries.

Appendix I

Summary of process of resistance risk analysis and registration (see also Fig. 1)

Stage 1: Resistance Risk Assessment

The risk assessed by resistance risk assessment is the unmodified risk and results from the inherent risk when the product is applied under unrestricted use conditions.

Assessment of the inherent risk

(1) Does the active substance belong to:

- 'new chemical group'? Depending on the type of product, the risk may be considered to be potentially high, unless experimental evidence exists to show that the risk is low.
- 'old chemical group', new compound? The risk can be assumed to be similar to that of other compounds in the same chemical group.
- 'old chemical group', old compound? Evidence for risk should be considered from previous practical use of the compound.

(2) Answer the following questions about the characteristics of the pest:

Does the pest have:

- short life cycle/many generations?
- high fecundity/widespread distribution of progeny?
- high inherent genetic variability?
- isolation of populations preventing the entry of sensitive forms?
- existence of a mechanism in the pest to metabolize a range of active substances?
- existence of cross resistance?
- high fitness of resistant strains?

Has the pest already developed resistance to other active substances?

(3) Answer the following questions about the characteristics of the plant protection product:

Does the product have:

- persistent activity?
- single-site mode of action?
- monogenic resistance?
- ease of metabolism?

(4) To obtain an assessment of inherent risk, consider the answers to steps 1–3. In general, the greater the number of positive answers to these questions, the higher the inherent risk of resistance.

Unrestricted use

(5) Define a pattern of use that will provide optimum yield improvement resulting from control of the pest. The chosen pattern of use will aim to minimize undesirable effects (e.g. phytotoxicity, sideeffects on the environment, etc.) but, at this stage, will not consider the avoidance of resistance. This is the unrestricted use.

Unmodified risk

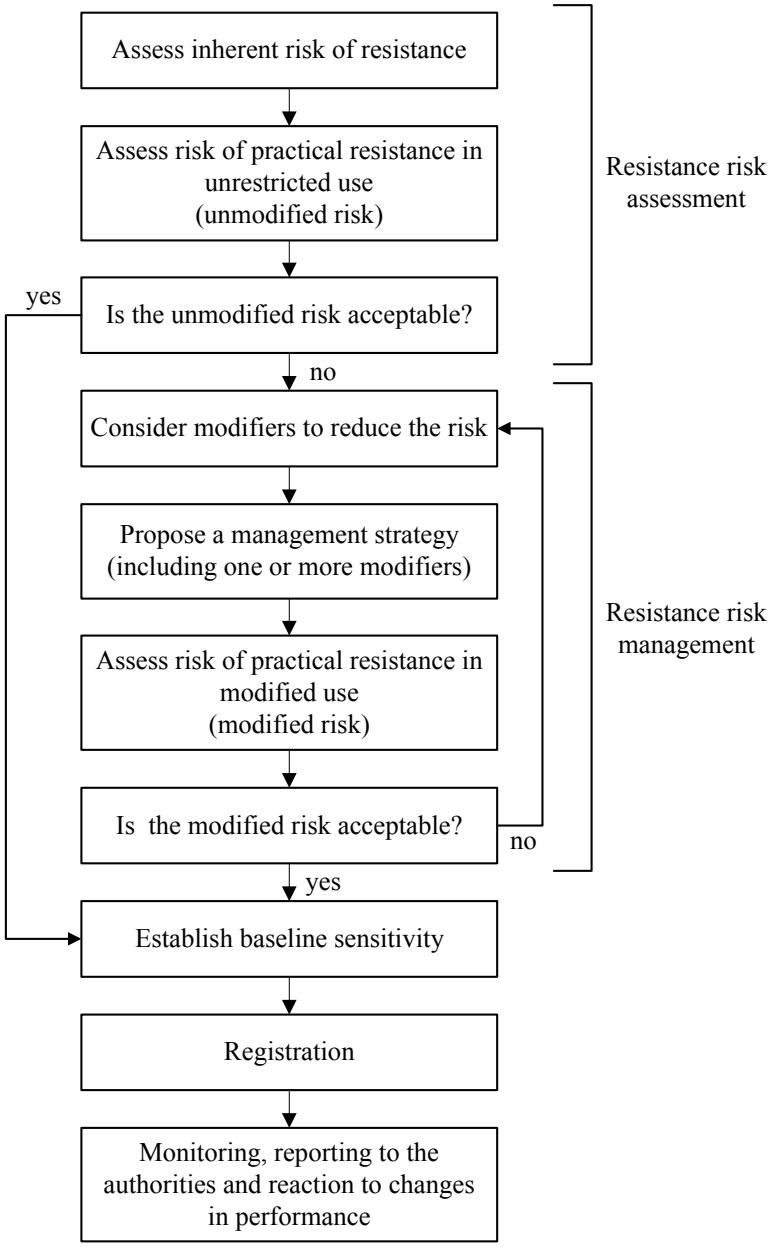
(6) Does the unrestricted use influence the risk of practical resistance? Does it cause an increase or decrease?

Factors to be considered include:

- widely grown crop with short rotations;
- monocropping or continuous cropping;
- application techniques;
- other cultural practices (e.g. fertilizers);
- need for high numbers of applications or long exposure to obtain control, because of the features of the crop environment;
- use of transgenic plants with genes expressing pesticidal activity;
- geographic isolation of populations preventing the re-entry of sensitive forms;
- climatic conditions favouring more frequent generations or higher population densities of the pest.

(7) The conclusion of the resistance risk assessment is an assessment of the level of unmodified risk.

Fig. 1. Diagram of the process of resistance risk analysis and registration



Stage 2: Resistance risk management

(1) Is the unmodified risk acceptable?

The acceptability of the risk will depend on a balance between the benefits to be obtained from the use of the plant protection product and the disadvantages if resistance develops or, in other words, whether the use without restriction would justify the risk of resistance. For example, the use of a 'risky' product might threaten the sustainability of other products or the development of resistance to a product may not be serious if sufficient suitable alternatives already exist.

If the unmodified risk is considered to be acceptable, the unrestricted use pattern could be proposed for registration.

(2) Is the unmodified risk unacceptable?

If the unmodified risk is not acceptable, specific strategies should be considered for applying modifiers in order to change the unrestricted use. Select the most appropriate that can be used alone or in combination to reduce the resistance risk to an acceptable level. Such modifiers may include:

- use of good plant protection practice;
- mixtures;
- alternations;
- application frequency, timing and dose rate;
- negative cross resistance;
- monitoring, reporting to the authorities and reaction to changes in performance.

The modified use pattern can be proposed for registration.

Stage 3: Sensitivity data

Sensitivity data is obtained and provided for registration.

Stage 4: Preparation of dossier

The elements in the dossier relating to resistance risk should be presented in the order of Section 6 of this standard.

Stage 5: Evaluation by Registration Authority

The registration authority re-evaluates the proposed use pattern using similar steps of resistance risk analysis; it considers the data presented, the methods used and the evaluation made by the applicant. The registration authority also takes account of the use pattern of other similar products already on the market. It decides whether the resistance risk resulting from the proposed use pattern is acceptable.

Stage 6: Monitoring

Continued efficacy of the plant protection product is monitored. Any changes are reported to the registration authority and appropriate action is taken.

Appendix II

Specific details on different types of plant protection products

1. *Fungicides*

1.1 *Inherent risk factors*

Fungi

Much can be learnt from the history of development of resistance in fungi. The pathogens shown as examples in Table 1 are believed to pose a high risk factor, inasmuch that they have shown themselves to have the capacity to become resistant to particular fungicides in a short time. The targeting of any new compounds to control any one or more of these fungi should thus automatically trigger concerns and stimulate more stringent examination of the data provided on the compound and its recommendations for use.

These fungi possess a combination or all of the following factors:

- short life cycle with many life cycles during the growing season;
- prolific spore production;
- means of achieving widespread dispersal of spores or other propagules in space and time;
- high genetic variability;
- extensively grown host crop with short crop rotations, monocropping and continuous cropping;
- ability to infect at all crop growth stages.

This does not mean, however, that fungi not included in Table 1 have no risk of developing resistance. It means only that, so far, resistance has not developed rapidly or has not been a limiting factor in disease control. Fungicide resistance is a dynamic phenomenon and other fungi may be added to Table 1 in future versions of this Standard.

Fungicide

Risk factors relating to the fungicide are very difficult to define for a new compound but more easily accepted for an established compound. Within the established compound groups, known compounds can be clearly categorized as having: (1) a high risk of resistance development if used without any restrictions; (2) a risk of shifts to lower efficacy; (3) a very low risk of loss of efficacy; or (4) a negligible risk, because they have been used over many years with no evidence of resistance development. For new compounds, unless data is presented to prove the risk is low, a significant risk of potential resistance development should be assumed.

For the fungicide groups described above as having either a high risk of resistance development or a risk of shifts to lower efficacy, these phenomena have been demonstrated in practice in certain pathogens. Experience has shown, however, that such phenomena can be managed and their effects minimized by the adoption of appropriate resistance management strategies. Only in very few cases has resistance led to the withdrawal of any of these compounds from specific uses.

Further information on resistance to fungicides can be found, for example, on the FRAC web page (www.frac.info).

Visualizing the inherent risk

When considering the risk posed by a fungicide product being used as recommended by a registration applicant, these simple questions should be asked:

- is the pathogen of known high risk (from Table 1)?
- does the fungicide pose a significant risk?

Logically, there are four combinations of these parameters which determine the inherent risk:

(1) High-risk pathogen + high-risk fungicide;

(2) High-risk pathogen + low-risk fungicide;

(3) Low-risk pathogen + high-risk fungicide;

(4) Low-risk pathogen + low-risk fungicide.

In practice, only the categories including a known and proven low-risk fungicide equate to a situation of little chance of resistance developing. For the other cases, modifiers should be introduced to reduce the resistance risk.

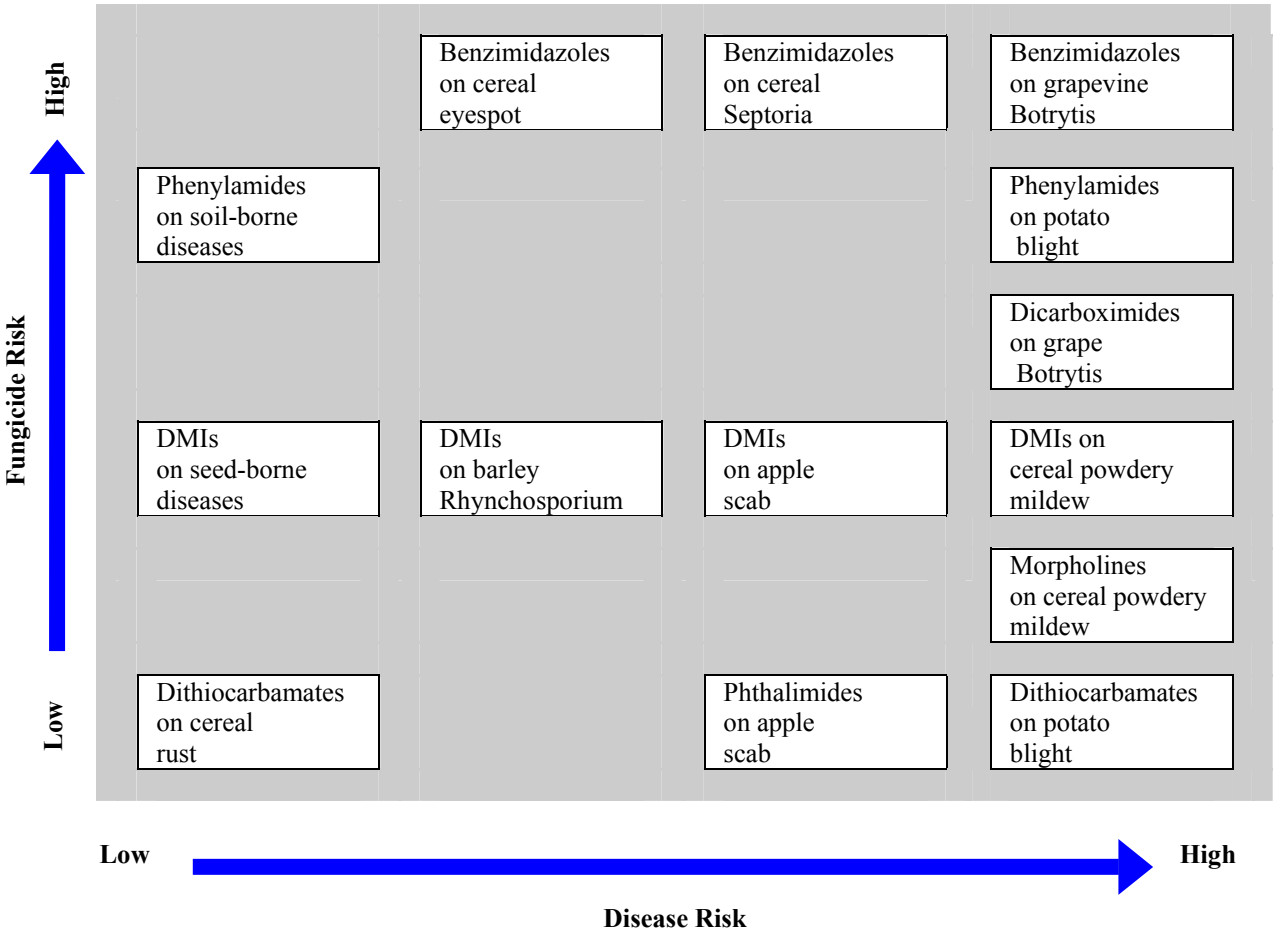
However, it is impossible, in practice, to put all situations into neat 'high-risk', 'low-risk' categories. Experience has shown that, even in situations that could generate a need for resistance management strategies, there have been differences in the rate at which resistance could develop. These differences have been influenced by the pathogen epidemiology and the properties of the fungicide. In order to appreciate these differences, it is convenient to visualize the issues as shown in Fig. 2.

The various combinations of risk factors are shown as the axes of the graph, each factor increasing in importance the further away from the origin it lies. Superimposed on the picture are some pathogen/fungicide combinations representing the risk given by unrestricted use of the fungicide on that fungus. The influence of pathogen biology and fungicide are clearly shown. The *P. infestans*/phenylamides and *B. cinerea*/dicarboximides (or MBC) combinations thus appear at the top right as very high-risk combinations. The *P. herpotrichoides*/MBC combination appears towards the upper left because the pathogen presents a relatively low risk (as signified by the time taken for resistance to appear) but is combined with a high-risk fungicide.

Table 1. Examples of plant pathogens considered to present a high risk of resistance development

Pathogen	Crop
Phytophthora infestans	Potato
Plasmopara viticola	Grapevine
Erysiphe graminis	Wheat and barley
Uncinula necator	Grapevine
Sphaerotheca spp.	Various
Mycosphaerella fijiensis	Banana
Pyricularia oryzae	Rice
Gibberella fujikuroi	Rice
Botryotinia fuckeliana	Various, especially grapevine
Venturia spp.	Apple and pear

Fig. 2. **A scheme for visualizing the inherent risk presented by the combination of a fungus and an established fungicide** (Note that the examples presented here are those existing in 1999).



By use of this visual representation, it is possible to place a proposed fungicide/fungus combination on the picture according to the unmodi- fied risk factors presented. An expert in the art of fungicide resistance and its management should reasonably be able to place a particular fungus attacking a particular crop at its correct position on the 'disease risk' axis. A judgement is then needed whether the resultant position within Fig. 2 represents an acceptable risk or not. In this situation it helps to draw on experiences with similar combinations of factors, if appropriate.

If the conclusion from the assessment of the unmodified risk is that it is acceptably low, there is no need for further assessment. If, however, the conclusion is that the risk is unacceptable, then modifiers should be introduced to reduce the risk to an acceptable level. Application of modifiers such as alternations, mixtures, programmes and timing will all move the risk vertically downwards on the 'fungicide' axis as they reduce the exposure and hence selection pressure on the pathogen. Factors including crop hygiene, resistant cultivars and cropping sequences will move the disease risk factor to the left. The ideal minimum risk position is at the lower left axis intersection. As an example, introduction of phenylamide/mancozeb mixtures for potato blight control has effectively moved the resistance risk for phenylamides vertically downwards into the lower right quartile.

1.2 *Cultural practices and forecasting*

The user is expected to make full use of any practice designed to generate better crop hygiene, which results in a lower primary inoculum pressure and the lowering of the ability of plant pathogen epidemics to develop. However, such 'agronomic' and 'cultural' practices can only be suggestions and cannot be enforced as label recommendations. Such methods include:

- sanitation, e.g. stubble burial, straw removal;
- use of host plant resistance;
- good agronomic practice, e.g. avoiding excess fertilizer, ensuring effective crop rotation;
- appropriate diagnostic techniques to guide and optimize application timings.

2. *Herbicides*

2.1 *Inherent risk factors*

Weed

Unlike insects and pathogens, weeds usually only produce one generation per year and development of resistance is usually a relatively slow process. In addition, until now, the phenomenon is not as widespread as resistance in insects and pathogens. It is therefore difficult to class any weed species as inherently more or less likely to develop resistance to a particular herbicide.

To assess the risk of a particular species developing resistance to a particular herbicide, the only information available is the past history of the development (or not) of resistance to other herbicides. Historical databases with such information exist and may be used as key references. HRAC, for example, funds the maintenance of such a database (Heap, 1997; http://www.plantprotection.org/HRAC/).

Herbicide

For an established compound or new compounds within a known chemical class (mode of action group), a historical analysis of resistance cases can show groups where there is a risk of resistance occurring. As this is a dynamic situation, current surveys should be consulted; for example, the HRAC database (Heap, 1997) maintains a classification of all herbicides by mode of action (see http://plantprotection.org/HRAC/moa 2002.htm).

In cases of new compounds, testing against biotypes of target species showing resistance to other herbicides should be carried out. For the chemical groups for which they are known to be valid, such tests can be a useful means of understanding the overall risk of the active substance and for determining the 'robustness' of the product with regard to resistance.

Where no cross resistance is evident and no cases of resistance have been recorded, it is considered reasonable that no specific resistance management strategy will be required. The applicant should, however, demonstrate that general herbicide resistance avoidance strategies are being recommended to the user and should provide a contingency plan for the steps to be taken if resistance does develop. This differs from pathogen and insect control, in which resistance can develop and spread very rapidly, and unknown compounds are considered as a high risk. However, once resistance has been confirmed (by, for example, a specific resistance test on seedlings), it will be necessary to develop a more detailed resistance management strategy.

2.2 *Cultural practices*

In many cases, the use of cultural practices can reduce weed density and therefore selection pressure. Such practices should be encouraged and should form part of any resistance management strategy wherever possible. Such practices can include cultivation (ploughing), stale seedbed techniques (using non-selective herbicides to control weeds germinating before crop sowing), mechanical weeding (manual or machinery), crop rotation and cleaning machinery. However, such 'agronomic' and 'cultural' practices can only be suggestions and cannot be enforced as label recommendations.

3. *Insecticides/acaricides*

3.1 *Inherent risk factors*

Target pest

Insect and mite pests have varying rates of reproduction, which have an impact on the possibility of developing resistance. In general, the greater the number of generations per cropping season, the greater the inherent capacity of that pest to develop resistance. To assess the capacity of a particular species to develop resistance, historical development of resistance to other products should be reviewed. The Insecticide Resistance Action Committee (IRAC) maintains a global resistance database (Tomlin, 1998) and web sites (http://plantprotection.org/IRAC/). This and other relevant databases may be referred to.

Pests exhibiting resistance as a result of a modified target site can be cross resistant to other products acting at the same site of action. However, where cross resistance develops, it is not necessarily brought about by this type of mechanism. Where a pest species is known to show modified target site resistance to other insecticides or acaricides, new compounds sharing the same mode of action will be assumed to be subject to cross resistance, unless proved otherwise. Where modified target site cross resistance is proved or suspected, use of modifiers should be proposed as part of a resistance management strategy.

Arthropod resistance is most commonly brought about by enhanced metabolism. This enhanced metabolic capacity is not normally compound- specific but can affect various product types. Resistance can also develop as a result of other non-specific mechanisms such as behavioural avoidance or reduced uptake. Like enhanced metabolism, these types of resistance can affect several modes of action and chemical types. However, it is possible for some, but not all, compounds from any one chemical class to be affected. Where target species are known to exhibit these types of non-specific resistance, evidence should be presented to establish whether or not cross resistance affects performance of the product in question. If performance is affected, modifiers should be developed as part of a resistance management strategy.

Insecticide or acaricide

For an established compound or new compounds belonging to a known chemical class, a historical analysis of resistance can highlight high-risk use patterns. As this is a dynamic situation, current surveys, such as IRAC's database (Tomlin, 1998) or web sites (http://plantprotection.org/IRAC/ or http://www.croplife.org) can provide useful information.

3.2 *Natural enemies and IPM*

Pest populations can be moderated by maintaining the beneficial capacity of introduced or naturally occurring predators and parasites. Under certain circumstances, normally as part of established integrated pest management (IPM) programmes, these beneficial organisms can be used to reduce selection pressure to insecticides and acaricides. Care should be taken to avoid dependence on too few product types in IPM programmes, as this can ultimately accelerate resistance development and result in use of non-IPM-compatible products. Selection pressure can be further reduced by use of agronomic practices, such as crop rotation, and planting times to avoid pest infestations.

Appendix III

Guidance on the presentation and use of sensitivity data

Introduction

Sensitivity data gives information about the level of resistance to a particular plant protection product in a pest population, as well as often providing a profile of the distribution of such resistance among individuals in that population. Sensitivity data allows for comparison between different populations and, in particular, between the same population at different times. It thus allows evaluation of changes in sensitivity to the plant protection product. In the context of the registration procedure, sensitivity data presented at the time of application for registration can be used to determine whether and how much resistance later develops during the commercial use of the product.

Sensitivity data may be considered as 'baseline' if it is obtained from pest population(s) that have not been exposed to the plant protection product or to related active substances of the same cross-resistance group and so have never been subjected to any relevant selection pressures, and if the pest population(s) concerned show no metabolic resistance to the product.

Sensitivity data for registration

Ideally, baseline sensitivity data should be presented in the registration dossier. However, it is not always possible to obtain baseline sensitivity data from field populations, for example due to widespread commercial use of established products containing the active substance (in the case of a re-registration of a product containing an established active substance) or containing another active substance from the same cross-resistance group (in the case of registration of a product containing a new active substance of a known chemical group). In that case, it may be possible to obtain 'historical' baseline sensitivity data (that is, data obtained from the original registration) produced from populations showing no resistance. Such data should be presented, even if gathered after the initial product launch. Baseline sensitivity data could also be derived from a reference population consisting of individuals kept in 'organism stores' (seed banks, fungal collections, or insect/mite cultures). However, in this case, the number of data points is likely to be less than desirable (see later in this text). Data for other cross-resistant compounds, if available, may also be relevant to the new compound. If neither of these possibilities exists, then data should be produced from typical field populations, even if these have been exposed to selection pressure.

If sensitivity data other than baseline sensitivity data from field populations is presented in the registration dossier, the justification should be provided.

Sources of sensitivity data

Where data on potential resistance is required for registration, it is desirable that sensitivity data should be derived from specific bioassays in glasshouse or laboratory (or from molecular biological techniques). The advantage of the specific bioassay methods is that they provide quantitative results, making it possible to measure the frequency of resistant individuals within a given sample or population and to determine how resistant these individuals are to the product in question. Since bioassay data is generated in controlled environments, this avoids the inevitable variations caused by other (uncontrollable) factors in field experiments.

However, in many cases, the generation of specific bioassay data is impractical, either because of the difficulty of handling the target pest or because specific reliable and reproducible bioassay methods are not available for the pest concerned. This is often the case, for example, with weeds. In these situations, field efficacy data, such as that gathered during the pre-registration phase of the product for demonstrating the efficacy of the product under near-practical conditions, is a suitable alternative as future reference. Field-collected data has the advantage of being a measure of the response of naturally occurring organisms under realistic conditions. It can also measure the impact on a much larger sample size than would be possible under laboratory conditions.

If bioassay sensitivity data is not presented in the registration dossier, the applicant should justify why field trial data is used, and explain how this information should be interpreted as a measure of sensitivity.

Pests for which sensitivity data is needed

In order to decide for which pests to generate sensitivity data, the risk of the development of resistance should be assessed for each target pest (using the criteria for risk assessment in this standard) and sensitivity data should be presented for those species which are considered to be other than low risk.

Since many product labels have a large number of target pests, and these vary from country to country, it may be difficult and expensive to produce sensitivity

data for all the target pests on the label. In these cases, sensitivity data should be required only for the major pests on the label. However, it should be noted that the development of resistance in a minor pest of one crop may have serious consequences in another crop for which this same pest is a major pest.

Several important pests are recognized to present a high risk of development of resistance to plant protection products. Examples of those that occur in the EPPO region are shown in Table 2. In general, sensitivity data is always expected for these pests. However, if an applicant believes that sensitivity data should not be required for a high-risk species, a reasoned case should be made to justify the absence.

Specific sensitivity testing

Specific sensitivity testing is normally done by bioassay testing under laboratory conditions. Great advances are currently being made in the development of molecular biological tools for the determination of pesticide resistance in certain target species. Such tools may determine, for example, the frequency of individual genes leading to resistance in a population. But these methods have so far been developed for only a limited number of pest species.

The method used in bioassay should be appropriate for the pest species and the type of plant protection product, especially in relation to exposure and method of application. It should be reliable and reproducible to allow a realistic estimation of the inherent population variation in response to the test substance and to ensure that any variability observed is due to variation in the pest population rather than to variation caused by the method itself. Test methods have been published for a number of pests and types of plant protection products (see, for example, methods published by the Resistance Action Committees). For a new type of plant protection product or an additional species, there may be no published methods available and new test methods are needed. As a general principle, if the method used is not already a known and widely accepted method, the applicant should explain the need for a new method and comment on its appropriateness and reliability for the present situation.

In a bioassay, the test material may be the active substance or the commercially formulated product. If the product exists only as a co-formulated mixture, only the single active substance under investigation should be used. This is because the changes in the sensitivity range of an active substance may be masked, when used in a co-formulated mixture, by the effectiveness of the partner active substance. For the testing of co-formulated product in field trials, see later in this text.

It is essential to test a dose range capable of including, as far as practicable, the full range of sensitivity in the population. In addition, it may be useful for the sensitivity data to include data from at least two seasons/ years in order to cover variability over time.

Presentation of sensitivity data

The sensitivity profile should present the distribution of sensitivity values according to an established criterion. This may be, for instance, an EC50 (or LC50) or EC90 (or LC90) value or a MIC value (minimum inhibitory concentration) for the test population(s). The profile may then be presented as a basic curve (or histogram) showing the proportions of populations having, for instance, an EC50 within a certain class, or as a cumulative frequency distribution curve.

The sensitivity data are used as a reference point against which future assessments of sensitivity are compared to establish whether or not sensitivity values have changed. This can be done by visually comparing graphic representations of the sensitivity distributions. Appropriate statistical techniques may also be used to form straight-line data plots, or curvilinear or cumulative frequency distributions, to allow comparison.

The shape of a sensitivity distribution the natural population (e.g. the presence of cross resistance or the existence of strains of different sensitivity).

It may be possible to determine a ‘discriminating dose’ from the sensitivity distribution so that individuals in a population controlled below the discriminating dose are considered as ‘sensitive’ and that any growth, development or survival of the organism at that dose should be investigated further. The use of a discriminating dose can reduce the labour involved in conducting large-scale monitoring after product launch, but the discriminating dose should be selected with care. If the dose is set too high, there is a danger of missing low levels of resistance, whereas if the dose is too low, there will be too many false positives.

Number of samples needed

For any population, the sensitivity data should represent an adequate measure of the population variability in response to the test compound and should therefore be constructed from an adequate sample size. It is not, however, possible to be prescriptive about how many data points are required for all possible situations. The more variable the response, the greater the number of points that will be required to establish a statistically reliable dose/response curve. The variability of the response can depend not only on the genetic variability within the population but on the characteristics of the test product and on the method used. In general, expert judgement will be needed to determine the level of investigation required to achieve the desired objective.

Sources of data

It is recognized that it is generally not scientifically justified to present a general sensitivity profile based on samples from only a limited area (for example, from one field) as all samples may come from one fairly homogeneous population. It is preferable to construct the sensitivity profile from test samples from a diverse

range of populations from different locations in order to gain a broader view of the genetic composition of the species, to determine variation in response due to location, and to avoid focusing on isolated or unrepresentative strains. Locations could include different geographical areas within a country or even different countries.

As a general principle, the origin of samples should reflect the major areas of intended use of the compound as well as major areas of occurrence of the target pest. However, it is also useful to have data points from regions with low intensity of product use. Such data can give information on whether there is a general shift in sensitivity due to other aspects than the product use (e.g. climate) or whether there are differences in sensitivity even before the product is used on the market (e.g. metabolic resistance).

Similarly, sensitivity data may consist solely of populations taken from a single country if the importance of that species is greater than in any other country, especially if it has exhibited differential responses to existing plant protection products in the past. Where samples come from diverse locations within one country, it should be possible for the resulting data to be relevant also for neighbouring countries. If this is claimed, the applicant should provide a reasoned argument to support the claim.

The population for testing should, in general, come from the crop on which the product will be used, since there may be differences between the strains in different crops. However, it is also possible that a sensitivity profile constructed for a particular pest on one crop may be valid for the same pest on another crop. This is of particular relevance for registration for a minor crop, when the sensitivity data may come from a major crop. Whenever the sensitivity data come from a crop other than the intended use, the applicant should provide arguments to support the relevance of the data.

The samples should be taken over a period of more than one cropping season. The sampling method should be described in the application for registration and, where possible, should comply with existing guidelines.

The use of efficacy data

As mentioned previously, specific (bioassay) sensitivity data is preferred for registration purposes. However, where there may be problems in obtaining such data, field efficacy data can be used to demonstrate the sensitivity of populations of the target pest(s). The data can be derived from efficacy evaluations produced under field conditions during product development (and as such, may have been the efficacy data submitted as part of the registration application) before resistance could reasonably be expected to have influenced performance. If efficacy data on current field populations is provided for registration, it should be obtained from an area where the product gives adequate performance (thus indicating that resistance is absent or low in the field).

Efficacy data for co-formulated products should be produced only from the commercially co-formulated product, as it is the performance of the product as marketed that will be the first indicator of lack of efficacy and therefore of a possible resistance problem. In order to determine whether resistance is the true cause of lack of field performance, the applicant can usefully provide initial glasshouse or field data to demonstrate the efficacy of the component which has a risk of resistance when used alone. Such data can then be used as a 'second line' reference point when investigating reports of field failure.

Table 2 Examples of species in the EPPO region which have developed resistance and for which sensitivity data should normally be provided.

Depending on the crop and region, other species might be more relevant than the examples given here

I Pathogens/Pathogènes	II Invertebrates/Invertébrés	III Weeds/Adventices
Botryotinia fuckeliana	*Aphis gossypii*	*Alopecurus myosuroides*
Erysiphe graminis	*Bemisia* spp.	*Amaranthus retroflexus*
Phytophthora infestans	*Cydia pomonella*	*Avena* spp.
Plasmopora viticola	*Frankliniella occidentalis*	*Chenopodium album*
Sphaerotheca spp.	*Leptinotarsa decemlineata*	*Conyza canadensis*
Uncinula necator	*Myzus persicae*	*Echinocloa crus-galli*
Venturia spp.	*Panonychus ulmi*	*Lolium* spp.
	Phorodon humuli	*Phalaris minor*
	Spodoptera exigua	*Senecio vulgaris*
	Tetranychus urticae	*Solanum nigrum*
	Trialeurodes vaporariorum	*Stellaria media*

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