

## RESISTANCE MANAGEMENT AND THE REGISTRATION OF PESTICIDE PRODUCTS IN EUROPE

Phil Russell of Aventis CropScience at Lyon in France discusses the increasing importance of resistance risk analysis within the European pesticide registration process

### Background

Resistance to pesticides (insecticides, herbicides, fungicides) by pests (insects, weeds, fungi) can have very serious consequences to the user, the producer and the environment. For the user, the build-up of resistance will lead to loss of pest control leading to loss of marketable crop and consequential loss of income. For the producer, resistance can mean severe loss of sales and a considerable loss on the investment made in developing new products. For the environment it can mean overuse of a product in an often desperate attempt to control a resistant pest or, eventually, the possible reliance on older, less environmentally friendly products.

Up until the early 1990s there was no requirement for a product to be marketed and used in accordance with an approved resistance management strategy. Resistance management and the strategies employed to maintain product efficacy were voluntary. Because of the problems that resistance could cause, the vast majority of producers marketed their products within the resistance management guidelines issued by the Resistance Action Committees (RACs) of the Global Crop Protection Federation (GCPF). Most users abided by the advice given and so reaped the benefits.

### The introduction of regulation

This position changed with the introduction and implementation of EC Directive 91/414/EEC (Anon, 1991) and subsequently Commission Directive 93/717/EEC (Anon, 1994). There was now a requirement, as part of the registration process for new active ingredients and the products containing them, and the re-registration of established products, for information on the actual or possible occurrence of resistance to be provided together with details of a management strategy to avoid resistance or to manage it if it was already present.

This was a major step forward and was generally welcomed by the agrochemical industry. It did, however, present many problems. The published directives were felt to be vague, gave no guidance to the registration applicant on what information was required to support the application and similarly gave no guidance to the regulators on what information to expect, nor on how to interpret it when provided. It was soon recognised that confusion could develop, that different applicants would adopt different standards for data supplied, and that different regulators could apply different standards to the evaluation of the submitted dossiers. Eventually the European and Mediterranean Plant Protection Organisation (EPPO) was asked by regulators from its member countries

to produce a Guideline for use by applicants and regulators in order to help them construct the dossier and interpret it respectively. A review of the process by which this Guideline was produced is given by McNamara and Smith (2000) and the Guideline is published in OEPP/EPPO (1999).

### The data requirements and risk analysis process

The Guideline sets out a suggested way of approaching the problem of assessing the risk of resistance developing and of then developing strategies to prevent, limit or manage its development such that the product has as long an active life as possible. The Guideline is not a 'statutory requirement' as such, but it is realistically expected that applicants will follow the suggested formats and that regulators will follow the advice contained within it.

Probably the most important aspect is that the onus is on the applicant to produce the analysis and to justify the conclusions and proposed resistance management strategies. The process requires the applicant to consider several factors that affect the risk of using the product on a particular crop to control a particular pest under particular conditions. If the risk factors without any resistance management are considered too high, then a management strategy has to be proposed and justified. Full details of the steps involved are contained in the Guideline but will be summarised here:

#### *Inherent risk*

This is a risk factor that is generally beyond our control and applies to both the pest to be controlled and to the at-risk active ingredient. Many pests, e.g. cereal powdery mildews, aphids, potato late blight, grey mould (*Botrytis cinerea*) are well known to be able to develop resistance quickly. Introduction of a new chemical for their control would automatically generate concern. For all types of pest management, but especially plant disease control, history has shown that we should expect a moderate to high risk of development of resistance to new treatments in the absence of management strategies. As very few actual risk data may be available at the time of registration of a new active ingredient from new chemistry, it would be wise to regard all new chemistry as showing a potential risk of resistance development. These risk factors need to be considered and explained in the registration dossier, drawing on historical experience where applicable.

### *Agronomic risk*

The risk produced by the combination of the pest and product risks analysed as the 'inherent risk' leads to a consideration of the *agronomic* risk when no resistance management strategies are employed. This needs to be considered and a decision made as to whether or not the risk is acceptable or whether measures need to be introduced to reduce the risk. As an example, consider a potential new fungicide to control *Phytophthora infestans*. We know that there is no cross resistance between our new active and established fungicides. We have no information on the mode of action of the active, nor on the possible mode of resistance. We know that *Phytophthora infestans* is a high risk pathogen and that, potentially, we could base a control programme around applying our new active for every spray of the season, maybe upto or over 14 applications. Is it reasonable to expect that such a proposal would not lead to development of resistance? The logical answer is 'No'. So our assessment of the agronomic risk is that it is too high to be accepted for unrestricted or unmodified use of our new active and we come to the conclusion that we must alter the pattern of use of our product in order to reduce the risk to an acceptable level. This leads to the development of a resistance management strategy by the introduction of 'modifiers'.

### *Modifiers*

Modifiers can be considered to be any means by which the unacceptable risk posed by unrestricted use of our product is reduced to an acceptable level. They include:

- Reducing the number of applications of our product
- Selling the product as a coformulated mixture with a non-cross-resistant partner, or recommending application in tank mix with a non-cross-resistant partner
- Recommending specific application programmes including non-cross-resistant partners. These take several forms:
  - recommending alternations with our new product
  - recommending restrictions on the number of sequential applications (blocks) of our new product
- Recommending specific spray application timings to avoid excessive selection pressure for resistance
- Any combination of the above

Of course, different modifiers could be used in different environments for the same pest-crop system, and it is not expected that the same modifier strategy will apply to all crops that the product is to be used on.

The applicant is expected to produce a management strategy based on stated modifiers and explain why it will work.

### *Supportive data*

**Baseline studies.** It is obviously necessary to have a means of determining whether or not resistance develops to an active ingredient. This means that an activity or sensitivity reference point needs to be established for the response of the non-resistant population before exposure to the new active substance. This reference point is termed the 'baseline'. For

most fungi it can be established by appropriate *in vitro* or *in vivo* techniques, but for weeds, some fungi and some insects these laboratory processes are very difficult or not available, so initial field efficacy has to be relied upon as the reference. The applicant is expected to provide evidence of having obtained the baseline reference data together with a method of assaying possible resistance should it be suspected. It must also be remembered that the baseline data cannot be used as any predictor as to whether the risk of development of resistance is high or low.

**Biochemical mode of action, mode of resistance and cross-resistance.** These parameters can be very useful in assessing the risk of resistance developing. Unfortunately they are rarely known for a new active substance from new chemistry at the time of a registration application. For this reason, the Guideline requests that evidence on these parameters should be provided where known, but that if not known, information should be provided on the tests completed. As an example, the biochemical mode of action may not be known, but the fact that it is not a known mode of action should be established by testing for known actions, and reported. Similarly, evidence of cross-resistance, or lack of it, to known molecules with resistance problems should be provided.

**Evidence to support the strategy.** Wherever possible, the applicant should provide data to illustrate that the proposed management strategy including the various modifiers will not select for resistance and allow it to dominate the population to be controlled. Of course, this can be difficult to do given the timescales of a new product development programme before a registration submission, but it is considered that in most cases some data can be gathered. This will include application of the proposed strategy, monitoring of the response of the pest population to the application, and comparison with the baseline.

### *Strategy implementation and monitoring*

The applicant is expected to provide an example product label which should explain to the user how to use the product in order to manage resistance. The applicant should also inform the regulator how the proposed strategy will be promoted in the marketplace, and what steps will be introduced to allow the success of the strategy to be monitored.

## **Further considerations, problems and developments**

### *Placing the risk analysis in the registration process*

It is obvious that the true risk analysis is specific to the use of a product to control a particular pest on a particular crop in a specific environment. For this reason it has been suggested by industry that the Risk Assessment is not applicable for consideration of the registration process for the active ingredient (Annex I and II) but is only of use for registration of a formulated product (Annex III) which is done at individual member state level.

### *Registration of new active substances from known chemistry*

Registration of known chemistry has some advantages in that there should be a wealth of information available on the occurrence of resistance, mode of action etc. But it also presents some problems, especially if the applicant desires to introduce a different resistance management strategy to that already employed for products in the same cross resistance group. For most established chemistry for which two or more companies sell products, regulators will look towards the RACs to establish agreed management strategies, but it could happen that a company may wish to recommend different use patterns. This can happen for several reasons *e.g.* access to particular mixture partners, or due to a specific, unique, biological property of the new active. Means of resolving possible conflicts are currently being considered.

### *Re-registration of established products*

For established products there should be information available on mode of action, cross resistance, mode of resistance and the presence of resistance, if appropriate. What may not be available, especially for older molecules, are extensive baseline sensitivity data, particularly from laboratory assays. In these situations it should be permissible to use field efficacy data to illustrate that a product is still functioning as expected, and hence there is no evidence of resistance.

### *Links between registration data sets*

Potential problems are seen between the need to establish various toxicological parameters, *e.g.* Maximum Residue Levels (MRLs) and the development of a resistance management strategy. This is because the MRL trials process starts quite early in the development process for a new active, and a decision has to be taken on a number of applications of the product under consideration. Data are thus gathered on the basis of this number of applications. If, however, later studies show that for resistance management purposes the application number or sequence has to change, or indeed a change is imposed by the regulator, an imbalance in data sets is generated as the MRL data will not refer to the proposed use pattern. This problem has been highlighted and is under consideration as industry believe that registration should not be unduly delayed in these circumstances.

### *Disagreement between applicant and regulator*

It is hoped that this will not happen, and applicants are advised to consult with the appropriate regulator during the process of developing the risk analysis and management strategy to ensure that no nasty surprises appear on examination of the dossier. If, however, disagreement does occur which cannot be resolved between the applicant and the regulator, a means of resolving the conflict still needs to be determined.

### *What constitutes a baseline?*

There has been much debate over what constitutes a base-

## RESISTANCE ACTION GROUPS (RACs)

For further details on RACs see the following:

*FRAC (Fungicide Resistance Action Group)*

see <http://www.gcpf.org/frac/frac.html>  
and *Pesticide Outlook*, 1999, **10**(5), 213

*HRAC (Herbicide Resistance Action Group)*

see <http://www.gcpf.org/hrac/hrac.html>  
and *Pesticide Outlook*, 1998, **9**(4), 17

*IRAC (Insecticide Resistance Action Group)*

see <http://www.gcpf.org/irac/irac.html>  
and *Pesticide Outlook*, 1994, **6**(5), 29

*RRAC (Rodenticide Resistance Action Group)*

see <http://www.gcpf.org/rrac/rrac.html>

line in terms of number of data points and what baseline is applicable. The industry view, is that the number of data points should be determined by the applicant and justified in the dossier. For what baseline is applicable, the industry view is that the most appropriate and available one should be used. In this context it is important to note that generation of laboratory baseline data is a very expensive operation as many man-years of effort may have to be expended in order to produce an assessment method and more man-years then used to obtain data. In these circumstances, and for some minor crops or minor pests, it may not be financially worthwhile to generate laboratory data. In these circumstances it is suggested that field efficacy data are used.

### *Acceptance of data between countries*

Annex III will be considered at individual country level. However, it could happen that not all data will be gathered in all countries, particularly data to support baseline laboratory studies, or to support the proposed management strategy. Concern has been expressed that some countries may demand data from their own country, but industry feels that provided the applicant can give a reasoned argument why data from a neighbouring country can be used, this should be allowed. The question is still open.

## Conclusion

The pesticide registration process has changed in Europe to place far more emphasis on resistance management. The Resistance Risk Analysis component of a registration submission dossier is now of equal importance to all other components. Without it, registration is likely to be delayed until it is provided. Industry has accepted these changes, and is working actively with regulators to produce a fair, understandable system for appraisal of the Analyses and resultant resistance management strategies.

The EPPO panel that produced the original Guideline is currently working to resolve the outstanding issues.

## References

- Anon. (1991). Council Directive (91/414/EEC) concerning the placing of plant protection products on the market. *Official Journal of the European Community*, **L230**, 19 August 1991, 1–32
- Anon. (1994). Commission Directive (94/37/EC) amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. *Official Journal of the European Community*, **L194**, 22 July 1994, 65–81

- McNamara D.; Smith I. M. (2000). Development of an international standard on resistance risk analysis. Proceedings of *The BCPC Conference – Pests & Diseases*, **2**, 765–770
- OEPP/EPPO (1999) EPPO Standard PP 1/213(1). Resistance Risk Analysis. *Bulletin OEPP/EPPO Bulletin* **29**, 325–347

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