Managing Resistance for Sustainable Use of Plant Protection Products

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Abstract

It is estimated that EU re-registration will result in approximately 65% of 1st ,2nd and 3rd list active ingredients being removed from the market. It is more difficult to estimate how many uses will remain on product labels following member state re-registration. Up to 60 or 70 % of target species and crops could be lost, if use patterns which fall outside the representative GAP (one safe use concept) are not re-registered at member state level, following Annex I inclusion.

Faced with the massive cost of updating Annex II and III dossiers, companies are rationalising product portfolios, formulations and use patterns. Limited research and development resources are therefore increasingly being focused on uses that offer best prospects for re-registration and commercially acceptable returns on investment.

Diversity of control mechanisms (including chemical and non-chemical methods used in IPM and ICM) is an essential component of resistance management, and therefore also of sustainable agriculture. Loss of crop protection products, resulting from re-registration, will drastically reduce resistance management options, as rotation and mixing partners are removed from the market. Companies and national regulatory authorities will increasingly face this problem as they attempt to implement the European and Mediterranean Plant Protection Organisations' Resistance Risk Analysis Guideline PP1/123(1).

While regulatory compliance remains of paramount importance, pragmatism when interpreting guidelines is necessary to avoid further unnecessary loss of product diversity. Failure to use pragmatism will result in companies no longer supporting commercially less attractive uses.

Loss of product diversity will be greatest, but not limited to minor crops. There are already cases where product diversity is too restricted for effective resistance management in major crops.

While "essential uses" have been granted in certain cases, it may not be commercially viable for companies to support these applications in isolation. The limited market potential of these derogations may not be sufficient to justify fixed costs required to keep products on the market.

It is therefore important for stakeholders to recognise that:

- *Once lost, products and use patterns are effectively gone forever.*
- *Maintaining product diversity is essential for resistance management, IPM, ICM and sustainable use of crop protection products.*
- *Further use restrictions, are likely to increase resistance management problems.*
- *The greatest loss of product diversity is likely to occur in minor crops.*
- *Crop protection products and non-chemical alternatives remaining on the market after re-registration will be subject to increased risk of resistance.*

New modes of action and use patterns are badly needed to reverse this trend.

1 Introduction

Resistance is defined by the European and Mediterranean Plant Protection Organisation (EPPO) as:

"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." (Anon, 2001-a)

Importantly, this definition is qualified by use of the term "practical resistance". The guideline distinguishes between the appearance of resistance in the laboratory and which is observed under agricultural conditions,

" 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).

This paper sets out to demonstrate that resistance management is an essential component of sustainable agriculture and integrated pest management (IPM). This paper also sets out to illustrate that loss of product diversity resulting from EU re-registration will increase resistance risk and that as a result resistance management is all the more important.

2 Loss of Diversity

2.1 Impact of EU re-registration

It is estimated that EU re-registration will result in approximately 65% of 1st ,2nd and 3rd list active ingredients removed from the market in 2004 (See figure 1).

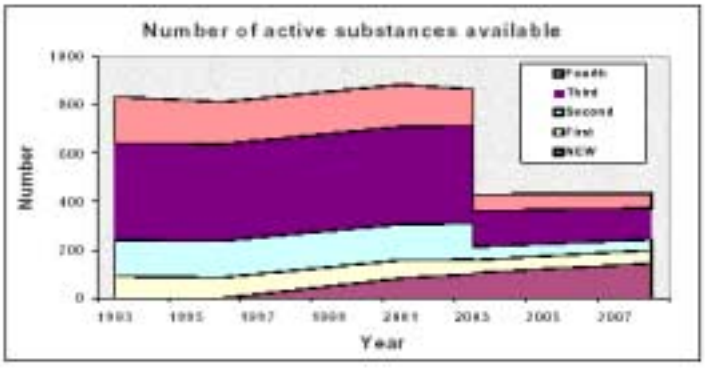

Figure 1, Estimates of the total number of active ingredients available for authorisations during the period 1993 –2008. (Anon, 2001-b).

While many of these active ingredients are not the most commonly used, and in some cases are not even in active use, this loss nonetheless represents a significant reduction in diversity of available tools for resistance management. Likewise, while it may be argued that many of these products share modes of actions with notified actives, they have often been developed for different and mutually exclusive use

patterns. As a result, it may not be possible to replace de-registered products with those that are successfully re-registered.

This regulated loss of active ingredients will be further accentuated by:

- Product portfolio rationalisations
- The impact of member state re-registrations
- The rate of discovery of new modes of action and
- The current rate of new active ingredient approvals

These processes are examined in more detail below:

2.2 Impact of product portfolio rationalisation

It not possible to know in advance how many uses will remain on product labels following member state re-registration. It is however likely that of those actives which are supported through EU re-registration, from 40 to 50% of their respective formulated products will be withdrawn from the market, as crop protection companies rationalise their product portfolios. This is being driven by two related processes:

- Companies are increasingly focussing on fewer formulations to reduce the cost of updating Annex III dossiers to manageable levels and
- Many formulations require modification to comply with recent guidance on the acceptability of formulation components. In order to reduce costs and improve operational efficiency, fewer products are being used to replace these.

2.3 Impact of member state re-registration on product use

It is difficult to estimate and predict with accuracy what proportion of approved use patterns will be lost from following Annex I inclusion, as a result of member state re-registration. However, in order to gain an insight into the sort of situation, which could be anticipated, a retrospective analysis was conducted for a representative List 1 active ingredient. Results of this analysis are summarised below in Table 1.

Table 1.
Potential loss of registered uses resulting from member state re-registration, following Annex I inclusion. A case study with one representative List I active ingredient

Process	Crops	Target species
1995 Dossier submission	68	230
Use patterns that rely on applications not covered by the representative GAP – based on original dossier	59 (87%)	192 (83%)
Use patterns that rely on applications not covered by the representative GAP – following investment in an extensive Annex III dossier revision	49 (72%)	153 (67%)

A total of 68 crops and 230 target organisms were notified in 1995. Of these, 59 crops and 192 target organisms involved use patterns in excess of what subsequently became the representative safe use good agricultural practice (GAP), upon which evaluation for Annex I inclusion is now based. If this one representative GAP is used

as a cut-off criterion for member state re-registration (as is currently the practice in Italy), 87 per cent of the diversity of crops and target organisms would be removed from the existing product label. However, following substantial investment in upgrading the Annex III dossier, the impact of such a cut-off criterion on diversity of approved crops and target pests for this compound could be reduced to 72 and 67 per cent respectively.

While this case study is based on a single representative List I compound, it serves to illustrate the significant impact that cut-off criteria based on the representative GAP could have on product diversity. This is even more significant when one considers that it would be in addition to a 60 to 70 per cent loss of active ingredients and a loss of something in the region of 40 to 50 per cent of formulated products.

2.4 Rate of discovery of new modes of action

Rates of discovery vary from time to time, and from one product type to the next. However, in the case of herbicides, there has been a marked lack of discovery of new modes of action over recent years. For example, the latest group of products with a new mode of action, the HPPD-inhibitors, was discovered roughly 20 years ago. By contrast, more than 20 different herbicidal modes of action were discovered and brought to market following the 2nd world war and up to the mid 1980's. This trend is compounded by the fact that investment in discovery research is under increasing pressure as the cost of regulatory compliance escalates.

2.5 Rate of new active ingredients approvals

Figure 1 shows “availability of active ingredients for authorisation from 1993 to 2008”. However, this graph could be misleading, as it does not represent the actual status of new active ingredients on Annex I. Actual numbers of inclusions to date show a slow rate of replacement. At the time of writing this paper, based on the recent “State of Main Works” SANCO/629/00.rev56, 17 July 2002, of the 80 new “new chemical substances” in the system, only 21 have been included on Annex I.

There is also a disproportionate loss of diversity of insecticidal and acaricidal active ingredients. To date only one new insecticidal compound and one insecticidal micro-organism has been included on Annex I. Likewise, the relative difficulty of registering insecticidal compounds can be witnessed by the fact that two of the five new chemical substances to receive “non-inclusions” so far are insecticides. Based on current status, it is clear that registration of new active ingredients and modes of action does not offer a solution to the scale and pace of lost diversity; at least not for the foreseeable future.

3 Competing for Limited R&D resources

Faced with the massive cost of updating Annex II and III dossiers, companies are rationalising product portfolios, formulations and use patterns. Limited research and development resources are therefore increasingly focused on uses that offer best prospects for re-registration and commercially acceptable returns on investment. In this respect, quantitative financial measures such as return on investment, net present value and internal rates of return, are increasingly being used to make difficult

decisions regarding which products and projects can be financed. In an increasingly competitive global agricultural economy, this inevitably means that limited R&D funds are increasingly directed toward major crops and the most important target organisms. Conversely it is increasingly difficult for less economically important crops, pests and geographical regions to compete for these limited funds.

3.1 Minor crops and "Essential Uses"

The declining availability of products and uses for minor crops has become increasingly apparent in recent years. The Commission responded to requests from the member states by publication of a draft regulation granting "essential use derogations" for 49 of the 321 active ingredients that that have been identified as not being included on Annex I of Directive 91/414 (SANCO, 2002). These derogations provide member states with the opportunity to authorise use of these identified active ingredients in specified situations up to June 2007, "in the absence of an efficient alternative". In the context of the need to invest in sustainable agriculture and sustainable use of crop protection products, it would be prudent for competent authorities to develop an interpretation of the phrase "absence of an efficient alternative" that includes the need to manage resistance. Furthermore, the impact of essential use derogations is likely to be limited in practice. With approved uses being heavily restricted, it may not be commercially attractive for companies to supply plant protection products, even though essential use derogations have been granted. This type of situation is likely to occur when potential revenues are insufficient to justify fixed costs associated with maintaining products on the market.

3.2 Major crops

For commercial reasons, it is likely that loss of product diversity will be greatest for, but not limited to, minor crops. There are already cases where product diversity is too restricted for effective resistance management in major crops. The emergence of pollen beetle (*Meligethes* spp.) resistance to pyrethroid insecticides highlights this problem. This is causing concern as there are few, if any, viable alternatives to the pyrethroids for control of *Meligethes* spp. on oil seed rape.

Having originally developed in France, there are now signs that similar problems are developing in Switzerland, Germany and in Denmark (Dr. U. Heimbach, BBA. personal communication). The situation situation in Germany is problematic as alternatives to pyrethroids are already very limited, and will be non-existent following EU re-registration. Under the circumstances applicants to compare not able to comply with the requirements of Directive 91/414 EEC and EPPO's PP 1/213(1) resistance risk analysis guideline. Likewise, it is not possible for authorities to ensure that unacceptable resistance risks are not authorised (see also Section 5 below).

In the case of herbicides, there is a lack of sufficient product diversity in cereals for resistance management. Control of blackgrass (*Alopecurus myosuroides*) and *Lolium* spp. is increasingly difficult as resistance and cross-resistance to the majority of available herbicide products and modes of action is already widespread in the region.

4 Resistance Management, IPM Sustainable use of crop protection products

The concept of Integrated Pest Management (IPM) is often associated with sustainable agriculture. However, the sustainability of IPM programmes is often neglected from a resistance management perspective. This is important as IPM without resistance management (RM) can create the "worst of all worlds". Without due consideration for resistance management, development and use of IPM programmes based on too limited diversity of IPM compatible chemistries can result in accelerated selection of resistance to these most valuable IPM compatible products.

The pressing problem of Codling moth (*Cydia pomonella*) resistance was recently discussed at a "Symposium on the Current Status of Resistance in Codling Moth, a Global Perspective", which was organised by IRAC in collaboration with the 7th European Congress of Entomology in Thessaloniki. The rapid development and spread of this resistance across the region since 1990 provides a useful model of the relationship between IPM and RM.

The acyl urea, diflubenzuron, was widely used in IPM programmes in France from 1989 to 1992. Being selective to important species of beneficial arthropods, use of these compounds was favoured in IPM orchards. As a result, they were extensively used and enabled growers to establish IPM programmes. However, resistance soon developed, which reduced the effectiveness of these and other related compounds. In France, the situation was compounded by development of several different resistance mechanisms: enhanced esterase, enhanced acetylcholine esterase, enhanced glutathion S-transferase and Kdr.

Today, two to three times as many insecticide applications are required to control codling moth in south eastern France compared with what was required before resistance developed in 1990 (Sauphanor et. al., 2002). At the Thessaloniki workshop, entomologists working in Switzerland, Italy, Belgium and Greece also reported similar resistances in developing in their respective countries.

Although not possible to prove, it is possible to speculate that this challenging resistance would have been avoided if resistance management had been incorporated as part of the IPM programmes that relied so heavily on use of diflubenzuron from 1988 to 1992. Whatever the actual cause, the value of diflubenzuron and other codling moth insecticides has been reduced as a consequence. In addition, because of the non-specific nature of this resistance, other IPM compatible resistance management tools (including other acylureas) are now restricted or no longer available for use. This loss of control options is serious as it puts further pressure on remaining alternatives, and has resulted in greater numbers of insecticide applications being required to produce marketable crops.

This example helps to illustrate that IPM without due regard for RM can result in high levels of selection pressure and therefore risk of resistance to the very compounds that are increasingly required to contribute to sustainable agriculture.

5 Resistance Risk Analysis

Commission Directive 91/414 EEC on the inclusion of new and existing active substances requires assessment of the risk of resistance being developed by target organisms and, where necessary, that management strategies be introduced to address these risks. The European and Mediterranean Plant Protection Organisation (EPPO) worked with regulatory authorities and industry to develop a resistance risk analysis guideline to provide guidance to applicants addressing this need. The resulting guideline, PP 1/213(1), was published in 2000 and is now increasingly used by both applicants and regulatory authorities when evaluating resistance risk for registration purposes in the EU (Anon 2001).

While regulatory compliance remains of paramount importance, pragmatism when interpreting guidelines such as PP 1/213(1) is necessary to avoid further unnecessary loss of product diversity. With increasing demands on limited R&D resources, failure to apply pragmatism when interpreting this guideline will not solve the underlying problem of reduced chemical diversity. While the guideline stresses the need for pragmatism, it also identifies the benefits of establishing baseline sensitivities and investing in post-market susceptibility monitoring. However, because of the nature of the work, these processes can be exorbitantly expensive and logistically challenging, especially when implemented on a region-wide basis. A failure to focus these requirements where they are most needed could result in companies electing to no longer support labels for commercially less attractive crops and target organisms. Again, the only solution here is common sense and pragmatism on the part of both applicants and regulatory authorities when implementing the guideline.

6 Conclusions and Key Messages for Stakeholders

Each registered active ingredient, formulation and use represents an investment of intellectual capital by both private and public sectors. It is important for stakeholders to recognise that once registrations are lost, these investments are gone forever. Likewise, it is important for stakeholders to recognise that maintaining diversity of pest control techniques is essential for resistance management, IPM, ICM and sustainable use of crop protection products. EU re-registration will result in an imminent and substantial lost diversity of crop protection products. As a result, remaining crop protection products and non-chemical alternatives will be subject to increased risk of resistance. Stakeholders are encouraged to be mindful of this prognosis when interpreting regulatory guidelines and making decisions related to member state re-registrations.

Further use restrictions at member state level, are likely to increase resistance management problems. For economic reasons, the greatest loss of product and use diversity is likely to occur in minor crops. However, this problem is not limited to minor crops. There are already cases within the EU where there are no viable resistance management alternatives for major crops. The problem posed by blossom beetles (*Meligethes* spp.) on oil seed rape provides a timely reminder of the potential for resistance problems in major EU crops.

New active ingredients, modes of action and use patterns are badly needed to reverse this trend. However, the current rate of approval of new active ingredients in the EU

is not likely to solve the problem in the foreseeable future. Sustainable use of crop protection products will therefore be increasingly dependent on resistance management to maintain efficacy of a rapidly decreasing tool box of existing chemistries.

7 References

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