

FUNGICIDE RESISTANCE ACTION GROUP (FRAC)

Phil Russell from Aventis CropScience, Lyon, France, and Chairman of FRAC, outlines the latest news from this important action group

Changes in structure

The past two years have seen major upheavals and changes in the agrochemical / crop protection industry. Mergers and take-overs have led to some product portfolios being merged, while in other cases products have been divested as a condition of merger; e.g. trifloxystrobin from Novartis is now a Bayer product. These changes are reflected in the FRAC Steering Committee for 2001 (Table 1).

News from the Working Groups

FRAC no longer publishes hard-copy resistance status reports for the Working Groups, because the information is gathered at different times of the year and any publication is likely to be out of date. Readers are thus directed to the FRAC web site (<http://www.gcpf.org/frac/frac.html>) for the latest position.

MBC, Dicarboximide, Phenylamide Working Groups

For these areas of chemistry the resistance situation and management strategies are considered well established. Little industrial monitoring now takes place and the Groups are considered as 'Sleeping Groups', but advice and information is still available from the respective Chairman.

Anilinopyrimidine Working Group

Monitoring sensitivity of *Botrytis cinerea*, particularly from vines, is of major importance to this Group. It is, therefore, encouraging to note that despite up to 10 years of

commercial application of anilinopyrimidines there is no indication of resistance development in the field.

An issue that should be raised, however, concerns sensitivity monitoring methods. Many years of research by the industry has shown that monitoring based only on *in-vitro* techniques can be unreliable. Isolates can be found which appear to be resistant yet are not so when tested *in vivo*. For reliable data, all assays must finally be based on an *in-vivo* evaluation. Even then, care must then be taken with data interpretation, because it is known that natural populations contain a very small proportion of less sensitive isolates. Many years of research has shown that even when exposed to selection pressure from the anilinopyrimidines, this small proportion has not increased, so its presence is not an immediate sign of the breakdown of disease control. Furthermore, it is quite normal to discover this small proportion in a vineyard one year and not find it the next, despite the use of an anilinopyrimidine. Approved methods for assessment of *Botrytis cinerea* sensitivity to anilinopyrimidines have been published (EPPO, 1996).

QoI Working Group.

This may be a new name for many people. The Group has formerly been known as the Strobilurin Working Group, then the STAR Working Group and more recently as the interim name, QoI-STAR Group. The change of name has arisen because of the inclusion in the Group of the non-strobilurin compounds famoxadone (an oxazolinedione) and fenamidone (an imidazolinone). All compounds share a

Table 1. FRAC Steering Committee, 2001.

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common biochemical mode of action (site Qo inhibition) and the demonstration of cross-resistance between Group members – the term ‘Qo’ referring to the location of the active site on the outside of the mitochondrial membrane. All companies involved with QoI based products, Syngenta, BASF, Bayer, DuPont and Aventis CropScience are conducting extensive monitoring surveys in many crops, the latest resistance position and management guidelines being available on the FRAC web site. The speed at which resistance developed, particularly in *Erysiphe graminis* on wheat in Northern Europe and both powdery and downy mildew on cucurbits, particularly in Japan was unexpected and the QoI Working Group are anxious that recommendations for resistance management are followed. Resistance is not, however, a universal phenomenon with this group and there are several instances where no evidence of resistance has been found despite extensive monitoring. Although strobilurins are no longer being recommended for control of wheat mildew, to date no resistance to QoI compounds has been found in other cereal diseases (*Septoria tritici*, *Puccinia recondita*, *Pyrenophora teres*), *Uncinula necator* on vines or in *Alternaria solani* and *Phytophthora infestans* on potatoes. Active resistance management is, however, still strongly advised in all these cases, and for other applications.

Monitoring of resistance could be greatly helped by the use of molecular analysis techniques. It is well known that the point mutation at the G143A codon of the cytochrome b gene can be used to identify resistance in several fungi. This has been a major breakthrough and is allowing resistant gene frequencies to be determined in monitoring samples. However, the difficulty faced is that the relationships between gene frequency and field effects of resistance are not established. It is thus possible to detect resistant genes in field populations that show no apparent resistance in terms of loss of efficacy. More research is urgently needed to clarify the relationships, but until the answers are known, researchers should not make assumptions of the onset of field resistance based on a chance discovery of a low proportion of resistant genes in a population. A further complication is that it is quite possible that alternative resistance mechanisms could also operate, but again these need further clarification.

FRAC Guidelines and strategy development

Guidelines and criticism

Over the past year, comments have been received by FRAC members that the Guidelines produced by the FRAC Working Groups are not always of direct relevance, and hence value, to the end user of products. Criticism of guidelines relating to cereal disease control have been particularly prominent. In contrast, little criticism has appeared for such crops as vines or top fruit. Why? The reason probably lies in the way in which products are used in practice and in the purpose of the guidelines. Vines and fruit are both crops which have suffered because of problems of fungicide resistance, particularly with mbc and dicarboximide fungicides. Grape and fruit producers are well aware of the problems that resistance can cause, resistance management strategies are developed with advisors and

growers and are built into the crop management systems. The crops are also high value, so the importance of effective resistance management is of direct economic benefit to the user and guidelines are followed. For cereals the situation is different. In general terms the cereal farmer in Europe has never been faced with a total or near-total crop loss because of the development of fungicide resistance. Resistance has developed in certain cases, e.g. eyespot and mbc fungicides, powdery mildews to DMI and strobilurin fungicides, but in all cases disease control has been possible by judicious use of alternative chemistry. At the same time there has been the need for very strict economic management of inputs on cereals in order to generate profit. This has led to the subsequent trend for reduction of fungicide dose rates and a mix-and-match policy between products. FRAC Guidelines, advocating full dose rates have thus been regarded as of no practical value, but users still want advice.

This creates a dilemma for FRAC, and it is necessary to understand the nature of the Guidelines to understand the situation. FRAC represents the industry. The Guidelines it produces are based on a careful evaluation of the scientific data available *at the time* and indicate the perceived best ways to use *particular types of chemistry* in order to prevent or manage resistance problems within that type of chemistry. The Guidelines are not allowed to recommend use of particular products. To do so would be extremely difficult bearing in mind the multitude of products available and would also be of dubious legality. FRAC will also not recommend specific product mixes or coformulations, except for the advice on mixing different types of chemistry and to use mixture partners from a different cross-resistance group when necessary. For this reason, it is expected that advisers or users will use the Guidelines in selecting products for disease control programme, but will also select products for their biological benefits. FRAC will also not recommend reduced doses in such cases unless the reduced dose is recognised by the company as permissible in a tank mix or co-formulation.

Status of science and resistance management

The Guidelines, and particularly the criticism of them, reflect the precarious nature of the science of resistance management, particularly for new chemistry. Resistance and its management depends on the interaction between the fungus concerned and the chemical used to control it. From history it is possible to predict that certain fungi present a high risk of resistance development and that certain areas of chemistry are also high risk (e.g. phenylamides, mbc fungicides). This is not easy to do for new chemistry, although it is wise to make the assumption that the risk will not be low until it can be proved. The result of the interaction and additional factors such as effect of dose rate and management strategies (number of applications, tank mixtures, coformulations) on the risk of resistance development is especially difficult to predict without extensive research, which can be difficult to carry out and interpret. Development of resistance occurring after testing a particular management strategy in a particular environment is a clear indication of an unsatisfactory strategy, but if the strategy does not show resistance, the dilemma is to know

whether the strategy *per se* is the true reason for success or whether some other factor(s) in the original hypothesis relating to the pathogen or the chemical are wrong. The time factor could be a major limitation. A strategy that appears sound over 1 or even 3 seasons may really be allowing an undetected build-up of resistance that in true exponential style could explode at a given season in the future. Of course, molecular diagnostic techniques may provide the answer to the detection of low levels of resistance development, but they will by their very nature depend on the generation of resistance for their discovery and until such techniques are widespread this leads to a very debatable conclusion that at present we can only produce an effective management strategy and explain its scientific logic by first of all generating resistance through use of an ineffective strategy. But this in itself is not wise. We should not willingly try to generate resistance, especially in the field in case it spreads and dominates the population. What we very often do in practice, of course, is to adopt an acceptable strategy in the absence of definitive data to explain why it is working, even though we can put strong scientific hypotheses to support the strategy.

The impact of dose rate on resistance selection and development poses many problems. Do low doses impart a higher risk, and if so, over what timescale? Can effects be predicted to appear after one season, or are we looking at a cumulative effect over many seasons? Only research will tell, but this research will have to be conducted at the same time as a resistance management strategy has been proposed and implemented in the field for marketed products – there is not enough time in the R&D process to answer all questions before market introduction. Can mathematical modeling help? The answer must be a qualified ‘yes’ because the production and testing of models normally rely on an historical data set being present. This set may not be present for new chemistry, so the model will yet again rely on hypothesis and (educated) opinion. This is not to say that any model would be of no value, it could be very valuable in illustrating the effects of different options and circumstances, but knowing which is correct would still be an imprecise judgement.

The dose rate debate will thus continue. My personal prediction is that it will be impossible to produce a general model to cover all pathogen-chemical options except in the broadest sense and that each individual combination will have to be treated differently to obtain a definitive answer, maybe even including environment as an additional factor. More research is urgently needed.

Resistance risk analysis

All applications for registration of a new active, or re-registration of an established active in Europe must now include an assessment of the likelihood that resistance could develop to the active. If resistance is likely in the absence of resistance prevention measures, then suitable measures must be proposed to prevent or manage the problem. FRAC, in collaboration with HRAC and IRAC has represented the industry and collaborated with representatives of the

regulatory authorities in Europe on an EPPO Working Group to produce a Guideline for use by registration applicants to help them prepare registration submissions, and by regulators to help them interpret the data provided. The Guideline was published (OEPP/EPPO 1999) and the implications and contents summarised Russell (2001). After publication, it was felt necessary to introduce the Guideline to the industry and regulators in a more formal manner. A workshop was thus organised by EPPO in June 2000 at the Institute of Plant Protection in Poznan, Poland. Many representatives from industry and regulatory bodies throughout Europe and Japan attended, with the members of the EPPO Working Group acting as presenters and trainers throughout. As could be expected from such a gathering, many questions arose that will need further clarification. The work of the EPPO Working Group is thus continuing and the Guideline will be updated following comments on its implementation in practice.

Chemical Group Codes

The identification of cross-resistance potential is of great importance, as it can prevent a user from using inappropriate mixtures or product alternations in a resistance management programme. FRAC has therefore produced a list of Chemical Group Codes based on cross-resistance potential (available on the FRAC website).

The United States Environmental Protection Agency (EPA) Office of Pesticide Programs is also about to announce voluntary pesticide resistance management labeling guidelines based on mode/target site of action for agricultural uses of herbicides, fungicides, bactericides, insecticides and acaricides. The scheme will also operate in Canada under the auspices of the North American Free Trade Agreement (NAFTA). Although the scheme will not be mandatory, it is proposed that product labels should contain resistance management guidance information and that the product should be clearly labeled with a code or codes to indicate the cross-resistance group of the active(s) in the product. The FRAC Chemical Group codes have been adopted for this purpose. The codes also appear in *The Pesticide Manual* published by BCPC and it is hoped that they will become the international standard.

References

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