Combined risk: 1 = low, 2-6 = medium, 9 = high

benzimidazoles dicarboximides phenylamides	**high (3)**	**3**	**6**	**9**
carboxanilides DMIs phosphorothiolates anilinopyrimidines phenylpyrroles strobilurins	**medium (2)**	**2**	**4**	**6**
coppers dithiocarbamates melanin inhibitors phthalimides sulphur SAR-inducers	**low (1)**	**1**	**2**	**3**
basic fungicide risk ↑ / basic disease risk →		**low (1)**	**medium (2)**	**high (3)**
		seed-borne (eg. *Pyrenophora, Ustilago*) soil-borne (eg. *Phytophthora*), cereal eyespot cereal rust rice sheath blight	**barley *Rhynchosporium* wheat *Septoria***	**apple scab banana *Sigatoka*, cereal powdery mildew, grape *Botrytis*, potato blight, citrus *Penicillium*, rice blast**

Fig 3.
This diagram exemplifies interactions between basic (or inherent) fungicide and disease-associated risks of resistance development. The risk categorisation is approximate and the scores are arbitrary. Nevertheless, these are probably the best estimates that can be made in the light of current knowledge. Operation of resistance management strategies, such as roatation or mixture of different types of fungicide, and integrated use of non-chemical control measures, could decrease the combined risk scores by at least two points.

RISK MODIFIERS

Much practical experience, together with a certain amount of experimentation, indicates that the inherent risk of resistance, as determined by the fungicide and the target pathogen, can be modified by the operation of different disease management strategies. Some strategies can intensify the risk. Others, fortunately, can decrease the risk, and increasingly these are being adopted from the start of commercial use of new fungicides. The most important risk-modifying factors are considered to be:

- avoidance of repeated application of the at-risk fungicide; the more frequent the treatment is applied to selectable populations of the fungus, the more rapid the selection of mutants.
- avoidance of depending wholly on the at-risk fungicide for control; the more uniform the treatment, the more sustained the selection pressure; alternation or combined application with other types of fungicide can reduce risk.
- fragmentation of the area and predominance of use of this fungicide; the greater the area that requires treatment, locally or regionally, and the greater the uniformity of use, the more widespread the selection and build-up of resistant variants.
- reduction in the period of exposure of the pathogen, whilst it is actively growing and/or reproducing, to the at-risk fungicide; the longer the persistence of action of the fungicide the greater the risk.
- use of integrated disease management; the greater the use of non-chemical methods, such as disease-resistant varieties, rotation of crops, or hygienic practices, the lower the fungicide selection pressure.
- the amount, or 'dose', of fungicide used for each application may be an important risk-modifying factor; relationships of dose to resistance development, which are not yet clearly understood, are discussed below.

It is a common practice for farmers to economise by applying fungicides at rates lower than those recommended by the manufacturer, whilst retaining the normal frequency of applications. In some circumstances, for example where the crop variety has a degree of disease resistance, or where conditions permit only light disease development, the use of reduced rates can give satisfactory results, and is supported by some advisory services. Sometimes the manufacturer will indicate a range of application rates which can be used according to conditions. The question of whether and how the dose rate affects the risk of resistance development has been debated for many years. Unfortunately the experimental data concerning this issue are few and somewhat conflicting (Brent, 1995).

There is a consensus view, which is supported by the mathematical models considered in the next section, that the risk of major gene resistance increases as the dose increases, just as the effectiveness of disease control increases with dose. This is because the degree of disease control is proportional to selection pressure in favour of high-level resistant mutants. There is also a widely held view that the risk of development of polygenic resistance, which appears to be a stepwise process, will be low at very low dose rates, because these will exert little or no selection pressure, will rise to a maximum at an intermediate rate, which will select low-level mutants, and will decline at higher rates because the low-level mutants will be killed or stopped from growing and multiplying. Of the two mathematical models that apply to polygenic resistance, one (Shaw, 1989) supports the above hypothesis, and the other (Josepovits, 1989) indicates that dose rate will have little if any effect on resistance development. It should be stressed that the dose-resistance relationships outlined above, and illustrated in Figure 4, are not firmly established, even qualitatively. Much more experimental evidence needs to be produced and analysed before the effects of dose can be considered as a part of the risk assessment procedure.

MATHEMATICAL MODELS

A number of mathematical models were proposed some years ago, for the prediction of the rate of development of resistance in relation to different regimes of fungicide use (Delp, 1980; Kable and Jeffery, 1980; Skylakakis, 1982; Skylakakis, 1982; Wolfe, 1982; Levy et al, 1983; Josepovits and Dobrovolszsky,

1985; Chin, 1987; Milgroom and Fry, 1988)). These relate to single-step resistance, assuming that two distinct biotypes, differing widely in sensitivity due to one major-gene mutation, occur in different proportions according to the degree of selection exerted by fungicide treatments.

R = recommended dose (typically ED_{95})
E = ED_{100} for original population

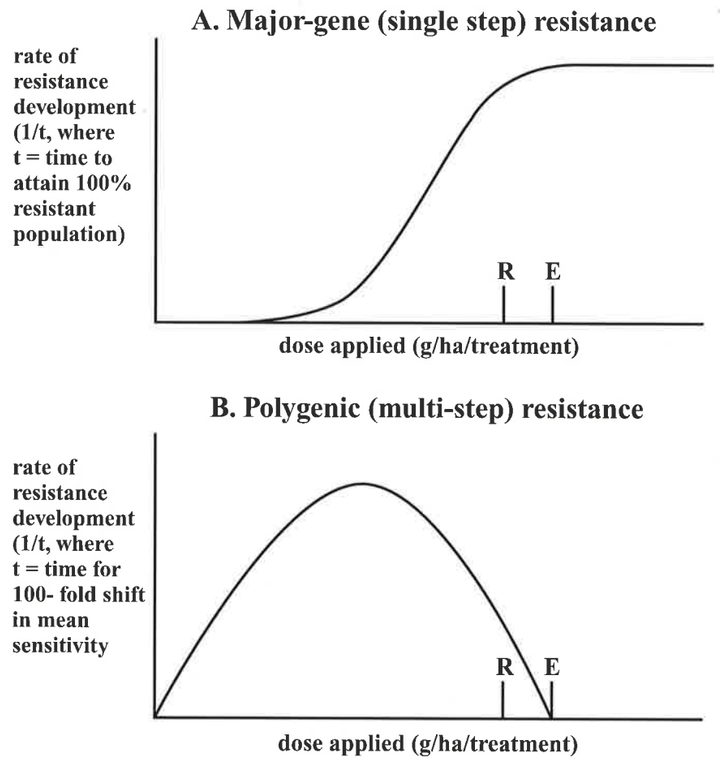

Fig.4. Hypothetical relationships of the rate of development of resistance to the dose of fungicide applied. It is assumed that the different doses are applied in an identical number and timings of treatments. Experimental data relating to such relationships are few, and more research is needed.

The general conclusions from these models are similar and accord with conclusions drawn earlier from existing knowledge of population genetics and epidemiology. They predict, for example, that rapidity of resistance development will be associated with frequent pathogen reproduction, highly effective and persistent action of the at-risk fungicide, greater initial frequency and fitness of resistant mutants, and the sole use of the at-risk fungicide. Rotation or mixture with another fungicide to which mutants remain sensitive are both predicted to delay, but not totally prevent, resistance development. Indications of the relative value of using mixtures or rotations of single fungicides vary between models and according to the assumptions made within some of the models. For example in the model of Kable and Jeffery (1980) complete spray coverage, not allowing escape of any part of the pathogen population, favours the use of alternating fungicides, whereas as coverage decreases the use of mixtures becomes more effective.

The predicted time-scales of resistance development seem to be of the same order of magnitude as those encountered in practice (Skylakakis, 1982), and some examples for one model are given in Table 3. However, verification of the accuracy of each model under a range of conditions has not been attempted. This would be very difficult because of the inaccessibility of data on key aspects such as the relative frequency of mutants at the time of first treatment, the fitness of mutants in the field, and the uniformity of fungicide exposure.

The models considered so far do not apply to the multi-step or polygenically based development of resistance. Models proposed by Shaw (1989) and Josepovits (1989), relate specifically to this type of resistance. Again parameters such as rapid pathogen growth and reproduction and the repetitive use of one fungicide tend to favour resistance development. The mean level and the spread of fungicide resistance that are ultimately attained in response to a particular fungicide regime will be determined largely by the extent to which fitness is affected as the number of mutations towards resistance increases. Unfortunately relationships of this type are not at present measurable, and verification of these models has not been achieved. A further model, which relates to pesticide resistance generally, incorporates effects of pesticide dose and indicates factors that determine the suitability of pesticides for use in mixtures (Birch and Shaw, 1997).

Overall, the range of mathematical models that have been published have

provided a valuable theoretical background to resistance studies. However, they have not, to our knowledge, been used in the practical assessment of resistance risk because of the lack of verification and the difficulties of getting the data required both to verify and to work the models.

Table 3 Predicted and observed duration of selection pressure required for practical resistance to occur

Pathogen	Fungicide	Standard selection time* (days)	Duration of selection pressure	
			Predicted	Observed
Cercospora beticola	Benomyl	9.5 - 14.3	130 - 263 d	140 - 200 d
Phytophthora infestans	Metalaxyl	3.7 - 3.8	57 - 70 d	200 - 400 d
Sphaerotheca fuliginea	Dimethirimol	8.5 - 16. 5	98 - 236 d	112 - 224 d
Ustilago nuda	Carboxin	158	5 - 7 y	11 y

*Time for proportion of resistant sub-population to increase by e (2.7 times)

Source: Skylakakis, 1982

INTEGRATION OF RISK FACTORS

The study of case histories of resistance development in practice, and consideration of the underlying genetic, biochemical and epidemiological processes, indicate that a very complex, interacting and continually changing set of factors determine the rate and severity of development of fungicide resistance. It is a daunting task to attempt to fit together all available data, and to identify

and find further data, in order to make a reasonably reliable assessment. However, it is necessary to do this, not only to guide the manufacturer in decision-making on product introduction and label recommendations, but also registration authorities who now regard the assessment of resistance risk and establishment of appropriate use strategies as a key component of the efficacy statements required to permit decisions on pesticide approval.

Each main usage of a new fungicide requires a separate risk assessment, which must draw together the fungicide risk factors and the disease risk factors discussed earlier. This should be done in a systematic way. It is possible to draw up a checklist of different factors. An example is given in Table 4. Another example was presented by Gisi and Staehle-Csech (1988). It is also possible to allocate risk categories or scores to each factor, and to add them up to give an overall risk assessment.

Whilst such a scheme gives a useful framework for reviewing available information, any effort to quantify each risk factor, or to produce an overall numerical score for risk, is beset by problems. Not all the factors are at present measurable with any degree of precision; the 'fitness' of resistant mutants under field conditions is probably the most critical and difficult factor to measure. Nor are they equally important, and it is virtually impossible to ascribe weightings to each factor other than by personal judgement. At our present state of knowledge, probably the best that can be done is to note information relevant to each factor and to make a high, medium or low risk rating accordingly. The resulting risk profile can be used as a basis for assessing the prospects of obtaining durable performance under a range of possible use strategies, and of the need for monitoring in the different use situations.

If the overall risk assessment for a particular pattern of use of a new fungicide is anything other than 'low' then it becomes very desirable of course to attach a reliable time-scale with regard to the speed of build-up of resistance under different circumstances of use. This cannot be done at present. Studies of case histories of resistance development, which have similar fungicide-associated or disease-associated characteristics to those considered to apply to the test fungicide, may give some idea of how many years it may take for problems to arise. It remains vitally necessary, however, to maintain a very close watch for any sign of deterioration of practical performance, and if possible also to monitor for the sensitivity of representative samples of the target pathogen taken from treated crops.

The framework in Table 4 applies specifically to the assessment of risk for a new fungicide. If a fungicide that is already in commercial use is submitted to assessment for the risk of resistance arising during use in a new region or against a new target disease, then the record-to-date of the fungicide in established uses or locations, regarding either the build-up or the absence of resistance, of course becomes a major additional factor, particularly if the fungicide has been in commercial use for a considerable time.

CURRENT TRENDS AND FUTURE DEVELOPMENTS

Risk assessment and fungicide development

It is encouraging that, over the past ten to fifteen years, the assessment of the risk of resistance has become a routine part of the development of a new fungicide by most if not all the companies concerned. The amount of attention given, and the procedures adopted vary to some extent between companies, and for commercial reasons disclosure of the methods used, and of the results, are often restricted or delayed. In general, however, consideration of the factors presented in Table 4 is used as the basis of risk assessment. This work may be done entirely in-house by the industrial developer of the fungicide, or it may be contracted to a public-sector or private-sector laboratory.

When two or more companies are concurrently developing fungicides which have the same mode of action or are subject to cross-resistance, then there is much to be gained by collaborating in risk assessment. This approach is fostered by FRAC, which in such situations endeavours to set up working groups as early during commercial use of a new fungicide as possible. Those formed most recently are the Anilinopyrimidine and Strobilurin Working Groups. Their main aim is to establish agreed recommendations for use that will offer the best prospects for product durability. As an example, a set of recommendations that has recently been issued by the Strobilurin Working Group is shown in Figure 5. The establishment of such recommendations automatically involves the shared assessment of risk under a range of use scenarios, as well as the sharing of results of observations on performance and of sensitivity monitoring in order to verify the risk assessments and the effectiveness of the adopted strategy of use.

Table 4 A framework for the assessment of risk of the development of resistance during commercial use of a new fungicide

Factor	**Positive indication of resistance risk**
Fungicide -associated	
Fungicide class	When the test fungicide is a member of a class which has a record of resistance problems
Site of action in target fungus	If there is a single site of action; or if the site is known to be capable of change to a form that is unaffected or less affected by other fungicides
Cross-resistance	If there are target pathogen strains resistant to existing fungicides which also resist the test fungicide
Response to mutagenic agents	If treatment with mutagenic agents causes the target fungus to produce resistant, fit mutants
Response in sexual crossing experiments	If sexual crossing cause the target fungus to produce resistant, fit recombinants
Response to repetitive fungicide application	If repeated exposure of the target fungus to the test fungicide, in the laboratory or in field plots, causes the appearance of resistant, fit strains at detectable levels; the distribution of sensitive and resistant isolates (bi-modal or uni-modal) can indicate whether major-gene or polygenic resistance is likely to occur

Factor	**Positive indication of resistance risk**
Disease-associated	
Generation time	If multiplication cycles of the target pathogen,and hence fungicide applications are frequent
Amount of sporulation	If sporulation of the pathogen is abundant
Isolation	If populations of the target pathogen are isolated and/or non-migratory
Modifying	If fungicide applications need to be frequent, if the test fungicide (or fungicides related to it by cross-resistance) will be used continually or throughout crop or regional areas, if alternative chemical treatments or non-chemical measures will not be used

Registration requirements

Pesticide registration authorities world-wide are increasingly demanding information relevant to the assessment of resistance risk, the development of use strategies, and the establishment of base-line data. Consideration of such information is now considered to be a necessary part of the assessment of efficacy and of the information and instructions given on product labels. It is not an easy matter to specify what data should be provided, and how such data should be judged in relation to approval and to the conditions attached thereto.

The EU Registration Directive (91/414/EEC) stipulates that registration data should include 'information on the possible occurrence of resistance'. At present an *ad hoc* panel of the European Plant Protection Organisation (EPPO) is working on the establishment of guidelines for use by EU member states

regarding the specifications for, and the assessment of, data to be submitted to registration authorities concerning the risk of potential pesticide resistance problems and strategies for avoidance. In the absence of such guidelines, individual registration authorities are handling the question of resistance risk in their own ways. So far, the trend has been for acceptance of company information and plans, and there has been little intervention.

Some general views of the agrochemical industry on this topic have been presented by Urech et al (1997). The need to include resistance risk assessment and management strategy in applications for registration is recognised, and a harmonised approach to this across all OECD countries is desired. The scheme should be simple and workable, and based on voluntary action rather than on command. Data requirements should be descriptive, qualitative and straightforward to interpret. The industry will be making appropriate proposals in due course.

It has to be fully understood by those concerned with pesticide registration that resistance risk assessment, like weather forecasting, is a useful process but an imprecise one, and that any improvement in its accuracy will be very gradual. Because of the complexity of the interacting factors that determine resistance development, and because our knowledge and skills in this area are still very limited, it is not appropriate to establish the formal categorisation of the resistance risk attached to each new fungicide. Dutch workers (Rotteveel et al, 1997) have recently proposed the establishment of six official resistance risk categories, ranging from negligible to very high and including an 'unknown' category, which would be allocated by the use of a dichotomous key. A scheme of this type seems to us more likely to raise either over-confidence in product durability or undue alarm regarding resistance development, rather than to promote more effective use or a longer product life. In the authors' view, any overall judgement of risk to product performance that goes beyond low, moderate or high is at present attaching a degree of predictive precision and confidence which has not been achieved.

Nevertheless it does seem entirely right for pesticide registration authorities to expect to receive an account of the methods used for resistance risk assessment, the results and the conclusions, together with a statement on the avoidance strategy to be adopted, if any, on the results of base-line sensitivity monitoring , and on plans, if any, for further monitoring of sensitivity or for monitoring effectiveness in practical disease control.

It is also reasonable that such submissions should have to be arranged in a set frame-work, to ensure that key questions are addressed and to permit ready comparison with other assessments done on related products.

Research priorities and support

It is encouraging that agrochemical companies now put considerable effort into risk assessment and other resistance studies relevant to the development and use of new products. As discussed earlier this increasingly involves inter-company collaboration, fostered by FRAC. To some extent, industrial results are now published in journals and conference proceedings, and are shared with public-sector researchers through joint action groups such as the UK Fungicide Resistance Action Group (FRAG). It is important that such results should be published as soon as possible since in conjunction with a knowledge of subsequent product use and performance they give valuable guidelines for future risk assessment methodology.

It becomes very clear from the foregoing sections that there are huge gaps in our knowledge of the many interacting factors that determine resistance development and of their relative importance, and that consequently our ability to predict the severity and the time-scale of practical resistance development, in relation to options for use strategies, is at present very limited indeed. Improvement requires the identification of key research projects, and financial and institutional support for their completion.

The genetic and the biochemical or biophysical changes that underlie resistance development, are reasonably well understood for only two fungicide classes, the benzimidazoles and the carboxanilides. There is a growing knowledge, but very far from complete, regarding the complex of mutations and mechanisms that appear to give rise to resistance to the DMI fungicides. Much more genetic and biochemical research on this class is needed, both at the cellular level and in relation to shifts in sensitivity under field conditions. The same applies to the phenylamides, the dicarboximides, and the anilinopyrimidines and some important individual fungicides such as dimethomorph.

Inroads into knowledge of the behaviour of mutant genes and their products in field populations of crop pathogens, particularly at very early stages of resistance development, will only become achievable if very sensitive and specific detection methods can be developed and used. Possibilities for this are discussed on page 25.

The influence of different strategies of fungicide use on the rate of development of resistant populations is often discussed, and views are expressed and prescriptions recommended which, through necessity, are out of proportion to the small amount of relevant experimental data that is available. Many more long-term studies should be done on the effects of application factors such as dose rate, timing of sprays in relation to stage of the disease, persistence of action and mixture or rotation of fungicides.

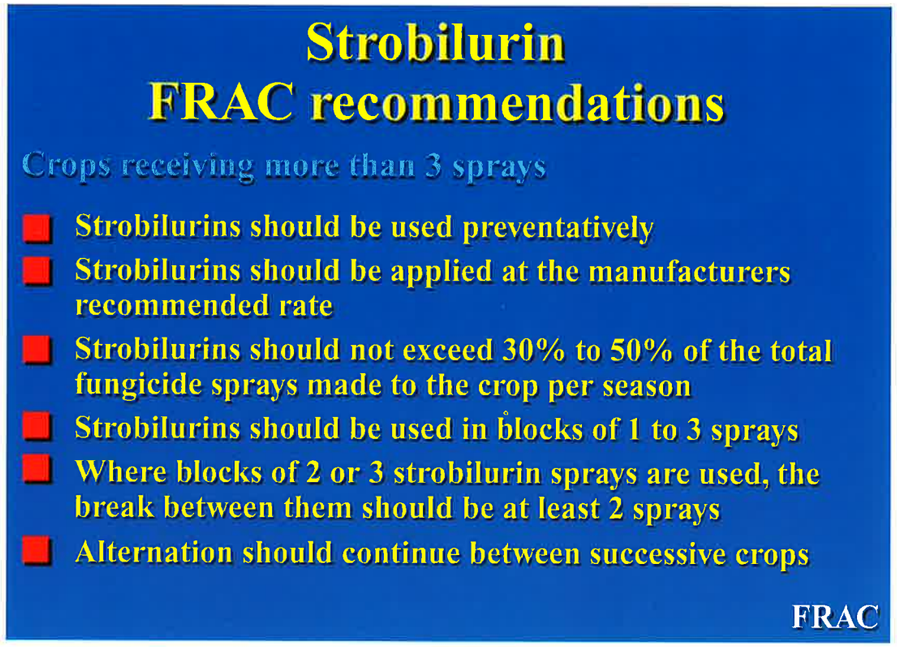

Fig. 5.

A recent example of a set of FRAC recommendations concerning the management of resistance in a new class of fungicides. They are based on a risk analysis made by the Strobilurin Working Group.

The full recording, publication and up-dating of case histories must be strongly encouraged. If possible these should describe risk assessment and base-line studies, then the selection and implementation of use strategies adopted, and finally the outcome in terms of practical resistance development or non-development, including results of sensitivity and performance monitoring. Valuable guidelines for the assessment of risk, and also the formulation of avoidance measures, have emerged from records of past experience, and this should be a continuing process.

The main limiting factors with regard to the progress of basic research relevant to fungicide resistance risk assessment are lack of funding, and low prioritising of this area of work by official research policy-makers world-wide. Industrial organisations do fund a number of projects in public-sector laboratories concerned with risk assessment. Often these are short-term, typically being relatively routine cross-resistance or mutagenesis tests. Longer-term research on resistance mechanisms and genetics, and on field behaviour of mutant populations, must mainly depend on government funding. This is well justified and should be increased, because of its basic scientific thrust, which is considerable, and also because of its importance with regard to registration of pesticides and to their most economic and environmentally safe use.

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After graduating at London University in Botany and Microbiology, Keith Brent worked for over twenty years in ICI, now Zeneca. At first he studied the biochemistry of filamentous fungi, at the Akers Research Laboratories, Welwyn. In 1964 he moved to Jealott's Hill Research Station where he led research on fungicides discovery and development and tackled some of the initial problems of fungicide resistance. In 1979 he was appointed Head of the Crop Protection Division at Long Ashton Research Station, University of Bristol, where he also became Deputy Director. During this period he continued to be involved in fungicide research, and also taught in international courses on fungicide resistance in seven countries world-wide. Since 1992 he has worked as an international consultant in crop protection and agricultural research management and in 1995 he authored the first FRAC Monograph.

Derek W Hollomon PhD

Having gained a degree in Agricultural Botany at Reading University, Derek Hollomon started his plant pathology research at Hull University and was awarded a doctorate in 1965. After several years of post-doctoral research in Canada, Australia and the USA, he returned to the UK to initiate research at Rothamsted on the mode of action of the systemic fungicides that were then beginning to be used for cereal disease control. His research soon extended to resistance problems, and these have continued to be a major interest since he moved to the Long Ashton Research Station in 1985. His work has involved much collaboration with the agrochemical industry, and also has kept him in close contact with the growers. He was awarded the British Crop Protection Council Medal in 1995, and is currently Chairman of the Crop Protection Group of the Society of Chemical Industry.