11 Disease Management by Chemicals

'It was, finally, a matter of trying a large number of remedies, assuring myself of their merits, making them easy of execution, of taking into special account their economy of application, and of winning the confidence of the farmer.' [M. Tillet, 1714–1791]

In an age of increasing environmental awareness, the use of chemicals to control pests, pathogens and weeds is now questioned. This is part of the wider debate about intensive agriculture and its effects on the environment, but the issue of chemicals has become particularly emotive. There is nowadays no shortage of critics eager to discredit the manufacturers and users of pesticides. But this state of affairs is a recent development, and should not obscure the relief and excitement which greeted the discovery of the first effective pesticides, which provided growers with a quick, economic means to control previously destructive infestations and diseases. The stability and security of food supplies in the developed world is due in part to the success of this strategy. While assessing the current status of the chemical control of plant diseases it is important to maintain this historical perspective, and to consider the achievements as well as the problems posed by the use of chemicals in crop management.

The following account will focus on fungicides, as these are the chemicals most frequently used to control plant diseases. Many of the basic principles discussed, however, apply equally well to other important types of crop protection chemicals, such as insecticides and herbicides.

Fungicides

The evolution of fungicides

The fungicidal properties of certain chemicals have been known for many years. The first fungicides, based on sulphur and copper, were discovered in 1846 and 1882, respectively. The discovery of Bordeaux mixture, based on copper sulphate and lime, by Pierre Millardet in France, is one of the most familiar stories in plant pathology, starting with the chance observation that copper salts applied to grapevines to deter thieves also controlled infection by the downy mildew pathogen, *Plasmopara viticola*. Millardet's achievement was to translate this observation into practical use by developing formulations of copper for effective commercial application on crops. During the century since this discovery, fungicides have diversified and changed dramatically (Fig. 11.1; Tables 11.1 & 11.2). The early inorganic compounds have now been superseded by organic chemicals which are active at very low doses, are effective against a wide range of fungal pathogens, and can be applied with precision by machinery appropriate to a small plot or a 1000-ha plantation. However, if pioneers such as Millardet were still alive today, two features of the current fungicide market (Fig. 11.2) would surprise them. Firstly, many of the old, original compounds are still widely used. Secondly, almost all the modern generation of fungicides were discovered by a process not dissimilar to Millardet's initial observation, with the most effective compounds being selected by random screening for activity against a few fungi chosen to represent the most important target pathogens. Only in the past few years, with advances in molecular biology, structural chemistry, and computer technology, has the prospect of designing molecules to perform specific tasks become a reality.

The perfect fungicide

It is relatively easy to compile a list of the desirable properties one would like any new fungicide to

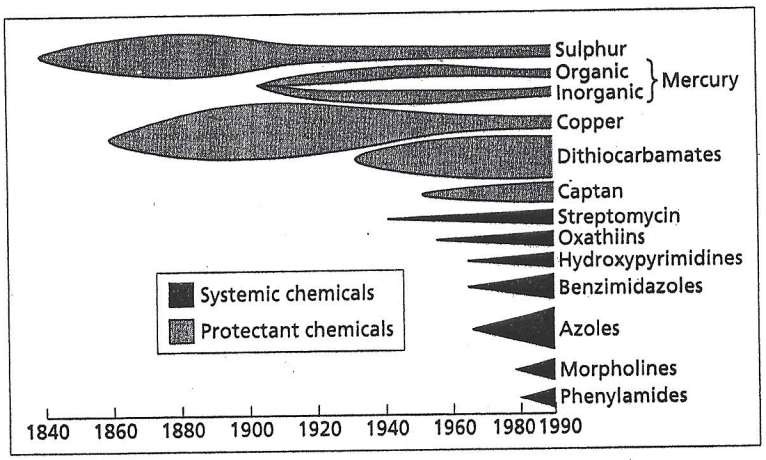


Fig. 11.1 Evolution of fungicides, types available, origins and relative importance.

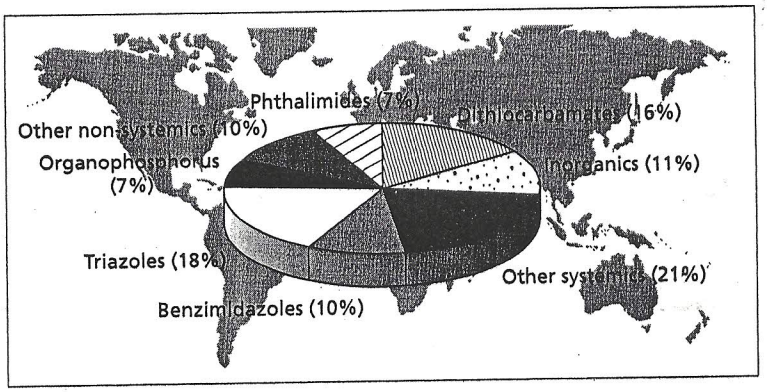


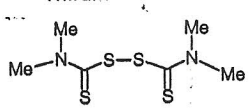
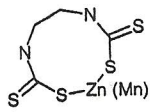
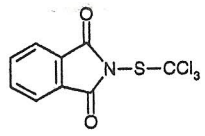
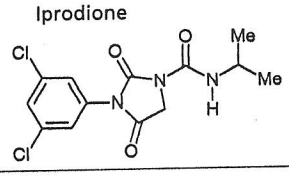
Fig. 11.2 Fungicides world market 1991. (After Lyr 1995.)

possess (Table 11.3). In practice, it is difficult to satisfy all these requirements. The biological considerations listed are attainable for many fungicides applied to aerial tissues or seeds, but targeting pathogens found in the soil is more problematical. Soil sterilants such as chloropicrin and methyl bromide are broad-spectrum biocides which have drastic effects on the soil microflora and fauna, and have now been withdrawn in many countries due to concerns about their safety. Similarly, the use of certain systemic compounds which are taken up by plants raises questions over the persistence of residues in crop products. Such residues may be beneficial in terms of reducing post-harvest diseases, such as fruit rots, but persistence into the food chain is regarded as less acceptable. All new agrochemicals are subjected to rigorous toxicology testing (see below), and the most common reason for a compound failing to make it to the market is some question mark, however, small, about safety. Alternatively the cost of production, or the economics of use by comparison with existing products, may lead to the demise of otherwise promising novel compounds.

The discovery process

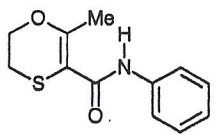
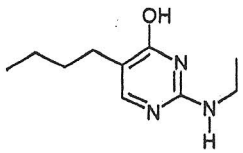
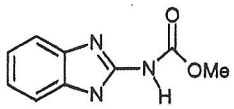
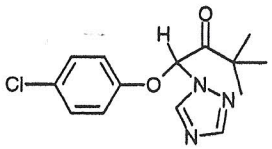
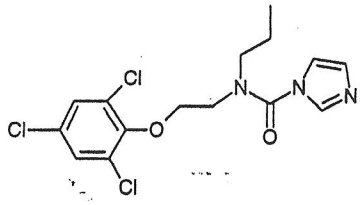
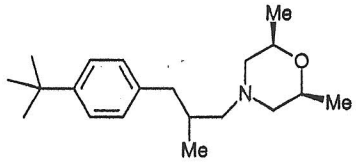
The starting point in the search for compounds with potentially useful biological activity is synthetic chemistry. Most agrochemical companies employ teams of chemists who continuously make new compounds. Each compound is screened for activity against a range of target organisms, including plant pathogens, pests and weeds. A selected few are then chosen for more intensive evaluation as candidate compounds for possible commercial development.

Table 11.1 Major groups of protectant fungicides, with examples.

Type	Example	Mode of action (where known)
Metal-based fungicides		
Copper fungicides	Bordeaux mixture $CuSO_4 + Ca(OH)_2$	Non-specific
Tin fungicides	Fentin acetate $Ph_3SnOCOCH_3$	Non-specific?
Mercury fungicides	Phenyl mercury acetate $PhHgOCOCH_3$	Non-specific
Sulphur fungicides		
	Elemental sulphur	Respiration
Dithiocarbamates	Thiram 	Thiol proteins
	Zineb (Zn), Maneb (Mn) 	
Others		
Pthalimides	Captan 	Proteins
Dicarboximides	Iprodione 	?

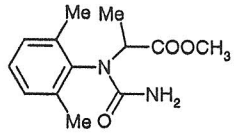
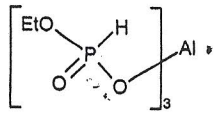
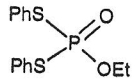
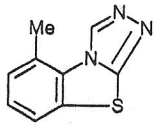
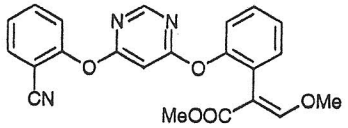
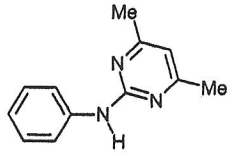
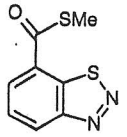
In practice this apparently random process, known as **empirical screening,** is carefully designed and controlled (Fig. 11.3). Because developing agrochemicals is a commercial enterprise, it is vital not to waste time and resources on compounds which, for one reason or another, are unlikely to make it to the market. The initial biological screens used are designed to identify chemicals with the most promising activity. Many highly active compounds are discarded at this stage if their mode of action is shown to be identical to existing products already on the market. Rigorous toxicology tests reject those which might fail on safety grounds. Only a tiny proportion of chemicals screened eventually become commercial products. Original estimates of one in 10 000 chemicals tested have been revised downwards to less than one in 20 000. This no doubt is a reflection of the difficulty of finding new compounds with a significant advantage over existing products, along with the increased stringency of registration requirements, particularly

Table 11.2 Major groups of systemic fungicides, with examples.

Type	Example	Mode of action (where known)
Oxathiins	Carboxin 	Enzyme in citric acid cycle
Hydroxypyrimidines	Ethirimol 	Adenosine deaminase
Methyl benzimidazoles (MBC)	Carbendazim 	β-Tubulin
Ergosterol biosynthesis inhibitors		
Azoles	Propiconazole Triadimefon 	Sterol 14α-demethylase
Imidazoles	Prochloraz 	Sterol 14α-demethylase
Morpholines	Fenpropimorph 	Sterol isomerase and reductase

Continued

Table 11.2 *Continued*

Type	Example	Mode of action (where known)
Phenylamides	Metalaxyl 	RNA polymerase
Phosphonates	Fosetyl-Al 	?
Organophosphorus fungicides	Edifenphos 	Membrane function
Melanin biosynthesis inhibitors	Tricyclazole 	Inhibits polyketide pathway
Strobilurins	Azoxystrobin 	Mitochondrial electron transport
Anilinopyrimidines	Pyrimethanil 	Protein secretion? Methionine biosynthesis?
Defence activators	CGA 245704 (a benzothiadiazole) 	Induces systemic acquired resistance (SAR)

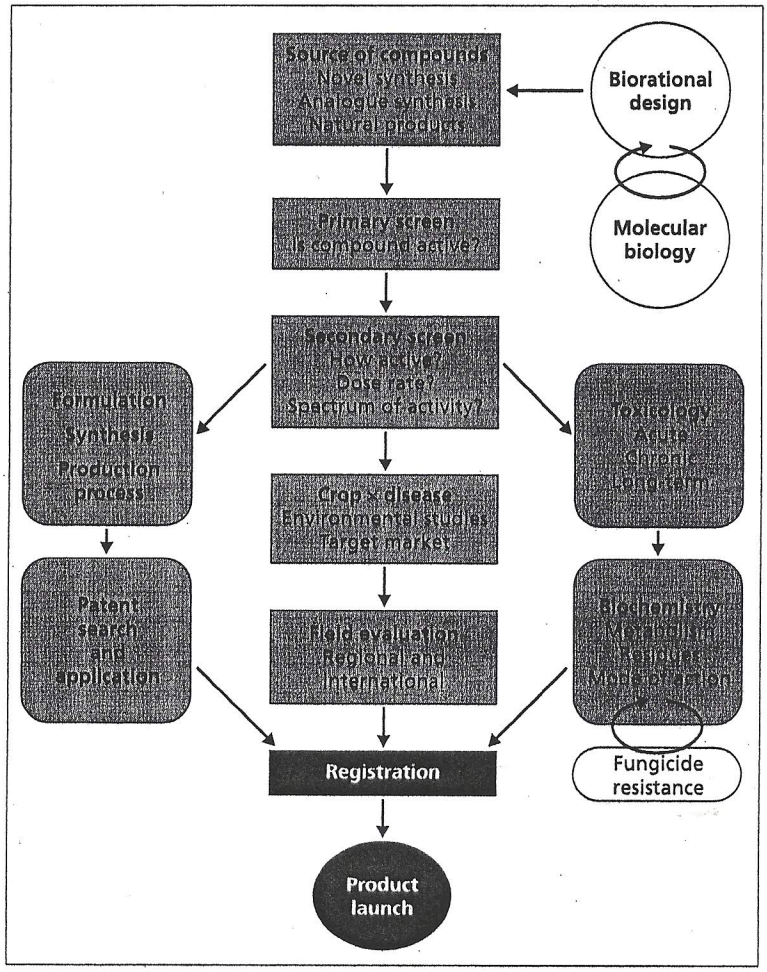


Fig. 11.3 Activities involved in the discovery and development of new agrochemicals.

concerning product safety. As a consequence, agrochemical development is a multi-million dollar exercise which can only be tackled by large, international companies. The notion that agrochemical companies are all involved in some fiercely competitive discovery race is, however, misleading. In reality companies cooperate as well as compete, through licensing agreements to permit manufacture or marketing of each other's compounds, often in mixtures. The virtue of such collaboration is not only commercial, as it can encourage concerted action to combat problems such as fungicide resistance.

The main steps in fungicide development are shown in Fig. 11.3. There are in fact several possible sources of the new molecules required in phase 1. Novel, or 'blue sky' synthesis, is only one approach. Another is analogue synthesis, in which chemists produce a series of modified molecules related to compounds with known activity. The best recent examples of these are the azoles (Table 11.2), a family of fungicides with the same mode of action (inhibition of sterol biosynthesis), which account for a significant proportion of the world fungicide market (Fig. 11.2). Alongside synthesis of analogues is the more contentious business of 'patent-busting', in which rival companies try to identify chemical loopholes in existing patents which might allow production of a similar, but legally distinct, compound. An alternative, and increasingly popular, approach to chemical synthesis is to screen natural products, usually obtained from microbial cultures. This has of course been particularly fruitful in the discovery

Table 11.3 Specifications of a perfect fungicide.

Biological considerations
It must offer effective and consistent disease control
It should not be phytotoxic at the recommended dose level
It should not adversely affect other parts of the crop ecosystem
Toxicological considerations
It must not constitute a hazard during application
Residues in the crop should not pose a problem for the consumer
Formulation factors
It should be safe to store and transport
It should be simple to apply at a precise dosage level
The method of formulation should increase its efficiency as a fungicide
Economic considerations
The financial return should exceed the cost of the fungicide and its application

of antibiotics for clinical use, but some recently developed fungicides, such as the strobilurins (Table 11.2), also derive from natural chemicals, in this case metabolites found in certain species of mushrooms. The biochemical diversity of living organisms is now seen as a potentially limitless source of novel activity.

Whatever the origin of the new molecule, identification of useful biological activity depends upon a phased selection process (Fig. 11.3). The aim of the primary screen is to rapidly identify compounds with promising properties. Typically this will include a range of fungal pathogens representing on the one hand biological diversity, and on the other, known economic importance. There is little commercial purpose in selecting compounds with excellent activity against minor pathogens, for which there is no significant market. Hence most screens will include a downy mildew such as *Plasmopara*, a *Phytophthora* species, a powdery mildew, a rust, and several other fungi known to be significant on a world scale, such as rice blast (*Magnaporthe grisea*), *Botrytis*, apple scab (*Venturia*), and *Rhizoctonia*.

There are of course many variations on this theme, and no two company screens will be identical. There may also be subtleties in the type of activity searched for. Originally, many companies screened compounds *in vitro*, against cultures of pathogenic fungi. Quite apart from the problem of testing non-culturable biotrophs, this approach potentially overlooked useful interactions on or in the plant. For instance, a compound might be converted into a more active form through plant metabolism, or might activate endogenous plant defences. For these reasons almost all screens nowadays use more natural systems which assess the effects of the test chemical on the particular plant–pathogen interaction.

Once a promising compound has been selected in the primary screen, more intensive evaluation begins (Fig. 11.3). The secondary screen seeks to estimate the potency of the chemical and more clearly define its spectrum of activity. Additional target pathogens are often included at this stage. Further properties of the compound, such as its uptake, movement and persistence in the plant, will be investigated. Work may also start on structure–activity relationships, with chemical modification of the molecule to optimize its activity. Next it is important to assess the field performance of the new compound by comparison with existing standards, and to initiate toxicology tests to evaluate safety. Environmental studies are included to monitor the fate of the chemical in the ecosystem, and to detect any adverse effects on non-target species. Due to the increasing awareness of the potential problem of fungicide resistance (see p. 208), there will most likely be some work aimed at assessing the risk of resistance developing, for instance genetic studies using fungal mutants. It is also essential for the company to protect its discovery as early as possible by filing an appropriate patent.

Further development aims to progress the compound from a promising candidate molecule to a commercial product in practical use. This involves several different activities, from development of a chemical production process, through formulation and recommendations for use, to the final stages of product registration and marketing. Each country has its own regulatory requirements and in practice this can prove one of the most time-consuming and difficult steps in launching a new agrochemical.

In spite of the complexity and expense of this long process, the agrochemical industry has been remarkably successful in finding and developing a succession of new types of molecules to aid the fight against plant disease. Predictions of the rapid demise of chemical control through a combination of economic, environmental and biological changes, includ-

ing pathogen evolution, have proved premature. But a number of problems remain. To date there are no commercially effective compounds active against plant viruses, and few effective bacteriocides. Several fungal targets remain elusive, including some vascular wilts, root pathogens, and other soil-borne diseases. Only one class of compounds, the phosphonates, has significant shoot to root mobility, providing control of root infection following aerial application. And added to the commercial and legal pressures of patent life and product registration are the increasing problems of environmental acceptability and pathogen resistance.

Rational design of fungicides

A quite different, and potentially more efficient means of inventing pesticides than the hit-and-miss business of empirical screening, is to specifically design molecules with a particular target in mind. This is really an extension of structure–activity studies into the realm of molecular modelling and the prediction of chemical configurations with optimum biological activity. Given the power of modern computers this is, in theory at least, now feasible. This approach, however, depends upon a fundamental understanding of the specific target, and the likely effects of interference with the target on the pathogen.

The basic idea is shown in Fig. 11.4. First a biochemical process essential for the growth, development or pathogenicity of the fungus is identified. This might be a particular step in a metabolic pathway leading to production of a vital molecule such as a component of a membrane or a cell wall, or a pathogenicity factor such as a toxin. It should be obvious that this biochemical step should not be present, or at least not be essential, in the host plant, otherwise any intervention will damage the crop as well as the pathogen. The next step is purification of the protein, usually an enzyme, responsible for carrying out the process. Three-dimensional modelling of the protein then identifies the active site, and permits the design of molecules which should fit into the site and thereby disrupt normal function. The ultimate test is to synthesize the predicted molecule and assess its activity against the pathogen.

This approach may be refined by using the tools of molecular genetics. If one can identify the gene encoding the target protein (Fig. 11.4) then there are a number of possibilities. Sequencing the gene will assist prediction of the encoded protein structure and conformation. The gene may be expressed in another organism, usually a bacterium, to produce large quantities of the protein. Such recombinant DNA technology might also permit the development of alternative, or 'smart' screens, in which a microorganism expressing the gene of interest, rather than the pathogen itself, is used to rapidly test compounds for their biological effects.

Molecular biology can also aid target validation. It is vital to have information on the likely biological effects of inhibiting the target process. Replacing the gene encoding the target protein with a defective copy (known as gene disruption) will abolish function altogether. If the biochemical step concerned is vital to the fungus, such genetic intervention will be lethal. But while this may confirm the importance of the target, it is not a definitive test. The argument is as follows. It is unlikely, in practical terms, that any fungicide will completely abolish the activity of a target enzyme, due mainly to the difficulty of getting a sufficient dose to the specific cellular site. A more likely scenario is that the compound will reduce rather than abolish activity. What is required is a more precise test of what happens if target protein X is reduced in activity by 10%, or 50%, etc. One way of doing this is to reduce the amount of protein X by attenuating expression of the gene encoding the protein. It may be possible to modulate gene expression by means of antisense RNA, which effectively ties up a proportion of the message for the target protein. This approach is now routinely used to attenuate gene expression in plants, but it should be noted that to date its application in fungi remains largely unproven.

Types of fungicides

There are several different ways of classifying the diverse range of chemical compounds currently used as commercial fungicides. One is by chemical class: for instance, inorganic vs. organic compounds. Another is by mode of action: for example, compounds which have toxic effects on a variety of cellular processes vs. those which interfere with a specific process (see below). A further classification is based on the behaviour of the compound on or in the plant.

Prior to 1960, nearly all the fungicides discovered came under the general description of protectant

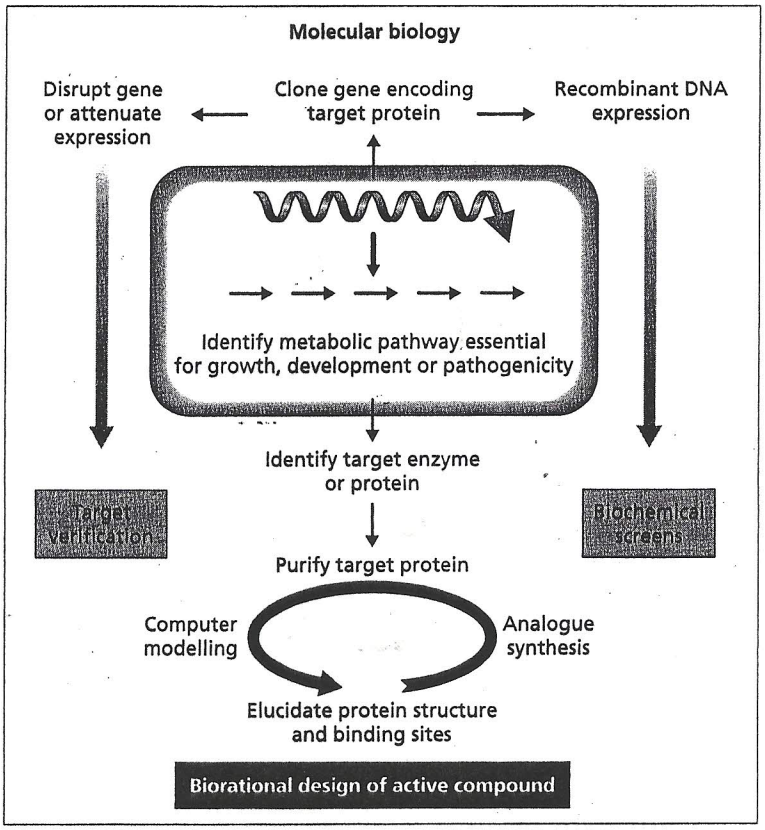


Fig. 11.4 Rational approach to fungicide design.

compounds (Table 11.1). These materials supplement the defences of the plant by forming a superficial chemical barrier to prevent, or protect against, infection. While protectant compounds are effective against a wide range of fungi, they have limitations in practical use. By the very nature of their mode of action they must be applied before the pathogen attempts to penetrate the host. Hence there is a need for reliable, early warning of an infection risk (see p. 64) if protectant compounds are to be used effectively and economically. Because they form surface coatings, such fungicides are subject to degradation and erosion by light, rain and other environmental factors. Last, but not least, applications to growing plants rapidly become ineffective as new leaves, flowers and fruits continue to develop. For this reason protectant fungicides may need to be applied to a crop at regular intervals throughout the season.

Due to these limitations there was a sustained hunt for compounds with a different type of activity, which are actually taken up by the plant and poison the pathogen from within. The advantages of such systemic chemicals should be obvious (Table 11.2). These compounds offer opportunities for therapy, i.e. they may eradicate an established infection. In this way the use of chemicals in plant pathology would resemble human medicine, where the emphasis has always been on developing cures as well as preventing disease.

Some of the first compounds to be used as systemic pesticides were in fact antibiotics, such as streptomycin, but the real breakthrough came in the 1960s with the advent of the benzimidazoles, such as benomyl and carbendazim. These compounds are active against many different plant-pathogenic fungi, and also move through tissues so that accurate and widespread distribution of the chemical over the host is not necessary (Table 11.4). Better still, it is possible to apply such fungicides in the form of seed-dressings, where continual uptake by the growing seedling can protect the plant for many weeks after germination.

Table 11.4 Effect of distribution on the efficiency of the protectant fungicide dinocap and the systemic fungicide benomyl on control of cucumber powdery mildew, *Sphaerotheca fuliginea*. For each fungicide the same amount of material was applied per leaf in either one or a number of drops. After a period of incubation in an atmosphere laden with pathogen spores, the effects of the fungicides were assessed in terms of the area of leaf affected by the pathogen. The results are expressed as percentage reductions from control values. (After Evans 1977.)

No. drops per leaf	Fungicide concentration per drop	Disease control (% reduction)	
		Dinocap	Benomyl
1	0.0250	5	20
2	0.0125	10	40
4	0.0067	20	100
8	0.0033	55	100
16	0.0017	100	100

The large majority of systemic compounds, however, move only in the apoplast, and hence tend to travel from the base to the top of the plant, accumulating in leaves and shoot apices. For this reason they are usually ineffective against soil-borne pathogens infecting roots or other subterranean organs. The notable exceptions are the phosphonates, such as fosetyl-Al (Table 11.2), which are phloem-mobile and can therefore travel from the shoot to the root, providing effective treatment for diseases such as root rot caused by *Phytophthora* species (see p. 208).

The discovery of systemic fungicides provided an enormous step forward in the chemical control of plant disease. Previously intractable problems such as deep-seated infections of fruits or seeds could now be effectively tackled. But one of the apparent strengths of these new compounds, their highly specific mode of action, soon proved to be a weakness. Within a short period of time after their introduction a significant number of target pathogens began to develop resistance to these chemicals.

Mode of action of fungicides

Most first-generation, protectant fungicides (Table 11.1) are known to be **multisite** inhibitors, which interfere with the central metabolic processes of the target fungus. Indeed the majority of these fungicides appear to affect the production of energy or ATP, either by inhibiting respiration or by uncoupling oxidative phosphorylation. Metal-based fungicides such as copper or mercury inhibit a wide range of enzymes involved in various metabolic pathways. Similarly, dithiocarbamates complex with thiol groups on proteins, thereby inactivating enzymes and ultimately causing cell death. This fatal disruption of core processes probably explains why few fungi have evolved systems able to circumvent the toxic effects of these fungicides. Thus for decades the copper, sulphur and dithiocarbamate fungicides have remained as effective as when they were first discovered. One remarkable exception to this rule is the case of *Pyrenophora avenae*, which managed to overcome the toxic effects of mercury applied as a seed-dressing to oats.

By contrast, most of the systemic compounds discovered to date act at a **single site** in the cell, inhibiting a specific enzyme or process. For example, early work on the mode of action of benzimidazole fungicides showed that these compounds inhibited cell division. It was later shown that the specific site of action is β-tubulin, a polymeric protein found in microtubules — essential components of the cytoskeleton. Binding of the fungicide to the tubulin molecule prevents polymerization, and hence disrupts the normal activities of the cytoskeleton, including spindle formation during cell division. The widely used azole fungicides interfere with the biosynthesis of sterols, which are molecules found in fungal cell membranes. These 'sterol biosynthesis inhibitors' (SBIs) affect membrane structure and function, with widespread consequences for the cell. The specific interaction is with an enzyme protein catalysing a single demethylation step in the sterol biosynthesis pathway. Such azole fungicides are therefore referred to more precisely as 'demethylation inhibitors', or DMIs. A second class of SBIs are the morpholines (Table 11.2), which act on the same pathway but at different steps affecting sterol isomerization and reduction. This property is useful as fungi which have become insensitive to DMIs are often still sensitive to morpholine fungicides. Other examples of single-site inhibitors listed in Table 11.2 include the phenylamides, which affect nucleic acid synthesis, and the recently introduced strobilurin fungicides, which block mitochondrial electron transport.

Table 11.5 Comparison of protectant and systemic fungicides.

	Protectant (multisite inhibitors)	Systemic (single-site inhibitors)
Action	Prophylactic	Therapeutic
Basis of toxicity	Many metabolic systems affected	Few metabolic systems affected
Phytotoxicity	Common, especially if applied to wrong tissue or an inappropriate host	Rare
Pathogens affected	Numerous	Variable—some extremely specific, others are effective against a broad spectrum
Pathogen resistance	Rare	Common
Movement	Confined to redistribution on surfaces	Translocated, usually in apoplast (xylem, cell walls)

The highly specific mode of action of single-site inhibitors means, perhaps inevitably, that small changes in the fungus, for instance in the target protein, may alter the efficacy of the compound. In many cases only a single mutation in the fungus is sufficient to abolish activity, and hence lead to resistance. The implications of this are discussed in more detail below.

The contrasting properties of protectant and systemic fungicides are summarized in Table 11.5.

Formulation and application

Discovering chemicals with useful biological activity is only one part of fungicide development. It is also necessary to produce the compound in a form suitable for storage and subsequent application to the crop. Therefore, alongside the constant hunt for better compounds, efforts are continually made to optimize activity in the field by improving formulation and devising better ways of delivering the chemical to the target fungus. The goal is not only to ensure effective control of the disease, but also to reduce the amount of fungicide applied to the crop. This lowers costs and also minimizes any risk to non-target species in the crop ecosystem.

Much of the mystique of the agrochemical industry concerns formulation. The tricks of how to get insoluble compounds into a form suitable for application, and then distribute them over a crop in such as way that they stick to water-repellent plant surfaces and remain active for days or even weeks, are closely guarded secrets. With protectant compounds the main problem is to ensure an even coverage of the plant, and to prevent loss of the active ingredient through weathering or degradation. The biologically active chemical is therefore mixed with carrier compounds which aid dispersion and adhesion to the crop. Such ingredients are often described as 'stickers' and 'spreaders'. They include surface-active detergents and polymers such as carboxymethylcellulose and alginates. With systemic compounds, uptake by the plant is important, and ingredients may therefore be added to aid penetration across the external cuticle of the plant.

The problems of formulation are closely allied to the method of application. Clearly this depends in large part on the type of pathogen to be controlled. Formulations designed to deliver an active ingredient to the leaf surface are unlikely to be fully effective as seed-dressings or treatments for soil. There is also the question of scale. Applying fungicides in a controlled environment such as a glasshouse is a very different proposition to treating a whole field or plantation. In the former case it may be possible to add a chemical to the irrigation system, or to fumigate the crop atmosphere, while the latter usually requires spray application from a tractor or the air. Figure 11.5 illustrates some of the different methods used to apply agrochemicals. The most common approach is to spray a diluted solution or suspension of the active ingredient through a hydraulic nozzle. Such conventional, high-volume sprays are relatively inefficient because a wide range of droplet sizes are generated and much of the active ingredient misses the target. The larger droplets tend to run off the plant, while the smaller droplets may be carried away in turbulent air, a phenomenon known as 'drift'. Less than 1% of the

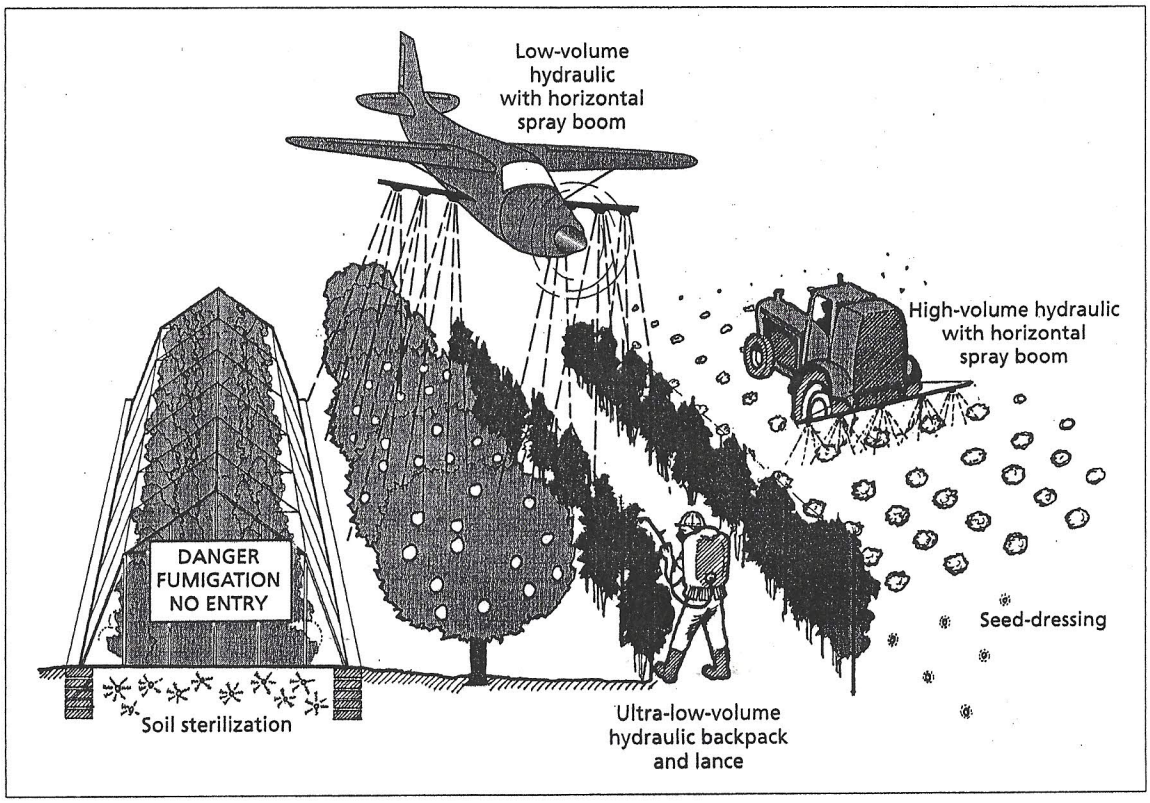
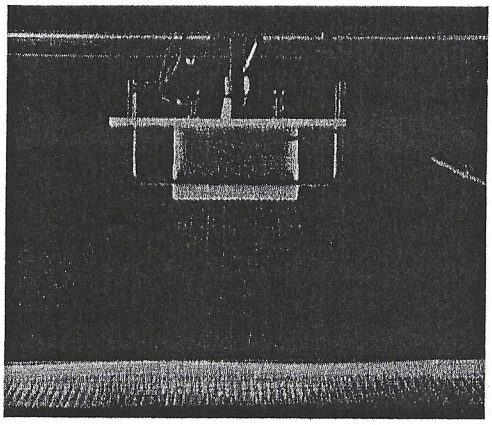


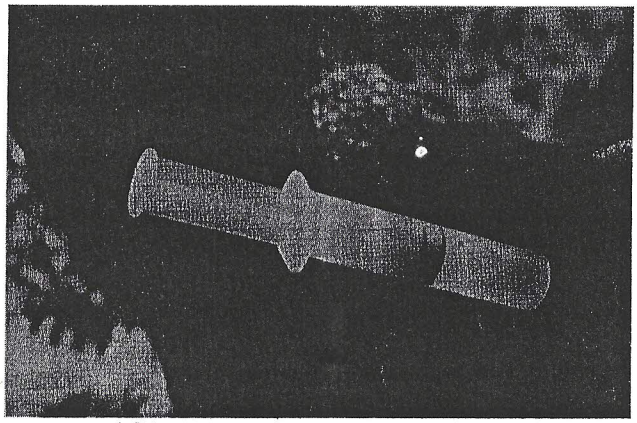
Fig. 11.5 Some methods used to apply pesticides to various crops.

chemical may reach the correct place. A cynic once observed that this method of delivery is analogous to treating the common cold by dropping aspirin tablets from an aeroplane and hoping to find a proportion of the human population looking skywards with their mouths open! While this is obviously an exaggeration it does illustrate the difficulty of reaching disease agents which may be present on the underside of leaves or, as in the case of the eyespot pathogen of wheat, *Pseudocercosporella herpotrichoides*, infecting the base of the stem. Interestingly, control of this disease has been shown to be more effective in instances where rainfall follows application of a fungicide spray, presumably due to the compound being washed down the leaf sheaths to the infection site. Due to the inefficiency of conventional hydraulic sprays, much effort has been expended on developing techniques for controlled droplet application, using improved nozzle designs or rotating discs to generate sprays of defined droplet size. Such improvements permit a lower volume of pesticide to be applied to the crop. Recently, ultra-low-volume methods have been developed, such as electrodynamic spray techniques (Fig. 11.6a). This technology generates electrically charged droplets which are attracted to plant surfaces, giving improved coverage from a smaller volume of liquid. The active chemical can be formulated in oil rather than water, which prevents evaporation and is also an advantage in regions where rainfall and hence the water supply is limiting. Electrostatic spraying has been successfully used to apply pesticides in tropical crops such as cotton and cowpea.

While spraying is the most widely used way of applying pesticides, other methods may be more suitable depending on the compound or the target pathogen. Sulphur, for instance, is easily applied as a dust rather than in suspension, while fumigation can be highly effective in protected cultivation such as glasshouses. Seed-dressing is a very efficient way of

(a)





(b)

Fig. 11.6 Some novel ways of applying fungicides. (a) An electrostatic sprayer generating charged droplets of controlled size. (Courtesy of Eric Hislop.) (b) Trunk injection of an avocado tree using a plastic syringe containing an aqueous solution of fosetyl-Al to control *Phytophthora* root rot. (Reprinted from Coffey 1987; copyright 1987, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.)

applying compounds to prevent seedling diseases such as damping-off, and, provided the fungicide is sufficiently mobile in the growing plant, can also protect against infection by airborne pathogens. For instance, systemic compounds such as ethirimol and some azoles, applied to cereal seeds, provide good control of powdery mildew, *Erysiphe graminis*. The advantage of this approach is that the compound can be applied in an appropriate formulation to batches of seed by the supplier rather than the grower, which saves time and money. There can, however, be drawbacks, as some fungicides are phytotoxic when applied to seed, and it has been argued that the more prolonged exposure of the pathogen to a fungicide originating from seed can increase the risk of resistance (see below).

Alternative methods are often necessary when the pathogen occurs in soil, or is difficult to target due to its growth habit in the host plant. Drenching soil with a pesticide, or treating by fumigation, may be costly and also can affect non-target species. In this situation, granular formulations of the chemical may be more appropriate, designed to gradually release the active ingredient into soil over a period of time. Pathogens which grow in inaccessible parts of the plant, such as deep within seeds, or in vascular tissues, may also present problems. Earlier this century smut fungi such as species of *Ustilago* and *Tilletia* were among the most damaging disease agents of cereal crops, due to transmission from season to season through seed. Techniques were devised to soak seeds in solutions of fungicide, but the real breakthrough in control of these diseases came with the introduction of organomercury treatments, which effectively eradicated most seed-borne fungi. Some smut fungi, however, such as loose smut (*Ustilago nuda*), infect the embryo rather than the seed coat, and are therefore not affected by treatments which are restricted to surface tissues. Control of loose smut was not achieved until the advent of truly systemic compounds such as carboxin which could penetrate and move within host tissues. Ironically, some smut diseases are now staging a comeback due to the withdrawal of organomercury fungicides on environmental grounds. Effective alternatives are available but are more expensive, and hence the use of seed treatments is declining in some crops.

Vascular wilt fungi are difficult to control with chemicals, especially those infecting woody perennial hosts. A good example is Dutch elm disease, caused by *Ophiostoma novo-ulmi*, which has decimated elm populations across much of the northern hemisphere. Attempts were made to protect specimen elms, e.g. those in city parks, by injecting fungicides into the sapwood, where the chemicals are carried upwards in

the transpiration stream. Some success was achieved using benzimidazole fungicides such as benomyl, but the treatment proved ineffective on large trees, mainly due to the relative insolubility of these compounds, which prevented them moving in sufficient concentrations to prevent infection of the upper branches. However, in some instances injection can be an extremely effective way of applying a fungicide to a woody plant. The most destructive disease of avocado groves is root rot, caused by *Phytophthora cinnamomi*. This soil-borne pathogen attacks the small, feeder roots of the tree, with often fatal consequences (see p. 251). *Phytophthora* root rot was not amenable to chemical control until the introduction of systemic fungicides active against oomycete fungi such as metalaxyl. This compound, applied as a root drench, controlled disease in young trees, but the prognosis for more mature trees remained gloomy. The advent of phosphonates such as fosetyl-Al, which can move from shoot to root, radically changed the situation, with foliar sprays at monthly intervals giving good control. Even better results were achieved by applying the compound by injection with a syringe which is left inserted in the trunk of the tree (Fig. 11.6b). The fungicide solution is gradually taken up by the tree, and only two injections a year may be sufficient to ensure control of this previously lethal disease.

It should be obvious that labour-intensive application methods, such as injection, are only feasible with high-value crops where protection of individual plants can be justified on economic or amenity grounds.

Fungicide resistance

Prior to the discovery of the first systemic, selective fungicides, there were very few instances when application of a protectant compound, at the correct time and dose rate, failed to control a pathogen. Thus for decades the copper, sulphur and dithiocarbamate fungicides have remained as effective as when they were first discovered. The few exceptions to this rule include the development of resistance to mercury-based seed-dressings in *Pyrenophora*, dodine in apple scab (*Venturia inaequalis*), and problems with the use of diphenyl compounds to control post-harvest rots of citrus fruits caused by *Penicillium* species (Plate 8, facing p. 12). But in general, the protectant, multisite inhibitors, have given long-term, durable control of many crop diseases.

Practical experience with the newer, systemic compounds has been different. There have been numerous cases in which an initially highly effective fungicide has subsequently failed to control a

Table 11.6 Some examples of fungicide resistance in practice.

Fungicide group	Pathogen	Crop	Date first reported
Organomercury	*Pyrenophora avenae*	Oats	1970
Dodine	*Venturia inaequalis*	Apple	1969
Pyrimidine	*Sphaerotheca fuliginea*	Cucumber	1970
Benzimidazoles	*Botrytis cinerea*	Various	1971–1973
	Cercospora spp.	Peanut, sugarbeet	1974
	Pseudocercosporella herpotrichoides	Wheat	1981
Dicarboximides	*Botrytis cinerea*	Grapevine	1978
	Monilinia fructicola	Stone fruit	1986
Phenylamides	*Phytophthora infestans*	Potato	1980
	Peronospora tabacina	Tobacco	1981
	Peronospora parasitica	Brassicas	1983
	Bremia lactucae	Lettuce	1983
Demethylation inhibitors (DMIs)	*Erysiphe graminis*	Cereals	1982–1986
	Pyrenophora teres	Barley	1985
	Penicillium digitatum	Citrus	1987

pathogen in a crop (Table 11.6). Sometimes such failures have occurred within a short time of first use of the compound. For example, the pyrimidine fungicide dimethirimol, introduced in 1968, showed outstanding activity against powdery mildews, and was recommended to control the cucumber powdery mildew pathogen *Sphaerotheca fuliginea* (Fig. 11.7) in glasshouses. Intensive use quickly led to the emergence of highly resistant strains of the pathogen, and by 1971 the compound was withdrawn in The Netherlands. Similarly, the phenylamide fungicide metalaxyl (Table 11.2) was launched in 1977 and recommended for control of many important oomycete pathogens such as the downy mildews, *Phytophthora* and *Pythium*. By 1979, isolates of cucumber downy mildew, *Pseudoperonospora cubensis*, able to tolerate 20 times the initially effective dose of the fungicide had been recorded, and, more dramatically, in the following season failures to control potato blight occurred in Ireland and The Netherlands. This was shown to be due to the incidence of metalaxyl-resistant strains of *Phytophthora infestans* in the field, and shortly after, formulations of fungicide containing metalaxyl alone were withdrawn. Similar experiences occurred with blue mould of tobacco, *Peronospora tabacina*, and other downy mildews such as *Peronospora parasitica* and *Bremia lactucae*. Table 11.6. lists some further examples where resistance to systemic fungicides has occurred.

Why did this happen, and what lessons can be learned from these setbacks? More importantly, can anything be done to prevent such 'boom-and-bust' episodes in the future?

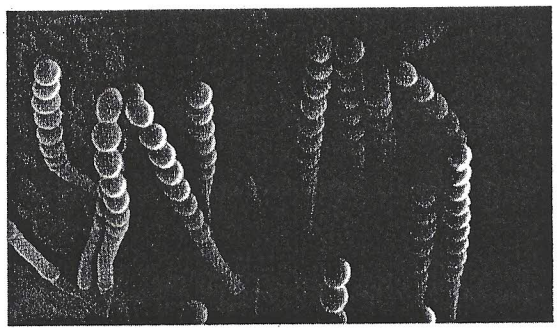


Fig. 11.7 Scanning electron micrograph of cucumber powdery mildew, *Sphaerotheca fuliginea*, showing surface mycelium, conidiophores and chains of spores. Scale bar = 100 μm. (Courtesy of Alison Daniels, AgrEvo UK.)

Some definitions

Before attempting to answer these questions, some terms used to describe the problem should be defined. **Insensitivity** and **tolerance** have both been used to indicate changes in the response of fungi to fungicides, but **resistance** is now the preferred term. It is essential, however, to distinguish between instances where the sensitivity of a target fungus to a particular chemical has changed, and the actual loss of efficacy of a fungicide in practical use. There are numerous examples of resistance being detected in some strains of fungi, yet the fungicide still gives effective control of the disease in the field. The phrase **resistance in practice** has therefore been recommended to describe situations where reduced sensitivity of a fungal pathogen to a fungicide results in poor disease control in the field. **Cross-resistance** is the phenomenon whereby development of resistance to one chemical in a particular class also confers resistance to other, related chemicals. For example, strains of *Botrytis cinerea* (Plate 7, facing p. 12) resistant to benomyl are also resistant to other benzimidazole fungicides such as carbendazim and thiabendazole. This has important practical implications, as strains altered in sensitivity to one fungicide in a particular group may simultaneously become resistant to all other compounds in that group.

The risk of resistance

Three factors determine the risk of resistance arising and the extent to which it will spread in the pathogen population and hence become a practical problem:

1 the nature of the fungicide;
2 the way in which the fungicide is used;
3 the biology of the pathogen concerned.

Single-site fungicides are much more likely to encounter problems of resistance since only a single mutation in the pathogen may be sufficient to counter the action of the compound. With multisite fungicides numerous mutations may be required, which greatly reduce the probability of resistance developing to such compounds.

Important aspects of fungicide use are the frequency of application, and whether a compound is

applied on its own rather than in combination with other chemicals. Ultimately, this is about selection pressure—the degree to which the presence of a fungicide in the crop ecosystem will favour strains of a pathogen less sensitive to the chemical concerned. If, for example, a pathogen population comprises a mixture of strains which differ in sensitivity to a chemical, exposure to that chemical will select those individuals able to withstand the treatment. It should be obvious that the more frequently a fungicide is used, and the more often a pathogen is exposed to it, the greater the likelihood that such resistant individuals will survive rather than the originally predominant sensitive strains.

Biological factors influencing risk are to do with the genetic system of the fungus, and its life cycle. The first consideration is the frequency of mutation to a resistant form; this provides the genes, or alleles, conferring resistance. However, for resistance in practice to occur, such genes must persist and spread in the pathogen population. If, for example, mutation to resistance to a fungicide has other effects on the fungus, such as reducing its growth rate or reproductive capacity, then resistant individuals may not survive in competition with sensitive strains. Genetic recombination may, of course, mix up genes and provide opportunities for fitter, resistant strains to arise. Then there is the extent to which such resistant strains are likely to spread. The types of spores produced and their mode of dispersal are therefore important.

Given these various considerations, it should be possible, at least in theory, to distinguish between 'high-risk' and 'low-risk' pathogens. Fungi with rapid reproductive cycles, producing large numbers of wind-dispersed spores, are more likely to pose problems of resistance than slowly reproducing fungi which are dispersed over only short distances. Practical experience to some extent supports such predictions, with resistance often developing rapidly in polycyclic airborne pathogens such as downy and powdery mildews. But not all incidences of resistance conform to this model. Eyespot disease of cereals (Plate 6, facing p. 12), caused by *Pseudocercosporella herpotrichoides*, developed resistance to methyl benzimidazole (MBC) fungicides during the 1980s, with field populations shifting to a predominance of resistant individuals within only a few seasons. Yet this pathogen was believed to be asexual and splash-dispersed, and the speed with which resistance built up took many people by surprise. More recently a sexual stage has been discovered in this fungus, but it is not known whether sexual inoculum played any part in the emergence of MBC resistance. It might simply be that mutations to MBC resistance can occur at a fairly high frequency, that such mutations have no discernible effect on fitness, and that MBC fungicides were widely used on a high proportion of cereal crops. The moral of this story is that risk assessment is far from simple, and with highly variable and adaptable organisms such as fungi a useful guiding principle is to expect the unexpected!

The evolution of resistance

The development of resistance to fungicides is an example of an evolutionary change in a fungal population caused by a human activity, the application of a chemical to a crop. The raw material for this evolution is genetic variation in the fungus, but the driving force, the selection pressure, is provided by crop management practices. Understanding the nature of this change in the pathogen, and how it came about, is essential if we are to counter the problem of fungicide resistance.

Monitoring changes in the response of fungal populations to fungicides, season by season, has become an important activity, both in defining the problem, and predicting future events. This relies on surveys of fungal isolates taken from the field to determine their dose–response to the chemical concerned. The usual way to measure fungicide sensitivity is to determine the dose which inhibits 50% of a particular physiological parameter. For example, if growth or spore germination is reduced by half, then this is described as the ED_{50} (effective dose) or EC_{50} (effective concentration) which gives 50% inhibition. Alternatively the minimum inhibitory concentration (MIC), the lowest concentration completely preventing growth of the pathogen, may be determined. Different isolates of a fungus can therefore be compared in a standardized dose–response test.

An important conclusion arising from this type of research is that not all pathogens or fungicides behave in the same way. For instance, in the case of MBC fungicides, the development of resistance was associated with the emergence of fungal strains which could withstand huge doses of the compound, 1000-fold more than sensitive strains. But with some other fungicides, such as the SBIs, resistance has developed

as a gradual shift in sensitivity, rather than as a dramatic change (Fig. 11.8). It is clear that more than one phenomenon is likely to be involved. These contrasting patterns in the development of resistance have been described in population terms as either **disruptive selection**, in which the population diverges into sensitive and resistant classes, or **directional selection**, in which the population overall shifts towards reduced sensitivity. This is shown in diagrammatic form in Fig. 11.9. Application of a fungicide either selects a subset of the population which is highly resistant to the compound, or alternatively eliminates

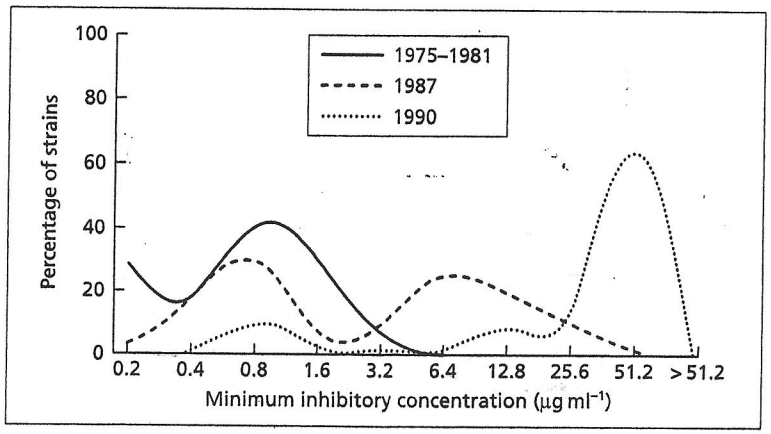


Fig. 11.8 Changes in the sensitivity of the barley pathogen *Rhynchosporium secalis* to the sterol biosynthesis inhibitor (SBI) fungicide triadimenol in populations of the fungus sampled between 1975 and 1990. (Redrawn from Kendall *et al.* 1993; copyright 1993, with kind permission from Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington OX5 1GB, UK.)

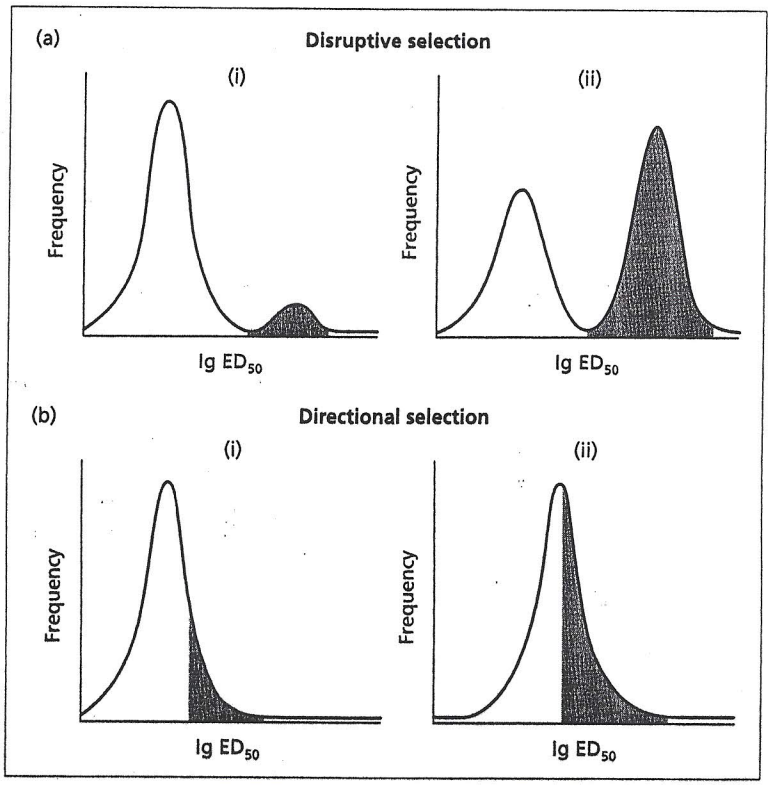


Fig. 11.9 Selection of resistance to fungicides in pathogen populations. Shading represents the more resistant individuals in the population. (a) Disruptive selection: (i) distribution before application of the fungicide; (ii) distribution after prolonged selection. (b) Directional selection: (i) distribution before application of the fungicide; (ii) 'shifting' of the distribution of ED_{50} values after fungicide application. (After Berg *et al.* 1990.)

the least resistant individuals. The former change causes a quantum leap in resistance (as in the case of MBC and phenylamide fungicides), while the latter causes a gradual erosion in the efficacy of the compound over a more extended time scale (e.g. Fig. 11.8).

These different scenarios are ultimately due to differences in the mechanism of resistance, and in its underlying genetic basis. Figure 11.10 shows some of the possible mechanisms involved in the resistance of a fungus to a particular chemical. Comparison of these mechanisms should clarify why the degree of resistance varies. Changes in the target site can, for instance, completely abolish the activity of the fungicide. This is essentially what happened with MBC fungicides, once the tubulin protein had mutated to prevent binding of the chemical. Some of the other mechanisms are likely to have less effect on the sensitivity of the pathogen, for instance changes in the rate of uptake, efflux or detoxification of the compound. Such alterations will reduce, rather than completely abolish, activity. This scheme also shows that more than one gene may affect the response of a fungus to a fungicide. Resistance due to changes in a target protein is usually encoded by a single gene, while other types of resistance may involve several processes encoded by multiple genes. This may explain why some forms of resistance develop gradually with incremental shifts in sensitivity over a period of time.

Combating fungicide resistance

Resistance to pesticides is now an established fact of life in the agrochemical industry, so the question is not so much will resistance occur, as when will it occur, and can it be managed? In fact, even where major reductions in the efficacy of a fungicide have taken place, experience has shown that the compound may still have a useful role to play in disease management, provided the rules of the game are understood.

The early, dramatic failures in fungicide use were due almost entirely to a 'quick fix' mentality in which continuous application of a single compound on its own led, perhaps inevitably, to the selection of resistant forms of the pathogen. To a large extent the first systemic, single-site compounds were victims of their own success. These fungicides were so active and effective that they were quickly adopted by growers and used sometimes indiscriminately in crops throughout the season. The selection pressure on pathogens was therefore considerable. With the benefit of hindsight manufacturers, advisors and growers are now aware of the potential scale of the problem, and measures have been put in place to minimize the risk of resistance occurring. The agrochemical industry has coordinated its response by establishing the Fungicide Resistance Action Committee (FRAC), which is a forum aiming to prolong

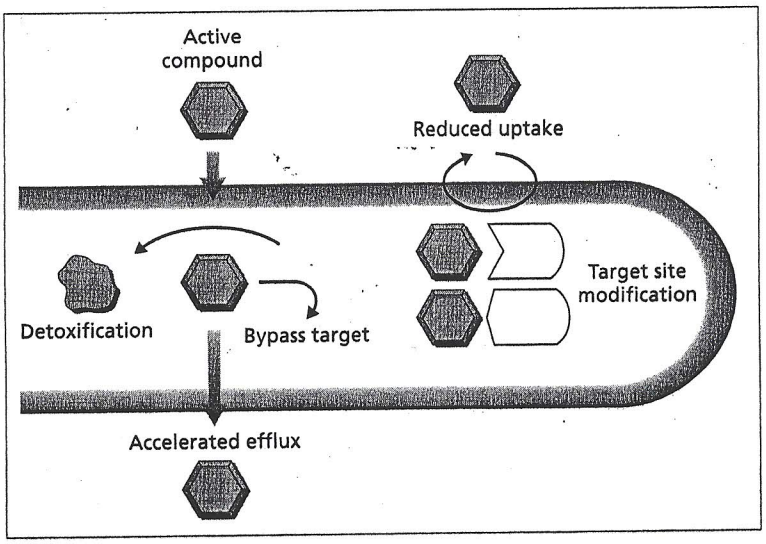


Fig. 11.10 Some mechanisms of fungicide resistance.

the effectiveness of fungicides liable to encounter resistance problems, and to limit crop losses during the emergence of resistance. Bodies such as FRAC identify existing and potential resistance problems, but their most important role is to develop guidelines for fungicide use which minimize the risk of resistance in practice.

Several commonsense strategies to combat fungicide resistance are summarized in Table 11.7. These aim to reduce selection pressure either by reducing the frequency of use of a fungicide, or by diversifying the chemicals the pathogen population is exposed to during the season. Thus, fungicides are used as mixtures with different modes of action, or treatments are alternated between compounds with different modes of action. One perhaps ironic aspect of this is that some of the older, multisite fungicides now play key roles as partners in mixtures, or as treatments in 'fungicide rotation'.

These ideas can be illustrated with examples from practical experience with different pathogens and contrasting compounds. The grey mould fungus, *Botrytis cinerea*, is a major threat to grape production in many parts of the world, and fungicides are routinely used to control this pathogen in vines. When MBC fungicides were first introduced they gave excellent results with *Botrytis*, but quickly lost their efficacy due to the emergence of highly resistant strains. Such resistant strains are as fit as sensitive strains, so they are able to persist in the pathogen population; reducing or abolishing use of MBC fungicides does not therefore significantly reduce the threat of resistance to these compounds. However, MBC resistance is often correlated with increased sensitivity to another group of chemicals known as phenylcarbamates. Hence for a while, mixtures of MBC and phenylcarbamate fungicides were recommended for control of *Botrytis*. This strategy has now been undermined by the emergence of strains resistant to both groups of chemicals. However, alternative fungicides with contrasting modes of action are available. These include the dicarboximides, such as iprodione (Table 11.1) and vinclozolin, and the recently introduced anilinopyrimidines (Table 11.2). *Botrytis* has also adapted to dicarboximides, but in this case resistant strains appear to be less competitive than sensitive strains, and hence the level of resistance in the pathogen population can be reduced, or at least stabilized, by rotation to other compounds. The currently highly effective anilinopyrimidines are from the outset being recommended as one treatment in an alternated spray programme, or formulated as mixtures with other compounds. Thus, even in a very difficult case, such as *Botrytis* in vineyards, effective options still exist for chemical management of the disease.

Another highly adaptable pathogen capable of exerting high disease pressure on a crop is *Phytophthora infestans* (Plates 1 & 2, facing p. 12). The rapid demise of the phenylamide fungicide metalaxyl in the potato crop in Europe in 1979–1980 has already been described above. However, metalaxyl is still used for the control of potato blight, formulated in mixtures with dithiocarbamates such as mancozeb, since such mixtures give control superior to the protectant compound alone. Figure 11.11 shows the incidence of metalaxyl-resistant strains of *P. infestans* in The Netherlands during the 1980s. Following the initial problem, use of the fungicide was suspended from 1981 to 1984, and the proportion of resistant strains declined. Metalaxyl was then reintroduced for use in mixtures co-formulated with multisite compounds, and the proportion of resistant strains rose again, albeit to a level lower than at the outset (Fig.

Table 11.7 Strategies to minimize the risk of fungicide resistance in practice.

Reduce fungicide use

Apply fungicides only when and where necessary, ideally based on a disease risk prediction

Use fungicides as part of an integrated control programme, e.g. combined with disease-resistant cultivars and cultural measures to reduce inoculum

Diversify fungicide treatments

Avoid repeated use of fungicides with the same mode of action

Use mixtures of fungicides with different modes of action

In a spray programme, alternate fungicides with different modes of action

Include multisite fungicides in mixtures or alternations

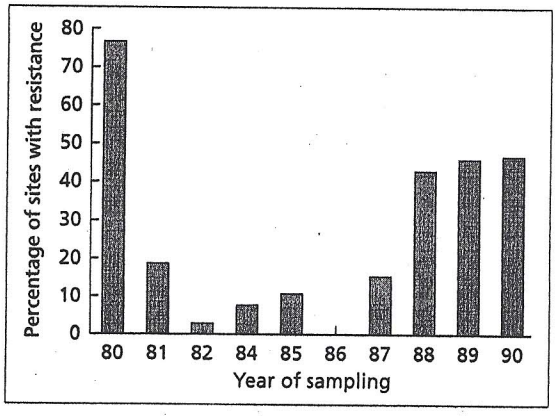


Fig. 11.11 Monitoring phenylamide resistance in *Phytophthora infestans* in potato crops in The Netherlands 1980–1990, showing the percentage of sites sampled at which resistance was found. (After Staub 1991.)

11.11). A rather similar pattern has also occurred in Ireland. The increases in resistance recorded in the late 1980s have been linked to several seasons when disease pressure was high, and the use of metalaxyl on seed crops, with the possibility of resistance being carried over to the next season. Current recommendations are to use alternative multisite fungicides on seed potato crops. This example illustrates the importance of understanding pathogen epidemiology in the management of fungicide resistance.

The final case histories concern experiences with SBIs. Unlike MBC and phenylamide fungicides, resistance to SBIs has developed more slowly, conforming to the directional selection model (Figs 11.8 & 11.9). In many cases such shifts in sensitivity have not led to any actual reduction of control in the field. Nevertheless, strategies to prevent any further erosion in the efficacy of SBI compounds are being pursued. One key component in these strategies is the morpholine fungicides, which act at different sites to DMIs in the sterol biosynthetic pathway. Thus, any reduction in sensitivity to DMIs does not affect sensitivity to morpholines. This provides a useful option for mixing or alternating SBI fungicides in the control of important diseases such as powdery mildew of cereals, *Erysiphe graminis*, or Sigatoka of bananas, *Mycosphaerella fijiensis*. The latter pathogen initially developed resistance to MBC compounds, while declining sensitivity to azoles has now been reported from banana crops in Central and South America. However, morpholines such as tridemorph still give consistent control, and are used in resistance management strategies which include alternation with different fungicides, and reductions in the number of sprays, and area of crop sprayed, whenever possible.

Putting resistance to practical use

Paradoxically, the occurrence of resistance can be an aid to understanding the mode of action of different fungicidal chemicals. Molecular genetic analysis of mutants altered in sensitivity to fungicides can provide detailed information on the target site of the fungicide, as well as clues as to why different classes of fungi differ in their response to particular compounds. For instance, analysis of laboratory mutants of model fungi such as *Aspergillus* confirmed that the site of action of MBC fungicides is β-tubulin. Isolating and sequencing the genes conferring resistance showed that loss of activity is due to changes in one or a few critical amino acids in the β-tubulin protein.

There are important practical spin-offs from such fundamental molecular studies. Firstly, detailed structure–activity interactions can be defined, indicating how particular chemicals bind to a target protein. This may aid rational design of molecules with improved activity. Secondly, molecular probes based on DNA sequences from specific resistance genes can be used to analyse resistance in natural fungal populations. Such probes can, for instance, detect the presence of individual resistance genes in field isolates of pathogens, thereby providing information on the distribution of resistance, and the likelihood of problems occurring with the use of a fungicide to control an epidemic. When combined with PCR it may even be possible to devise diagnostic kits for the rapid detection of particular resistance genes, thereby aiding decisions on practical disease control. Lastly, some genes for fungicide resistance have proved to be valuable tools for the genetic manipulation of commercially important fungi, as they can be used as dominant selectable markers for transformation. In other words, resistance to the fungicide confirms that the gene of interest has been successfully introduced into the fungus.

The future of fungicides

An appropriate comment to conclude this chapter is

that rumours of the complete demise of fungicides have been exaggerated! Gloomy predictions that the rapid adaptation of fungi to chemical selection would undermine the whole basis of control by fungicides have proved to be unduly pessimistic. Other worrying scenarios, such as exhausting the supply of new, safer chemicals to the extent that no new fungicides would ever be launched, have also been discredited. Following the comparative lull in discovery during the 1980s, the current decade has seen the introduction of several new chemical classes with high activity, low environmental impact, and novel modes of action. Compounds such as the strobilurins are likely to provide improved control of important diseases, such as *Septoria* on cereals, at lower dose rates and with greater flexibility in time of application, than previously available chemicals. In most major crops, growers now have a greater choice of effective fungicides than ever before. The status of chemical control of plant disease is therefore more encouraging than the current situation in clinical microbiology, where antibiotic resistance now threatens effective treatment of several previously tractable bacterial diseases.

There is, however, no room for complacency, both in terms of the ability of pathogens to adapt to new circumstances, and the continuing concerns about the environmental acceptability of chemicals. The age of blanket treatment of a crop with a single compound to combat one disease is to a large extent over. Chemicals are increasingly viewed as only one element in an integrated crop management system aimed at maximizing output while reducing inputs. It is of interest that many agrochemical companies have now merged with, or bought stakes in, seed companies marketing particular crop cultivars. This is part of the trend towards offering the grower an integrated control package, including host genetic resistance. At the same time several of the larger companies are investing in plant biotechnology, in the expectation that novel approaches to control, for instance using transgenic crops (see p. 228), will provide additional options alongside their portfolio of chemicals.

But what of the chemicals themselves? Already there is a greater emphasis on 'natural' approaches to pesticide discovery, not only through screening natural products for biological activity, but also in the search for chemicals which act via the endogenous defence systems of the plant. One of the most interesting recent developments has been the launch of CGA 245704, a benzothiadiazole compound (Table 11.2) which has no innate fungistatic or fungitoxic properties, but which nevertheless is active against a range of diseases. This and related chemicals, described as plant activators, switch on systemic acquired resistance in the host plant. There are hopes that because this is a completely different mode of action to conventional fungicides, such compounds will be invaluable in combating fungicide resistance. There may also be exciting possibilities in looking for chemical analogues of other, natural signal molecules, for instance hormones regulating fungal growth, so that processes such as sporulation or sexual reproduction might be inhibited. This would not prevent infections but would instead limit the rate of epidemic development by reducing inoculum. Such behaviour-modifying chemicals already form the basis for effective strategies for insect control, using analogues of volatile signal molecules known as pheromones. Another fruitful area may be to exploit natural chemistry which already serves a defence function. Recently, many small antifungal peptides have been isolated from plant seeds (see p. 143), and some of these show promise as natural fungicides, or even as defence proteins for engineering into transgenic plants. Thus the fields of fungicide discovery, biotechnology and biological control are now converging. Add to this the possibility of rational design of active molecules, and the prospects for further improvements in chemical control look bright.

Further reading

Books

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