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CENTENARY REVIEW

A century of fungicide evolution

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SUMMARY

Up until the 1940s chemical disease control relied upon inorganic chemical preparations, frequently prepared by the user. Key areas of use were horticulture and vegetable production with key targets being diseases that caused easily recognized damage. After this era and as the damaging effects of more crop diseases became obvious by the use of chemical control, the crop protection industry expanded rapidly and research to discover new active materials began in earnest. As new areas of chemistry were introduced, each one aiming to offer advantages over the previous ones, chemical families were born with research-based companies frequently adopting patent-busting strategies in order to capitalize on the developing fungicides market. Systemic fungicides offered new opportunities in disease control. The rise in Research and Development (R & D) and the increase in the number and quantity of chemicals being applied led to the introduction of regulation in the 1950s, initially on a voluntary basis, but now strictly controlled by legal obligations. In the 1960s, the market switched from horticulture and vegetables to one in which the main agricultural crops dominated. The cereal market, initially based on barley, moved to the current dominant market of wheat. The costs of R & D have risen dramatically in recent years and have become dominated not by the discovery process per se but by the provision of all the extra data needed to obtain registration. These rising costs happened at a time when markets showed little growth and are currently showing some decline. This has resulted in an industry that is continually striving to cut costs, normally by mergers and take-overs. As a consequence, many plant disease problems are not now being targeted by the industry and special measures have been introduced to ensure adequate disease control is available for these minor markets. Plant disease control will remain a necessity and fungicides will remain as a key factor in such control, although it is predicted that integrated control using chemicals, biological controls and biotechnology approaches will begin to dominate.

THE POSITION AT THE START OF THE TWENTIETH CENTURY

It is a reasonable assumption that plants have suffered from diseases and disorders ever since they appeared on earth. However, and no doubt due to lack of understanding of the causes of such plant health problems, diseases initially were not treated with as much concern as the direct effects seen on crops by natural phenomena such as floods, drought, hail, wind and frost. The situation for insects was different: they were visible, they could be identified one from another and their effects were very clear. Only when agriculture began to develop and people started to sow crops, primarily small grain cereals, did the diseases and disorders gain more attention. The first organized agriculture seems to have been based on growing barley (*Hordeum vulgare*) and the two wheats, *Triticum dicoccum* and *T. monococcum* in the Middle East about 5000 BC, from where it spread from the Mediterranean into Europe about 4500 BC and into England about 3500 BC (Behrens 1957; Braidwood 1963). To ward off the natural disasters, various rituals and traditions evolved and slowly the association between mildews, rusts and other diseases to natural phenomena would have been made. Of course, the identities of the true causes of plant disease were not known at this time, and would not be discovered for many centuries. To control plant diseases the rituals developed further, including the use of prayer to a particular God at specific times in the growth cycle of the crop. Diseases started to be given names, e.g. Samana disease of barley, possibly a rust but equally possibly another leaf parasite.

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Plant diseases receive frequent comment in the Bible, usually referring to mildews and blast. The terms 'mildew' and 'blast' are difficult to define by modern standards. Mildew could have referred to a general rotting of the crop or grain while blast could refer to a sudden affliction that seriously damaged the standing crop, but this is speculation.

As agriculture developed, so attempts were made to be more specific in the identity of the diseases and disorders and to adopt practical control measures. In Indian culture about 500 AD, there is an indication that it was considered plants could suffer from human type ailments, so diseases of trees and other crops were caused by, for example, 'phlegm', 'indigestion', 'wind', 'jaundice' and 'bile'. Remedies varied from dusting with ashes of cowdung to fumigating with fumes from '7 herbs' and nurturing with milk and honey. Should applied control measures have failed there was a general recommendation to transplant the affected plant into fresh soil. There was still a concept, however, that the fungal pustules, spots, deformities of the plants were the result of unhealthy conditions rather than the cause of them. As time went on this changed and the true nature of diseases became apparent. So began the age of collection and classification of the organisms responsible, coupled with the first studies into epidemiology and practical, scientific, disease control. Of course there was no crop protection chemical industry at that time (mid–late nineteenth century) and control centred on seed treatments and sanitation. As early as 1807 Prevost had demonstrated that bunt of wheat, caused by *Tilletia caries* was caused by a fungus and could be controlled to some degree by copper sulphate. He provided the first scientific evidence that the chemical would kill fungal structures. Previous scientists (e.g. Schulthess 1761) had simply observed that copper sulphate could provide some control of bunt but did not know why. It appears, however, that the observations of Prevost were not accepted for about 50 years, until De Bary published several accounts of studies on plant diseases in 1853–1867. By then, of course, the Irish potato famines (1840–1845) had resulted in the death of about a million people in Ireland and led to approximately half a million Irish emigrating to the USA. Interest in controlling the disease was intense, but many still held firm to the belief that the associated fungus (then called *Botrytis infestans*) was the result rather than the cause of the problem. Experiments in chemical control were tried; a mixture of lime, salt and copper sulphate was applied to the soil. It was not successful, and it is only to be pitied that the mixture was not applied to the foliage. It took another 10 years before the cause and effect relationship was accepted. Finally the fungus was placed into the new genus, *Phytophthora*.

It was in the latter half of the nineteenth century that chemical disease control really started to develop. Sulphur had long been known to have therapeutic properties. In 1824 a recommendation was made for it to be used to control powdery mildew of peaches (Robertson 1824) and in 1848 sulphur dust was recommended for control of vine powdery mildew (*Uncinula necator*) and other powdery mildews. Lime sulphur, prepared by boiling lime and sulphur together, seems to have been first mentioned in 1833 by Kenrick as a means of controlling vine powdery mildew. Copper sulphate was tried as a foliar spray for various diseases but was found to be phytotoxic on some crops. Sometime before 1862 lime was added to the copper sulphate to reduce its damaging properties, initially to reduce damage to wheat seed.

Lime sulphur did not control downy mildew of vines (*Plasmopara viticola*), but in 1882 Millardet noticed that where a liquid made from lime and copper sulphate had been applied to vines near roadways in order to discourage thieves from stealing the grapes, there was far less downy mildew. One of the best known fungicides, Bordeaux mixture, was thus announced in 1885.

Fungicidal preparations based upon the active ingredients sulphur, lime and copper sulphate dominated chemical disease control into the early twentieth century.

1900–1940: EPIDEMIOLOGY AND D.I.Y. DISEASE CONTROL

The twentieth century thus began with an increasing knowledge of plant diseases and their causes. Mycology and plant pathology were firmly established as scientific disciplines and the basic principles of plant disease control were being underpinned by studies on the epidemiology of the pathogens. The main interest, however, was with diseases that were obvious and that caused clear economic damage, either by direct effects on yield or were debilitating enough to the useful part of the crop to make it unattractive as food. In general, therefore, chemical disease control was aimed at horticulture, including all types of fruit, vegetables and established garden plants such as roses, and potatoes. The modern day concerns of the effects of the chemicals on the environment were largely non-existent.

Table 1 shows the history of fungicide development up to around 1940.

Rules and regulations concerning the safety of the operator while carrying out chemical treatments were also largely absent at this time and much was left to the common sense of the operator coupled with basic safety advice on the chemicals provided by the manufacturer. The provision of ready-made products or formulations was also in its infancy at the beginning of the century. Most users, primarily nurserymen, prepared their own fungicides from basic recipes (Table 2).

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Table 1. *Fungicides in use up to 1940*

Year	Fungicide	Primary use
BC	Natural products	Cankers, mildews
c. 60	Wine	Cereal seed treatment
1637	Brine	Cereal seed treatment
1755	Arsenic	Cereal seed treatment
c. 1760	Copper sulphate	Cereal seed treatment
1824	Sulphur (dust)	Powdery mildews and other foliar pathogens
1833	Lime sulphur	Broad spectrum, fruit, vines
1885	Bordeaux mixture	Broad spectrum
1891	Mercuric chloride	Turf fungicide
1900	$CuOCl_2$	Broad spectrum, especially *Phytophthora infestans*
1914	Phenylmercury acetate	Cereal seed treatment
1929?	Mercurous chloride	Soil applied fungicide especially for *Plasmodiophora brassicae*
1932	Cu_2O	Seed and foliar broad spectrum
1934	Dithiocarbamates patented	Broad spectrum protectants
1940	Chloranil, Dichlone	Broad spectrum, generally seed treatments

Table 2. *Early twentieth century recipes for preparation of fungicides and their uses* (*from Sanders 1910*)

Bordeaux mixture	Copper sulphate 2 lb Fresh burned lime 2 lb Water 10 gallons	Potato blight, apple and pear scab, cucumber and melon mildew, peach leaf curl, apple mildew, cherry leaf scorch, tomato leaf rust etc.
Woburn Bordeaux emulsion	Copper sulphate 10 oz Lime water 8·5 gallons Water to 10 gallons Paraffin (solar distillate, non inflammable)	As above. Also available ready made
Ammoniacal copper carbonate solution	Carbonate of copper 1 oz Carbonate of ammonia 5 oz Soft water 16 gallons	Tomatoes under glass. Recommended to 'wipe' tomatoes before marketing as preparation is poisonous
Potassium sulphide	Boil 0·5 oz in 1 gallon of water and add whites of two eggs to help preparation stick to leaves	Rose mildew plus other diseases
Violet fungicide	3 lb 4 oz copper sulphate 5 lb 8 oz copper carbonate 22 gallons of water Add 1 oz permanganate of potash	For various fungal diseases of violets, pansy and viola
Cupram, or copper carbonate	Carbonate of copper 1·25 oz Strong ammonia 16 liquid oz Water to 10 gallons	Roses, peaches, nectarines for shot-hole and peach leaf curl
Lime sulphur spray	Flowers of sulphur 1 lb Quicklime 15 lb Water 50 gallons	Apple and pear scab, leaf spot, mildew. Instructions include mixing ingredients in a wooden barrel with 6 gallons of water, when the mix will boil of its own accord. Stir and add the rest of the water when boiling stops
Iron sulphate	Iron sulphate 25 lb Sulphuric acid 1 pint Water 50 gallons	For disinfection of tomato houses. Prepare in a wooden vessel. Add acid to iron sulphate first then add water very cautiously

Proprietary products were available at this time for those who did not wish to take the time and trouble to make their own. They were to be obtained from 'any nurseryman, seedsman or dealer in garden sundries'. Various manufacturer's names and trade names appeared; 'Woburn' was a common trade name suffix while 'Voss' was a reputable manufacturer.

Application equipment was not refined compared with the standards of today, and certainly in the early part of the twentieth century the market was aimed at

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the gardener, allotment holder and fruit growers. Large, wheeled spraying machines were available to be used in orchards, usually with a manually operated pump that required two men to operate. Remote pumps were available with pipework to deliver the sprays up to 300 yards away. For smaller scale use, knapsack sprayers were available, often holding 3·5 gallons of spray. Many were primed by a hand pump or, in some cases, a bicycle pump. Hand sprayers and syringes were also common, and various bits of equipment were available for distributing dusts.

This state continued throughout the early 1900s, with investigations into activity spectra, appropriate doses and application timing making much progress. But some of the failings of the then current fungicides were becoming apparent. They did not always give good control, could be phytotoxic, they required frequent applications and dose rates were generally very high, typically in the 10–20 kg a.i./ha range. The need thus grew for better products. It could be argued that the seeds of the modern research-based crop protection industry were sown at this time. In 1930 McCallan (McCallan 1930), described laboratory techniques to discover new fungicides. The dithiocarbamate fungicides were the first success from this approach, originally produced as accelerators in the rubber vulcanization process, they were patented as fungicides in 1934 by Tisdale and Williams but took some time to reach the market as proprietary fungicides. The first to do so, tetramethylthiuram disulphide, known as thiram, was initially used as a turf spray and for controlling diseases of tulips before its major use as a seed treatment was developed. Thiram was not particularly good as a foliar spray and further compounds from this chemistry were based on heavy metal combinations, of which zineb, the combination with zinc, was one of the first to be introduced in 1943, closely followed by Nabam, based on sodium.

Other research around this time had discovered the chlorine-based quinones (Cunningham & Sharvelle 1940). They were not particularly effective as foliar sprays but chloranil and dichlone did find uses as seed treatments for crops such as cotton, legumes and brassicas.

During this time the UK Ministry of Agriculture and Fisheries were conducting annual surveys of crop diseases throughout England and Wales. It is interesting to note some of the comments made at that time (Table 3, Moore 1946).

The comments made on the diseases of wheat illustrate that the perception of the importance of diseases was very different when compared with today. The distribution of wheat diseases was obviously a factor; black stem rust was still common at that time but is rare in the UK today. Mildew, septoria and brown and yellow rust diseases were known but not considered very important. An indication that take-all was recognized as a problem is made, presumably because of its very visible effect on the crop, but the true impact of eyespot and the *Fusaria* were not appreciated. At no time was there any comment on controlling these diseases except by agricultural practice: varieties, cropping rotations and factors such as nitrogen application.

Even into the early 1940s the arsenal of available fungicides was very small.

1940–1960: THE RISE OF THE CHEMICAL CROP PROTECTION INDUSTRY

The war years were a period of great advances in the chemical industry in most countries and it is reasonable to conclude that on the cessation of hostilities some of the chemical resources that had been directed at the war efforts were redirected into agricultural research, particularly chemical crop protection. The period thus saw new chemistry and new compounds based on pre-war chemistry, e.g. dithiocarbamates, being introduced. Virtually all compounds were protectants i.e. they needed to be present on the crop at the time that the fungal infection arrived. Once infection was established they were virtually useless. The emphasis throughout this time was still on control of high value crops e.g. orchard crops, or control of diseases of obvious damage potential, e.g. potato late blight, cereal seed treatments for smuts and bunts and leaf spots of vegetables that reduced the market value of the crop. A notable addition to these was the introduction in 1955 of an antibiotic, blasticidin S, in Japan, specifically for rice blast control. This disease causes very severe and highly visible damage to rice. This was the first evidence that a systemic product could be applied on a field scale to small grain crops (accepting that fields in Japan are quite small and usually tended by a single family). Cereal mildew, yellow and brown rusts and wheat septoria were still not considered important and there were no practical moves to control them in the field. Black stem rust of wheat seemed to decline in the UK in the mid 1940s.

Many of the chemicals listed in Table 4 are still used today and most readers will be familiar with them.

What will be immediately obvious is that by the mid 1940s the emphasis had swung away from 'do-it-yourself' manufacture of simple copper, lime and sulphur based materials to reliance upon commercially produced products. Such products are still available, but the true age of the crop protection industry had begun. Most manufacturers were established chemical or oil companies, e.g. DuPont, Standard Oil.

Studies into aspects of plant pathology other than purely epidemiology were progressing rapidly with more interest being devoted to physiological aspects

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Table 3. *Some diseases of crop plants recorded by the UK Ministry of Agriculture and Fisheries, 1933–1942*

Crop and disease	Comments
Wheat	
Black rust (*Puccinia graminis*)	Most common in South-west Wales where barberry is common. Moderate attacks common elsewhere. Was epidemic in 1940
Yellow rust (*P. glumarum*, now *P. striiformis*)	Can appear in January, more usually in May. Can be widespread but generally slight. Deprez 80, Wilma and Wilhelmina varieties appear to be particularly susceptible.
Brown rust (*P. triticana*, now *P. recondita*)	Of little economic importance. Fairly common
Mildew (*Erysiphe graminis* now *Blumeria graminis*)	Can be seen in February, more commonly in May–August, more so in the east. Usually appears too late to do damage. Variety Wilma highly susceptible. Bad attacks linked to excessive nitrogenous manuring
Take-all (*Ophiobolus graminis*, now *Gaeumannomyces graminis*)	Most frequent where cereal follows cereal. Sporadic but bad in 1935 and 1937. Research is ongoing into the effect of soil conditions on the disease
Fusarium foot rot and ear blight (*Fusarium culmorum*)	Variable from year to year but presence does not indicate active parasitism. Other *Fusarium* spp. sometimes found
Eyespot (*Cercosporella herpotrichoides*, now *Pseudocercosporella herpotrichoides*)	First recognized in England in 1935, seeming most common in the East where up to 85% of fields can be infected. Is associated with lodging. Needs to be distinguished from Sharp Eyespot which is believed to be of fungal origin (proved to be caused by *Rhizoctonia solani* in 1943)
Leaf spot (*Septoria tritici*) and Glume blotch (*Septoria nodorum*, now *Stagonospora nodorum*)	Common diseases, mostly in the South but rarely do sufficient damage to be noticed
Ergot (*Claviceps purpurea*)	Generally found on cereals in small quantities every year. Reported on wheat in 1933, 1937 and 1942, but detected in seed samples every year from 1926 to 1943 by the Official Seed Testing Station
Potatoes	
Blight	Present every year but severe epidemics in 1931, 1936, 1941. Research is providing more information on the relationship between blight and weather conditions
Field beans	
Chocolate spot	The disease was recognized as being caused by *Botrytis* spp. in 1937, having previously been ascribed to a bacterium. May be severe
Apple	
Mildew (*Podospharea leucotricha*)	Very common, more so in 1938 and 1939. Less prevalent where lime sulphur is being used instead of Bordeaux mixture
Scab (*Venturia inaequalis*)	Common. Research has led to changes in control. Low pressure sprays superceded by a high pressure driving, or drenching spray, leading to improvements in spray apparatus. This led to a need to reduce phytotoxicity of fungicides and search for new ones. Bordeaux mixture being replaced by lime sulphur where phytotoxicity is a real problem

of plant infection and plant disease resistance, and to the biochemical action of the fungicides.

1960–1970: EXPANSION OF R & D, RAPID MARKET GROWTH

The 1960s was a time of considerable expansion in chemical crop protection (Table 5). The start of this period saw some consolidation of previous years with further introductions from established areas of chemistry. Mancozeb was introduced, a dithiocarbamate based on manganese and zinc, and went on to become possibly the most widely used of this chemical class. Captafol, a phthalimide fungicide, followed folpet into the fruit and vegetable markets for control of foliar diseases and was generally considered a better product because of its longer persistence which led on some crops to lower dose rates than folpet.

Thiabendazole (TBZ), originally introduced as an anti-helminthic in human and veterinary medicine

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Table 4. *Key fungicide introductions up to around 1960*

Year	Fungicide	Chemistry	Key uses
1942	thiram	dithiocarbamate	broad spectrum especially seed
1943	zineb, nabam	dithiocarbamate	broad spectrum foliar sprays
1944	biphenyl	aromatic hydrocarbon	citrus storage rots (impregnating wrappers)
1946	oxine copper	inorganic	broad spectrum seed treatment
	tecnazene	nitrobenzene	potatoes, Fusarium and sprout suppressant
1952	captan	phthalimide	broad spectrum, especially fruit and vegetables
	folpet	phthalimide	broad spectrum
1954	fentin acetate	inorganic	broad spectrum
1954	fentin hydroxide	inorganic	broad spectrum
1955	anilazine	triazine	leaf spots
	blasticidin S	antibiotic	rice blast systemic
	maneb	dithiocarbamate based on manganese	broad spectrum
1957	dodine	guanidine	foliar diseases, fruit and vegetables
1960	dicloran	nitroaniline	broad spectrum, especially *Botrytis* spp.

Table 5. *Key fungicide introductions 1960–1969*

Year	Fungicide	Chemistry	Key uses
1961	mancozeb	dithiocarbamate	broad spectrum
1962	captafol	phthalimide	broad spectrum
1963	dithianon	carbonitrile	foliar pathogens of fruit, but not powdery mildews
	propineb	dithiocarbamate	broad spectrum
1964	thiabendazole	methyl benzimidazole carbamate mode of action	broad spectrum systemic fungicide, also nematicide
	chlorothalonil	phthalonitrile	broad spectrum, now especially Septoria on wheat
	dichlofluanid	sulphamide	broad spectrum
1965	dodemorph	morpholine (SBI)	powdery mildews, ornamentals systemic, eradicant
	kasugamycin	antibiotic	bacteriocide and fungicide, especially *Pyricularia oryzae*
	polyoxins	antibiotic	Alternaria, Botrytis, Rhizoctonia (Japan)
	pyrazophos	organophosphorous	powdery mildews systemic
	ditalimfos	organophosphorous	powdery mildews
1966	carboxin	carboxanilide	smuts and bunts, systemic cereal seed treatment
	oxycarboxin	carboxanilide	rust diseases systemic
1967	drazoxolon	hydrazone	powdery mildew on soft fruit, roses; seed treatment
	tolyfluanid	sulphamide	broad spectrum, especially top fruit
1968	edifenphos	phosphorodithioate	rice blast specific systemic
	benomyl	methyl benzimidazole carbamate (mbc)	broad spectrum, not Oomycetes
	fuberidazole	mbc	seed treatment especially to control Fusarium. Systemic
	guazatine	diguanidine	seed treatments and foliar spray, broad spectrum
1969	dimethirimol, ethirimol	2-aminopyrimidine	powdery mildews, systemic
	triforine	piperazine DMI	broad spectrum systemic
	tridemorph	morpholine SBI	cereal diseases, especially powdery mildew

was introduced by Merck & Co. for control of a wide range of foliar diseases of fruit, vegetables and ornamentals and as a post-harvest treatment of fruit and vegetables to control post-harvest losses. Although not chemically a methyl benzimidazole carbamate (MBC), it shares the same biochemical mode of action and systemic properties as this major group, typified by benomyl introduced a few years later by Du Pont. The systemic property of the mbc fungicides (TBZ, benomyl, carbendazim, thiophanate, thiophanate-methyl) was unique and distinguished them from the other fungicides available at the time. They could be applied as foliar sprays or as root drenches and were transported around the plant in the transpiration stream. They were thus able to stop fungal development after the infection process had begun by attacking the pathogen from inside the plant. The root/soil application was really only

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successful for container grown crops or for furrow treatment of high value crops because the compounds are so tightly bound to soil particles (Peeples 1974).

1964 saw the introduction of chlorothalonil by the Diamond Alkali Company. It is a broad-spectrum protectant fungicide initially intended for control of a range of diseases of fruit, vegetables and glasshouse crops. Its primary agricultural use today is for control of *Septoria tritici* on wheat, especially as part of a resistance management programme with more modern 'at risk' chemistry.

The first of the 'morpholine' fungicides, dodemorph, was introduced in 1965, followed 4 years later by tridemorph. Dodemorph was introduced specifically for control of rose powdery mildew (*Sphaerotheca pannosa*) while tridemorph was introduced for control of barley powdery mildew (*Erysiphe graminis* f. sp. *hordei*). Ethirimol was also introduced at this time as both a seed treatment and foliar spray to control barley powdery mildew. These two fungicides possibly represent the first formal recommendations for specific fungicides to be applied as foliar sprays to cereals but exact information relating to the commercial introduction of such cereal foliar sprays is somewhat unclear. Research was certainly being conducted into the effect of several of the new fungicides from the new areas of chemistry (ethirimol, tridemorph, benomyl) and also maneb (dithiocarbamate based on manganese), on control of cereal foliar diseases. The main target appears to have been *E. graminis*, particularly on barley, but attention was turning to investigating effects of control of other diseases on both barley and wheat such as the rusts (*Puccinia* spp.), *Septoria* spp. and *Fusarium* spp. This research was being carried out throughout Europe (Benada 1972; Bruin 1972; Chery 1972; Meeus & Haquenne 1973; Mundy & Page 1973;). Leadbeater *et al.* (2000) indicate that both tridemorph and ethirimol were introduced 'at the end of the 1960s', but it is unclear whether they were commercially widely available at that time. Possibly as a warning for the future, barley and cucumber powdery mildew quickly became resistant to ethirimol (Brent 1982). Thomas & Turner (1998) report that in 1970 there were no recommendations for the use of foliar applied fungicides on wheat in the UK and such recommendations did not appear until 1975. It certainly appears that the main cereal of interest at that time was barley, with wheat only becoming a major market later.

Carboxin was introduced in 1966 as a systemic seed treatment specifically for smuts and bunts as it is inactive on other fungal groups and not effective as a foliar spray. It was especially useful in control of loose smut (*Ustilago nuda*) as seed is infected by the fungus being inside the seed tissue rather than contaminated where the fungal spores are on the outside and infect the newly emerging shoot on germination. Contaminated seed can thus be cleaned up by a surface-acting fungicide while infected seed needs a systemic product. Carboxin was quickly used in mixtures with thiram or organo-mercury compounds which provided control of other seed contaminants such as *Helminthosporium* spp. Its close relative, oxycarboxin, was introduced as a foliar spray for control of cereal rust diseases at the same time.

Despite the advances being made in chemistry and the developing market for chemical crop protection products, all the key active ingredients discovered and introduced at this time for control of foliar diseases were for control of Deuteromycetes (Fungi Imperfecti), Ascomycetes and Basidiomycetes. Control of diseases caused by Phycomycetes, the prime example being potato late blight (*P. infestans*) still relied upon the established chemistry, principally dithiocarbamates. This situation was not to change until towards the end of the next decade.

1971–1980: THE RISE OF REGISTRATION AND RESISTANCE

The 1970s was possibly the most significant decade for advances in crop protection chemistry. By this time there were a great number of research-based companies operating in the UK alone: Boots Agrochemicals, Dow, Fisons Agrochemical Division (previously Pest Control), ICI Plant Protection Division, May & Baker, Murphy, PBI and Shell (Copping 2003). All the major oil companies had joined the crop protection market race, including Elf, Gulf, Chevron and Occidental. Ciba and Geigy had merged to form Ciba-Geigy in 1969. In mainland Europe both BASF and Bayer were active, with extensive R & D facilities in Germany.

The increasing use of fungicides in agriculture, as distinct from the horticultural markets of previous years, had shown the benefits of controlling diseases of field crops such as barley and wheat, both large hectarage crops in developed countries and both offering significant market opportunities. Application systems were becoming more sophisticated, fungicide dose rates were falling and the chemicals becoming safer (Table 6). More systemic compounds were being introduced. This latter attribute was heralded as providing a means for reducing the number of applications by using extended spray intervals.

Table 7 shows the key fungicides introduced at this time. These introductions illustrate a very significant principle that has continued to the present day; that of analogue chemistry. At this time the agrochemical market was growing at approximately 6·3% per annum in real terms (Finney 1988) and all research-based companies wanted to gain a share of the increasing market. However, research was expensive and one of the easiest ways to generate an active compound was to 'patent bust' an area of known

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Table 6. *The decline of fungicide dose rates and increasing safety as chemistry expanded* (*toxicity data from The Pesticide Manual*)

Fungicide	Year of introduction	Typical dose rate kg a.i./ha	Oral $LD_{50\ mg}$ a.i./kg (mammalian)
Sulphur	19th century	10–20	400–500
Copper sulphate	19th century	10–20	472
Mercuric chloride	1891	seed treatment	1–5
Dithiocarbamates	1940s–1960s	1·5–3·5	>8000
Phthalimides	1950s–1960s	<2·0	>5000–>22 000
Chlorothalonil	1964	0·75–1·25	>10 000
MBC generators	1960s	0·25–1·0	>15 000
Dicarboximides	1970s	0·75	3500–10 000
DMI triazoles	1970s	0·125–0·25	568–>6200
Strobilurins	1990s	0·125–0·25	>5000

Table 7. *Key fungicide introductions 1970–1980*

Year	Fungicide	Chemistry	Key uses
1970	iprobenfos	phosphorothioate	*P. oryzae* systemic Japan
	thiophanate, thiophanate-methyl	mbc mode of action	broad spectrum
	validamycin	antibiotic	*Rhizoctonia solani*, especially rice (Japan)
1973	benodanil	benzanilide	rusts, systemic
	triadimefon	triazole DMI	broad spectrum systemic
	imazalil	imidazole DMI	broad spectrum, mainly post harvest and cereal seed treatment
1974	iprodione	dicarboximide	Botrytis and relatives, *Alternaria* spp.
1975	bupirimate	2-aminopyrimidine	powdery mildews (apple) systemic
	fenarimol	pyrimidine DMI	powdery mildews
	nuarimol	pyrimidine DMI	seed treatment and foliar, especially cereals
	buthiobate	pyridine DMI	broad spectrum on Ascomycetes/Deuteromycetes
	vinclozolin	dicarboximide	Botrytis and relatives
1976	carbendazim	mbc	broad spectrum
	procymidone	dicarboximide	Botrytis and relatives
	cymoxanil	cyanoacetamide oxime	Peronosporales, systemic, now available in mixture only
1977	fosetyl-Al	phosphonate	Phycomycetes, especially *Plasmopara viticola* systemic via phloem
	metalaxyl, furalaxyl	phenylamide	Oomycetes, foliar and soil borne, systemic
	triadimenol	triazole DMI	broad spectrum
	prochloraz	imidazole DMI	broad spectrum especially *Pseudocercosporella herpotrichoides*
1978	ofurace	phenylamide	Oomycetes
	propamocarb	carbamate	Oomycetes, soil and foliar
1979	bitertanol	triazole DMI	*Venturia inaequalis* (apple scab)
	diclobutrazol	triazole DMI	broad spectrum
	etaconazole, propiconazole		
	tolclofosmethyl	organophosphorus	Rhizoctonia, Sclerotium
	fenpropimorph	morpholine SBI	broad spectrum especially cereals

activity discovered by a competitor. Hence the initial introductions of new areas of chemistry e.g. MBcS, dicarboximides, triazoles, were soon followed by new molecules from these areas from other research-based companies. Research into the biochemical mode of action of fungicides was also becoming increasingly common as scientists strove to understand how and why the new chemistry worked. Discovering how new fungicides worked was difficult and introduction of new chemistry to the market before the biochemical mode of action was known was common; a situation that still exists today for much new chemistry. There was a concept at the time that by understanding how fungi and fungicides worked it may be possible to design a fungicide to disrupt an essential fungal process and so provide disease control. Such a desire

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was quite reasonable but has seen little success to date. It is hoped that current studies into fungal genomics may provide more opportunities for this approach.

In 1965 the first of the morpholine fungicides had been introduced, dodemorph. This was very successful in controlling powdery mildews but its use was limited to ornamentals. In 1969 it was followed by tridemorph, active against powdery mildews and rust diseases of cereals, especially barley, and against sigatoka diseases of banana. Tridemorph was followed in 1979 by fenpropimorph. Its activity against cereal diseases was generally considered better than tridemorph and it is now the more widely used of the two on cereals. The morpholine fungicides, like the azoles, are sterol biosynthesis inhibitors (SBIs). However, morpholines and azoles act at different parts of the SBI pathway. The morpholines (which include the piperidine fungicide fenpropidin) inhibit Δ8–Δ7 isomerase and Δ14 reductase while the azoles inhibit C14-demethylation. Azoles fall into the class collectively known as the DMIs, DeMethylation Inhibitors. The DMI group of fungicides was to expand further in the next decade to become a major group of fungicides with uses in most crop areas.

This period saw several market introductions for control of oomycetes. A major discovery was fosetyl-Al, a phosphonate fungicide with the unique property of being phloem mobile. Its mode of action is still unclear but is thought to be due to two factors; a direct effect of the product on the fungus and by the chemical reinforcing the defensive reactions of the plant (Fenn & Coffey 1984; Guest & Grant 1991). It was followed by the first of the phenylamides, metalaxyl. This was an immediate success and found many uses for foliar and seed treatments. Also introduced was propamocarb, a carbamate fungicide introduced for control of soil-borne *Pythium* and *Phytophthora* spp. and for various downy mildews in horticulture.

The new chemistry reaching the market at this time thus provided the user with excellent choice, excellent economic return on the investment of using the product, and much better disease control than had been possible with the older chemicals. As a consequence of this, use of the older established chemistry declined and in some cases disease control was based exclusively on the new chemistry. What was not appreciated at this time was that the new chemistry was generally based on a single site of action, a property usually accompanied by resistance to that chemistry being governed by a simple genetic change in the pathogen. Fungicide resistance thus developed as a major problem. Resistance had been known in the 1960s e.g. to organomercury seed treatments (Noble *et al*. 1966), but was not considered a major threat. Major fungicide groups thus began to suffer from severe cases of resistance due to overuse, primarily in crops which received several applications during the season, e.g. vines for control of *Botrytis cinerea* or, in the case of ethirimol and barley powdery mildew, where seed treatments were followed by foliar sprays (Brent 1982). The mbc compounds were the first to be affected in vines. When they began to fail, growers turned to the then newly introduced dicarboximides to control *B. cinerea*. Within a few seasons these too failed as resistance developed (Russell 1995). Attempts to manage the problems generated were made: mixtures of compounds were tried, compounds were withdrawn from particular uses for a while in a hope that resistant strains would disappear from the populations. All were useful strategies but not entirely successful, largely because any initiatives taken were being made at a local company level. The industry realized at the end of the 1970s that this situation was having a serious effect and was threatening the use of many products of similar chemistry from different manufacturers. Industry thus began a major collaboration scheme with the formation of the Fungicide Resistance Action Committee in the early 1980s (Russell 1995) in order to co-ordinate resistance management strategies for areas of chemistry at risk of resistance development. FRAC is still very active today as the issues continue with modern chemistry.

1980–PRESENT: INDUSTRY CONTRACTS, FIERCE COMPETITION

The past 20 years have been very productive in terms of the introduction of new chemistry and expansion of established areas (Table 8).

The 1980s began with more very successful compounds being introduced for control of downy mildews and potato late blight from the phenylamide group. By this time resistance to phenylamides was known (Russell 1995) but the industry reacted very quickly with common agreed resistance management strategies based on a policy of only selling the chemistry in mixture with a compound from a different mode of action, usually mancozeb, and limiting the number of applications allowed. The sale of seed treatments to control foliar diseases was stopped. These strategies worked and the area of chemistry is still in common use although cyprofuram was withdrawn for commercial reasons. In 1996 metalaxyl was replaced in the market by metalaxyl-m (mefenoxam), an optical isomer of metalaxyl.

Triazole chemistry also began to expand with the introduction of many more compounds. In general each successive compound offered some advantage over its predecessors in basic activity or activity spectrum or its persistency and mobility on the crop. But once again resistance appeared and began to limit the use of chemicals in certain areas. The first sign of a problem occurred with barley powdery mildew (Wolfe & Fletcher 1981) but was soon followed by

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Table 8. *Key fungicide introductions 1981–present*

Year	Fungicide	Chemistry	Key uses
1981	benalaxyl	phenylamide	Oomycetes
	flutolanil	anilide	basidiomycetes, especially *Rhizoctonia* spp.
	mepronil	carboxamide	basidiomycetes, especially *Rhizoctonia* spp.
	pencycuron	phenylurea	*Rhizoctonia solani*, especially rice
1982	cyprofuram	phenylamide	Oomycetes
	triflumizole	imidazole DMI	broad spectrum, especially fruit and vegetables
1983	flutriafol	triazole DMI	broad spectrum
	penconazole		
	flusilazole		
	diniconazole		
	oxadixyl	phenylamide	Oomycetes
1986	fenpropidin	'morpholine' SBI	broad spectrum, especially cereal foliar diseases
	hexaconazole	triazole DMI	broad spectrum
	cyproconazole		
	myclobutanil		
	tebuconazole		
	pyrifenox	pyridine DMI	broad leaf crops, leaf spots
1988	difenoconazole	triazole DMI	broad spectrum
	tetraconazole		
	fenbuconazole		
	dimethomorph	cinnamic acid	Oomycetes
1990	fenpiclonil	phenylpyrrole	cereal seed treatment, foliar especially
	fludioxonil		*Botrytis* spp.
	epoxyconazole	triazole DMI	broad spectrum
	bromuconazole		
1992	pyrimethanil	anilinopyrimidine	*Botrytis* spp., *V. inaequalis*
	metconazole	triazole DMI	broad spectrum
	fluquinconazole		
	triticonazole		
	fluazinam	dinitroaniline	Oomycetes, *Botrytis* spp.
	azoxystrobin	QoI	broad spectrum
	kresoxim-methyl		
1993	metaminostrobin	QoI	broad spectrum
1994	cyprodinil	anilinopyrimidine	*Botrytis* spp., *V. inaequalis P.herpotrichoides*
	mepanipyrim		
1996	famoxadone	QoI	Oomycetes
	mefenoxam	phenylamide	replaced metalaxyl
1997	quinoxyfen	phenoxyquinoline	powdery mildews
1998	fenhexamid	hydroxyanilide	*Botrytis* spp.
	fenamidone	QoI	Oomycetes
	trifloxystrobin		
	cyazofamid	cyanoimidazole	Oomycetes
2000	picoxystrobin	QoI	broad spectrum
	pyraclostrobin		
2002	prothioconazole	triazole DMI	broad spectrum

other diseases, e.g. cucumber powdery mildew (Schepers 1985). However, prolonged use of this chemical class against many pathogens on a wide variety of crops has shown that resistance is not always an issue. In some cases this can be attributed to the swift action by FRAC of introducing effective resistance management strategies, but in other cases the pathogen itself seems to be of low risk for resistance development. The chemical class has thus continued to expand. The azoles are now arguably the most successful class of fungicides to have been introduced, the most recent to be announced being prothioconazole in 2002 (Mauler-Machnik *et al.* 2002).

The third major morpholine fungicide, fenpropidin, was introduced in 1986 primarily for use on cereals. Despite being sterol biosynthesis inhibitors, the morpholines have not suffered the resistance problems of the DMIs. They are very popular fungicides today, often appearing in coformulated mixture with DMIs and other chemistry. Because of their different mode of action to DMIs they will support

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resistance management strategies for this group and are often used in mixture with them.

DMI fungicides, despite their broad spectrum of activity, are not good fungicides for control of *B. cinerea* on vines. Until recently, control of this pathogen relied upon careful manipulation of resistance management strategies for the key botryticides, dicarboximides and mbcs. In the early 1990s this changed with the introduction of the phenylpyrrole and anilinopyrimidine fungicides. Both groups immediately found ready markets for *Botrytis* control. However, the lessons learnt from the dicarboximides and mbcs were very clear: *Botrytis* was a high-risk pathogen, and both groups were introduced to the market with clear anti-resistance strategies.

In the early 1980s control of downy mildews was still reliant upon old chemistry (dithiocarbamates, chlorothalonil) and the resistance-limited phenylamides.

There were clearly market opportunities and dimethomorph was introduced in 1988 specifically for control of oomycetes. Despite the common name, this material is not a 'morpholine' fungicide. Propamocarb, not affected by resistance problems, was now developed in mixtures with either mancozeb or chlorothalonil to enter the *P. infestans* control market. It was joined by fluazinam, a compound that combines oomycete activity with activity against *Botrytis* in certain markets, primarily in Japan. Each compound had its attributes and several blight control programmes were put together to capitalize on the properties of each one.

In 1992 the most significant chemical group since the DMIs were introduced came to the market; the strobilurins. The group was derived from a naturally occurring fungicide, β-methoxy-acrylic acid. They are a truly remarkable group with activity against all major fungal genera. They show protectant, systemic and eradicant action, although different compounds have different activity spectra and show different properties. The first strobilurin fungicides to reach the market were azoxystrobin from Zeneca (now Syngenta) and kresoxim-methyl from BASF. Other similar compounds soon followed. Not all are from strobilurin chemistry but they all share the same biochemical mode of action. Collectively they are called the QoI group, a term derived from their mode of action in binding at the Q_0 site on cytochrome b. An excellent review of this area of chemistry is available (Bartlett *et al*. 2002). They quickly began to dominate key markets, especially cereal foliar sprays as they could control the majority of disease problems. Their biochemical mode of action, inhibiting mitochondrial respiration, had been known before product launch, as had possible modes of resistance. What was not foreseen, however, was the speed at which resistance would develop in *E. graminis* on wheat and *P. viticola* on vines (Heaney *et al*. 2000). Since then, more cases of resistance have appeared and the group is considered a high risk one. One of the most recent pathogens to be affected is *M. graminicola* (*S. tritici*) on wheat, a pathogen initially regarded as low–moderate risk based largely on its DMI risk analysis. Resistance in this pathogen was first noticed in 2001 and appears to have developed rapidly such that the compounds are no longer recommended for its control in the UK (HGCA 2004). All QoI compounds are now recommended for use within strict resistance management guidelines (FRAC 2004). The compounds also have the property of affecting cereal plant physiology such that yield benefits are seen in the absence of disease control. Possible causes of this effect include reduced respiration, stimulation of nitrogen metabolism, and reduced energy consumption in combination with effects on green leaf area duration (Dimmock & Gooding 2002, Oerke *et al*. 2004). There is thus a possibility that even where resistance could be a problem, the compounds may still find a use as 'yield enhancers'.

No QoI resistance has been found in *P. infestans* despite much exposure. This has been surprising given the history of this pathogen to exposure to the phenylamides. Recently a new compound, cyazofamid, has come to the market for potato late blight control. The biochemical mode of action of cyazofamid is related to the QoI materials but instead of acting on the outside of the mitochondrial membrane at the Qo site, it acts on the inside of the membrane at the Qi site. To date there have been no reports of resistance development.

SAFETY ISSUES: REGISTRATION AND PESTICIDE USE

The rise in the number of chemicals being introduced into agriculture and horticulture in the late 1940s led to some concerns over operator safety. In the UK, a Working Party was established in 1950 by the Minister of Agriculture and Fisheries to consider such matters. In 1952 its first report, the Agriculture (Poisonous Substances Act) was passed and the first regulations under the act introduced in 1953. A second report soon followed, this time covering the possible risks to consumers of treated crops and led directly to the formation of the Advisory Committee on Poisonous Substances used in Agriculture. In 1955 a third report extended concern to effects on the environment.

The second report recommended that new toxic chemicals and their formulations be notified to Government Departments before being put on the market. This led to the voluntary Notification of Pesticides Scheme being agreed between Government and the industry, represented by the Association of British Chemical Manufacturers, the Association of British Insecticide Manufacturers and the British Pest Control Association. The Association of British

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Insecticide Manufacturers was to become the British Agrochemical Association, now the Crop Protection Association.

In 1964 the scheme was brought up to date and the requirements strengthened with the introduction of the Pesticides Safety Precautions Scheme (PSPS). Under this scheme the manufacturer of a new chemical was required to provide data relating to the safety of the product. Data should include full chemical description, proposed uses, mode of action, toxicity and persistence. Data were to be relevant to the user of the product, to the consumer of treated produce and to domestic animals and wildlife. Data were considered by the Advisory Committee and its Scientific Subcommittee. The key outcome was that various recommendations on how the product could and would be used were agreed between the manufacturer and the committees/government departments. The recommendations were published and the key elements were included on product labels. These would normally include advice on operator safety, the crops able to be treated, the dose rate limitations and harvest interval to be observed. Environmental safety was covered by recommendations such as not to spray near ponds or not to spray crops in flower in order to protect bees.

The PSPS was accompanied by introduction of the Agricultural Chemicals Approval Scheme, a voluntary scheme under which the efficacy of crop protection chemicals could be approved for various uses. Chemicals submitted to the scheme were required to have been through the PSPS. Decisions on whether or not a chemical would be approved were based on trials efficacy data submitted by the manufacturer and, possibly, by trials carried out by Advisory Services or independent research organisations. Once approved, the product label would carry the recognized approval mark.

In 1984 it was announced that the UK Government would introduce legislation to give statutory force to arrangements to ensure the safe and efficient use of pesticides. In 1985 the Food and Environment Protection Act 1985 (FEPA) and in 1986 the Control of Pesticides Regulations (COPR) were introduced. The latter act requires that any chemical substance used as a pesticide must be tested and approved by the Ministry of Agriculture for safety and efficacy. Similar schemes operated throughout other countries. Harmonization of the registration processes throughout the EEC was begun by Council Directive 91/414/EEC. Its aim is to provide a framework whereby data requirements are standardized between countries such that registration of an active ingredient in one country should facilitate its registration in another. This system is presenting many challenges, especially concerning acceptability of data between countries and the approval of products for minor market use. Various reviews of the current situation are presented by Smeets (2003), Flynn (2003) and Rotteveel (2003).

The increasing regulatory requirements seen over the past decades, and especially in the past 20 years, have placed much financial pressure on the research-based crop protection companies. Increasing demands for toxicology, metabolism and environmental data to support registration applications have resulted in a cost of approximately £100 million to discover, research, develop and register a new product. This has had several consequences on the industry. Firstly, it has led to a rapid reduction in the number of research-based companies willing to make the large capital investments required to support research in an increasingly competitive market where farmers and growers are continually striving to cut costs. This reduction has been seen as a time of mergers and takeovers in which research facilities of two companies can be combined and rationalized to an extent that they can be supported by the combined profit of the new joint company. A history of how the industry has changed is provided by Copping (2003).

The other main effect of increasing research costs comes from the simple fact that a new product has to make a profit for the company introducing it to the market. Today there are very few fungicide markets that can almost guarantee a sales profit capable of supporting or justifying a major R & D investment. Whereas 40 or 50 years ago the horticultural and vegetable markets were targeted, today such markets are far too small to justify the investment in required regulatory studies and can only be considered as 'add-on markets' to be considered once success in a major market has been achieved. Markets must also be considered at the international level; no single country market would justify the investment. Possible exceptions exist for control of rice blast in Japan, where many rice blast specific products are introduced just into Japan by Japanese companies.

The views of different crop protection companies will vary a little in which markets they consider to be viable, such differences being related to their expertise in the market, their crop and market support infrastructure, and the other components of their portfolio. Table 9 shows typical markets. They are dominated by wheat, rice and vines. The omission of potatoes may seem strange, but when considered at a financial level there is much debate as to whether the profit to be generated from a blight only fungicide would support the research, development and registration costs. An inevitable consequence of these financial constraints is that many markets, especially the smaller horticultural and vegetable ones, are experiencing drastic reductions in the number of compounds available for use.

Council Directive 91/914 has also led to many chemicals coming under increased regulatory scrutiny, a process which has in many cases led to requests

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Table 9. *Key markets considered as being able to support an R & D programme for discovery of a new fungicide*

Pathogen	Crop, disease	Comments
E. graminis	Wheat powdery mildew	Activity against barley powdery mildew would be a bonus. If successful, market could be extended to other powdery mildews on other crops e.g. vines, apples
M. graminicola (*S. tritici*)	Wheat leaf spot	Activity against other leaf spots, especially sigatoka diseases of banana would be a bonus. May possibly lead to fungicides capable of controlling apple scab (*V. inaequalis*)
Plasmopara viticola	Vine downy mildew	A bonus would be control of potato late blight (*P. infestans*) and control of other Phycomycetes
Botrytis cinerea	Grey mould of vines	Possibly a marginal market, but could allow introduction into other *Botrytis* markets and control of fungi such as *Monilia*, *Sclerotium*, *Sclerotinia*, *Alternaria*, *Rhizoctonia*
Magnaporthe grisea	Rice blast	A viable market only in Japan where high yields justify the cost of protection

for more safety data to be provided. In some cases this has led to registrations for various uses being withdrawn as the costs of providing the extra data would not be recovered by continuing sales. In other cases, the costs of conducting necessary studies on a new molecule and supporting the molecule in the market may not justify a registration application. Such has been the concern at this situation that special consideration measures for 'off label' uses have been put into operation (Brooijmans & Heer 2000; Chapman 2000).

THE FUTURE FOR FUNGICIDES

The question as to whether we need new fungicides has recently been considered by Hewitt (2004). His general conclusion was 'yes' but that the overall need could be modified by advances in other technology. Many forces are operating to allow this conclusion to be reached. Market forces, driven by the profitability (or not) of research programmes aiming to provide the new chemistry are an overriding factor. As research costs increase so the available markets become less attractive. The global crop protection market in 2003 showed a nominal growth of 6·2% to US$26 710 million, but when the effects of trade weighted inflation and currency exchange rates are excluded, the real change was a decline of 1·6% (CropLife International 2004). This followed the trend seen since 1999 when the decline was 5·7%, 2001 with a decline of 6·8% and 2002 with 5·0%. Maybe a more stable picture will emerge for 2004. The global disease control market was worth US$5746 million in 2003.

Resistance development to new chemistry has to be considered also. Today's research methods seem prone to discovery of new molecules that present a significant risk of resistance development. Despite the efforts of FRAC in recommending use guidelines and resistance management now being a constituent part of the registration process, resistance is unlikely to be avoided altogether with most chemistry and the best people will achieve is a delay in the time to when it is first seen. Should fungicide research move to discover chemicals with multi-site modes of action which could avoid resistance problems? This may seem a good solution to resistance but could generate problems with registration. Such compounds are likely to be general toxophores and may thus not pass today's stringent regulatory processes. The discovery of single site of action chemicals that pose a low resistance threat is not ruled out, but unfortunately such a property is only to be realized in retrospect. A further threat to effective resistance management comes from the fact that several compounds used in resistance management strategies are the old multi-site compounds such as dithiocarbamates and phthalimides. It would create severe problems if such compounds were lost due to regulatory reviews.

Biocontrol will undoubtedly contribute more in the future, most likely allied with the use of more natural compounds. Individually these approaches have not been particularly successful except in niche markets, but recent research has shown that when combined they seem able to complement each other very well (Schmitt & Seddon 2004). Time will tell if these approaches will be viable. Biotechnology, which has seen growth of approximately 19% in 2003 to a market value of US$3940 million (CropLife International 2004) due to increased sales of herbicide-tolerant and insect-resistant crops, has not yet had an impact upon disease control. It may make contributions when public opinion swings into its favour. Unfortunately many people see biotechnology as a means to introduce a form of disease control that will not be broken down by the pathogen and as technology that will only need to be introduced once into the crop to provide lifelong disease control. I urge

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caution here. The fungi that attack plants have shown themselves to be extremely adaptable over the years, changing their abilities to overcome various conditions. I would predict that biotechnology could control them for a while but would not banish them for ever.

The overall conclusion must be that disease control will be an everlasting challenge that will require all available resources in order to provide affordable nutritious food for all. Fungicides will remain an essential part of the disease control effort, but the recent developments in the industry, the increasing difficulty of discovering new active molecules and the increasing costs of bringing new products to market must eventually reduce the hitherto productive past. It is doubted if new products will cease to be introduced, but disease control in the future is likely to be far more integrated than in the past with all technologies being employed, chemicals, biological controls and biotechnology.

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