3 The Fungicides Market

Key Points

- Fungicides are discovered and marketed mainly by large, international, private businesses.
- The discovery and development of a new fungicide is very expensive and risky.
- Sales of major fungicides need to amount to around US$1000 million to recoup costs.
- Fungicides are sold to nearly all countries; sales in middle-income countries are rising sharply.
- Cereals, fruit and vegetable crops, grapevines, soybean, rice and pome fruits make up 85% of fungicide use.

Introduction

The discovery, development and marketing of fungicides is (and always has been) almost exclusively performed within the private sector, by large, independent, multinational companies. In contrast, plant breeding and extension activities, which support genetic and cultural disease control methods, were until recently mainly in the domain of state agencies and universities. Fungicide development has received only very limited public-sector support, mainly through co-investment in upstream research. Thus, to stay in business, a company producing fungicides needs to provide a satisfactory rate of return for its investors and to generate resources essential to company growth and development.

The agrochemicals business is risky and the companies continually review their commercial objectives and tend to attack only those markets that are large enough to support additional products, or are dominated by product(s) that are vulnerable and are under-developed or new. Fungicide targets and their priorities in the discovery process are defined not by their biology, but by their economics. The exercise of target definition is straightforward and common to all companies, the only differences between companies being the level of return or risk deemed to be acceptable in the pursuit of a particular market goal. For example, the control of oilseed rape (canola) pathogens may appear an important target to farmers or to regional sales managers wishing to extend their influence in the market, but it may not be large enough to support a dedicated fungicide research programme. Similarly, the control of *Gaeumannomyces graminis* in cereals is estimated to hold very large financial benefits for both the farmer and the fungicide manufacturer, but to commit resources to a discovery effort directed towards a market that has not been proven through the successful introduction of a product is risky, as the commercial size of the problem is difficult to quantify.

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What level of return is required by industry in order for the control of a particular disease problem to become an acceptable commercial target? To answer that question it is necessary to understand the costs involved in the discovery and development process, and to appreciate the effects of financial thresholds that companies impose upon the sale of products.

Candidate fungicides enter the process of biological evaluation and commercialization from various sources and range in cost from several hundred to many thousands of dollars each. Passage through the screening and development system eliminates most candidates, with approximately one commercial product emerging for every 140,000 compounds screened (Sozzi *et al.*, 2010). This industry-wide measure of success worsens annually as new materials that meet increasing demands of performance, competition and legislative restrictions become more difficult to discover.

The current industry average cost for the development of a new fungicide is approximately US$256 million, committed over a period of about 10 years, prior to product launch (Walter, 2010). Two-thirds of the total cost is attributed to biological efficacy trials and, in particular, exhaustive toxicological and environmental safety tests which alone may account for 60% of the investment. The primary discovery research, including chemical synthesis, biological testing and toxicology, accounts for only US$85 million. The remaining US$171 million is taken up in production chemistry, field trials, compliance toxicology and registration. The current total compares with US$80 million in 1976 and highlights the contribution of compliance with increasingly stringent regulatory requirements.

Companies normally take out a patent (which in most countries last 20 years; see Box 3.1) near the beginning of the 10-year development period. A new product may not show an operating profit for at least 2 years after commercialization. Thereafter, there may be only 8 years of patent protection in which to recoup the research and development investment costs on all compounds tested, including those that failed at some point in the development process. Companies can expect a few years of maximum profit, before having to contend with direct competition after patent expiry. Clearly, company philosophy must embrace a responsibility to the shareholders, employees and the growth of the enterprise itself, and develop only those products that will achieve the status of a profit maker. Therefore, the projected value of a fungicide at maturity is a critical issue in making discovery and development decisions.

Although companies are reluctant to publicize their economic thresholds, a projected return on investment of up to US$200 million of sales per annum at product maturity may be required to support the development of a pesticide. Furthermore, using that as a measure of commercial acceptability, together with the assumption that even exceptionally good new products will capture only 25–33% of an existing market, it is possible to identify specific disease and crop targets for fungicides. On the basis of a threshold of US$200 million sales annually, and accepting that the industry aim is to produce market leaders, targets would have to possess a current or projected value of between US$800 million and US$1000 million of sales to merit inclusion, not only in the development process for a new product, but also at the level of research. Of course, targets of lesser value may be considered, depending upon the evaluation of investment risk. For example, the development of a biological fungicide may be cheaper than that of a synthetic, and in that case smaller markets may become commercially attractive. However, it is important to note that despite

Box 3.1. Patents and intellectual property

The patenting system has a 'bad press' among the general public, but without it, it is hard to see how we could have access to any of the technological advances, from pharmaceuticals to transport to communications, that make up our modern world. The patenting system is central to the operation of the fungicide companies and an understanding of the basic principles helps explain the nature of the industry.

The purpose of the patenting system is to encourage innovation in all manner of products and industries. It does this in three main ways; first it grants an inventor time to exploit his/her invention during which only the inventor can make and sell the product. Secondly, it forces the inventor to disclose full details of the invention so that competitors can benefit from the underlying knowledge – patent means 'open'; an alternative would be secrecy. Thirdly, it forces an inventor to use a patented invention; failure to do so can result in the granting of licences (permission) to other parties to develop the idea.

The patenting system operates via government agencies called Patent Offices. The European Union has a single office while most other countries have their own. Many countries are signatories to patent treaties that bind themselves to abide by the common principle of respecting the patent system and the free trade of products.

The process of patenting starts when an inventor submits a 'Provisional Application' to the local patent office. The inventor may be the fungicide company, a university or a private individual. This is typically a short document describing the invention and is cheap to file and process. The main purpose of the Provisional from the inventor's perspective is to establish a date from which the eventual Patent, if granted, will be dated. Provisionals are typically filed prior to the full development of the invention. The document is not made public but the inventor can disclose it to organizations to try and secure the financial backing to develop the invention; these might be fungicide companies or venture capitalists, research agencies or charities. If such an organization were interested, the organization might buy the invention and fund the research, granting the inventor a royalty or some other recompense.

The patent office will in due course examine the patent and determine whether the invention satisfies the criteria of patentability; these are novelty, non-obviousness and utility. Novelty is determined by reference to published material, whether other patents, academic papers or the general literature. These are collectively called the 'prior art' and lie in the 'public domain'. The non-obviousness criterion is designed to disallow trivial improvements. Utility is defined as conforming to natural laws (i.e. perpetual motion machines are not patentable) and being capable of commercial exploitation.

The patent office does not examine provisional patents at first. Provisional patents last only 1 or 2 years. If the inventor (or the new owner) wishes to pursue the patent, increasingly large fees need to be paid to the patent office and patent attorneys along with full descriptions of the patent. Furthermore, the inventor must file the patent in all countries in which s/he would like protection. New treaties are making this international filing more straightforward.

The key element of the description is the section called the 'Claims'. Key fungicide patents are typically descriptions of chemicals that can be marketed safely and economically as fungicides. It is likely that, at first, only a single compound is known to the inventor and described in detail. However, nearly all fungicides fall into classes of similar compounds that share a common structural feature and a common MOA. It would be futile to patent just a single compound. All a competitor would have to do,

Continued

Box 3.1. Continued.

following disclosure of the patent, is alter the compound in a variety of ways, find a variant with activity and patent that. The competitor would have saved the huge costs of chemical discovery and the inventor would find its market diminished. Hence the inventor will tend to inflate its discovery and claim the use of all related compounds, including many that may not even have been synthesized. In contrast, the Patent Office, encouraged by competitors, will insist that only tried and tested compounds are included. This tension is central to the day-to-day life of fungicide companies as they seek to outflank each others' patents.

Eventually the patent office may grant the 'Letters Patent'. The owner of the invention now has a specified period, typically 16 or 20 years from the time of the Provisional, for exploitation. In practice however, development of the patent may have taken 5–8 years so the effective period may be only 10 years or less. During this period the inventor not only needs to recoup the cost of manufacture and distribution, but also of research and development. After this period the compound(s) go 'off patent' and anyone can legally make and sell the product. They will have the benefit of full details of the manufacturing process upon which to base their version of the product. The price will inevitably drop. Some companies avoid the process of discovery altogether and choose to specialize in the manufacture of so-called 'generic' products. Furthermore, some countries do not operate a patent system and thus feel free to manufacture any product at any time. They are prevented from selling their products in countries that operate within the patent system by fear of sanctions from the World Trade Organization.

The patent system has many critics. Many complain that companies exploit the system by filing minor improvements as separate patents, thereby extending the effective length of the protection. The system is certainly slow and expensive. However the alternatives would be for companies to rely on secrecy, like Coca-Cola does with its recipes, or to rely on state research organizations to discover and develop the compounds.

the advances in unravelling the biochemical, physical and biological bases of fungicide activity, the discovery process is still serendipitous and it is more likely that products are made on the basis of 'develop what you discover' rather than through a strictly targeted approach.

The Global Fungicides Market

At about 23% of the total agrochemicals market, global fungicide sales are estimated to be US$13.3 billion, including seed treatments (2011 figure) (http://www.amis-outlook.org/). Figures from the USA indicate that 78% of fungicide use is in agriculture, with 18% in industry, commerce and government and 5% used in the home and garden market (http://www.epa.gov/pesticides/pestsales/07pestsales/market_estimates2007.pdf).

In the early phase of the development and use of modern fungicides (1960–1970), the growth of the fungicide market was slow compared with that of the more established herbicide and insecticide sectors. From about 1970, the potential use of fungicides as agents to protect the quantitative and qualitative aspects of yield became widely recognized and demand increased, stimulating an annual sales growth rate of 3–5% (Fig. 3.1). The increasing potency of the fungicides is illustrated by the slow decline in the weight of fungicides being made and used.

The increase in efficacy has been due the development of systemic fungicides which typically are active in the parts per million range. The increasing pace of new fungicide introductions is shown in Fig. 3.2 and Table 3.1.

The Western European temperate cereal and vine industry was traditionally the largest fungicide market but other countries and regions are fast catching up. Europe has 40% of world sales compared with 28% in the Americas. In Asia and the New World, fungicide sales were restricted due to low crop values or to the presence of yield-limiting factors other than disease, such as water deficiency. Even so, the early 1990s witnessed a fungicide sales growth of over 5% per annum in those regions, in response to increased usage in South-east Asia on rice and in South America on high-value crops such as bananas. Table 3.2 lists some of the incomplete data compiled by the Food and Agriculture Organization of the United Nations (FAO). Several major countries such as China do not report to the FAO. The numbers show that the traditional users of fungicides especially in Europe are reducing the quantity of active ingredient being applied. In contrast, many middle-income tropical countries are fast increasing their use of fungicides (Schreinemachers and Tipraqsa, 2012); see Table 3.2.

Fungicide sales by mode of action

Two fungicide classes dominate global sales (Table 3.3), with DMI and QoI making up over 50% of sales. The DMI group has been the mainstay of foliar disease protection

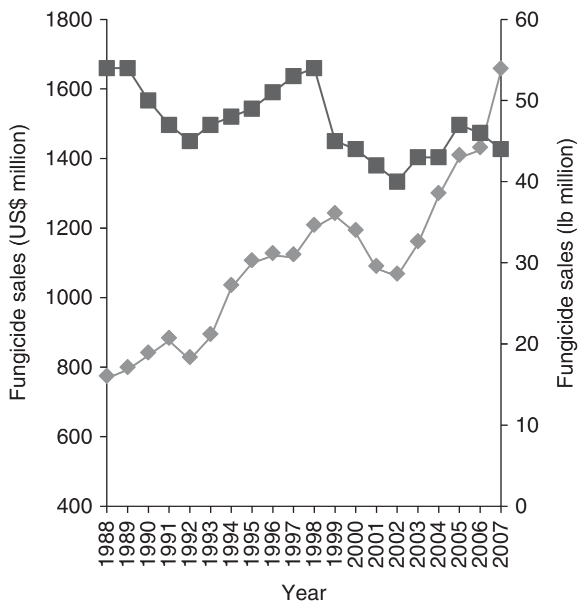

Fig. 3.1. The US fungicides market: increasing sales (—◆—) but declining weight (—■—).

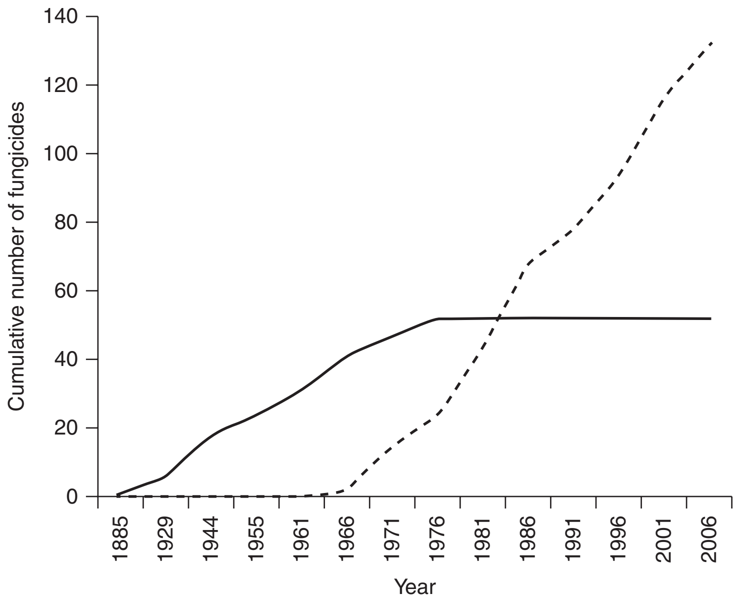

Fig. 3.2. Development of non-systemic (——) and systemic (– – –) fungicides.

Table 3.1. Fungicides introduced 1960–2005.

Date	Fungicides introduced
1940–1960	Thiram, zineb, nabam, biphenyl, oxine copper, tecnazene, captan, folpet, fentinacetate, fentinhydroxide, anilazine, blasticidinS, maneb, dodine, dicloran
1960–1970	Mancozeb, captafol, dithianon, propineb, thiabendazole, chlorothalonil, dichlofluanid, dodemorph, kasugamycin, polyoxins, pyrazophos, ditalimfos, carboxin, oxycarboxin, drazoxolon, tolyfluanide, difenphos, benomyl, fuberidazole, guazatine, dimethirimol, ethirimol, triforine, tridemorph
1970–1980	Iprobenfos, thiophanate, thiophanate-methyl, validamycin, benodanil, triadimefon, imazalil, iprodione, bupirimate, fenarimol, nuarimol, buthiobate, vinclozolin, carbendazim, procymidone, cymoxanil, fosetyl-A1, metalaxyl, furalaxyl, triadimenol, prochloraz, ofurace, propamocarb, bitertanoldiclobutrazol, etaconazole, propiconazole, tolclofos-methyl, fenpropimorph
1980–2000	Benalaxyl, flutolanil, mepronil, pencycuron, cyprofuram, triflumizole, flutriafol, penconazole, flusilazole, diniconazole, oxadixyl, fenpropidin, hexaconazole, cyproconazole, myclobutanil, tebuconazole, pyrifenox, difenoconazole, tetraconazole, fenbuconazole, dimethomorph, fenpiclonil, fludioxonil, epoxyconazole, bromuconazole, pyrimethanil, metconazole, fluquinconazole, triticonazole, fluazinam, azoxystrobin, kresoxim-methyl, metaminostrobin, cyprodinil, mepanipyrim, famoxadone, mefenoxam, quinoxyfen, fenhexamid, fenamidone, trifloxystrobin, cyazofamid, acibenzolar-*S*-methyl
2000–present	Picoxystrobin, pyraclostrobin, prothioconazole, ethaboxam, zoxamide, fluopicolide, flumorph, benthiavalicarb, iprovalicarb, mandipropamid, boscalid, silthiofam, meptyldinocap, amisulbrom, orysastrobin, metrafenone, ipconazole, proquinazid, penthiopyrad, isopyrazam, ametoctradin

Table 3.2. Major fungicide users. (From http://faostat.fao.org/site/424/default.aspx#ancor.)

Country	Year of data	Tonnes
Italy	1990	106,121
Australia	1992	94,193
France	1997	64,050
Mexico	2008	50,845
Colombia	2004	44,370
Japan	2000	40,612
USSR	1990	26,000
USA	1998	24,493
Turkey	2008	17,862
Ecuador	2004	15,505
India	2006	13,367
Portugal	2002	13,320
Spain	1990	12,312
Thailand	2004	12,292

Table 3.3. Market share of different fungicide groups. (From Krämer *et al.*, 2012.)

Fungicide group	Code	Market share (%)
Demethylation inhibitors (DMIs)	G1	29.2
Quinone outside inhibitors (QoIs)	C3	22.1
Dithiocarbamates	M3	6.8
Copper and sulfur	M1/M2	4.7
Phthalimides	M4	4.2
Methyl benzimidazole carbamates (MBCs)	B1	4.1
Succinate dehydrogenase inhibitors (SDHIs)	C2	3.5
Chloronitriles	M5	3.2
Phenylamides (PAs)	A1	2.5
Morpholines	G2	2.5
Melanin biosynthesis inhibitors (MBIs)	I1 and I2	2.4
Carboxylic acid amides (CAAs)	H5	2.1
Dicarboximides	E3	1.9
Anilinopyrimidines (APs)	D1	1.9
Others		8.1

for 30 years, whereas the QoI have established their market position only in the last decade. Many older contact fungicides with multi-site MOAs retain large market shares after many decades of use. This is a testament to the efficacy of their action, their safety record and the economic benefit they give to the grower. The strong sales of the sole chloronitrile, chlorothalonil, can be attributed to its value as a mixing partner with QoI, DMI and SDHI fungicides. One would expect a gradual decline in sales of MBCs and a corresponding rise in the sales of SDHI fungicides.

Global fungicides market by crop

Fungicide manufacturers focus resources on the research and development of new products that fit the most valuable markets. In terms of crops, vegetables, temperate cereals, rice, grapevine, soybean and pome fruit dominate the global fungicides market, representing nearly 85% of the global sales value in 2005 (Fig. 3.3). These ratios are fairly constant but there has been a large increase of value of the soybean market which has increased from 1.1% in 1990 to 8.3% in 2005.

Large fungicide markets are attractive not only because of their size, but also because they utilize long-established and well-understood technologies and present clear challenges for new-generation compounds. Absolute value, however, has to be balanced against the diversity of targets within a particular market, an assessment of current and potential competition, the level of technology required to succeed in that market and a view of future commercial and technical trends.

With a target validation threshold of US$800 million of fungicide sales, only vegetables (US$1.72 billion), temperate cereals (US$1.20 billion), rice (US$740 million), grapevine (US$700 million) and pome fruit (US$320 million) can be considered as potentially viable commercial targets for investment in the discovery and development of new fungicidal products.

The vegetable market is highly segmented, comprising many crops and a broad spectrum of pathogens. Accordingly, the registration of new products into this market is expensive and as a general target, vegetables do not offer a viable return on investment. Hence, fungicides sold into the vegetable market are always well established for use against pathogens in commercially more important sectors such as cereals. An exception is potatoes where fungicide use has become very intense in Europe. The inadvertent introduction of the *Phytophthora infestans* second mating type into Europe in the 1980s allowed the organism to circumvent numerous resistance genes that were previously effective (Haas *et al.*, 2009). As a result the fungicide companies have introduced ametocotradin and fluazinam to complement the established metalaxyl family of fungicides.

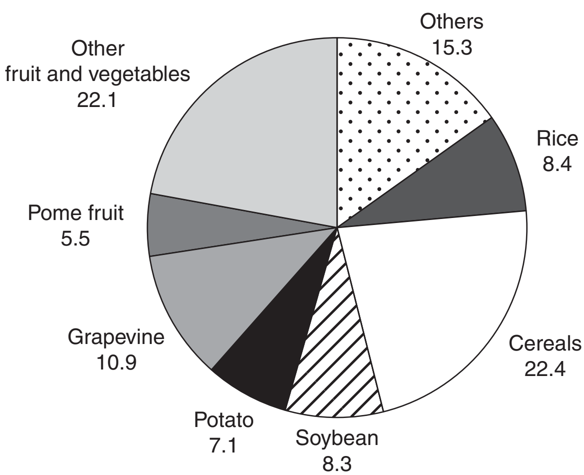

Fig. 3.3. Global fungicides market share (%) for the major crop groups in 2005 (total fungicides market in 2005 = US$7491 million). (Copyright: Phillips McDougall, 2006.)

Cereals

The cereals – wheat, rice, maize and many minor crops – are the mainstays of agricultural production worldwide. In 2011, annual production of rice was 722 million Mt, of maize was 883 million Mt, of wheat was 704 million Mt and of barley was 134 million Mt (http://faostat.fao.org/site/339/default.aspx).

Rice is grown in Africa, the Americas and Europe, but over 75% of the world's production is based in Asia. Average yields range from 1.4 t/ha in Brazil to 4.57 t/ha in Japan, with the most effective producers being Japan, South Korea, USA, China, Europe and Taiwan. Although rice cultivation in Japan accounts for only 1.5% of the global rice area, it commands 67% of the total rice fungicide sales market.

Following the Second World War, Japan began a period of intensive food production. Fertilizers, the use of high-yielding rice varieties and mechanization were encouraged in a bid to increase rice production. It is likely that these measures were also conducive to the incidence and severity of PYRIOR, rice blast, together with a range of other pathogens including *Rhizoctonia solani*, sheath blight and bakanae disease.

Disease control involves the use of cultural methods, resistant varieties and fungicides, usually employed in combination. The use of resistant varieties is a principal method in the control of PYRIOR. However, in Japan fungicide application is the main method of general disease control and this is reflected in the size of the market, currently estimated to be US$647.9 million, although the high price of rice and hence the level of fungicide sales would fall if the Japanese market was opened to wider competition.

Most rice fungicide products are of Japanese origin. Early rice blast control measures based on the use of organomercury products were abandoned with the removal of mercury compounds from Japanese agriculture in 1968. Since then a variety of products have been launched and the character of the market is now highly diverse and fragmented. Rice farmers tend to own small farms that are managed with few inputs or, commonly in Japan, act as an adjunct to another profession. Fungicide use reflects this situation, with products being sold in small packs of easily applied formulations.

Although some products, notably tricyclazole and probenazole, are equivalent in sales value to some successful temperate cereal fungicides, few achieve the high values of the leaders in that market. Tricyclazole is also unusual in that it originated from a non-Japanese company, Eli Lilly (now DowElanco), and has risen in popularity to become the market leader in rice blast control. Most companies will acknowledge the geographic and economic advantages of Japanese manufacturers in developing rice fungicides for Japan and South-east Asia and it is interesting that sources in the industry, including DowElanco, consider the current rice market to be difficult to exploit without a Japanese partner and to be economically risky, given the high return on investment that is required to support appropriate research and development programmes.

PYRIOR is found wherever rice is grown and in Japan is the most serious of all the rice pathogens. However, the climatic conditions in southern China, Sri Lanka, Taiwan, Indonesia, Vietnam and the Philippines favour sheath blight rather than rice blast. Sheath blight also occurs in South America and Africa. Disease control is through the use of fungicides, although in many tropical regions yields are too low to justify fungicide application, and protection from disease depends upon the use of less susceptible varieties and cultural control. Cropping patterns also differ between areas, with some rice being direct-seeded, some transplanted. Rice may be paddy- or upland-cultivated and, in areas of northern India, deep-water rice is common. The differences in cultivation impact directly on fungicide usage but also reflect the value of the crop, which in turn governs fungicide inputs.

The temperate cereals, i.e. wheat, barley, sorghum, oats and rye, are widely grown outside the tropics, throughout the world, with a total production of about 900 million Mt. Yields range from an average of 10 t/ha in Europe to less than 1–2 t/ha in the Former Soviet Union (FSU), China, India and Australia. However, yields vary between crops and regions, and within regions. In Western Europe wheat yields in excess of 10 t/ha are not uncommon, but yields in parts of Africa may not exceed 500 kg/ha.

Fungicide use in cereals is equivalent to 34% of the total input, or US$1700 million in sales, mainly in winter wheat but with significant usage in winter and spring barley. Because of the dominance of Asia and the FSU in cereal-growing area, it is to be expected that fungicide use and area under cultivation are not balanced. Europe, which supports less than 10% of the total cereals area, provides nearly 20% of the total production and is the primary cereal fungicide market, with an estimated value of US$1500 million.

In North America and Australia, cereal yields are limited more by water shortage than by the lack of disease control and hence the fungicide market is relatively small and localized. Generally, in order to be justified economically, foliar fungicide applications are restricted to areas where yields of over 2 t/ha can be achieved. Most treatments include a triazole, and QoI fungicides are becoming more popular. Specific mildewcides may be justified especially where malting barley production is threatened by triazole resistance as in Western Australia (Tucker *et al.*, 2014). Seed treatments are very widespread; these include triazoles such as fluquinconazole and SDHIs such as carboxin.

The development in Western Europe of techniques of intensive cereal production, in particular the use of fertilizers in continuous cultures of wheat and barley, while allowing for potential yields of over 10 t/ha to be achieved, was accompanied by increased disease levels. The use of fungicides in cereals was stimulated by the need to control disease and permit new levels of production, and profit, to be reached. The main target in Europe is now SEPTRI. Several fungicide groups are used and a remarkably large number of products are available to growers.

Triazoles are highly effective broad-spectrum products. Used as seed treatments and foliar fungicides, they form the most valuable segment of the cereal fungicide market. Their introduction into cereals heralded a revolution in disease control, providing the farmer with the means to control several pathogens for up to 4 weeks and, because of their ability to redistribute in the crop, to achieve a high level of reliability. The earlier appearance of morpholines into the cereal market was not as successful, probably because of their limited spectrum. However, the onset of resistance that eventually reduced the utility of triazoles against ERYSGT and ERYSGH acted to promote a re-emergence in the use of morpholines, which are now usually applied in combination products or tank mixtures with triazoles. Similarly, the failure of benzimidazole fungicides to control wheat eyespot led to the commercial success of the imidazole DMI fungicide prochloraz.

The cereal market is receptive to new product introductions, demonstrated by the rapid rise of the newer DMIs such as epoxiconazole, cyproconazole and prothioconazole (Tables 3.4 and 3.5). Their strength lies in their high activities and their reliability against other major cereal pathogens, particularly SEPTRI. The need to be aware of

Table 3.4. Cereal seed products. (From http://www.hgca.com/crop-management/disease-management.aspx.)

Fungicidal ingredient (products often include an insecticide)	Mode of action	Pathogen groups controlled
Carboxin	C2	B, GSA
Difenconazole	G1	GSA
Fludioxonil	G1	B, GSA
Fluquinconazole	G1	GSA, some control of GFA
Prochloraz	G1	GSA
Flutriafol	G1	GSA
Fuberidazole	G1	GSA
Ipconazole	G1	GSA
Triticonazole	G1	GSA
Prothioconazole	G1	GSA
Silthiofam	C7	Take-all
Thiram	M3	B, GSA

B, *Basidiomycota*; GSA, general soil or seed *Ascomycota*; GFA, general foliar *Ascomycota*.

potential resistance by employing fungicides with different biochemical MOAs encourages the use of a variety of fungicides. Farmers are being encouraged to use reduced frequencies or rates of fungicide application and to use appropriate mixtures to provide broad-spectrum control. There is a re-emergence of the use of non-systemic materials such as chlorothalonil which, although lacking the performance of systemics, have non-specific MOAs and are low-risk compounds with respect to resistance development. The QoIs introduced from 2000 have broad-spectrum activity and complement the triazoles. Many pathogens quickly developed resistance but with the judicious use of mixtures and alternations the QoI have achieved excellent sales.

Specific mildewcides, often developed initially for the grape industry, are also used on cereals. Examples include quinoxyfen, spiroxamine and metrafenone. Their MOAs differ from QoI and triazoles and hence they assist in resistance management strategies.

Many products are sold as mixtures. This is for two main purposes. One reason is to extend the spectrum of the product – i.e. the range of pathogens controlled. Selling products as formulated mixtures has obvious advantages for growers. It allows a range of pathogens to be controlled without having to make multiple applications across their field or having to make so-called tank mixtures of products that might not be compatible. Secondly it has a role in fungicide resistance management (Chapter 6). In addition to other fungicides, mixtures often contain insecticides or nematicides, again increasing the convenience for growers. Tables 3.4 and 3.5 illustrate the wide range of products with overlapping functions.

Grapevine

The principal vine fungicide market is in Europe but large industries also exist in Australia, New Zealand, South Africa and Chile. In all these places, fungicides are critical components of crop protection.

Table 3.5. Foliar products in use in UK for wheat. (From http://www.hgca.com/crop-management/disease-management.aspx.)

		Activity rating[a]					
Active ingredient(s)	Mode of action	Eyespot	ERYSGT	SEPTRI	Yellow rust	PUCCRT	Head blight
Cyflufenamid	U6		4				
Cyprodinil	D1	4	2				
Epoxiconazole + boscalid	G1 + C2	4	2	4	4	5	
Epoxiconazole + isopyrazam	G1 + C2	2	2	4	4	5	
Fluxapyroxad + epoxiconazole	G1 + C2	3	2	5	5	5	2
Prothioconazole + bixafen	G1 + C2	4	3	5	4	5	3
Metrafenone	U8	3	4	1			
Chlorothalonil	M5		1	3	1	1	
Mancozeb	M3		1	2	1	1	
Folpet	M4			2			
Prochloraz	G1	3	1	3	1	1	
Carbendazim	B1	1	1	1	1	1	2
Thiophanate-methyl	B1						2
Fenpropidin	G2		3	1	2	2	
Fenpropimorph	G2		2	1	2	3	
Quinoxyfen	E1		3				
Proquinazid	E1		4				
Spiroxamine	G2		2		2	2	
Azoxystrobin	C3		1	1	3	3	
Picoxystrobin	C3	1	1	1	4	3	
Pyraclostrobin	C3	1	1	1	4	4	
Trifloxystrobin	C3		1	1	2	2	

Dimoxystrobin + epoxiconazole	C3 + G1			3		5	3
Fluoxastrobin + prothioconazole	C3 + G1	4	2	4	4	5	3
Kresoxim-methyl + epoxiconazole	C3 + G1	2	1	4	4	4	
Kresoxim-methyl + fenpropimorph	C3 + G2		2	1	2	2	
Cyproconazole	G1	1	2	2	4	3	
Difenoconazole	G1		1	3	1	3	
Epoxiconazole	G1	2	2	4	5	4	2
Fluquinconazole	G1		2	3	3	3	
Flusilazole	G1	3	2	2	2	2	
Flutriafol	G1		1	2	2	2	
Metconazole	G1		2	3	3	3	3
Propiconazole	G1	1	1	2	2	2	
Prothioconazole	G1	4	3	4	4	2	3
Tebuconazole	G1		2	2	4	4	3
Tetraconazole	G1		2	2	2	2	

[a]From http://www.hgca.com/media/253724/wheat-fungicide-performance-2012-13-1-.pdf.
1, low activity; 5, highest activity.

The market is divided into the control of PLASVIT and UNCNEC, the causes of downy and powdery mildews. Other targets, particularly BOTCIN, grey mould, are economically significant but of secondary value compared with the two major pathogens in many markets. The grapevine is a particular challenge and opportunity for the fungicide industry. The value of a hectare of vintage grapes can exceed several thousand dollars so growers are very keen to ensure adequate protection. The three main pathogens are very diverse organisms (PLASVIT is from the *Oomycota*; powdery mildew and botrytis are from the *Ascomycota*) responding to different classes of fungicides. The crop is a perennial and thus subject to disease build-up in the environment of the vineyard. Being long-lived, the introduction of genetic resistance will always be very difficult to combine with quality.

The grapevine fungicide market is accordingly well established and supports many products (Table 3.6). The use of multi-site, surface-active protectants has always had a crucial role in disease management. Initially, control of PLASVIT was achieved solely through the use of Bordeaux mixture, with sulfur being employed to control UNCNEC. More recently, protectants such as mancozeb became widely used and now have an important technical and economic role within the market. Their immobility is a disadvantage as they cannot be used to protect the foliage or fruit that is not impacted during treatment or the extension growth that is subsequently produced. In addition, surface-bound protectants are subjected to the vagaries of the weather and are susceptible to loss through the action of rain. Characteristically, repeat applications of protectants are employed, with an interval between treatments as short as 10 days during periods conducive to disease or of economic importance, e.g. during fruit development.

Use of fungicides in grapes for wine production is constrained especially by the needs of the wine maker and the customer. The fermentation of wine is undertaken

Table 3.6. Fungicides used in Australian wine production. (Modified from Essling and Francis, 2012.)

Product active ingredient(s)	Mode of action	Pathogen targeted
Penconazole, tetraconazole, fenarimol, myclobutanil, tebuconazole, hexaconazole, triadimenol	G1	UNCNEC, BOTCIN
Spiroxamine	G2	UNCNEC
Fenhexamid	G3	BOTCIN
Metrafenone	U8	UNCNEC
Quinoxyfen	E1	UNCNEC
Boscalid	C2	UNCNEC, BOTCIN
Trifloxystrobin, azoxystrobin, pyraclostrobin	C3	UNCNEC, BOTCIN, PLASVIT
Dimethomorph	H5	PLASVIT
Benalaxyl, metalaxyl	A1	PLASVIT
Pyrimethanil, cyprodinil	D1	BOTCIN
Fludioxinil, iprodione	E2	BOTCIN
Chlorothalonil	M5	BOTCIN, PLASVIT
Captan	M4	BOTCIN, PLASVIT
Metiram, mancozeb	M3	PLASVIT

by yeast species that are susceptible to inhibition by fungicides that might persist in the must (pulped grapes). Furthermore, the large supermarket chains demand extremely stringent residues levels. In practice this limits the use of fungicides in two ways. First, many compounds can only be used early in the growth of the berries so as to allow time for the concentration to decline below that detectable in the bottled wine. Secondly, because limits are placed on the number of detectable compounds (including herbicides and insecticides and regardless of hazard) growers tend to use only one fungicide, to the detriment of resistance management strategies (Essling and Francis, 2012).

Pome (top) fruit

The main fungicide targets are in apples, comprising VENTIN (apple scab), *Podosphaera leucotricha* (apple powdery mildew), with the addition of *Alternaria mali* as a specific target in the Japanese fruit market. The control of VENTIN accounts for 50% and *P. leuchotricha* for 25% of the total sales value. Conditions favourable to infection are pathogen-specific and usually the pathogens do not occur simultaneously on the same host. For this reason different regions may be associated with particular disease problems, as in the Po Valley of northern Italy, which, because of its generally high humidity, is noted for severe outbreaks of apple scab. However, to be competitive, the most popular pome fruit fungicides are active against both major pathogens.

Several products make up the pome fruit fungicide market (Table 3.7). Early control measures relied on multi-site protectants, but the advantages of curative activity afforded by newer products were quickly adopted by growers and the major market share is now attributed to systemic materials such as the triazoles. Compounds under development include the broad-spectrum strobilurins. Resistance to the systemics was recorded soon after their introduction and a system of resistance management using mixtures or alternative applications of products with different MOAs is now a characteristic of the market and a feature of any development programme for new materials.

The objective of fungicide applications in pome fruit is to protect yield quality. The maintenance of leaf integrity, while essential to yield quantity, is of secondary value to the production of unblemished fruit. The dominance of apple scab control reflects the demands of the retailer and consumer for clean fruit, even though apples infected by VENTIN are not considered to be harmful and its eradication is purely cosmetic.

Table 3.7. Fungicides used for pome fruit.

Compound	Mode of action	Disease
Bupirimate	A2	*Podosphaera leucotricha*
Captan	M4	VENTIN
Copper	M1	*Alternaria mali*, VENTIN
Fenarimol	G1	VENTIN, *P. leuchotricha*
Fusilazole	G1	VENTIN, *P. leuchotricha*
Hexaconazole	G1	VENTIN, *P. leuchotricha*
Myclobutanil	G1	VENTIN, *P. leuchotricha*
Penconazole	G1	VENTIN, *P. leuchotricha*
Triforine	G1	*P. leuchotricha*

Leading Fungicide Manufacturers

In the past, companies focused upon their national markets but this is now unsustainable. The rising costs of the development of new fungicides and the maintenance of existing products due to increased regulatory pressures have encouraged the industry to consolidate. Consequently, companies have become increasingly international and, through merger, acquisition and considerable good luck in the discovery and development of key products, a few have emerged to dominate the market. Currently there are six major companies in the crop protection area: Monsanto, Syngenta, Bayer CropScience, DuPont, BASF and Dow. However, only three can be considered full-scale fungicide discovery and production companies: Syngenta (sales 2008: US$3142 million), Bayer CropScience (sales 2008: US$2501 million) and BASF (sales 2008: US$2297 million). Dow and DuPont retain niche activity in fungicide discovery.

Only 20 years ago there were ten large fungicide discovery companies. Of the current big three, Syngenta derives from Zeneca and Novartis; Sandoz and CIBA were previously acquired by Novartis; Bayer acquired AgrEvo and Rhone-Poulenc. BASF is unique is remaining a broad-based chemical company whereas Bayer and Syngenta are focused on crops and include seed businesses as well as chemicals.

Another group of companies specialize in manufacturing and distributing off-patent (or 'generic') compounds. They thus avoid the huge cost and risk of fungicide discovery and development. They do incur the costs of registration in smaller markets. On the other hand, they will only survive if they undercut the original patent holder so their profit margins will always be limited. The biggest generics company in the fungicide area is MAI (sales 2008: US$415 million) followed by Nufarm (sales 2012: US$200 million).

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