doi: 10.17221/83/2015-PPS

Recent Developments and Challenges in Chemical Disease Control

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Abstract

Leadbeater A. (2015): **Recent developments and challenges in chemical disease control**. Plant Protect. Sci., 51: 163–169.

The use of chemical fungicides to control plant diseases is an integral component of crop management. Although fungicides have been used to good effect in agriculture since the 1940s, the introduction of new fungicides is an essential element to provide sustained control of major crop diseases. The need for new and innovative fungicides is driven, among other factors, by resistance management, regulatory hurdles, and increasing customer expectations. New fungicides can be discovered either within established mode of action groups, ideally with low resistance risk (robust modes of action), or in areas with completely novel modes of action. Compounds having a novel mode of action are of course of special interest, since they play a key role in resistance management strategies, but equally important are new fungicides with enhanced characteristics such as systemicity, curativity, and longevity of disease control. With the background of increasing registration hurdles, increasing costs, and increasing market needs, the current market position of major crop protection fungicides needs to be reviewed, along with the consideration of current and future market needs. An analysis of the situation regarding new fungicidal compounds in late development or recently introduced to the market suggests that considerable innovation continues to be delivered in the chemical fungicide area. New modes of action are quite rare in some segments (major new fungicides are mainly SDHIs), but seem to be more frequently discovered for the control of oomycetes. Potential reasons for this are discussed.

Keywords: fungicides; research and development; fungicide resistance; strobilurins; triazoles; carboximides

The history of using chemical fungicides in agriculture started as early as 1807 when B. Prévost discovered the effectiveness of copper for the control of seedborne bunt disease in wheat. Since that time, fungicides have been used to good effect in agriculture to protect crops against the damaging losses caused by plant diseases and are recognised as an essential element in crop protection programmes. Despite the apparently wide range of fungicide products available on the market, there is a clear need for new and innovative fungicides, driven by resistance management, regulatory hurdles, increasing customer expectation, and new or spreading crop diseases. The effective control of some plant diseases (e.g. soil borne diseases such as *Pythium* spp., Fusarium Head Blight of wheat, and various bacterial and viral diseases) with current disease control products continues to be a challenge. Valuable and innovative new fungicides can be discovered within established mode of action groups, or in areas with completely novel modes of action (more of a challenge since a good balance has to be found between high activity against the target plant disease and safety to humans and the environment). Fungicides having a novel mode of action (preferably with low resistance risk) are of course of special interest, since they play a key role in disease control in modern, adapted population of plant pathogens, and also in resistance management strategies, but equally important are new fungicides with established modes of action with enhanced characteristics such as systemicity, curativity, and longevity of disease control.

According to recent studies (McDougall 2010), a new crop protection product takes around 10 years and approximately 260 million USD to be developed (from discovery to first sales). This high cost of product development, which is driven by the extensive studies required on efficacy, safety to humans, safety

doi: 10.17221/83/2015-PPS

to the environenment, safety to other organisms, production optimisation etc., is on the one hand a burden to industry. On the other hand, this high investment and the science required to successfully bring a new product to market and maintain it is an assurance of the safety of the fungicides and other plant protection products on the market today to consumers. It has also resulted in new advances and innovation in fungicide invention which includes high activity against plant diseases at very low use rates (reducing the environmental burden), the development of more toxicologically benign chemistries, and the achievement of crop protection via new technologies such as seed treatment, tree injection, and others. The process of identifying an active ingredient is only the start of the Research and Development process. For every active ingredient tested, only one in tens or hundreds of thousands actually makes it to the market. This is because there are a number of different obstacles that need to be overcome before a crop protection product is ready to go to market. Despite these high hurdles, it is clear that industry has been very successful in discovering and bringing new fungicides to the market over the past 75 years (Table 1). It is interesting to note that in numerical terms the rate of innovation in new fungicide has been maintained over the past 15 years (and arguably even increased since Table 1 does not include the many new Demethylation Inhibitors (DMI) and strobilurin type fungicides which have been invented in China over the past few years since they seem to have only local scope and have not yet been commercialised outside China; these include pyrisoxazole, flufenoxystrobin, mandestrobin, metominostrobin, pyrametostrobin, and pyraoxystrobin).

The need for new fungicides – resistance as a driver

Although a study of the 2015 FRAC Mode of Action Classification of Fungicides (www.FRAC.info) lists more than 200 fungicides from 57 mode of action groups, the reality is that the fungicide market by value is dominated by only a small number of modes of action (Tables 2 and 3). Due to this is it apparent that around 70% of the global fungicide market by value is represented by high to medium resistance risk fungicides. These numbers are a little misleading since high resistance risk fungicides are generally

Table 1. Key fungicide introductions from 1940 to the present day

Year	Fungicides	Number
1940–1960	thiram, zineb, nabam, biphenyl, oxine copper, tecnazene, captan, folpet, fentin acetate, fentin hydroxide, anilazine, blasticidin S, maneb, dodine, dicloran	13
1961–1970	mancozeb, captafol, dithianon, propineb, thiabendazole, chlorothalonil, dichlofluanid, dodemorph, kasugamycin, polyoxins, pyrazophos, ditalimfos, carboxin, oxycarboxin, drazoxolon, tolyfluanide, difenphos, benomyl, fuberidazole, guazatine, dimethirimol, ethirimol, triforine, tridemorph	24
1971–1980	iprobenfos, thiophanate, thiophanate-methyl, validamycin, benodanil, triadimefon, imazalil, iprodione, bupirimate, fenarimol, nuarimol, buthiobate, vinclozolin, carbendazim, procymidone, cymoxanil, fosetyl-Al, metalaxyl, furalaxyl, triadimenol, prochloraz, ofurace, propamocarb, bitertanol, diclobutrazol, etaconazole, propiconazole, tolclofos-methy, fenpropimorph	29
1981–2000	benalaxyl, flutolanil, mepronil, pencycuron, cyprofuram, triflumizole, flutriafol, penconazole, flusilazole, diniconazole, oxadixyl, fenpropidin, hexaconazole, cyproconazole, myclobutanil, tebuconazole, pyrifenox, difenoconazole, tetraconazole, fenbuconazole, dimethomorph, fenpiclonil, fludioxonil, epoxiconazole, bromuconazole, pyrimethanil, metconazole, fluquinconazole, triticonazole, fluazinam, azoxystrobin, kresoxim-methyl, metaminostrobin, cyprodinil, mepanipyrim, famoxadone, mefenoxam, quinoxyfen, fenhexamid, fenamidone, trifloxystrobin, cyazofamid, acibenzolar-S-methyl)	42
2001 to present	picoxystrobin, pyraclostrobin, dimoxystrobin, prothioconazole, ethaboxam, zoxamide, fluopicolide, flumorph, fluoxastrobin, benthiavalicarb, iprovalicarb, mandipropamid, boscalid, silthiofam, meptyldinocap, amisulbrom, orysastrobin, metrafenone, ipconazole, isotianil, proquinazid, ametoctradin, valifenalate, sedaxane, penflufen, isopyrazam, penthiopyrad, bixafen, fluopyram, fluxapyroxad, benzovindiflupyr, pyriofenone, pyribencarb, fenpyrazamine, isofetamid, oxathiapiprolin	35 plus other pipeline products

Source: reproduced and updated from Russell (2005)

doi: 10.17221/83/2015-PPS

Table 2. Reported sales of fungicides in the year 2013 by chemical class/mode of action

Chemical class	Worldwide sales 2013 (USD × 1000)[a]
DMI (Triazoles)	4 492
QoI (Strobilurins and others)	3 430
SDHI	1 061
Other multisites	788
Mancozeb	640
Copper fungicides	585
Benzimidazoles	526
Phenylamides	435
Chlorothalonil	345
Amines	292
Carboxylic acid amides	292
Anilinopyrimidines	241
Dicarboxamides	195
Other fungicides	2 352
Total	15 674

[a]calculated values based on Phillips McDougall market data published 2014 (www.phillipsmcdougall.com), using FRAC Chemical Classification

used in mixture with other, lower resistance risk fungicides, plus the value does not completely correlate with the crop area receiving the fungicides. On the other hand it can clearly be seen that a greater diversity of modes of action is needed to help growers manage the threat of resistance. In addition, there is a clear need for regulatory authorities to maintain the continued availability of existing modes of action in the market.

The challenges for industry in fungicide discovery

During the period 2000–2013, the value of Research and Development (R&D) expenditure on conventional chemical crop protection products by the 15 leading companies in the agrochemical sector has grown at a compound annual growth rate (CAGR) of 3.5%, raising the level of R&D expenditure from USD 2160 million, i.e. 2.16 billion in 2000 to a total of USD 3385 million, i.e. 3.385 billion in 2013 (McDougall 2014). In chemical crop protection, the investment of companies into R&D represents 6–7% of sales. While the overall level of R&D expenditure has increased, the same period has seen a change in the focus of R&D by the leading fifteen agrochemical companies with the level of R&D expenditure targeted at the seeds and traits sector increasing at a rate ahead of that devoted to conventional crop protection chemistry (CAGR of 9.9%). The ratio of R&D investment to sales (7.2% across the top 15 companies including seeds and crop protection) places the plant science industry among the most R&D intensive business sectors.

Fungicides, as is the case of all crop protection chemicals, must be targeted to meet the needs of farmers and growers, to resolve the problems which occur regularly and limit the productivity (yields) and quality of products. They must answer these "biological crop needs" and at the same time must be cost-effective to make their use worthwhile. At the same time the target markets need to be viable to the company inventing and producing the products to justify the large investment of money and resources required to fully develop the products,

Table 3. Global sales of fungicides according to resistance risk (Fungicide Resistance Action Committee (FRAC) Code List 2014)[a]

Resistance risk classification	Number of fungicide groups (FRAC Code List)	Number of fungicides	Worldwide sales 2013[a] (USD × 1000)[b]
High	4	34	4 401
High to medium	5	26	1 376
Medium	10	53	4 947
Medium to low	12	37	1 436
Low	4	29	2 693
Not known	21	29	653
Others (bactericides etc.)	1		168
Total	57	208	15 674

[a]excluding biologicals; [b]calculated values based on Phillips McDougall data published 2014

doi: 10.17221/83/2015-PPS

bring them to the market, and support them in the market place. In addition to these requirements, products must meet modern day requirements for human and environmental safety, and be compatible with other crop protection practices, avoiding undesired effects on, for example, beneficial organisms. Fungicide markets change and therefore do the market potential of crop/disease combinations. For example whilst the worldwide market for the control of powdery mildews has traditionally been targeted by most agrochemical companies for new product, it has become apparent that on its own this market has become critical in terms of a cost-benefit ratio for industry. In other words, the high level of investment required to bring a new, powdery mildew specific fungicide to the market is becoming difficult to justify against the rather crowded and limited market. On the other hand, new opportunities have opened up and rust control in soybeans in Latin America is today an important target for new fungicides. Forecasting these market changes is difficult and challenging, thus being another factor in the complexity of a new product invention and development. It will be seen that from a business perspective therefore, broad spectrum disease control is very attractive (to control a very wide range of diseases in a wide range of crops and countries with a single "blockbuster" fungicide makes the R&D investment most cost effective). Examples of this are the triazoles, strobilurins, and SDHI fungicides explaining the current "SDHI wave" of new product introductions.

It will be realised that the search for the "ideal" fungicide is complex and difficult. This is because there is a wide combination of properties of the fungicide that need to be considered and met which include biological effectiveness on the target disease(s), good crop safety, user friendly formulation and packaging, suitability for IPM, a good cost/profit ratio for the farmer as well as being environmentally sound and safe for users and consumers. Ideally the new fungicide will also have a low risk of resistance occurring.

To meet all these needs and successfully bring a new active substance to the market is a real challenge to industry. To achieve a high level of potency (activity) against a target pathogen whilst having minimal or no effect on the crop, on beneficial organisms, and on humans and other mammals is extremely difficult. There has been a large effort by academia and industry in recent years to use target site modelling in order to produce "designer molecules" to selectively inhibit fungi at specific target sites and in that way find new modes of action for products and at the same time avoid target sites which are known to be problematic in terms of mammalian toxicology. However, this has proved to be extremely difficult in practice and there has been, to the author's knowledge, no product which has been successfully discovered and developed utilising these techniques. It also appears that the trend, which started a number of years ago, of the so-called "high throughput screening" and combinatorial chemistry, where a huge number of randomly selected chemicals are screened for biological activity against a number of key target diseases, has proved not more successful than other approaches. This approach however has proved to be somewhat too untargeted and has been largely abandoned.

The current approach in industry is still very much around optimisation in known chemical classes and modes of action, although at the same time much research goes into the area of discovering new classes of fungicidally active chemistry and hopefully, new modes of action. All companies have their own key "search targets", that is a clearly defined research strategy defining what they want a new product to look like, what should be its characteristics, and therefore what will be the market potential. These search targets include elements such as a completely new mode of action against the key diseases, and maybe also multiple sites of action (multisite) or at least a very low risk of resistance occurring. These requirements are easy to define and state – but success in discovering such solutions remains a real challenge. As a consequence, many of the novel fungicides brought to the market recently, as well as several due to be introduced to the market over the next few years, are site specific fungicides, acting against the pathogens at a single binding site in a biochemical pathway. From a product safety point of view this tends to be a good thing, especially if the target pathway is one that does not exist in mammals. However, from the consideration of resistance risk, and consequently the long-term sustainability of the product in the market, this might not be so favourable, depending on the nature of the mode of action, the pathogen and to consequences to the pathogen of the genetic changes needed to adapt to the fungicide.

The successes of fungicide development

As mentioned already, despite increasing costs of developing and registering new agrochemicals

doi: 10.17221/83/2015-PPS

(McDougall 2010) and maintaining their continued availability to growers, industry has been successful in inventing and introducing new fungicides (Table 1). The rate of invention and introduction has been maintained at the rate of about 20 new active ingredients per decade, even within the last 20 years during which new and more stringent legislation has been introduced (Leadbeater & Gisi 2010; Leadbeater 2011). It appears that it is harder to find truly novel mode of action of chemical fungicides, and it is easier to innovate around known modes of action; new tools and technologies will hopefully address this difficulty in the future. Reasons for this include the fact that laboratory assays exist already for the known modes of action, the risks associated with existing modes of action in terms of environmental and mammalian toxicity are known and understood, and the chances of success of finding highly active new fungicides in a known area of chemistry are much higher. Some areas of plant disease control are in greater need of innovation in the area of new fungicides and modes of action than others at the present time. For example in recent years, industry has been very successful in discovering, introducing, and maintaining a diverse number of modes of action to control oomycete diseases, especially the late blight fungus *Phytophthora infestans* (Table 4). Since resistance is virtually unknown in this disease outside the phenylamides (e.g. mefenoxam), growers have a wide range of choices for disease control. The reasons for this high level of success in fungicide invention in the oomycetes are not clear but might relate back simply to research objectives in companies. In the 1980s, when the phenylamides were the key new class of fungicides for oomycete control and major resistance issues were arising, every major R&D company stepped up the efforts to find a new oomycete modes of action. At the same time questions were being raised about the future of the EBDC fungicides, specifically mancozeb. This added momentum into the search for new oomycete modes of action. It is quite likely that much of the success over the past 10–15 years in oomycete fungicide invention dates back to high priority research projects set up at this time. Conversely, it is clear that options for the control of the key wheat disease *Zymoseptoria tritici* are very few since the QoI and SBI fungicides lost performance, at least in West Europe (Table 5). It is difficult to imagine that a shortage in novel modes of action targeting this disease is due to lack of priority in companies. On the contrary, this is a high priority disease target in R&D of all major companies. It does however seem that a certain reliance was put on this "medium resistance risk" disease being controlled by the DMI and QoI fungicides, with many innovation projects being centred around these two modes of action. Fortunately the SDHI fungicides have recently been introduced, offering a high level of control of this disease. Equally fortunately a robust, multisite fungicide to control this disease exists, namely chlorothalonil. However, to ensure the longevity of successful control of this

Table 4. Key modes of action for oomycete disease control

Fungicide/example	Group/mode of action	FRAC code	MoA group resistance status	
			late blight	Downy mildews
Mancozeb	dithiocarbamates	M3	not known	not known
Folpet	phthalimide	M4	n/a	not known
Chlorothalonil	chloronitrile	M5	not known	not known
Mefenoxam etc.	phenylamide	4	common	common
Fluazinam	2,6-dinitro-aniline	29	rare	not known
Cymoxanil	cyanoacetamide oxine	27	not known	occasional
Azoxystrobin etc.	Strobilurin (QoI)	11	not known	common
Cyazofamid, amisulbrom	QiI	21	not known	occasional
Mandipropamid etc.	CAA	40	not known	common
Zoxamide, ethaboxam	β-tubulin inhibitors	22	not known	not known
Ametoctradin	QoSI	45	not known	not known
Oxathiapiprolin	OSBP	U15	not known	not known

QoI – quinone outside inhibitor; QiI – quinone inside inhibitor; CAA – carboxylic acid amide; QoSI – Quinone outside inhibitor, stigmatellin binding type; OSBP – oxysterol binding protein inhibitor; n/a – fungicide is not used in the affected crops

doi: 10.17221/83/2015-PPS

Table 5. Key modes of action for *Zymoseptoria tritici* control in wheat

Fungicide/example	Group/mode of action	FRAC code	MoA resistance status
Chlorothalonil	chloronitrile	M5	not known
Epoxiconazole, prothioconazole etc.	Triazoles (SBI)	3	common
Azoxystrobin etc.	Strobilurin (QoI)	11	common
Isopyrazam, fluxapyroxad etc.	carboxamides (SDHI)	7	no field resistance

QoI – quinone outside inhibitor; SBI – sterol biosynthesis inhibitor

major plant disease, new innovation in modes of action is desperately needed in this area. It is interesting that ametoctradin, an oomycete fungicide recently brought to market, blocks respiration at a step that is common to both oomycetes and true fungi, and stigmatellin has activity against a wide range of microbes. However this fungicide appears to only be biologically active against the oomycetes (at least at registered use rates). This is an example of an area which might justify further research in the future in the search for activity against other fungal diseases.

Recent advances and future trends

An analysis of new listings of fungicides by the International Organisation for Standardization (ISO) over the past 18 years is given in Table 6. This shows clearly that novel fungicides continue to be discovered and introduced by companies, but that the rate of introduction of truly new modes of action is declining steadily.

Success in finding new modes of action is however clearly possible, as demonstrated by several recent inventions such as the oomycete fungicides ametoctradine and oxathiapiprolin. The experience with the SDHI group of fungicides also demonstrates that although the mode of action may be well known, innovation can broaden the disease control spectrum into totally new crops and pathogen species (Glättli *et al.* 2011). This has resulted in a proliferation of new SDHI fungicides recently introduced or still in the R&D phases. The justification of these many fungicides of the same chemical class and mode of action lies in their differential disease control spectra, their different uses (foliar spray or seed treatment), and also their subtle differences in cross resistance patterns (Sierotzki & Scalliet 2013) which means that some of the SDHI fungicides may still give effective disease control even if resistance has arisen to others in the group, at least for some time.

A clear disadvantage with the approach of following known modes of action is an increased risk of resistance problems arising due to the greater market presence of a single mode of action class containing many fungicides which are cross resistant due to the presence of target site mutations, plus the fact that the fungicides entering the market late after resistance has already occurred, will have a lower commercial potential. Advances in molecular genetics, modelling, reactomics, and other new technologies may help exploit the known modes of action in new ways. Finally, a proliferation of one mode of action, such as has happened with the DMIs, QoIs, and more recently the SDHIs, tends to result in fewer alternative modes of action. This has an impact in terms of resistance management of the remaining modes of action – mode of action diversity is usually lower.

Table 6. History (1997–2014) of new ISO approved names for fungicides

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Existing MoA	3	3	4	1	1	7	0	2	1
New MoA	3	1	2	1	3	1	0	1	0
Total	6	4	6	2	4	8	0	3	1
	2006	2007	2008	2009	2010	2011	2012	2013	2014
Existing MoA	5	0	2	4	3	1	7	1	2
New MoA	0	0	1	2	0	0	2	1	0
Total	5	0	3	6	3	1	9	2	2

MoA – Mode of Action

doi: 10.17221/83/2015-PPS

The current and future situation with increasing generic producers of fungicides in the market may become critical for resistance management once the initial manufacturer's patents have expired. It is therefore also important that fungicide resistance management practices established for the current groups of fungicides, usually via FRAC, continue to be applied also to generic products when they enter the markets.

From the above given it is apparent that it will be important in the coming years to continue to innovate in new fungicides, to provide even more user-friendly products for the grower, to offer new disease control possibilities (e.g. control of new species or offer better control of difficult to control diseases), to make further advances in human and environmental safety, and also reduce the pressure on existing fungicides and their modes of action with regard to the risk of resistance arising. It is likely that due to the challenges already described, future novel fungicides may need to be targeted to a rather narrow disease and crop spectrum to ensure the required safety profiles. Indeed it is difficult at the present time to forecast the next big "blockbuster" fungicide chemical class – those recently described new mode of action fungicides (mainly from Japanese companies which include flutianil, pyriofenone, fenpyrazamine, tolprocarb, tebufloquin, picarbutrazox) tend to be rather narrow spectrum which itself is a challenge to financial hurdles in companies. Pressure on conventional chemistry will need to be reduced through the implementation of different technologies, such as crop disease resistance, perhaps through advances in conventional plant breeding and genetic modification, natural products research as a new source of chemical diversity, and also through the integrated use of biological control agents. In parallel, the search for conventional or natural chemicals which have an inherently low risk of resistance occurring to them in plant pathogens must continue. This search will hopefully be supported by new technologies to allow such chemistries to be found which do not suffer from the toxicological issues surrounding many of todays low resistance risk products, notably the multisites.

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Received August 14, 2015
Accepted after corrections September 7, 2015

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