New developments in weed management from industry

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Summary The herbicide market has reached maturity but is highly receptive to new weed management solutions. These comprise truly innovative herbicides as well as new application technologies. In this article we will discuss the fate of conventional herbicide technologies and the impact of herbicide tolerant crops. The herbicide industry has established new herbicide discovery and screening platforms. We will describe how these novel technologies will foster herbicide innovation.

Keywords Herbicide, herbicide market, herbicide tolerance, herbicide resistance, glyphosate, glufosinate, precision farming, UHTVS, UHTBS, VTBS, research platform.

INTRODUCTION

Weed competition accounts for approximately 15% of total pre-harvest crop losses. To protect against these losses and preserve yield quality, appropriate weed management is essential. Herbicides are by far the most important weed management tools; with about €12 billion turnover the herbicide market represents nearly 47% of the total chemical crop protection market (Bayer CropScience in-house data 2004).

Currently nearly 400 herbicides are registered globally but only a small number of active ingredients dominate the herbicide market. The leading herbicide is glyphosate, which today achieves a turnover of approximately €1.8 billion in the non-selective market and *ca.* €0.8 billion in glyphosate tolerant crops (Bayer CropScience in-house data 2004).

The current portfolio of herbicides has been generated in a crop science industry that has been undergoing a massive global consolidation process for more than 15 years. In 1990, 13 multinational companies were actively pursuing agricultural chemical research and development. These companies represented about 80% of the total agricultural market. Today, only six companies represent the same market share. Only four to five companies are significantly investing in the discovery of novel herbicides (Figure 1).

A few multinational producers of herbicides are gaining more and more importance. Many factors are responsible for this consolidation process. We will discuss the reasons for these developments as well as the changing demands of the global herbicide market in this presentation.

FACTORS CAUSING CHANGES IN WEED CONTROL SYSTEMS

Core issues driving changes in herbicide technology Agricultural production is undergoing drastic changes specifically in the countries of the western hemisphere. Between 1975 and 1995 more than 1.4 million farms went out of business in Europe. The most badly affected countries were Italy, Spain, Portugal and France. In these four countries, the number of people employed in agriculture shrank by at least one third between 1987 and 1997 (Wagenhofer and Annas 2006). The number of people employed in agriculture

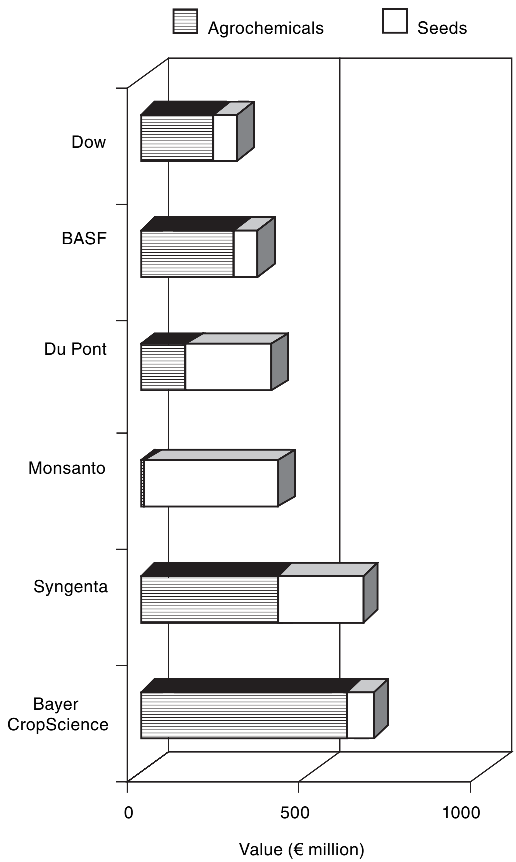

Figure 1. R&D expenses of selected companies 2005 (Bayer CropScience in-house data).

is continuously declining and has reached a low level of around only 5% of the total population in Europe (BBC News December 2, 2005). In Germany, less than 2% of the population are employed in agriculture (www.bmelv-statistik.de/tabellen/f2420.1.xls).

In the EU-15 approximately 70% of the crop protection business is done by 700,000 farmers. This number is going to decrease further with the anticipated agricultural reform initiated by the EU commission for the extended community. We will see bigger farms with an increasing level of professionalism and specialisation. Agricultural production will be shaped by both regional and global demands. Consumers will have an increasing influence on the farm production processes. Public awareness of farming is forecast to grow. Prescribed use of farm inputs (e.g. crop varieties, fertilisers, herbicides, insecticides, fungicides) might go along with these developments. Application technology may see drastic changes as agronomic characteristics will be recorded via global positioning systems and yield data will be directly recorded from harvesters on intensively used agricultural areas. The continued improvement of tools for precision farming is expected to assist the further implementation of integrated crop management practices.

Major political and regulatory factors leading to changes Subsidies in Europe and in the USA have a great impact on cropping and weed management decisions. The European CAP reform was based on overproduction and budget crises, pollution, food scares and pressures arising from the expansion of the EU to countries highly dependent on agriculture. These factors resulted in a switch from production to area related subsidies. This includes biodiversity measures and a wider protection of the environment (Table 1, Baylis 2005). Cross compliance with so-called Good Farming Practices defines which weed control tools are accepted by officials in Germany when farmers want to claim Pillar 1 (production related payments) or Pillar 2 (public goods or sustainability related payments) money. Policies and payments are set by member states co-financed by Brussels. The German BBA has developed the program Neptun to create crop protection indices, which may be used to reduce the amount of pesticide application (Gutsche and Rossberg 2004).

The US 2002 farm bill programs appear to be less restrictive when it comes to agrochemicals. However, they contain environmental projects as well, such as the Environmental Quality Incentives Program (EQIP) or the Conservation Security Program (CSP) (see USDA 2006a, USDA 2006b).

Table 1. EU Agri-Environmental programs by externality (Baylis 2005).

Externality	Agri-environmental programs
Soil erosion	Landscape
Chemical and nutrient run-off	Organic; stocking rates
Water pollution	Reduction of inputs
Habitat destruction	Natura
Habitat creation	Natura, anti-abandonment
Landscape	Landscape
Biodiversity	Rare breeds, anti-abandonment
Rural development	LFA
Cultural heritage	Traditional methods, less favoured areas
Habitat creation	Natura, anti-abandonment

Weed resistance Since the first observation of resistance to triazines in the late 1960s, further herbicide resistant biotypes with resistance to most of all herbicide classes have been identified worldwide in more than 154 different weed species (Vaughn 2003).

Weed tolerance or weed resistance to glyphosate was not known for many years after the introduction of this herbicide. In 1996, glyphosate-resistant *Lolium rigidum* Gaudin was identified in Victoria, Australia (Powles *et al*. 1998). In the next 10 years, glyphosate-resistant goosegrass (*Eleusine indica* (L.) Gaertn.), *Lolium multiflorum* Lam., horseweed (*Conyza canadensis* (L.) Cronq.), hairy fleabane (*Conyza bonariensis* (L.) Cronq.), buckhorn plantain (*Plantago lanceolata* L.), common ragweed (*Ambrosia artemisiifolia* L.) and Palmer amaranth (*Amaranthus palmeri* S.Wats.) have been identified in more than seven different countries (Heap 2006). The impact of resistance development on herbicide usage has remained limited on a global scale, although local weed management systems have had to be adapted. Even resistance to glyphosate did not limit the use of this most common herbicide.

The spectrum of resistant biotypes varies from crop to crop. Table 2 lists resistant weeds in the US cotton growing area, Table 3 resistant rice weeds (Burgos 2006). Of course, the growth conditions for rice weeds are completely different from those of weeds in other crops. However, some species prevail in production areas where the same products are used in different cropping systems. Often, these biotypes can grow under varying climatic conditions, e.g. *Amaranthus* species. Others however exist only under defined conditions. *E. indica* is restricted to warm climates, such as the southern US states or to special areas in the Brazilian Mato Grosso. *P. lanceolata* grows

Table 2. Resistant weeds in US cotton growing areas (Burgos 2006).

Weed	Herbicides	MOA[A]	States
Amaranthus palmeri	pyrithiobac	ALS inhibitor	AR, NC, SC, GA
	glyphosate	EPSPS inhibitor	GA
	trifluralin	Mitotic inhibitor	SC, AR
Conyza canadensis	glyphosate	EPSPS inhibitor	AR, MS, NC, TN
Xanthium strumarium L.	pyrithiobac	ALS inhibitor	AR, KS, MO, MS, OK, TN
	MSMA	unknown	AL, AR, LA, MS, NC, SC, TN
Eleusine indica	trifluralin	Mitotic inhibitor	AL, AR, GA, MS, NC, SC, TN
Sorghum halepense (L.) Pers.	clethodim, fluazifop, quizalofop	ACCase inhibitors	KY, LA, MS, TN

[A] MOA = mode of action.

Table 3. Resistant weeds in US rice growing areas (Burgos 2006).

Species	Herbicide	States
Ammania auriculata Willd.	bensulfuron	CA
Ammania coccinea Rottb.	bensulfuron	CA
Echinochloa crus-galli (L.) P.Beauv.	thiobencarb, molinate	CA
	cyhalofop, fenoxaprop	CA
	propanil	AR, LA, MO, TX
	quinclorac	AR, LA
Echinochloa oryzicola Vasing.	cyhalofop, fenoxaprop	CA
	thiobencarb, molinate	CA
Echinochloa phyllopogon (Stapf.) K.-Pol.	thiobencarb	CA
Cyperus difformis L.	bensulfuron	CA
Sagittaria montevidensis Cham. & Schltdl.	bensulfuron	CA

primarily under cooler climates, such as in summer in the northern US states or in winter in southern areas. Some of these species produce large numbers of small seeds, which are easily dispersed by wind. The high number of seeds guarantees a considerable proportion of individuals with mutated target sites for herbicides or with varying abilities to degrade agrochemicals.

It is a great challenge for the agrochemical industries to monitor resistance against their products in order to provide correct labelling, to propose alternative control strategies or to develop new molecules with new properties. Modern tools are used to characterise weed resistance on a molecular basis (Wagner *et al.* 2002). The exact description of resistance; however, is time and resource consuming. In some cases the incentive to search for new products is not high enough as the prices for current standards, such as glyphosate, are very low or the area infested with resistant weeds is too small and does not guarantee a return on investment (Hager 2003).

Herbicide tolerant crops In the mid 1990s herbicide tolerant crops were introduced, which enabled the selective application of originally non-selective herbicides, namely glyphosate, imidazoline herbicides and glufosinate. These HT crops have significantly changed the herbicide market environment in some regions.

The introduction of glyphosate tolerant soybeans and cotton in North America was extremely successful in turning around the practices for dicot weed management practices within several years. The imidazolinone herbicides, which once were key players in the American soybean market, are today niche products and RR-soybean is planted on more than 90% of the North American fields. Similar developments completely changed the soybean cultivation systems in Argentina too. These developments are leading to a drastic reduction in the diversity of active ingredients applied to soybean fields in the Americas; one single herbicide is dominating the weed management systems (Figure 2). In fields with crop rotation dominated by soybean cultivation, herbicide selection pressure led to the appearance of new weed communities. Some weeds have developed tolerance or even resistance to glyphosate and are now dominating some weed populations. Some of those biotypes even show insensitivity to more than

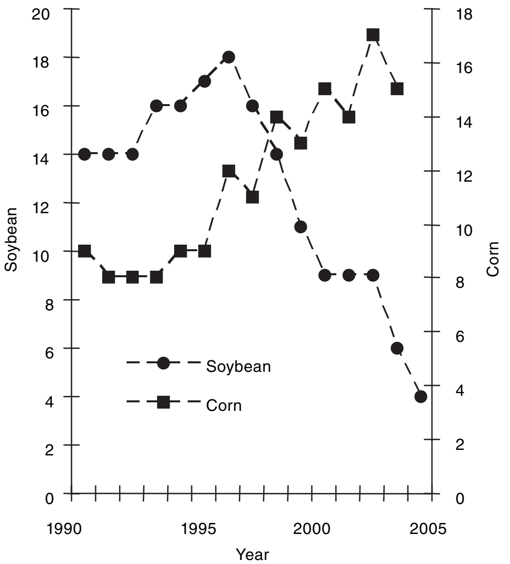

Figure 2. Number of active ingredients applied on five or more per cent of treated corn and soybean acres in top producing US states (USDA, NASS data according to VanGessel 2006).

one herbicide, such as to glyphosate plus certain ALS inhibitors (sulfonylureas, imidazolinones etc.).

In the near future additional countries will follow the North American and Argentinean model. For example, a significant increase in glyphosate tolerant soybean cultivation is forecast for Brazil. If we want to control the development of insensitive weed populations, we will have to alternate the use of herbicides with different modes of action or combine glyphosate with residual herbicides. Several mixture partners can be used to control such weed populations (e.g. Krausz and Young 2003).

The decrease in the number of soybean selective herbicides and the dominant position of glyphosate cause concerns about the availability of alternative herbicide solutions in the future. New soybean varieties with stacked glyphosate- and dicamba-tolerance traits are in development. They will allow the control of some important glyphosate-resistant weeds in crop (Fraley 2006). In the mid-term glyphosate will stay available as an efficient weed control tool but only if it is integrated in herbicide rotation programmes.

Adaptation of weeds to new habitats Apparently, some weed species in Brazil have adapted to cooler climates in the intercropping season, the safrinha. Weed control in the intercrops is not as intensive as in the main season. This leads to an increase of seedbanks and competition for the following crop (Dionisio Gazziero, EMBRAPA pers. comm.). Weed shifts can be attributable to ecological adaptation and are expected to occur where a single crop and herbicide combination are used (Owen and Zelaya 2005).

Several non-endemic weed species from southern Europe are penetrating into northern countries, e.g. *Abutilon theophrastii* Med. (Meinlschmidt 2006), *Ambrosia artemisiifolia* L. (Bohren *et al.* 2006) and *Setaria* spp. These invasive weeds require new weed control tools.

Impact on the herbicide portfolio With the invention and introduction of selective herbicides in the late 1940s a constant flow of innovative new active ingredients provided farmers with highly effective weed control tools. Today approximately 400 herbicides covering more than 17 different mode of actions offer weed management solutions in a broad range of crops.

The key herbicide market segments for selective herbicides are corn, cereals, soybeans and rice followed by dicot segments like sugar beets and cotton. The biggest single market segment however, covers non-selective herbicides in fruits, vines, plantations and other non agricultural uses.

The average approval rate for novel herbicides has been 10 to 12 active ingredients per year over the last three decades. This figure has been significantly less in the recent years as a consequence of increasing performance demands in crop production as well as ever increasing regulatory hurdles. It is likely to be even less in coming years as only a few new herbicides are predicted for introduction over the next six years (Table 4).

After decades of strong growth from the late 1940s to the 1980s, the herbicide industry is now facing a period with slow growth of 1–2% p.a. only or even stagnation. The herbicide market has reached a level of maturity leading to decreasing price levels for herbicides in the market. Some older products have been forced to step out of the market. The reasons are that they no longer fulfil today's agronomic or regulatory

Table 4. Predicted introduction of new herbicides and safeners between 2006 and 2012 (according to Credit Suisse 2006).

Company	2006	Thereafter
BASF	0	2
Bayer CropScience	0	4
Syngenta	1	2

requirements or do not possess sufficient economic benefits necessary for a sustainable return on investment. This development is also supported by the fact that many of the 'old' herbicides are running out of patent protection.

The innovation deficit Today, herbicides addressing only six different modes of action occupy approximately 75% of the total herbicide market. The vast majority of these herbicides are older than 10 years. As discussed above, the discovery rate of active ingredients has slowed down significantly. The latest discovery of a commercially relevant new mode of action dates back to the early 1980s. This is accompanied by a steep decline in the number of patent applications for new active ingredients. In 1990 more than 250 herbicides patent applications were filed, this number dropped to less than 70 applications in 2003 (Figure 3).

Unique research platforms striving for success The successful conventional herbicide discovery process is based on the optimisation of active chemical classes along with proven greenhouse screening technologies and will continue to play an important role in the future. In order to increase efficiency however and to counteract the declining innovation rate (see above) the remaining global herbicide companies have revised their discovery strategies. With the advent of miniaturisation and automation in screening technologies and in chemical synthesis (combinatorial chemistry, automated synthesis) new discovery platforms were established. In addition, pharma-like target-based discovery technologies were added to the platforms. The new screening platform builds a unique network consisting of:

1. Ultra-High-Throughput-in-Vivo-Screening (UHTVS) for the discovery of new compounds.

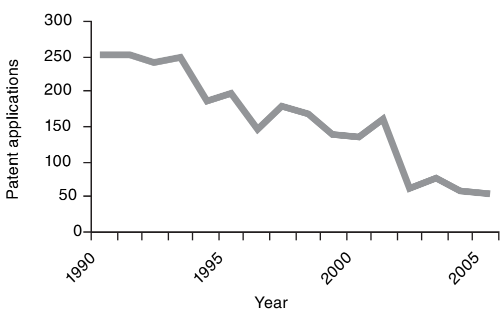

Figure 3. The number of herbicide patent applications between 1990 and 2005 (according to Stuebler 2006).

2. Target-based Ultra-High-Throughput-Biochemical Screening (UHTBS).
3. Virtual-Target-Based-Screening (VTBS) as an exemplifying tool for rational design approaches.

UHTVS opens a new dimension for discovery through rapid and reliable screening of whole plants. Several hundred thousand compounds can be tested annually for their herbicidal potential. The miniaturisation makes it possible to test even compounds available only in minute amounts, thus potentially increasing chemical diversity.

In parallel, a target-based screen (UHTBS) is implemented for the directed discovery of compounds interacting with novel targets. These targets have been identified through either systematic genomic knock-out programmes or by mode of action analysis of herbicidal hits from UHTVS. These targets also provide the basis for elucidating the three-dimensional (3D) target protein structure. If we know the protein structure and especially the 'active site' where its function is located, we will be in a position to use rational design approaches for chemical optimisation. Once we know the structure binding to the active site, we are able to use what is known as 'molecular modelling'. This technology (VTBS) offers direct proposals for optimised synthesis.

We are convinced that the new research platform will deliver high quality lead molecules, which fulfil the demanding requirements to the invention of new herbicide standards.

OUTLOOK AND TRENDS

The global herbicide market exhibits all typical parameters of maturity: stagnating growth, price pressure and increasing competition, expiry of patents, establishment of regional generic industries, portfolio consolidation and concentration of the industry on a small number of global players. Increasing regulatory demands triggering high development costs refrain the industry from serving smaller (niche) markets, which remain without adequate weed management solutions.

The global herbicide market will be nevertheless highly susceptible to truly innovative active ingredients offering added value to the environment, society and farmer:

1. Broad spectrum efficacy against grass and dicotyledonous weeds.
2. Flexibility for pre- and post-emergent use.
3. Outstanding selectivity in respective crop production systems.
4. Mode of action suitable to complement the herbicide rotation regimes (e.g. resistance management).

5. Low application rate.
6. Favourable environmental behaviour.
7. High level of safety.

Herbicides that no longer fulfil the requirements of modern agriculture can be expected to be replaced in the market. In addition to these opportunities, herbicide technology will be influenced by different tools and technologies developed for precision farming (see Gerhards *et al.* 2002a, Gerhards *et al*. 2002b):

1. Field mapping supported by GPS.
2. High precision, patch spray integration.
3. Online weed detection systems.
4. Seed bank monitoring.

For these technologies to succeed significant progress in cost-competitiveness is required. In order to further develop and to finally introduce precision weed control into the market, the co-operation of all application technology suppliers, herbicide industry and scientific community is essential.

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