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Global Herbicide Development – Opportunities and Constraints

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Summary

Herbicides have been essential tools in agricultural production for decades. With the global introduction in Canada of herbicide tolerant (HT) crops in 1996, agriculture has changed drastically. More than 90% of Canadian canola production is represented by three HT systems. In a few major crops like wheat (*Triticum aestivum* L.), barley (*Hordeum vulgare* L.) and pulse crops, HT systems have not yet achieved acceptance. New HT systems will be available soon. Companies with a tradition in conventional agrochemicals have changed objectives due to the growing importance and opportunity of the seed business resulting in reduced investment in conventional herbicide research. Clearly, there is still a need, however, for compounds with new modes of action to prevent and remedy weed resistance problems.

Introduction

As early as 1990, agrochemical market research indicated that the crop protection market was approaching maturity and it was becoming increasingly difficult to discover new agrochemicals with significant advantages over existing products[3]. Indeed, annual global turnover for crop protection products reached a maximum in the mid 1990's, and has fluctuated back and forth between US$25 and $35 billion per year over the last 15 years with herbicides representing almost 50% of this amount. A number of things have contributed to the dynamics in the crop protection business: politics (i.e. the EU CAP reform, US Ag policy), exchange rates, commodity prices, environmental factors such as drought and flooding, economical development in key agricultural countries (i.e. Brazil), and the introduction and spread of new diseases such as Asian soybean rust. As well, there has been an increase in the market participation of generic crop protection products, which are produced in low-cost business environments such as India and China. This has resulted in a decline in the value of crop protection products globally, and a consequent re-evaluation of where research dollars are spent. The most drastic change in agriculture however, has been the introduction of genetically modified crops which have revolutionized and changed weed control completely.

HT systems in major arable crops

Five HT systems have been commercialized in eight major crops (Table 1).

Table 1. HT systems in major arable crops

HT System	Herbicides Employed	Crops
Roundup Ready	glyphosate, sulphosate	Canola, corn, cotton, soybean, sugarbeet
Liberty Link	glufosinate	Canola, corn, cotton
Clearfield	imazapyr, imazamox, imazapic, imazethapyr	Canola, corn, rice, sunflower, wheat
STS (Sulfonyl-urea tolerant soybeans)	chlorimuron-ethyl, thifensulfuron-methyl	soybean
Triazine Tolerance	atrazine, simazine	canola

These systems involve changing crops by modifying or mutating genomes through gene technology (biotechnology) or from cell and tissue cultures (not modified by gene technology). HT crops offer some advantages over other crops; the herbicides employed are typically broader spectrum products which can be applied at different growth stages, and farmers can wait to evaluate weed problems without having to apply prophylactic sprays. Also, HT crops guarantee a hitherto unknown high degree of selectivity because they are specifically developed to be completely resistant to a given herbicide. HT systems differ from country to country and from crop to crop on the basis of need and political will. In Canadian canola (*Brassica napus* L.) production, where biotechnology has been embraced, Roundup Ready and Liberty Link are the prevailing technologies. Triazine tolerant varieties have dominated in Australia, where biotechnology has not yet seen widespread acceptance by the general public. In the near future new HT systems will enter the market: Liberty Link soybeans (*Glycine max* (L.) Merr.) and Optimum-GAT crops. Optimum GAT crops will contain genes for glyphosate, sulfonylurea and even glufosinate tolerance. Dicamba and 2,4-D tolerant crops are also in development.

How have HT crops changed agriculture production and crop protection research?

The number of new weed control solutions is decreasing

The number of different herbicides used to produce soybeans has decreased dramatically due to the high proportion of glyphosate tolerance in the germplasm. Like canola in Canada, HT soybeans and cotton (*Gossypium hirsutum* L.) play a major role in US agriculture.

Impact on the herbicide portfolio

With the invention and introduction of selective herbicides in the late 40's, a constant flow of new active ingredients provided crop producers with highly effective weed control tools. As a result, there are almost 400 world-wide herbicides covering more than 17 different modes of action. The average global government regulatory approval rate for novel herbicides has been 10-12 active ingredients per year over the last three decades. This figure has been slowing in recent years as a consequence of increasing demands in product performance as well as higher regulatory hurdles. HT crops have also contributed to this trend.

Many companies have reacted by shifting more of their research resources into biotechnology activities. Monsanto doesn't screen for new agrochemicals any more and DuPont's research efforts are primarily breeding and trait driven.

The Innovation Deficit

Today, herbicides involving only 6 different modes of action occupy approximately 75% of the total herbicide market, and most of them have been around for more than 10 years. The discovery rate of active ingredients has slowed significantly. The most recent discovery of a commercially relevant mode of action dates back to the early 80's (sulfonylureas). There has been a steep decline in the number of patent applications and publications for new active ingredients.

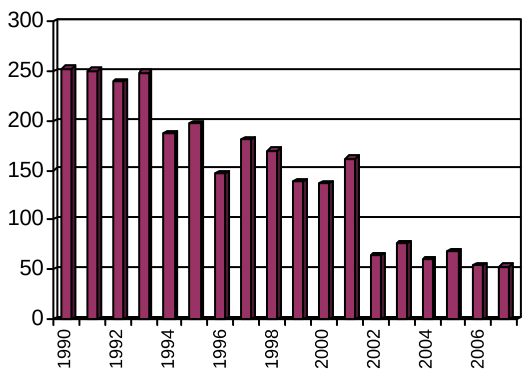

Figure 1. Decline in patent publications for herbicides, 1990-2007

In 1990, more than 250 herbicide active ingredient patent applications were filed. This number dropped to less than 60 in 2006, and does not look as if it will rebound (Figure 1). This decrease is a reflection of not only the reduced number of companies with activity in herbicide discovery, but also as a result of the ever decreasing success rate of those companies still willing to invest. Whereas 20 years ago it was sufficient to screen 10,000 new chemistries in the greenhouses of an ag-chem company in order to discover one novel herbicide, this number has increased today to several hundred thousand[11]. As a result of regulatory demands and due to the high standards in the market, costs for the development of new molecules have soared. Phillips McDougall recently published increases of R&D costs for agrochemicals between 1995 and 2005 from $150 to almost $250 million per developed product.[8,9]

Weed Resistance and adaptation to changing environments

Weed resistance in HT systems

Since the first observation of resistance to triazines in the late 60's, further herbicide resistant biotypes with resistance to almost all herbicide modes of action have been identified in more than 154 different weed species around the world [2,6].

Weed tolerance or resistance to glyphosate was not known for many years after its introduction. In 1996, glyphosate-resistant rigid ryegrass (*Lolium rigidum* Gaudin) was identified in Victoria, Australia[10]. In the following 10 years, glyphosate-resistant goosegrass (*Eleusine indica* Gaertn.), Italian ryegrass (*Lolium perenne* L. ssp. *multiflorum* (Lam.) Husnot), horseweed (*Conyza canadensis* (L.) Cronq.), hairy fleabane (*Conyza bonariensis* (L.) Cronq.), plantain (*Plantago spp*.), common ragweed (*Ambrosia artemisiifolia* L.) and Palmer amaranth (*Amaranthus palmeri* S. Wats.) have been identified in one or more of 7 different countries. The impact of resistance on global herbicide use has remained limited and regional. Resistance to glyphosate, however, has not yet significantly limited the use of this most common herbicide. ALS (Group 2) resistance has been widely described in many geographies[7]. Although metabolic resistance has been identified as the mechanism in ALS inhibitors in some circumstances, it is usually mediated by an altered enzyme target site. Some of the biotypes now show cross resistance to different imidazolinone and sulfonylurea herbicides.

Characteristically, resistant weeds prevail in production areas where the same types of herbicides are used within different cropping systems resulting in the lack of rotation of different modes of action. The end result is increased selection pressure for weeds resistant to these limited modes of action, which further results in the appearance of uncontrolled weeds in farmer fields. Product stewardship programs with the identified target site mutations will be necessary to reduce the risk of the spreading of herbicide resistance[13].The agrochemical industry is challenged to deal with resistance through label changes, alternative control strategies and the economics of developing new molecules for what sometimes can be a limited market opportunity.

Weed shifts in HT systems

Introduction and intense adoption of single approach weed management tools, such as the use of limited number of herbicides, often results in a shift in the population of the weed flora[4,12]. For example a recent survey sent to weed scientists across the USA indicated that populations of morningglory (*Ipomoea spp*.), dayflower (*Commelina* spp.), pigweeds (*Amaranthus spp*.), nutsedge (*Cyperus spp*.) and certain types of annual grasses are increasing in Roundup Ready crops. Shifts can be the result of incomplete control or changes in the timing of emergence.

What causes some companies to continue with active herbicide research?

Existing HT programs will not solve all problems

The search for new corn (*Zea mays* L.) herbicides appeared unattractive in the 80's when 2 lbs/ac or 2.24 kg/ha of atrazine dominated production. However, atrazine has lost its registration in many countries, and has been severely limited in application rates in others. These restrictions are primarily based on risks of soil leaching and resultant ground water contamination. HT corn solutions are also not providing all the solutions for weed control (Figure 3). Corn differs from soybeans insofar as it is more susceptible to early weed competition and wide row spacing reduces crop competition. Single glyphosate or glufosinate treatments are often not sufficient when weeds emerge over long periods of time after planting. Sometimes farmers cannot enter fields because of bad weather conditions or workload conflicts at spraying time. Yield penalties are the consequences of late weed control. Therefore, pre-emergence herbicides are still a common practice in corn even when glyphosate or glufosinate tolerant varieties are used. Figure 2 demonstrates the benefit of soil residual compounds through the early reduction of weed competition. The number of new herbicide molecules developed for corn, especially those with soil activity, has actually increased over the last decade, the opposite of what is observed for soybean or canola. Unlike Canada, HT systems are not used in European oilseed rape (*Brassica napus* L.) production, produced primarily for biodiesel. Predictions for area produced are variable for oilseed rape, as the political view on energy crops continuously changes in the food vs. fuel debate. Increasing energy prices globally may contribute to an increase in demand for this crop and stimulate conventional agrochemical discovery outside of North America. Other countries which have yet to establish biotechnology crops are also opportunities for conventional product development.

Figure 2: Weed control in corn. Left: untreated. Right: Pre-emergence treatment with metolachlor. Grasses compete with corn for light, water and nutrients. Corn in untreated plot heavily affected.

Agriculture needs to overcome resistance and shifts in weed communities

If we want to reduce the development of difficult-to-control weed populations, we will have to alternate the use of herbicides with different modes of action and to combine glyphosate with residual herbicides (Figure 3). The addition of different herbicide mixtures in most HT crops could be used to control such weed populations. The decrease in the number of new selective soybean herbicides and the dominant position of glyphosate will cause concerns about the availability of alternative herbicide solutions in the future for this crop [5,12]. New soybean varieties with stacked glyphosate and dicamba tolerance traits are in development which will allow in-crop control of some important glyphosate-resistant weeds. However, glyphosate will only maintain its current status as an efficient weed control herbicide if it is integrated in a herbicide rotation program.

Figure 3: Glyphosate resistant horseweed treated with 1.3 kg/ha glyphosate.

Objectives of agrochemical companies in the development of new herbcide technologies.

Companies developing new plant protection molecules using conventional chemistry search for compounds with certain characteristics.

1. Broad spectrum efficacy against grass and dicot weeds (to reduce the complexity and number of compounds required per unit area)
2. Flexibility for pre- and post-emergence use (to increase the utility and opportunity for individual molecules to participate in more than one market segment)
3. Outstanding selectivity (demanded by customers)
4. Modes of action suitable to complement the existing herbicide rotation regimes (for the management of weed resistance)
5. Low application rate (small environmental footprint and better cost position)

Existing herbicides which do not fulfil the requirements of modern agriculture will be replaced, and new ones falling short will simply not be developed.

Outlook

Consolidation of the crop protection industry will continue. Less than a handful of companies will maintain the critical resources for regular launches of new herbicides. The increasing demand for food and energy has already led to considerable changes in crop production strategies. Subsidies for ethanol production and increasing Indian and Chinese demand increased US corn acreage by 20% in 2007, to the detriment of US cotton acreage, which decreased by almost 30%. Corn acres stayed high in 2008, and soybean and wheat grew due to stronger commodity prices[1]. Fertilizer costs almost doubled between 2005 and 2008, and are returning to historical averages only now. The global crop protection market exceeded the $35 billion plateau in 2007, and further growth in 2008 is expected. Farmers will try to avoid energy costs where possible, and will apply mixtures of broad-spectrum herbicides with those possessing residual performance instead of applying the same herbicide twice or three times as they do today in some crops. In Latin America, 12 litres of glyphosate/ha can be a normal application amount per year. Such an intensive use of one single product will inevitably lead to the selection of resistant and more tolerant species. Resistance monitoring has become a necessity for modern agriculture.

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