

Why have no new herbicide modes of action appeared in recent years?

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Abstract

Herbicides with new modes of action are badly needed to manage the evolution of resistance of weeds to existing herbicides. Yet no major new mode of action has been introduced to the market place for about 20 years. There are probably several reasons for this. New potential products may have remained dormant owing to concerns that glyphosate-resistant (GR) crops have reduced the market for a new herbicide. The capture of a large fraction of the herbicide market by glyphosate with GR crops led to significantly diminished herbicide discovery efforts. Some of the reduced herbicide discovery research was also due to company consolidations and the availability of more generic herbicides. Another problem might be that the best herbicide molecular target sites may have already been discovered. However, target sites that are not utilized, for which there are inhibitors that are highly effective at killing plants, suggests that this is not true. Results of modern methods of target site discovery (e.g. gene knockout methods) are mostly not public, but there is no evidence of good herbicides with new target sites coming from these approaches. In summary, there are several reasons for a long dry period for new herbicide target sites; however, the relative magnitude of each is unclear. The economic stimulus to the herbicide industry caused by the evolution of herbicide-resistant weeds, especially GR weeds, may result in one or more new modes of action becoming available in the not too distant future.

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1 INTRODUCTION

No new major herbicide mode of action has been introduced in a commercial herbicide active ingredient in the last 20 years. Before this drought, a new mode of action was introduced approximately every 3 years, leading to current use of approximately 20 known modes of action (Table 1). The same is not true of insecticides and fungicides, for which major modes of action such as ryanodine receptor insecticides and fungicides such as the strobilurins that attack the QoI binding site of respiration have been introduced within the past two decades. Gerwick⁴ reported 137 new herbicide active ingredients introduced from 1980 to 2009. They all had modes of action of herbicides introduced before 1990. The uses of some older herbicides and new herbicides with old modes of action have sometimes been expanded through the use of herbicide safeners, a strategy unavailable for insecticides and fungicides. Gerwick's analysis of 2009 US, Japanese and PCT patent applications found that the total composition of matter patents for insecticides (57), fungicides (78) and herbicides (51) did not differ that much. However, the patents in which the modes of action were not obvious from the chemical structure were quite different: ten insecticides, ten fungicides and only two herbicides. New herbicides launched or scheduled for launch during 2010–2012 all target old target sites (aminocyclopyrachlor, an auxinic molecule; pyroxasulfone, a very-long-chain fatty acid synthesis inhibitor; bicyclopyrone, a hydroxyphenylpyruvate dioxygenase inhibitor; indaziflam, a cell wall biosynthesis inhibitor). Why are herbicides lagging behind in introducing new modes of action, and what are the prospects for a major new mode of action being introduced in the future? This review sets out the author's thoughts regarding

this question. The views expressed are quite similar to those espoused by Gerwick in his recent short review.⁴

2 WHY NEW HERBICIDE MODES OF ACTION ARE NEEDED

According to the sixteenth-century physician and writer François Rabelais, 'Nature abhors a vacuum'. This is certainly the case with the ecological vacuum caused by highly efficient herbicides, where any weed that can inhabit the unoccupied ecological niche formed by a highly efficient herbicide has the marked advantage of reduced competition. However, as the playwright Tennessee Williams wrote in one of Big Daddy's lines in *Cat on a Hot Tin Roof*, 'sometimes I think a vacuum is a hell of a lot better than the stuff that nature replaces it with'. In the case of herbicide-resistant weeds occupying the ecological vacuum created by herbicides, farmers would agree with Big Daddy's sentiments.

Since the advent of synthetic herbicides in the mid-twentieth century, weeds have readily evolved to fill the ecovacuums formed by herbicides.⁵ With some modes of action the delay between introduction of the herbicide and evolved resistance has taken only 3 or 4 years [e.g. acetolactate synthase (ALS) inhibitors], whereas with others the evolution of resistance has taken

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Table 1. Modes of action of currently used commercial herbicides.^{1–3} The numbers of the target sites are given in bold

Herbicide or herbicide class	Target site
<i>Amino acid metabolism</i>	
Glyphosate	1 EPSPS
Glufosinate	2 Glutamine synthetase
Sulfonylureas, imidazolinones, triazolpyrimidines, pyrimidinyl(thio)benzoates and sulfonylamino-carbonyl-triazolinones	3 Acetolactate synthase
<i>Auxin receptors</i>	
Pyridine carboxylic acids, benzoates, phenylcarboxylic acids, quinolinecarboxylic acids and others	4 F-box proteins
<i>Auxin transport inhibition</i>	
Naptalam and diflufenzopyr-sodium	5 ABCB proteins
<i>Carotenoid synthesis</i>	
Trifluoroheterocyclic compounds such as fluridone and nonflurazon	6 Phytoene desaturase
Triketones, isoxazones and benzoylpyrazoles	7 Hydroxyphenylpyruvate dioxygenase
Clomazone	8 Deoxyxylulose-5-phosphate synthase
<i>Cellulose synthesis</i>	
Nitriles, isoxaben, alylazines and flupoxam	9 Cellulose synthase
<i>Folate synthesis</i>	
Asulam	10 7,8-Dihydropteroate synthase
<i>Lipid synthesis</i>	
Aryloxyphenoxypropionates, cyclohexanediones and pinoxaden	11 Acetyl-CoA carboxylase
Acetamides, oxyacetamides, chloroacetamides, tetrazolinines and others	12 Very long-chain fatty acid synthase
<i>Mitosis</i>	
Dinitroanilines, benzamides, pyridines, phosphoramidates and DCPA	13 Tubulin
Carbamates	14 Other sites related to microtubule organization
<i>Photosynthesis</i>	
Triazines, ureas, nitriles and many others	15 D-1 of PSII
Bipyridyliums	16 Accepts protons from PSI
<i>Porphyrin synthesis</i>	
Diphenyl ethers, phenylpyrazoles, thiadiazoles, pyrimidinediones and others	17 Protoporphyrinogen oxidase
<i>Protein phosphatase</i>	
Endothall	18 Serine/threonine protein phosphatases
<i>Uncoupler</i>	
Dinitrophenols	19 Membrane disruptors

decades [e.g. glyphosate, the inhibitor of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS)]. The lag time between introduction and the first reported case of evolved resistance is a complex function of many factors, including weed species, selection pressure, existing genetic diversity and the nature of the target site. The mechanism of resistance is usually an altered target site.⁶ Thus, applying a herbicide with a different mechanism of action would generally eliminate the herbicide-resistant weeds.

Before the 1990s, farmers could rely on new mechanisms of action being introduced every few years. Thus, site-of-action resistance could usually be easily countered, even in cases of multiple resistance, based on site-of-action mutations of several herbicide target sites within the same species. There were cases of cross-resistance based on metabolic degradation of herbicides with different modes of action owing to a single gene or two or more genes for enzymes involved in metabolic alteration of xenobiotics.⁶ Even in these cases, there were usually effective herbicides that were not degraded by these weed biotypes.

There are now many examples of multiple resistance, as well as fields with mixtures of weed species with resistance to different

herbicides with different modes of action. In some situations, farmers have run out of cost effective and/or even technologically effective herbicide options.

From a biological standpoint, glyphosate-resistant (GR) crops have made the situation worse. In 1996, the same year that the first GR weed was reported,² GR soybeans were introduced.⁷ Since then, the adoption of GR soybean, maize, cotton, alfalfa and sugar beet has been rapid, now accounting for about 85% of the more than 1 billion accumulated hectares of transgenic crops grown worldwide.^{8,9} Many of the farmers who adopted this technology used it year after year, with glyphosate as the only herbicide for weed management.¹⁰ Adoption of this technology provided several environmental and toxicological benefits.^{11,12} However, the extensive selection pressure exacerbated the evolution of glyphosate resistance.

Natural site-of-action mutations can give a more resistant form of EPSPS, but a one codon change in the gene does not provide a high level of resistance.¹³ Alteration of more than one codon, as was done by site-directed mutagenesis to produce the GA21 version of EPSPS, provides a much higher level of resistance.¹⁴

However, such double mutations of EPSPS have apparently not occurred in nature. The most resistant weed biotypes have other mechanisms of resistance based on gene amplification^{15,16} or sequestration of glyphosate in the vacuole.^{17,18} Weeds with these two mechanisms of action have been highly problematic in some places where GR crops have been grown continuously for several years, such as GR cotton in the southeastern United States¹⁹ and GR soybeans in the mid-southern and mid-western United States.^{5,20}

There are now fields in the mid-western United States that have *Amaranthus tuberculatus* individuals with resistance to ALS, protoporphyrinogen oxidase inhibitors (PPO) and glyphosate in every possible combination.²¹ Of 18 fields sampled, all fields with glyphosate resistance (10 out of 18) also had ALS inhibitor resistance, and four had resistance to all three modes of action with the *A. tuberculatus* population. In addition to these target-site resistances, non-target-site resistance to photosystem II (PSII)-inhibiting herbicides is also found in this species in some of these fields. One field had an *A. tuberculatus* population with resistance to all four herbicide classes, and all four resistances were found in some individuals within this field. This level of multiple resistance greatly reduces the farmers' options for effective and economical weed management. Furthermore, some populations of this species in the same area have evolved resistance to hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicides.²² HPPD was the last new target site introduced for herbicides. Stacking of HPPD resistance with the other herbicide resistances of *A. tuberculatus* can be expected.

In addition to the problem with this species within these fields, there are other weed species with their own arrays of herbicide resistances. *A. tuberculatus* is only one of several weed species with resistance to multiple herbicides.⁵ Tranel *et al.*²¹ concluded that there is an urgent need for new herbicide options or a new weed management paradigm. As efficacy of herbicides is lost owing to the evolution of herbicide resistance, herbicides with new modes of action are needed more than ever. Furthermore, some of the older herbicides with unique modes of action are being lost from the marketplace in some countries or states (e.g. the banning of paraquat in some European countries) owing to regulatory factors.

3 THE CHANGING ECONOMICS OF HERBICIDE DISCOVERY

The fact that there have been no new herbicide modes of action for over two decades is partly due to three major economic factors. The first of these is the adoption of GR crops. There was massive reliance on glyphosate alone by farmers who had previously used combinations of several herbicides for weed management before GR crops. This led to the devaluation of other herbicides, as their use substantially decreased in cotton, soybean and maize.²³ The price of seed with the glyphosate resistance gene(s) was higher than that of conventional seed, so a significant portion of the cost of weed control was shifted from herbicides to a 'technology fee' added to the price of seeds. Even with the technology fee, the cost of superior weed management was generally reduced by GR crops.²⁴

The reduction in the price of glyphosate after the patent expired exacerbated the situation.²⁴ Also, during the past two decades, the patents for many other herbicides have expired, leading to further devaluation of the herbicide market by generic herbicides.

Before the evolution of GR weeds began to threaten this technology, companies involved in pesticide discovery had good reason to think that the utility of GR crops would remain high for decades. At this time, the general view was that evolution of GR weeds would be a very minor problem, with very slow evolution of very low levels of resistance, if it happened at all.²⁵ Weed species shifts to those with a low level of natural resistance to glyphosate²⁶ were thought by many to be controllable with higher rates of glyphosate. Considering a devalued herbicide market for three major crops and the possibility that GR wheat²⁷ and rice²⁸ might be eventually introduced, companies reduced their discovery efforts for new herbicides in relation to those for insecticides and fungicides. This can be seen in the dramatic decrease in herbicide patents in less than 5 years after GR soybeans were introduced, which was followed by a clear reduction in the number of herbicide active ingredients introduced (~5.5 per year before 2001 and only ~2 per year after 2001) (Fig. 1).

The second economic factor that has slowed mode-of-action discovery involves the consolidation of the pesticide discovery

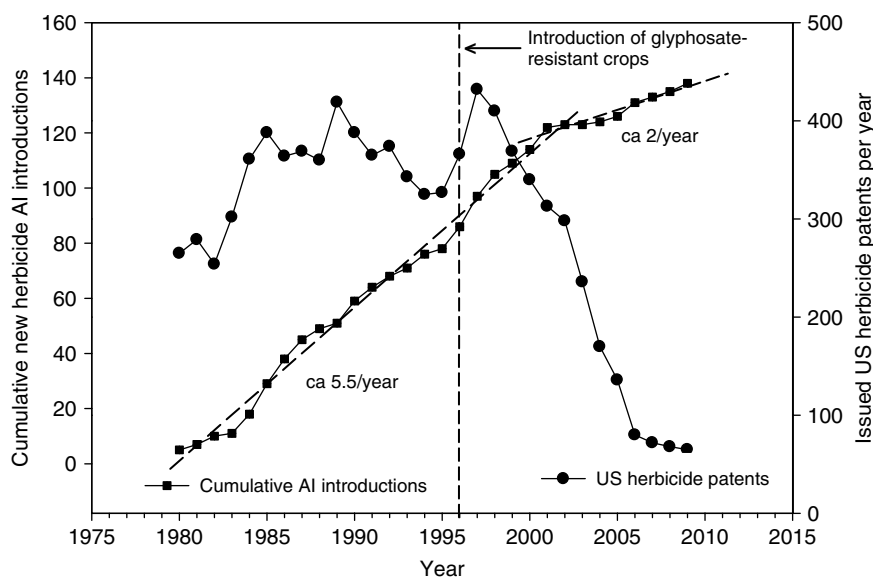


Figure 1. US herbicide patents and new active ingredient introductions over the past 30 years. Redrawn from Gerwick.⁴

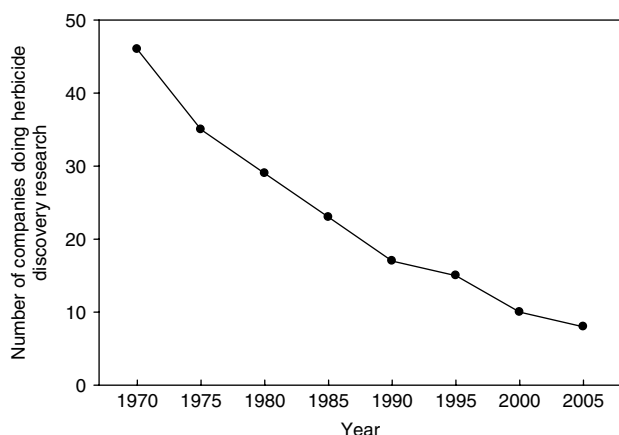


Figure 2. Attrition of companies involved in herbicide discovery. Drawn from data provided by Appleby.²⁹

industry over the past 50 years. The 20 or so currently utilized herbicide modes of action were discovered at a time when there were many companies involved in herbicide discovery research compared with the past 20 years. This can be seen graphically in Fig. 2.²⁹ Examination of the changes in the number of members and membership affiliations of scientific societies to which herbicide discovery scientists belong reveals that the consolidation of this industry has resulted in tremendous attrition in the number of scientists engaged in this type of research, even before GR crops were introduced. Different cultures and philosophies between different companies, different countries in which those companies operated and cultural differences between sites within the same company maximized invention. The contribution of this diversity to discovery is something that cannot be quantified. The reduction in diversity between the relatively few remaining research groups has probably contributed to the stagnation in the growth in numbers of herbicide modes of action.

Lastly, the cost of discovery, development and meeting regulatory requirements has increased. The cost of bringing a synthetic pesticide to the market increased from \$184 million in 2000 to \$246 million in 2008.³⁰ This is partly due to the fact that many more compounds must be evaluated to discover a viable active ingredient than in the past. All the low-hanging fruit may have been picked already. Furthermore, after discovery, the toxicological and environmental hurdles that must be cleared are increasingly higher and, thus, more costly. This increased cost has partially fueled the merger of pesticide companies. These costs have also made it attractive to introduce familiar compounds with old modes of action for which the results of testing are more predictable than for an entirely new chemical class with a new mode of action and an unpredictable toxicity profile.

To paraphrase Gerwick,⁴ not only has the cost of getting a new product to market risen, but getting the new product on the market has been of less value owing to glyphosate-resistant crops and generic herbicides.

4 WHAT MAKES A GOOD HERBICIDE TARGET SITE?

From what is known of the target sites and modes of action of commercial herbicide active ingredients, there is no easy answer to this question. One can list desirable properties of a herbicide target site (Table 2). However, there is no rule of thumb, as there

Table 2. Desirable properties of a herbicide target site

Critical for plant survival
No similar target in non-target organisms, particularly mammals
Subject to irreversible inhibition
Inhibition of a relatively small percentage of the target causes lethality
Inhibition causes accumulation of a toxin
No alternative isozymes or pathways around the target
Inhibitor binding site that binds compounds with physicochemical properties compatible with good uptake and translocation

are exceptions to almost any criterion that might be formulated, apart from the essential one – that the molecular target is essential for plant survival. For example, chemical descriptor criteria have been proposed for predicting whether a compound might be a herbicide,³¹ but the most ideal herbicide thus far introduced, glyphosate,³² does not fit these chemical parameters.

Clearly, there are many more potential target sites for herbicides than are currently being used. The companion paper by Dayan *et al.*³³ and a recent review³⁴ describe a number of natural phytotoxin target sites that are different to those of commercial herbicides. In a few cases, these compounds are as active as some commercial herbicides. However, a significant fraction of the target sites of natural phytotoxins are suspect in terms of mammalian toxicity and even general cytotoxicity. Furthermore, many of these excellent natural phytotoxins are too structurally complex to be economical and/or lack the proper physicochemical properties required for sufficient uptake, translocation and/or environmental stability.

One criterion for a mode of action is that the target site not be one that is present in relatively great abundance in the plant cell. For example, it might be thought that the enzymes of the dark reactions of photosynthesis would be good herbicide target sites, but these enzymes are found at high concentrations in order to process the large amount of carbon dioxide fixed by plants. For example, ribulose-1,5-bisphosphate carboxylase oxygenase (RuBisCo) is the most abundant protein in green plant cells. The fact that it is a rather inefficient enzyme requires the plant to have even larger amounts of it. Inhibiting only a small fraction of this enzyme in target plants would take kilograms of herbicide per hectare. A number of inhibitors of the enzymes of carbon assimilation, including RuBisCo, have been studied as potential herbicides, but none has been commercialized.³⁵

Good inhibitors with similar *in vitro* K_i values of the six enzymes of the branched-chain amino acid pathway have been found, but only inhibitors of acetolactate synthase (ALS) have been commercialized.³⁶ This is partly because ALS is a low-abundance enzyme that is rate limiting in the pathway. The irreversible inactivation by ALS inhibitor herbicides also contributes to their effectiveness. Still, 60–80% inhibition is required for lethality. The enzyme that precedes ALS, ketol-acid reductoisomerase (KARI), is present in higher amounts, and 95% *in vivo* inhibition is needed to kill a plant.³⁶ The best ALS inhibitor herbicides are effective at less than 1 g ha⁻¹.

Low-use-rate herbicides are more desirable than those with higher use rates, and the target site strongly influences the use rate of a herbicide. However, if a herbicide is safe, effective and inexpensive, the use rate may be less important. For example, glyphosate is used at relatively high rates, but it is perhaps the most perfect herbicide yet discovered.³² Nevertheless, when the

number of molecules of EPSPS is significantly increased by gene amplification, the amount of glyphosate needed for effective use becomes too high to be used in the field.^{15,16}

A desirable feature of a target site is that inhibition of a relatively small part of the pool of the enzyme is lethal. Protoporphyrinogen oxidase (PPO) has this property. Inhibition of PPO leads to the substrate moving to parts of the cell where it is oxidized to the PPO product, protoporphyrin IX (ProtoIX).³⁷ ProtoIX is very toxic in the presence of light and molecular oxygen, causing rapid cell death. Other enzymes of the porphyrin pathway are not good herbicide targets, presumably because the unique accumulation of a highly photodynamic porphyrin intermediate (ProtoIX) in a vulnerable cellular compartment does not occur when they are inhibited. There is some evidence that accumulation of a toxic substrate, α -ketobutyrate, may play a role in the toxicity of acetolactate synthase (ALS)-inhibiting herbicides.³⁸ Toxic intermediates do not accumulate when other enzymes of branched-chain amino acid synthesis are inhibited. This may be another reason why good inhibitors of the enzymes prior to ALS in the branched-chain amino acid pathway are not good herbicides.³⁶

As stated by Wittenbach and Abell,³⁶ the limitation for obtaining new herbicide modes of action is not due to failures in finding good inhibitors of essential plant enzymes, but rather to the difficulty of finding sensitive, lethal target sites. The best herbicides are generally those that translocate to target sites that are essential to meristematic tissue. Thus, compounds that are good inhibitors of such target sites *in vitro* but that are poorly or not translocated are not good herbicides.

5 CURRENT APPROACHES TO HERBICIDE DISCOVERY

The traditional method of discovering a mode of action was to discover a herbicidal or phytotoxic compound and then determine its mode of action using physiological and biochemical approaches. The mode of action of relatively few herbicides introduced before 1980 were understood before the herbicide was marketed. The modes of action of these herbicides were often discovered by public sector scientists. There are still several older herbicides that have unknown modes of action (e.g. the organic arsenical herbicide MSMA).² In some cases, the lack of knowledge may be due to more than one target site for the same herbicide, but the lack of interest in exploring the modes of action of old herbicides that have relatively little market share is probably the major cause of this knowledge gap.

Another approach has been to pick a new molecular target site without knowing its potential for herbicides and to find efficient inhibitors with *in vitro* screening. This approach has been facilitated by evaluating vast combinatorial chemistry libraries of compounds using high-throughput *in vitro* screens. At the time that this strategy was first implemented, most pesticide discovery companies were affiliated with companies that were using this method for pharmaceutical discovery. The pharmaceutical industry has used this approach successfully. There is no published claim that any commercial herbicide mode of action has been discovered in this way. This may be because the herbicide discovery efforts with this approach did not have the resources of the pharmaceutical discovery endeavors that used it. To use this method on unvalidated target sites may often be unsuccessful, even when excellent *in vitro* inhibitors are discovered.

More recently, 'omics' approaches have been used to determine the mode of action of phytotoxins with unknown modes of action.

Table 3. Examples of studies to determine the modes of action of phytotoxins by 'omics' approaches

Approach(es)	Phytotoxin	Reference
Metabolomics	Ascaulitoxin	40
Metabolomics	Pyrenophorol	41
Metabolomics	Several herbicides	42
Physionomics and metabolomics	Cinmethylin	43
Genomics	Glyphosate	44
Genomics	Cinidon-ethyl, tribenuron-methyl, 2,4-D	45
Genomics	2,4-D	46
Genomics	Flufenacet	47
Genomics	Atrazine and bentazon	48

Using this strategy, a library of response profiles to compounds (both commercial and experimental) with known modes of action is first generated. Then, the response profile to a compound with an unknown mode of action is produced and compared with those of known mode of actions. If a new compound does not fit the profile of any of the known modes of action, it can be assumed that it has a new mode of action, for which the profile might provide clues.³⁹

Going from the most fundamental to phenotypic responses, 'omics' approaches include transcriptomics, proteomics, metabolomics, physionomics and phenomics. The last two of these approaches have been used for many years. The first three were ushered in with the introduction of powerful genomics tools, advances in proteomics methods and powerful analytic capabilities for quantitative analysis of hundreds of metabolites in plant extracts. Table 3 provides examples of papers using these approaches to determine new modes of action. Herbicide discovery company data are generally not published, so the published information is only a hint of what has been done. Such studies have generally not resulted in discovery of a published new mode of action. However, even if a new mode of action is not found, the study eliminates known target sites and provides clues as to what the actual target site is.

There are several difficulties with this approach. First, the effort and cost in generating a robust database is high, especially for transcriptomics through metabolomics. Dose and sampling times are problems, in that comparing two compounds with very different modes of action, for example one that acts fast (e.g. a PPO inhibitor) and another that acts slowly (e.g. glyphosate), is difficult. All lethal phytotoxins eventually cause many secondary and tertiary effects that can be confounding. Therefore, most researchers use sublethal doses and hope that there are clear indicators of the mode of action soon after treatment. Compounds with multiple target sites will also provide confounding results.

Other approaches to mode-of-action discovery include gene expression manipulation, such as overexpression, and reducing or eliminating expression via knockout or gene silencing methods.⁴⁹ Several potential herbicide target sites have been identified using antisense or RNAi technologies (Table 4). Calibration methods are needed to get realistic answers, as herbicides never inhibit all of the target-site molecules. These methods can be used partially to knock out gene expression. Finding a new potential target site is just the first step. Discovery of a good herbicide for that site may be more daunting than finding the site. Indeed, in spite of the

Table 4. Examples of herbicide target sites identified by antisense or RNAi methods

Target site	Reference
Aldolase	50
Biotin synthase	51
Carbonic anhydrase	52
Chlorophyll synthase	53
Coproporphyrinogen oxidase	54
Cystathionine β -lyase	55
Dehydroquinase dehydrase/shikimate dehydrogenase	56
Ferredoxin : NADP reductase	57
Flavanone 3-hydroxylase	58
Geranylgeranyl reductase	59
Glutamine-semialdehyde amino transferase	60
Mg protoporphyrin monomethylester cyclase	61
Pectin esterase	62
Sphingolipid 4-hydroxylase	63
Thioredoxin	64
Transketolase	65
Uroporphyrinogen decarboxylase	66

Table 5. Herbicide-resistant crops likely to be introduced within the next 5 years. Data are from Gewick⁴

Crop	Herbicide(s)	Mode of action or target site
Maize	2,4-D/aryloxyphenoxys	Auxin mimic and ACCase
Maize	ALS inhibitors	ALS
Maize	Dicamba	Auxin mimic
Soybean	ALS inhibitors	ALS
Soybean	2,4-D/glufosinate	Auxin mimic/GS
Soybean	Isoxaflutole	HPPD
Soybean	Glufosinate/isoxaflutole	GS/HPPD
Soybean	Mesotrione	HPPD
Cotton	Dicamba/glufosinate	Auxin mimic/GS
Cotton	2,4-D	Auxin mimic

many potential target sites found by gene silencing methods, no herbicides have been introduced with any of these target sites.

Multiple approaches to a mode-of-action discovery are probably more productive than reliance on a single method. After a putative target site has been identified, the ultimate proof of this site is engineering a plant with a resistant form of the putative target site.

6 FUTURE DEVELOPMENTS AND CONCLUSIONS

The spectre of increased evolution and spread of glyphosate-resistant weeds has apparently caused the agrochemical industry to increase investment in herbicide discovery. This renewed interest has not yet resulted in significant increases in herbicide patents. A number of new herbicide-resistant crops, some with stacked resistances to more than one herbicide, are due to be launched in the near future (Table 5).^{4,67} However, in every case, the herbicides to be used with these crops have modes of action to which there are already examples of evolved resistance.⁵ If used properly, they will give farmers new tools to prevent and mitigate evolved resistances. However, if the past is a predictor of the future, it would be optimistic to predict that farmers will use these products as part of a robust resistance management strategy. In places where multiple resistance to several of these modes of action has already occurred,²¹ the utility of some of these new transgenic crops is questionable.

Thus, a better solution to such weed problems would be herbicides with new modes of action for which no resistance has evolved. Although there is no clear timeline for the introduction of new modes of action, considering the need and thus the economics, there is little doubt that such products will be introduced eventually. It would be naïve to believe that a pipeline of herbicides with new modes of action will be a long-range solution to weed management problems without farmers guarding the long-term utility of such products by using them as only part of a diverse array of weed management tools to delay or avoid evolution of resistance.

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