Common mechanisms endowing herbicide resistance in weeds

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Summary Plant populations evolve resistance to herbicides through the selection of individuals with phenotypes allowing survival when exposed to herbicides. As a general rule herbicides are strong selecting agents causing intense mortality to populations. Whilst any mechanism that improves survival when exposed to the herbicide can be selected, certain types of biochemical resistance mechanisms tend to be favoured, particularly those that endow substantial resistance. The two most important resistance mechanisms are target site modifications and increased rates of herbicide detoxification. More recently, important examples of resistance where the mechanism is reduced herbicide mobility within the plant have been described.

By far the most commonly reported herbicide resistance mechanism is modification of the target enzyme for the herbicide. During the 1970s and 1980s, the mechanism of triazine resistance in a number of weed species was elucidated and the mutation within the *psbA* gene determined. Since then resistance due to a modified target enzyme has been reported for herbicides inhibiting acetolactate synthase (ALS), acetyl-coenzyme A carboxylase (ACCase), tubulin polymerisation, and 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). In all of these examples, resistance has been found to occur as a result of a single nucleotide change within the coding region of the gene leading to an amino acid modification in the protein.

Several enzyme systems have been implicated in resistance due to increased herbicide detoxification. Increased activity of aryl acylamidase (AAA), an enzyme that cleaves the propanil molecule, endows resistance in two *Echinochloa* spp. Likewise, increased activity of a glutathione transferase (GST) that conjugates atrazine endows resistance to atrazine in some populations of *Abutilon theophrasti*. In both of these examples, resistance occurs to the selecting herbicide and a few chemically related compounds. More complicated examples of resistance are the result of increased cytochrome P450 monooxygenase (Cyt P450) activity. A number of weedy species, mainly grass weeds including *Lolium rigidum* and *Alopecurus myosuroides*, have populations with resistance as the result of elevated Cyt P450 activity. These resistant populations frequently have wide resistance across chemical modes of action.

Paraquat resistance in a number of weeds, including weedy *Hordeum* spp., and glyphosate resistance in *Lolium rigidum* are correlated with reduced translocation of herbicide to the shoot base. The hypothetical mechanism in both cases is exclusion of the herbicide from the cell.

A number of weed populations have complex patterns of resistance that are the result of the accumulation of two or more different mechanisms. These examples of multiple resistance may have more than one of the mechanisms described above.

Keywords Herbicide resistance, resistance mechanisms, selection, fitness.

INTRODUCTION

Herbicide resistance in weeds is an evolutionary response to the selective pressure of herbicides. Herbicides cause massive mortality in weed populations leaving few individuals surviving. Some of the surviving individuals do so because they contain a biochemical change that allows the plant to survive the herbicidal onslaught. Over time, the resistant individuals within the population are favoured and eventually their progeny dominate the population.

A number of distinct biochemical mechanisms could potentially endow resistance in plants. To understand why certain mechanisms are favoured and others appear rarely or not at all, it is important to understand the selective process. This review will briefly describe the selective process, discuss why certain mechanisms are favoured and detail the three main types of mechanisms that have been reported for herbicide resistant weeds.

SELECTION OF RESISTANCE

Selection for herbicide resistance occurs because susceptible individuals in the population are killed, but resistant individuals survive and contribute seed to the seed bank. Selection for resistance is driven largely by the intensity of the herbicide selection pressure and the pre-existing frequency of herbicide resistant individuals in the population (Jasieniuk *et al.* 1996, Preston and Powles 2002a). The rate of selection may be further influenced by other factors, such as seed

bank characteristics, or the dominance of expression of resistance.

Selection pressure Selection pressure is often considered as the fraction of the weed population killed by the herbicide application. However, more correctly the fractional reduction in seed set caused by the herbicide should be the measure of selection pressure. In either case, in the context of annual cropping systems, the number of years of herbicide applications made becomes a simple substitute for selection pressure (Preston *et al.* 1999). The rationale for this is that there is often little difference in the impact of selection pressure on the rate of resistance evolution unless weed control drops below about 80%. Herbicide efficacy is rarely allowed to fall too far as weed control will be compromised.

Initial frequency of resistance alleles Mutations within genes from susceptible to resistant types occur at a constant rate. Such mutations occur on average at about 10^{-9} (Haughn and Somerville 1987, Davies 1994). However, individuals carrying mutations do not occur at this frequency, but may occur at much greater frequencies (Jasieniuk *et al.* 1996, Preston and Powles 2002a). The reason for this is that mutations occur all the time and are passed on to progeny. Therefore, where the number of susceptible individuals is vastly greater than the number of resistant individuals, the number of individuals changing from susceptible to resistant will outnumber the number of individuals changing from resistant to susceptible. This results in a slow increase in the number of resistant individuals to an equilibrium frequency. This is further subject to genetic drift and other processes that can dramatically change allele frequencies in small populations. However, for a neutral mutation in a large population the equilibrium frequency will approximate 50% (where there are only two alleles).

What stops the frequency of a mutation reaching 50% is the fitness differential between the wild type (susceptible) and the mutant (resistant) alleles. For an allele with partial or full dominance, the relationship between the equilibrium frequency of resistance (q_e) and the fitness penalty against the resistant allele (s) can be approximated by the following equation where μ is the mutation rate and h the degree of dominance:

$$q_e = \mu/hs$$ (Jasieniuk *et al*. 1996)

From this equation it is clear that an allele providing little fitness penalty will be present at high frequencies and one with a significant penalty will be present at low frequencies in populations.

HERBICIDE RESISTANCE MECHANISMS

Use of herbicide will select for any individual that can tolerate application of that herbicide. These survivors may contain any of a number of biochemical changes that contribute to plant survival. The possible resistance mechanisms are detailed in Table 1.

Table 1. Potential herbicide resistance mechanisms and their consequences for herbicide behaviour.

Resistance mechanism	Consequence
Target site mechanisms	
Insensitive target enzyme	Herbicide binds less well to the target and enzyme is not inhibited
Over-expression of target enzyme	Herbicide binds to target enzyme, but sufficient enzyme remains uninhibited
Absorption mechanisms	
Reduced interception of herbicide spray (e.g. narrower leaves)	Reduced concentrations of herbicide inside the plant
Reduced absorption of herbicide (e.g. waxier cuticle)	Reduced concentrations of herbicide inside the plant
Detoxification mechanisms	
Increased herbicide detoxification	Insufficient active herbicide reaches the target enzyme
Detoxification of toxic compounds produced by herbicide action (e.g. oxygen radical detoxification)	Reduces speed of herbicide action, but requires removal of herbicide by some other mechanism
Translocation mechanisms	
Binding of herbicide (e.g. cell walls, lignin or other compounds)	Herbicide is immobilised
Intracellular sequestration of herbicide (e.g. vacuole)	Herbicide translocation is limited, herbicide stays near point of application
Reduced cellular uptake of herbicide	Herbicide translocation is limited and herbicide accumulates in tips of treated leaves
Expulsion of herbicide from cells	Herbicide is expelled from cells and flows to tip of treated leaves

In practice, most reported examples of herbicide resistance in weeds are the result of an insensitive target site. There are fewer examples of increased herbicide detoxification and even fewer of reduced translocation. Of the other mechanisms listed in Table 1, none have been conclusively established as important in resistant weed populations.

The impact of fitness on selection of mechanisms
One reason why only a subset of the resistance mechanisms have been observed could be that these mechanisms occur at much higher frequencies in unselected populations. For example, target site mutations might suffer a much lower fitness penalty compared to mutations that endow other types of resistance mechanisms. Another explanation for the preponderance of target site modifications could be that target site mutations are much easier to document than other types of resistance. However, work examining resistance to aryloxyphenoxypropanoate herbicides in *Lolium rigidum* Gaud. and *Avena* spp. in Australia would suggest that target site mutations are selected much more commonly than increased detoxification mutations and other types of resistance (Preston, unpublished data, Maneechote, Preston and Powles, unpublished data). The same is true of *L. rigidum* with resistance to sulfonylurea herbicides (Gill 1995, Llewellyn *et al.* 2001).

The fitness of individuals carrying the resistance allele under selection should also be considered. As a general rule, target site mutations provide greater resistance to herbicides than other types of mechanisms. This means the heterozygotes are less affected by the herbicide and will have greater fitness in the presence of the herbicide. Therefore, selection by herbicides will tend to favour target site insensitivity mechanisms. The exceptions are situations where target site mutations are fatal (e.g. paraquat resistance), or where target site modifications result in lower resistance than other mechanisms.

In the early stages of selection, more than one resistance mechanism may be present in the population; however, with continued selection the stronger resistance mechanism, because it has greater fitness under selection, will be expected to dominate. Therefore, the selection of resistance mechanisms is influenced by the combination of fitness in the absence of selection and fitness in the presence of selection. A further factor is chance, particularly in smaller populations. Resistance alleles would be expected to have a clumped rather than even distribution across the landscape. Therefore, some populations may not contain certain resistance alleles. In these populations, other resistance mechanisms may be selected.

INSENSITIVE TARGET SITE

Herbicides act by binding or otherwise interacting with one or more proteins, the effect of which is to interfere with plant growth or metabolism. Plants may become resistant to the effects of herbicides through changes within these proteins that reduce or eliminate the ability of the herbicide to bind or interact. Mutations that result in enzymes with reduced sensitivity to herbicides are known from weeds for photosystem II (PS II), acetolactate synthase (ALS), acetyl-coenzyme A carboxylase (ACCase), α-tubulin and 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS).

Photosystem II The first resistance mechanism to be carefully documented in weeds was resistance to the PS II-inhibiting triazine herbicides. Resistance to triazines was shown to be the result of an inability of the triazine herbicides to inhibit photosynthetic electron transport (Pfister *et al*. 1979). Subsequently, a mutation of Ser264 to Gly within the D1 protein of PS II was shown to be the cause of resistance (Hirschberg and McIntosh 1983). Since then a large number mutant D1 proteins from resistant weeds have been sequenced and most have contained the same mutation (Gronwald 1994, Preston and Mallory-Smith 2001).

Selection of PS II-inhibitor resistant photosynthetic algal populations in the laboratory turned up a number of mutations other than Ser264 Gly within the D1 protein that reduced the ability of herbicides to inhibit PS II (Trebst 1996). Some surprised has been expressed that these mutations had not been more widely observed in resistant weed populations. Only recently have two of these mutations, Ser264 to Thr and Val219 to Ile, been reported in herbicide resistant weed populations (Masabni and Zandstra 1999, Mengistu *et al.* 2000). Significantly both of these populations were selected with substituted urea herbicides rather than triazine herbicides.

Our understanding of PS II allows an appreciation of why certain mutations endow resistance to herbicides and why certain patterns of cross resistance may occur. The insights gained can be used to understand the effects of mutations in other herbicide target sites. Usually only one or a small number of amino acid modifications are possible in an enzyme to endow resistance to herbicides yet retain adequate catalytic activity. Mutations endowing resistance may remove an amino acid side chain essential for herbicide binding, result in a change to a larger, more charged or more hydrophobic side chain that causes steric or charge interference with herbicide binding, or may cause larger subtle or unsubtle changes to the shape of the herbicide binding pocket. Some of these changes are evident in herbicide resistant PS II (Figure 1). As the

different herbicides that inhibit the same enzyme bind in subtly different ways (see Figure 1), different mutations may result in resistance to one herbicide, but not others. The Ser264 Gly modification within the D1 protein that reduces binding of triazine herbicides also slows electron transport and result in inefficiencies in photosynthesis (Holt and Thill 1994). This mutation will clearly carry a fitness penalty in the absence of herbicide. However, the much higher triazine resistance endowed by this mutation, and hence fitness under selection, compared to the other two mutations (Trebst 1996, Devine and Preston 2000) will mean this mutation is most likely to be selected by triazine herbicide use.

Acetyl-coenzyme A carboxylase The widespread use of herbicides that inhibit ACCase has resulted in a large number of grass weeds with resistance to these herbicides (Devine 1997). Many examples of target site-based resistance to the ACCase inhibitors are known. However, it has proved difficult to sequence the ACCase gene and only one mutation endowing resistance has been reported. This mutation, Ile1780 to Leu is known from a resistant population of *Setaria viridi*s (L.) P.Beauv. (Delyé *et al.* 2002).

Different populations of ACCase-resistant weeds have different patterns of cross resistance to ACCase-inhibiting herbicides (Table 2). These variations suggest that a number of different mutations within ACCase are possible in weed populations. Indeed it is likely that most of the resistant populations of *L. rigidum* in Table 2 will carry different mutations within ACCase.

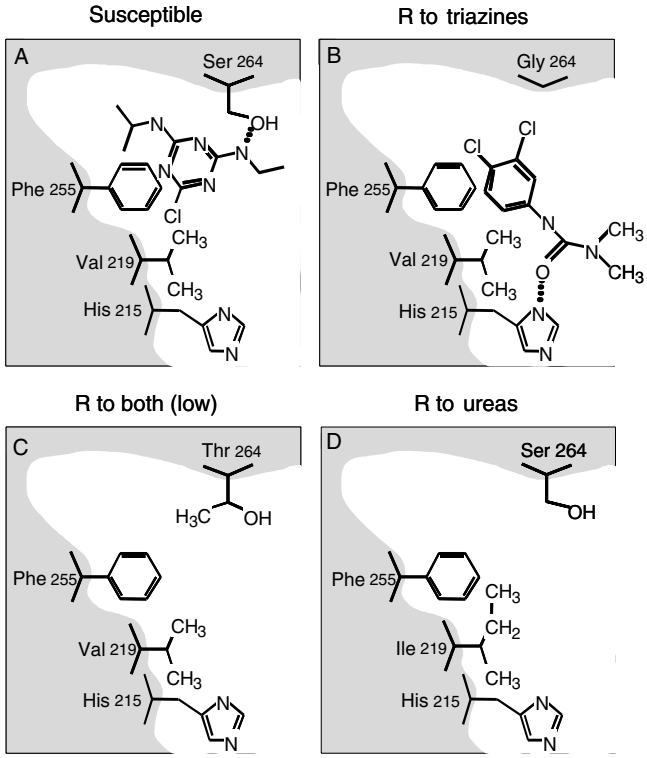

Figure 1. Diagrammatic representation of PS II with binding of atrazine (A) and diuron (B) to the binding pocket. A) Susceptible, B) Resistant due to Ser264 Gly mutation, C) Resistant due to Ser264 Thr mutation and D) Resistant due to Val219 Ile mutation (after Preston and Mallory-Smith 2001).

Table 2. Variations in resistant ACCase in *L. rigidum* populations (adapted from Preston and Powles 2002b).

Population	Resistance index (R/S) for herbicides		
	Diclofop acid	Fluazifop acid	Sethoxydim
SLR 3	>37	>>3	8
SLR 31B	6	55	26
SLR 74	50	17	>50
VLR 69	29	4	1
WLR 33	368	>60	6
WLR 96	>217	>>7	>2

A**cetolactate synthase** A large number of weed species have evolved resistance to ALS-inhibiting herbicides. In many of these examples, resistance is conferred by a mutation within the ALS gene (Saari and Maxwell 1997). Mutations are known within five different sites in the ALS gene (Figure 2). The most common mutations observed are those in Domains A and B. A total of eight different amino acid substitutions are known for the proline in Domain A (Devine and Preston 2000). Each of these mutations endows resistance to sulfonylurea and sulfonamide herbicides and some also provide some resistance to imidazolinone herbicides. A single amino acid substitution is known for Domain B and this mutation endows resistance to all three classes of ALS inhibiting herbicides (Bernasconi *et al*. 1995).

Selection with sulfonylurea herbicides has tended to select for mutations within Domains A and B, whereas selection with imidazolinone herbicides has selected for mutations in Domains B to D, but not

Domain A. Like resistance to PS II-inhibiting herbicides, this can be understood by differential fitness of the different mutations under selection by different herbicides.

Mutations at Domain A often also result in resistance of the ALS enzyme to feedback inhibition by branched-chain amino acids. This results in changes in amino acid pools in leaves and seeds of resistant plants (Eberlein *et al.* 1999). This is a clue to the fitness penalty of these mutations. At present it is not clear whether other mutations of ALS also alter feedback inhibition.

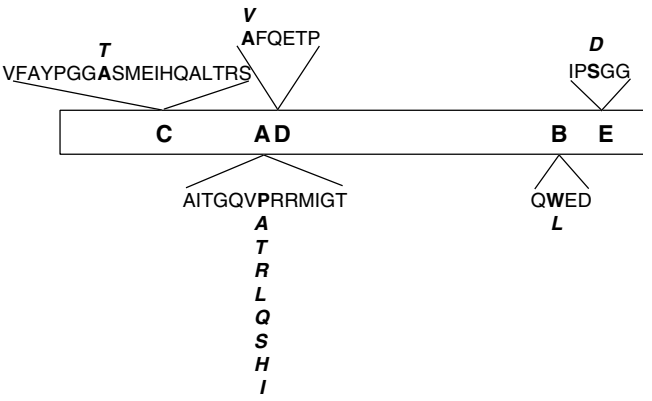

Figure 2. Highly conserved domains within ALS where amino acid modifications are known to endow resistance to ALS-inhibiting herbicides in weeds. The letters in bold are where amino acid changes endowing resistance occur. Known changes are in italics (after Devine and Eberlein 1997).

Target site resistance to other herbicides Populations of several weed species have evolved resistance to dinitroaniline herbicides. Of these, *Eleusine indica* (L.) Geartn. has been the most extensively studied. There is a highly resistant as well as an intermediate resistant population of *E. indica*. Both populations contain amino acid modifications within the α-tubulin protein. The R population contained a change from Thr239 to Ile whereas the I population had a change from Met268 to Thr (Yamamoto *et al.* 1998).

Resistance to glyphosate in *Eleusine indica* from Malaysia is the result of an amino acid modification within the EPSPS protein. This population has a Pro106 to Ser modification. This modification gives only modest resistance to glyphosate and also impairs EPSPS function (G. Dill, personal communication).

INCREASED HERBICIDE DETOXIFICATION

Most herbicides, with the exception of non-selective herbicides, such as paraquat and glyphosate, can be detoxified to some extent by plants. Indeed the very concept of selective herbicides, those lethal to weed species but not the crop, usually depends on more rapid metabolism of the herbicide by the crop species. Generally, similar enzymatic systems are responsible for metabolism of herbicides in crops and weeds, the difference being the rate and extent of metabolism are much greater in the crop. Weed populations have evolved resistance to herbicides through increased activity of aryl acylamidase (AAA), glutathione transferase (GST) or cytochrome P450 monooxygenase (Cyt P450) enzymes.

Cytochrome P450 monooxygenases Cyt P450s are a large family of enzymes that add oxygen to hydrophobic substrates. In plants these enzymes play significant roles in secondary metabolism, but are also known for their ability to detoxify herbicides. Cyt P450s have been implicated as the mechanism of herbicide resistance in several weed species, most notably *L. rigidum* and *Alopecurus myosuroides* (Table 3). Substituted urea, sulfonylurea and aryloxyphenoxypropanoate herbicides are most often involved; however, cyt P450-mediated resistance to triazine, triazinone, imidazolinone, pyrimidinylbenzoate or auxin mimic herbicides is also known.

One feature of populations with resistance due to Cyt P450-dependent increased detoxification is the common occurrence of cross resistance across chemical groups. For example, populations of *A. myosuroides* selected with chlorotoluron may show resistance to ACCase inhibitors and other herbicides (Kemp *et al.* 1990). Likewise, populations of *L. rigidum* resistant to diclofop-methyl may also be resistant to ALS inhibitors (Heap and Knight 1990).

Cyt P450 enzymes can have narrow or broad substrate specificities. It is likely that selection with herbicides in different species, and possibly in different populations within a species, can select for different enzymes with different substrate specificities (Preston and Mallory-Smith 2001). For example, fenoxaprop-P-ethyl selection in *A. myosuroides* in France has selected for a population resistant to both fenoxaprop-P-ethyl and flupyrsulfuron (Letouzé and Gasquez 2001). In this example, the activity of both herbicides on resistant individuals was increased by adding the cyt P450 inhibitor malathion. An alternative example is provided by *D. sanguinalis* with resistance to fluazifop-P-butyl and imazethapyr, where malathion

Table 3. Weed species with populations resistant to herbicides as a result of enhanced herbicide detoxification catalysed by Cyt P450s (compiled from Preston and Mallory-Smith (2001), and references therein, Fischer *et al*. (2000), Hidayat and Preston (2001), and Letouzé and Gasquez (2001)).

Species	Herbicides
Alopecurus myosuroides Huds.	Chlorotoluron Diclofop-methyl Propaquizafop Chlorsulfuron Fenoxaprop Flupyrsulfuron
Avena sterilis L.	Diclofop-methyl
Digitaria sanguinalis (L.) Scop.	Fluazifop-P-butyl Imazethapyr
Echinochloa phyllopogon (Stapf.) Koss.	Bispryibac-sodium
Lolium rigidum Gaud.	Diclofop-methyl Chlorotoluron Chlorsulfuron Simazine Metribuzin
Phalaris minor Retz.	Isoproturon
Sinapis arvensis L.	Ethametsulfuron-methyl
Stellaria media (L.) Villars	Mecaprop

increased activity of imazethapyr, but decreased activity of fluazifop-P-butyl (Hidayat and Preston 2001). It is likely that a single Cyt P450 that can metabolise both fenoxaprop and flupyrsulfuron has been recruited in *A. myosuroides*, whereas two different Cyt P450s have been recruited in *D. sanguinalis*. In a more extreme example, several Cyt P450s with different substrate specificities have been recruited in a population of *L. rigidum* resistant to a wide range of herbicides (Preston *et al.* 1996a).

Other herbicide detoxifying enzymes Resistance to the PS II-inhibiting herbicide propanil has evolved in *Echinochloa crus-galli* (L.) P.Beauv. in USA and other areas and *E. colona* (L.) Link. in Central and South America (Valverde and Itoh 2001). In both species increased activity of AAA, an enzyme that hydrolises propanil, is responsible for resistance (Leah *et al.* 1994, Carey *et al.* 1997). This enzyme only metabolises propanil and a few related compounds and no cross-resistance is reported.

Increased GST-mediated detoxification of triazine herbicides, particularly atrazine, has been shown to endow resistance in some populations of *Abutilon theophrasti* Medikus in the US (Anderson and Gronwald 1991). GSTs are well known to be involved in the detoxification of a large number of herbicides (Marrs 1996); however, in the resistant *A. theophrasti* populations resistance is restricted to the triazine herbicides.

ALTERED HERBICIDE TRANSLOCATION

Variations in translocation patterns of herbicides between populations are occasionally measured, but rarely have such variations been shown to be important in resistance. Two examples where altered translocation patterns are proposed to be responsible for resistance are paraquat resistance in *Hordeum* spp. and glyphosate resistance in *Lolium rigidum*.

Paraquat resistance has evolved in several populations of *Hordeum glaucum* Steud. and *H. leporinum* Link. in Australia following extensive selection with these herbicides. Resistance in these populations has been proposed to result from reduced translocation of paraquat from the leaves to the shoot meristem (Preston *et al.* 1992). A reduction of about 50% is observed in the amount of herbicide translocating out of the treated leaves in resistant populations compared to susceptible populations. The resistant populations are more sensitive to paraquat under warm conditions and this greater sensitivity is correlated with greater translocation of paraquat to the shoot meristem with higher temperatures (Purba *et al.* 1995).

Glyphosate resistance has evolved in several populations of *Lolium rigidum* in Australia following 15 or more years of application of glyphosate for total weed control. A number of possible resistance mechanisms have been examined in one resistant population of *L. rigidum*. The pattern of glyphosate translocation in the resistant population is significantly different to that of susceptible populations (Lorraine-Colwill *et al.* 2002). Glyphosate is well translocated in susceptible *L. rigidum* plants with large amounts of herbicide being translocated to roots. In contrast, in resistant plants glyphosate is only poorly translocated to roots and large amounts end up in the leaf tips. For glyphosate to be lethal to plants sufficient herbicide must accumulate within the shoot and root meristematic tissue to inhibit the shikimate biosynthetic pathway. If glyphosate can be kept away from the meristematic tissue, such as through accumulation in the leaf tips, the plants will survive (Lorraine-Colwill *et al.* 2002).

MULTIPLE RESISTANCE

Multiple resistance in weeds occurs when more than one mechanism contributes to resistance (Preston and Mallory-Smith 2001). This occurs through the accumulation of resistance mechanisms, either as a result of sequential selection, or interbreeding of

individuals with different resistance mechanisms (Preston and Powles 2002b). Such multiple resistant individuals may contain two or more of the resistance mechanisms that are outlined in Table 1.

While multiple resistant populations of weeds occur in several species (Preston and Mallory-Smith 2001), multiple resistant populations of *L. rigidum* are the most complex. Studies on one multiple-resistant population of *L. rigidum*, VLR 69, show the extent of multiple resistance that can occur. This population has an ACCase resistant to aryoxyphenoxypropanoate herbicides, an ALS resistant to sulfonylurea and imidazolinone herbicides (in 5% of the population) and enhanced detoxification of many herbicides catalysed by at least 4 different Cyt P450s (Preston *et al.* 1996b). It is now known that at least five genes are responsible for the wide extent of multiple resistance in this population (Preston 2002).

CONCLUSIONS

Of the 10 possible herbicide resistance mechanisms listed in Table 1, only two occur commonly in weed species. These are target site insensitivity and increased herbicide detoxification. The reasons for the preponderance of these two mechanisms is likely to be their much greater fitness under selection pressure, but also may be influenced by relatively small fitness penalties in the absence of herbicide selection. It is only where target enzyme modifications and metabolism of herbicide are impossible, such as for paraquat, that other resistance mechanisms are more often observed.

For most herbicide target enzymes, several different amino acid modifications are known to endow resistance. However, only one or a few these mutations may occur primarily in field-selected weed populations. The over-representation of certain amino acid modifications is clearly related to the selection history of populations, but these mutations might also be more common in unselected populations. As with selection of resistance mechanisms, fitness during selection together with fitness in the absence of selection will also determine the specific mutations selected.

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