Weed Science, 50:700–712. 2002

Review

Resistance of weeds to ALS-inhibiting herbicides: what have we learned?

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Herbicides that target the enzyme acetolactate synthase (ALS) are among the most widely used in the world. Unfortunately, these herbicides are also notorious for their ability to select resistant (R) weed populations. Now, there are more weed species that are resistant to ALS-inhibiting herbicides than to any other herbicide group. In most cases, resistance to ALS-inhibiting herbicides is caused by an altered ALS enzyme. The frequent occurrence of weed populations resistant to ALS inhibitors can be attributed to the widespread usage of these herbicides, how they have been used, the strong selection pressure they exert, and the resistance mechanism. In several cropping systems, ALS-inhibiting herbicides were used repeatedly as the primary mechanism of weed control. These herbicides exert strong selection pressure because of their high activity on sensitive biotypes at the rates used and because of their soil residual activity. Several point mutations within the gene encoding ALS can result in a herbicide-resistant ALS. From investigations of numerous R weed biotypes, five conserved amino acids have been identified in ALS that, on substitution, can confer resistance to ALS inhibitors. Substitutions of at least 12 additional ALS amino acids can also confer herbicide resistance in plants and other organisms but, to date, have not been found in R weed populations. Mutations in *ALS* conferring herbicide resistance are at least partially dominant, and because the gene is nuclear inherited, it is transmitted by both seed and pollen. Furthermore, in many cases there is apparently a negligible fitness cost of the resistance gene in the absence of herbicide selection. Although resistance to ALS-inhibiting herbicides has been a bane to weed management, it has spurred many advances within and beyond the weed science discipline. As examples, resistance to ALS-inhibiting herbicides has been exploited in the development of herbicide-resistant crops, studies of weed population dynamics, and in developing protocols for targeted gene modification. Resistance to ALS-inhibiting herbicides has greatly affected weed science by influencing how we view the sustainability of our weed management practices, what we consider when developing and marketing new herbicides, and how we train new weed scientists.

Key words: Acetolactate synthase, acetohydroxyacid synthase, AHAS, sulfonylurea, imidazolinone, triazolopyrimidine, pyrimidinylthiobenzoate, mutation, genetics, molecular biology, genetic variability, cross-resistance, herbicide-resistant crops, fitness, molecular modeling, selectable marker, outcrossing, interspecific hybridization, genetic recombination.

Although herbicides are extremely effective weed management tools, overreliance on a single herbicide (or group of herbicides with the same site of action) is likely to result in weed populations that are resistant to that herbicide (or group of herbicides). In particular, acetolactate synthase (ALS)-inhibiting herbicides have been plagued by the development of herbicide-resistant weeds. In 1998 ALS-inhibiting herbicides overtook all other herbicide classes in terms of the number of weed species for which a resistant (R) population had been reported (Figure 1). What is remarkable about this is that the first ALS-inhibiting herbicide was commercialized in 1982, whereas triazines have been used extensively since the 1960s.

The discovery of ALS-inhibiting herbicides was a significant accomplishment in the history of weed science. These herbicides, used at grams per hectare rates as opposed to the kilograms per hectare rates typical of many other herbicides, were largely responsible for the decline in the total amount of herbicide active ingredient applied to crops during the 1980s (Bellinder et al. 1994). Additionally, these herbicides were considered a boon to weed management because of their broad-spectrum weed control, soil residual activity, wide application windows, high margins of crop safety, and low mammalian toxicities (Mazur and Falco 1989). However, the Achilles' heel of these herbicides—their propensity to select R weed populations—not only threatens their future utility but also has significantly influenced how the weed science community views the sustainability of weed management practices. Consequently, it is fitting to review the effects of resistance to ALS-inhibiting herbicides during the 50th anniversary of *Weed Science.*

The purpose of this review is to summarize what we have learned about resistance to ALS-inhibiting herbicides during the past two decades. We begin with a brief introduction to

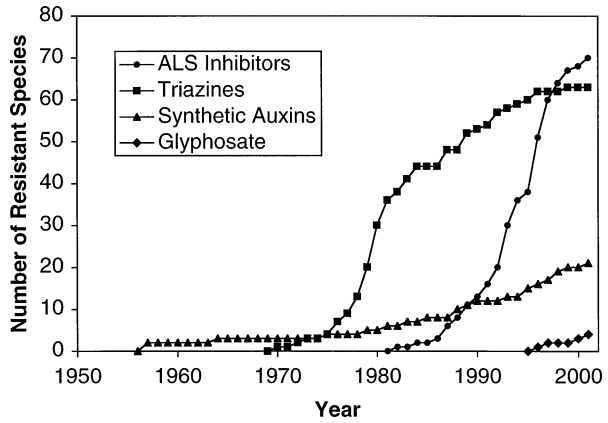

FIGURE 1. Global tally for the appearance of herbicide-resistant weed species for selected herbicide–herbicide groups. Adapted from Heap (2002) with permission.

ALS-inhibiting herbicides and then focus on the mechanisms, physiology, and genetics of resistance to them. We also describe how plant and agricultural scientists have exploited resistance to ALS-inhibiting herbicides and conclude with a discussion of how resistance to these herbicides has influenced weed science.

ALS-Inhibiting Herbicides

Herbicide technology advanced tremendously in 1982 with the introduction of the first ALS-inhibiting herbicide, chlorsulfuron, for broadleaf weed control in cereals (Saari et al. 1994). Chlorsulfuron as well as other sulfonylurea (SU) herbicides are effective at low rates related to their highly specific inhibition of the ALS enzyme (Ray 1984).

ALS, also referred to as acetohydroxyacid synthase or AHAS, is the first enzyme that is common to the biosynthesis of the branched-chain amino acids isoleucine, valine, and leucine (Umbarger 1978). Inhibition of ALS leads to the starvation of the plant for these amino acids, and it is this starvation that is thought to be the primary mechanism by which ALS-inhibiting herbicides cause plant death. But other secondary effects of ALS inhibition, such as buildup of 2-ketobutyrate, disruption of protein synthesis, and disruption of photosynthate transport, have also been implicated in the mechanism of plant death (Shaner 1991). More detailed discussion of the biochemistry of the branched-chain amino acid pathway and of ALS inhibition can be found in Chipman et al. (1998), Duggleby and Pang (2000), and Kishore and Shaw (1988).

Since the introduction of SU herbicides, three other classes of herbicide chemistry that also inhibit ALS have been commercialized: the imidazolinones (IMIs) (Shaner et al. 1984), the triazolopyrimidine sulfonanilides (TPs) (Gerwick et al. 1990), and the pyrimidinylthiobenzoates (PTBs) (Takahashi et al. 1991). Compounds in other chemistry classes also inhibit ALS activity and are under investigation for potential herbicide commercialization (Babczinski and Zelinski 1991; Heap 2002).

Large differences in weed control spectrum and selectivity can be achieved by dramatic changes in herbicide structure (i.e., between herbicide classes); however, significant shifts in herbicide potency, selectivity, and weed control spectra are also achieved by relatively minor molecular alterations within a herbicide family (Ladner 1991). Consequently, many chemical manufacturers continue to discover and develop ALS-inhibiting herbicides with better properties or new uses. Today, there are more than 50 commercial ALS-inhibiting compounds used for selective weed control in an immense variety of grass and broadleaf crops (Heap 2002; Saari et al. 1994) in nearly every part of the world where chemical weed control is practiced.

Evolution of Resistance to ALS-Inhibiting Herbicides

That selection by ALS-inhibiting herbicides could rapidly lead to R weed populations became apparent in 1987, only 5 yr after the introduction of the first SU, with the discovery of chlorsulfuron-resistant biotypes of prickly lettuce (*Lactuca serriola* L.) (Mallory-Smith et al. 1990) and kochia [*Kochia scoparia* (L.) Shrad] (Primiani et al. 1990). Now, there are at least 22 monocot and 48 dicot weed species with resistance to ALS-inhibiting herbicides (Heap 2002). Resistance to ALS inhibitors in some weed species is not limited to a few isolated populations but rather is so widespread and common as to pose a real threat to the continued use of ALS-inhibiting herbicides. In Illinois, for example, so much of the waterhemp [*Amaranthus rudis* Sauer and *A. tuberculatus* (Moq.) Sauer] is resistant to ALS inhibitors that these herbicides are no longer recommended for waterhemp control (Hager et al. 1997; Patzoldt et al. 2002). Similarly, widespread occurrence of kochia resistant to ALS inhibitors in the intensive wheat (*Triticum aestivum* L.) production areas of the United States and Canada has limited the use of chlorsulfuron (Guttieri et al. 1995).

A feature common to many weed populations resistant to ALS inhibitors is that their selection involved reliance on ALS-inhibiting herbicides for their control (Hall and Devine 1990; Mallory-Smith et al. 1990; Primiani et al. 1990; Saari et al. 1992; Schmitzer et al. 1993). Predominantly, resistance occurs as a result of reduced sensitivity of the target ALS enzyme to inhibition by the herbicide. A second mechanism of resistance is increased herbicide metabolism resulting in rapid detoxification of the herbicide. This mechanism generally has resulted in a low magnitude ($<$ 10-fold) of cross-resistance to herbicides with very different modes of action (Hall et al. 1994). The two most notable weeds that have gained resistance to multiple modes of action, including ALS-inhibiting herbicides, caused by enhanced herbicide metabolism are rigid ryegrass (*Lolium rigidum* Gaud.) (Christopher et al. 1991; Cotterman and Saari 1992; Holtum et al. 1991) and blackgrass (*Alopecurus myosuroides* Huds.) (Kemp et al. 1990; Moss and Cussans 1991). Interestingly, these R biotypes were not selected by ALS-inhibiting herbicides: in rigid ryegrass, enhanced metabolism was selected with acetyl coenzyme A carboxylase (ACCase) inhibitors (Christopher et al. 1991) and in blackgrass, with photosystem II inhibitors (Kemp et al. 1990). Cross-resistance in rigid ryegrass to ALS inhibitors was reported (Heap and Knight 1986) before the reports of ALS inhibitor resistance in prickly lettuce and kochia mentioned at the beginning of this section.

One of the most interesting aspects of the evolution of weed populations resistant to ALS inhibitors has been the high frequency of occurrence. What is it about the ALS-

inhibiting herbicides that explains this? Factors that are likely to speed the selection of R biotypes by a herbicide include the repeated use of that herbicide over large areas, little or no use of the alternative herbicide modes of action, high efficacy of the herbicide on sensitive (S) biotypes at the rate used, and soil residual activity of the herbicide. All these factors have contributed to the high number of weed populations resistant to ALS inhibitors. But these factors also apply to other herbicides, triazines in particular, and thus one or more additional factors must account for the high occurrence of resistance to ALS inhibitors. As mentioned previously, resistance to ALS inhibitors in most weed biotypes is caused by an altered ALS. In the following section, we address the question regarding the high frequency of resistance as we discuss the physiology, genetics, and molecular biology of target-site ALS inhibitor resistance.

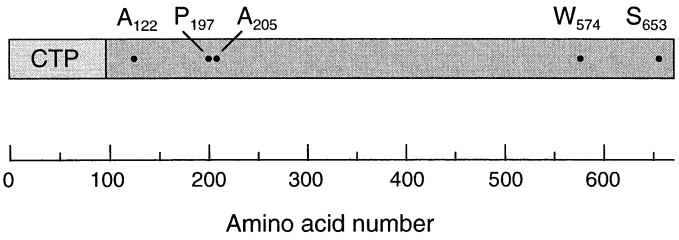

FIGURE 2. Schematic representation of acetolactate synthase (ALS) showing five highly conserved amino acids. In every case investigated thus far—excluding laboratory selections—target-site resistance to ALS-inhibiting herbicides has been attributed to a change in one of these five amino acids. The chloroplastic transit peptide (CTP) targets the precursor protein to plastids, whereupon it is removed to yield mature ALS. Total ALS precursor length, CTP cleavage site, and numbering of amino acids are based on the precursor ALS from *Arabidopsis thaliana* (Sathasivan et al. 1990).

Genetics, Molecular Biology, and Physiology of ALS Target-Site Resistance

Genetics and Molecular Biology of Resistance

Under herbicide selection, R *ALS* alleles are dominant over S alleles. Although the degree of dominance varies among plant species or alleles (Foes et al. 1999; Hart et al. 1993; Sebastian et al. 1989; Wright and Penner 1998a), R alleles are selected even when present in the heterozygous condition. This contrasts with target-site resistance to dinitroanilines, in which the R allele is recessive to the S allele (Jasieniuk et al. 1994; Zeng and Baird 1997); therefore, the R allele is expected to be selected only in the homozygous condition. Although ALS functions in plastids, *ALS* is a nuclear gene and follows normal Mendelian inheritance. R *ALS* alleles are therefore disseminated by both pollen and seed. This is in contrast to target-site triazine resistance, in which resistance is disseminated only by seed in most species because the gene encoding the target site is a plastidic gene (Souza-Machado et al. 1978). Thus, simply the genetics of ALS-inhibiting herbicide resistance, i.e., that resistance is conferred by a single, dominant, nuclear-encoded gene, might partially account for the high frequency of occurrence of resistance to ALS inhibitors relative to some other herbicides.

Natural Variability of ALS

Selection drives evolution, but genetic variability is the fuel upon which selection can act. Thus, the amount of natural variability of *ALS* among individual weeds will affect the likelihood that R biotypes are selected by ALS inhibitors. Variability among alleles is largely caused by spontaneous mutations. Theoretically, a particular high mutation rate in *ALS* relative to other herbicide target-site genes could account for the relatively high-occurrence frequency of resistance to ALS inhibitors. Although mutation rates are typically estimated to be in the range of 10^{-8} to 10^{-10} per nucleotide base-pair per generation (Gardner and Snustad 1984), the actual mutation rate of *ALS* or of any other particular gene is not known and there is no evidence that *ALS* mutates at an unusually high rate. What is known, however, is that the variability of *ALS* is not the same in all weed species.

In the only study we are aware of in which the variability of a herbicide target-site gene was compared among species, a 436-nt region of *ALS* was compared among common cocklebur (*Xanthium strumarium* L.) and common ragweed (*Ambrosia artemisiifolia* L.) plants (Jiang and Tranel 2002). The DNA sequence of this region was determined and aligned from 24 plants of each species, which were collected from six sites in three states. Results from this study revealed that *ALS* was highly variable in common ragweed but not in common cocklebur: 54 and 0 of the 436 nt were polymorphic among the common ragweed and common cocklebur plants, respectively (Jiang and Tranel 2002). These findings provide an explanation for the recent identification of numerous common ragweed populations resistant to the relatively new ALS inhibitor, cloransulam (Patzoldt et al. 2001; Schultz et al. 2000), but do not address variability of *ALS* relative to other herbicide target-site genes. The recent advent of low-cost, high-throughput DNA sequencing procedures makes studies of herbicide target-site variability feasible, and such studies in the future should provide interesting results. For example, it would be interesting to determine whether the variability of the herbicide target-site genes other than *ALS* is high in common ragweed as well.

Regardless of the level of variability of *ALS* within a population, high *ALS* variability in and of itself does not ensure that R *ALS* alleles will be present. Genetic polymorphisms may not equate to protein polymorphisms, and only certain protein polymorphisms will result in resistance. As discussed in the next section, however, a surprisingly large number of *ALS* point mutations result in herbicide-resistant ALSs.

Herbicide-Resistant ALS: A Multitude of Mutations

Several single amino acid substitutions that are sufficient to convert ALS from a herbicide-sensitive to a herbicide-resistant enzyme have been identified. Excluding laboratory selections, target-site resistance to ALS inhibitors in all weed biotypes investigated thus far has been caused by a substitution of one of five conserved amino acids. Three of these five amino acids (Ala_{122}, Pro_{197}, and Ala_{205}) are located near the amino-terminal end of ALS and the other two (Trp_{574} and Ser_{653}) are located near the carboxy-terminal end (Figure 2). Of known plant ALS sequences, these five amino acids have been found at equivalent positions in nearly all cases. Common cocklebur and common ragweed, however, have an alanine rather than a serine residue at position 653 (Bernasconi et al. 1995; Patzoldt et al. 2001).

Despite the high conservation of ALSs among plant species (Chipman et al. 1998; Guttieri et al. 1996), ALSs differ in length because of nonconserved additions and deletions; consequently, exact positions of the conserved residues often vary among species. Additionally, although amino acids are usually numbered starting from the beginning of the precursor ALS protein, some investigators have designated amino acids by numbering from the beginning of the mature protein (i.e., with the chloroplastic transit peptide removed) (Bernasconi et al. 1995; Kakefuda et al. 1996). Different lengths among ALSs and different amino acid numbering schemes have resulted in much confusion (as well as mistakes) in the literature regarding the identification of analogous ALS mutations. For example, the Arabidopsis equivalent of Ala_{122} has been variously referred to as Ala_{56}, Ala_{57}, Ala_{90}, Ala_{100}, and Ala_{113} (Bernasconi et al. 1995, 1996; Wright et al. 1998). To help avoid additional confusion, we suggest that researchers reference ALS amino acid substitutions with the corresponding amino acid in the Arabidopsis precursor ALS, as we have done in this review. Arabidopsis is the model organism for plant genetics research and also, conveniently, has the longest ALS reported from higher plants to date.

In Table 1, weed biotypes with target-site resistance to ALS inhibitors are grouped by the five amino acids at which resistance-conferring substitutions have been identified. A version of this table, along with instructions for providing additions or updates, will be maintained within The International Survey of Herbicide Resistant Weeds web pages (available at www.weedscience.com). We encourage researches to add new weed biotypes to this list as they are identified.

In addition to the fact that substitutions of at least five different amino acids in ALS have been identified in R weed populations, multiple substitutions have been identified for two of these amino acids (Table 1). In fact, eight different amino acid substitutions for Pro_{197} have been reported in herbicide-resistant weed populations. Thus, there is a relatively large amount of flexibility in the herbicide-binding site of the ALS enzyme, in that this site can tolerate substitutions at each of the several conserved amino acids with apparently minimal consequences to normal catalytic function of the enzyme. A likely explanation for this is that the herbicide-binding site of ALS is different from its active site, although the two sites are probably in close proximity (Ott et al. 1996; Pang et al. 2002; Schloss et al. 1988).

Thus far, we have limited our discussion of R ALS isozymes to those from weed biotypes identified from natural populations. Intentional selection of plants resistant to ALS inhibitors has led to the identification of many of the same mutations listed in Table 1, as well as other mutations not yet identified from natural weed populations. Experiments with yeast and bacteria have yielded even more resistance-conferring ALS mutations (Duggleby and Pang 2000). To date, at least 17 different amino acids have been identified that, on substitution, can confer herbicide resistance in at least one organism (Table 2). It will be interesting to see if any of the 12 amino acid substitutions that have been identified thus far only by laboratory selections will be eventually identified in field-selected R weed populations.

In contrast to the situation with ALS target-site resistance, few resistance-conferring mutations in genes encoding target sites of other herbicides have been identified in weed populations. For example, although several mutations in the psbA gene that confer a triazine-resistant D1 protein have been identified experimentally, a glycine for Ser_{264} is the predominant resistance substitution found in weed populations (Gronwald 1994). Only recently has a second D1 protein substitution, an isoleucine for Val_{219}, been found in a triazine-resistant weed biotype (Mengistu et al. 2000). Substantial research several years ago by Monsanto and others failed to identify mutations in the enolpyruvylshikimate-3-phosphate synthase (EPSPS) gene that would confer significant glyphosate resistance while maintaining the normal EPSPS function (Bradshaw et al. 1997). To date, only two weeds, goosegrass [*Eleusine indica* (L.) Gaertn.] and horseweed [*Conyza canadensis* (L.) Cronq.], have been identified with target-site resistance to glyphosate, and the EPSPS mutation in each was at the same amino acid codon (Dill et al. 2000; G. Dill and G. Heck, personal communication). These comparisons indicate that even if the variability of *ALS* among plants is similar to that of other herbicide target-site genes, one would expect a higher initial frequency of R *ALS* alleles relative to other target-site genes simply because there are so many variations in the *ALS* gene that confer R ALS enzymes.

That several different mutations can lead to an R ALS is especially well illustrated by biotypes of kochia that are resistant to ALS inhibitors because of a substitution of Pro_{197}. The Pro_{197} codon is CCG in wild-type (S) kochia (Guttieri et al. 1995). Nine different codons can result from a single point mutation within a codon (three nucleotide substitutions times three codon positions). For the Pro_{197} codon in kochia ALS, three of these nine possible codons (substitutions at the third position) will still encode a proline residue. The other six possible codons, however, will each code for a different amino acid residue. All six of these amino acid substitutions have been identified in kochia biotypes resistant to ALS inhibitors (Guttieri et al. 1995). Additionally, a kochia biotype with a leucine substitution for Trp_{574} has been identified (Foes et al. 1999). Thus, there are at least seven point mutations that can occur, and in fact have occurred, in a kochia *ALS,* each of which resulted in a herbicide-resistant biotype.

Physiology of ALS Target-Site Resistance

Cross-resistances Conferred by Different ALS Substitutions

Several ALS substitutions will result in resistance to ALS inhibitors; the magnitudes of resistance to different ALS-inhibiting herbicides, however, vary widely among substitutions. Although data for all ALS-inhibiting herbicides and ALS substitution combinations are far from complete, several trends have become apparent in recent years. Although exceptions exist, resistance caused by an altered ALS can be generally classified into three types on the basis of cross-resistance: (1) SU and TP resistant, (2) IMI and PTB resistant, and (3) SU, IMI, TP, and PTB resistant (broad cross-resistance).

The list of ALS resistance–conferring substitutions in Table 1 includes corresponding information on the resistance to SU and IMI herbicide classes. TP and PTB herbicides are relatively new chemistries and cross-resistance tests to these classes with many herbicide-resistant isolates have not

TABLE 1. ALS amino acid substitutions that confer herbicide resistance and that were identified in herbicide-resistant weed populations. Resistance-conferring ALS mutations that were intentionally selected (i.e., laboratory selections) are not included in this table.[a,b]

Amino acid residue and number[c]	Substitution conferring resistance	Weed species	Resistance[d]		Reference
			SU	IMI	
Ala 122	Thr	*Xanthium strumarium* L.	S	R	Bernasconi et al. (1995)
	Thr	*Amaranthus hybridus* L.	S	R	Hager and Tranel, unpublished data
	Thr	*Solanum ptycanthum* L.	S	R	Milliman et al. (2000); D. Riechers, personal communication
Pro 197	His	*Lactuca serriola* L.	R	r	Guttieri et al. (1992)
	Thr	*Kochia scoparia* (L.) Shrad	R	S	Guttieri et al. (1995)
	Arg	*Kochia scoparia* (L.) Shrad	R	ND	Guttieri et al. (1995)
	Leu	*Kochia scoparia* (L.) Shrad	R	ND	Guttieri et al. (1995)
	Gln	*Kochia scoparia* (L.) Shrad	R	ND	Guttieri et al. (1995)
	Ser	*Kochia scoparia* (L.) Shrad	R	ND	Guttieri et al. (1995)
	Ala	*Kochia scoparia* (L.) Shrad	R	ND	Guttieri et al. (1995)
	Ala	*Brassica tournefortii* Gouan	R	S	Boutsalis et al. (1999)
	Ile	*Sisymbrium orientale* L.	R	r	Boutsalis et al. (1999)
	Leu	*Amaranthus retroflexus* L.	R	R	Sibony et al. (2001)
Ala 205	Val	*Xanthium strumarium* L.	r	r	Woodworth et al. (1996a)
Trp 574	Leu	*Xanthium strumarium* L.	R	R	Bernasconi et al. (1995)
	Leu	*Amaranthus rudis* Sauer	R	R	Woodworth et al. (1996b)
	Leu	*Amaranthus hybridus* L.	R	R	Schmenk et al. (1997)
	Leu	*Kochia scoparia* (L.) Shrad	R	R	Foes et al. (1999)
	Leu	*Sisymbrium orientale* L.	R	R	Boutsalis et al. (1999)
	Leu	*Ambrosia artemisiifolia* L.	R	R	Patzoldt et al. (2001)
	Leu	*Ambrosia trifida* L.	R	R	Patzoldt and Tranel (2002)
Ser 653	Thr	*Amaranthus powellii* S. Wats.	S	R	McNaughton et al. (2001); F. Tardif, personal communication
	Thr	*Amaranthus retroflexus* L.	S	R	McNaughton et al. (2001); F. Tardif, personal communication
	Asn	*Amaranthus rudis* Sauer	S	R	Patzoldt and Tranel (2001)
	Thr	*Amaranthus rudis* Sauer	S	R	Patzoldt and Tranel (2001)

[a] Additions and updates are available at www.weedscience.com.
[b] Abbreviations: ALS, acetolactate synthase; ND, not determined.
[c] Amino acid number is standardized to the *Arabidopsis thaliana* sequence.
[d] S, r, and R indicate little or no resistance (sensitive), moderate resistance (< 10-fold relative to S biotype), and high resistance (> 10-fold) respectively, to sulfonylurea (SU) or imidazolinone (IMI) herbicides. S, r, and R classifications should be considered generalizations (the 10-fold cutoff between r and R classifications in particular) because different herbicides within the SU and IMI classes may provide different responses and results from only one or a few herbicides within each herbicide class have been reported for most R biotypes.

TABLE 2. ALS amino acids that have been implicated in herbicide resistance in either field selections from natural weed populations (natural selection) or from intentional selection of plants, green algae, yeast, or bacteria.[a]

Amino acid residue and number[b]	Organism	Reference
Gly 121	Yeast	Bedbrook et al. (1995)
Ala 122	Plant—natural selection	See Table 1
	Plant—intentional selection	Bright et al. (1992) (plus others)
	Yeast	Bedbrook et al. (1995)
	Bacteria	Yadev et al. (1986)
Met 124	Plant—intentional selection	Ott et al. (1996)
Val 196	Bacteria	Hill and Duggleby (1998)
Pro 197	Plant—natural selection	See Table 1
	Plant—intentional selection	Haughn et al. (1988) (plus others)
	Yeast	Bedbrook et al. (1995)
Arg 199	Plant—intentional selection	Ott et al. (1996)
Ala 205	Plant—natural selection	See Table 1
	Yeast	Bedbrook et al. (1995), Yadev et al. (1986)
	Bacteria	Friedberg and Seijffers (1990)
Phe 206	Plant—intentional selection	Kakefuda et al. (1996)
Lys 256	Yeast	Bedbrook et al. (1995)
	Green algae	Kovar et al. (2002)
Met 351	Yeast	Bedbrook et al. (1995)
His 352	Plant—intentional selection	Oh et al. (2001)
Asp 376	Yeast	Bedbrook et al. (1995)
Met 570	Bacteria	Ibdah et al. (1996)
Val 571	Yeast	Bedbrook et al. (1995)
Trp 574	Plant—natural selection	See Table 1
	Plant—intentional selection	Lee et al. (1988) (plus others)
	Yeast	Bedbrook et al. (1995)
Phe 578	Yeast	Bedbrook et al. (1995)
Ser 653	Plant—natural selection	See Table 1
	Plant—intentional selection	Sathasivan et al. (1991) (plus others)

[a] Abbreviations: ALS, acetolactate synthase.
[b] Amino acid number is standardized to the *Arabidopsis thaliana* sequence.

been reported; thus, the herbicide cross-resistances described earlier have often been described as (1) SU-specific resistance, (2) IMI-specific resistance, and (3) broad cross-resistance. For biotypes for which it has been investigated, R–S responses were often similar between the SU and TP classes, and between the IMI and PTB classes (Devine et al. 1991; Mourad et al. 1994; Wright et al. 1998).

Substitutions of Ala_{122} or Ser_{653} result in IMI but not SU resistance, whereas substitutions of Pro_{197} usually result in SU but not IMI resistance (Table 1). In some cases, low to moderate levels of IMI resistance have also been observed in biotypes with the Pro_{197} substitution, but the resistance has typically been less than 10-fold and not consistent among various IMI herbicides (Saari et al. 1994). Probably, the greatest cross-resistance to IMI herbicides conferred by a substitution of Pro_{197} was reported in redroot pigweed (*Amaranthus retroflexus* L.), in which resistances to four IMI herbicides ranged from 4- to 63-fold (Sibony et al. 2001). Substitutions of Trp_{574} result in high levels of resistance to both IMI and SU herbicides (as well as the TP and PTB herbicides). The one example of a weed biotype with resistance caused by an Ala_{205} ALS substitution also displayed broad cross-resistance; however, the levels of resistance (approximately 10-fold) were much less than that observed relative to biotypes with the Trp_{574} ALS substitution.

Resistance to one compound of a particular class of ALS-inhibiting herbicides has not guaranteed cross-resistance to all members of that chemical family. This is particularly true of the SU herbicides for which differential resistance (or lack thereof) has been reported in several biotypes (Devine et al. 1991; Hart et al. 1993; Saari et al. 1992; Sibony et al. 2001). In tobacco (*Nicotiana tabacum* L.) selected for SU resistance, for example, a serine for Pro_{197} substitution provided about threefold resistance to primisulfuron while resistance to chlorsulfuron was over 30-fold (Harms et al. 1992).

Effects of ALS Target-Site Resistance on Plant Fitness

Since the identification of plant biotypes with a triazine-insensitive D1 protein, several studies have investigated whether there was an associated decrease in plant fitness in the absence of herbicide selection (Holt and Thill 1994; Jasieniuk et al. 1996). The general conclusion from these studies is that reduced affinity of the D1 protein for triazine herbicides is accompanied by reduced electron flow through photosystem II and consequently reduced fitness (Holt and Thill 1994).

In the absence of herbicide selection, a fitness cost associated with herbicide resistance will decrease the likelihood or rate of weed populations developing resistance. Consider, for example, a random mating population and assume that an S allele mutates to an R allele at a frequency of 1×10^{-6} and that the R allele is completely dominant over the S allele. Population genetics theory predicts that the equilibrium frequency of R plants in such a scenario and in the absence of herbicide selection would be 2.0×10^{-4} if the R plants are 99% as fit as the S plants. In contrast, the

equilibrium frequency of R plants would be 2.7×10^{-6} if they are only 75% as fit as the S plants (Jasieniuk et al. 1996). Thus, whether an R ALS has a low or high fitness cost in the absence of herbicide selection could affect the initial frequency of R biotypes by 100-fold or more.

Do mutations that alter ALS-inhibiting herbicide sensitivity reduce plant fitness? Holt and Thill (1994) have concluded that resistance-conferring mutations in *ALS* do have subtle effects on plant growth and development but do not consistently reduce plant fitness. For example, comparisons of R and S kochia biotypes failed to identify a significant difference in biomass production, the number of seeds produced, or competitiveness (Christoffoleti et al. 1997; Thompson et al. 1994b). In contrast, an S biotype of prickly lettuce produced 31% more aboveground biomass relative to a biotype with target-site resistance to ALS inhibitors, although the two biotypes still had similar competitiveness (Alcocer-Ruthling et al. 1992).

Care must be taken in interpreting studies of plant fitness comparisons because often the R and S biotypes used are not genetically similar (near-isogenic), and thus differences observed may be caused by genetic polymorphisms other than the resistance mutation. Eberlein et al. (1999) minimized this confounding effect by comparing R and S biotypes of lettuce (*Lactuca sativa* L. 'Bibb') derived from five generations of backcrossing. Although the R *ALS* allele came from prickly lettuce in this case and additional prickly lettuce genes likely were carried along in the backcross progeny, the two lettuce lines were expected to be greater than 96% similar (Eberlein et al. 1999). Two conclusions obtained from comparison of these two lines were that the specific activity of ALS was lower in the R than in the S biotype and that ALS from the R biotype was less sensitive to feedback inhibition by branched-chain amino acids, resulting in greater amino acid accumulation. Fitness differences between the two lines were not described in this report; it seems likely, however, that under certain environmental conditions such physiological differences could confer at least subtle fitness differences.

Findings from previous comparisons of the branched-chain amino acid physiology between plants resistant or sensitive to ALS inhibitors corroborate the findings by Eberlein et al. (1999) (Dyer et al. 1993; Eberlein et al. 1997; Thompson et al. 1994a). Interestingly, however, these findings point to a possible fitness advantage (rather than disadvantage) of the R plants in the absence of herbicide selection: greater accumulation of branched-chain amino acids in R vs. S plants may allow seeds from R biotypes to germinate more rapidly, especially under cool temperatures (Dyer et al. 1993; Eberlein et al. 1999; Thompson et al. 1994a). It is interesting to speculate that this potential fitness advantage, under some circumstances, could help maintain a relatively high frequency of R *ALS* alleles in the absence of herbicide selection.

Several crop species that have target-site resistance to ALS inhibitors have been commercialized (see below). Initial reports indicated that these crops (which were obtained either from selection or from genetic transformation with a foreign R *ALS*) did not differ from their herbicide-sensitive counterparts in observable growth properties or yield (Blackshaw et al. 1994; McHughen and Holm 1991). We are not aware of any reports of decreased fitness or yield potential or of any significant growth and development differences in crop plants that have been attributed to an ALS inhibitor resistance gene in these crops. Brandle and Miki (1993) reported decreased yields of tobacco transformed with a resistance-conferring *ALS* from Arabidopsis. As the authors of this report discuss, however, reduced yield potential of the transgenic lines may have been caused by secondary effects introduced during the transformation–regeneration procedure and not specifically by the R ALS.

One of the few reports of a substantial fitness cost of an ALS inhibitor resistance gene has come from a study with Arabidopsis (Bergelson et al. 1996). Plants transformed with the *Csr-1* allele (which contains an asparagine for Pro_{197} substitution [Haughn et al. 1988]) as well as the originally selected mutant line produced about 35% fewer seed than did control plants, when grown in the field. Reduced fitness was attributed to the production of fewer siliques, rather than fewer seeds per silique, and no differences among lines were observed for biomass production (Bergelson et al. 1996). Inclusion of both transgenic lines and the original mutant line allowed Bergelson et al. (1996) to make a strong argument that the observed fitness difference was specifically caused by the *Csr-1* allele and not other genetic differences.

Given the large number of different R *ALS* alleles, it is to be expected that all have not been investigated for fitness effects. Depending on the genetic background (e.g., weed species), the number and expression pattern of *ALS* loci, and the specific *ALS* mutations, fitness costs caused by resistance will vary. From the studies conducted, it is clear that target-site resistance to ALS inhibitors can have pleiotropic effects under at least some conditions and plant fitness may be affected. Nevertheless, reductions in plant fitness of R relative to S biotypes do not, in general, appear to be as great for ALS inhibitor resistance as that observed for triazine resistance. This would suggest that the initial frequency (i.e., before herbicide selection) of individuals resistant to ALS inhibitors would be relatively high. In fact, Preston and Powles (2002) recently reported that the initial frequency of rigid ryegrass individuals with target-site resistance to ALS inhibitors was as high as 1.2×10^{-4}. On the basis of this, they reasoned that the fitness cost of resistance in the absence of herbicide selection should be 0.01%.

On the basis of the preceding discussion on the genetics, molecular biology, and physiology of ALS target-site resistance, factors that may contribute to the high-occurrence frequency of resistance to ALS inhibitors may be summarized. These factors, in addition to cultural and chemical elements mentioned previously (repeated use of ALS-inhibiting herbicides over large areas, their high efficacy, and their soil residual activity) include single-locus–semi-dominant genetics of resistance, minimal effects of the R alleles on plant fitness in the absence of herbicide selection, and a large number of possible point mutations that can confer resistance to one or more ALS-inhibiting herbicides.

Exploiting ALS Target-Site Resistance

Weed resistance to ALS-inhibiting herbicides has undoubtedly provided resistance management and prevention challenges to chemical manufacturers, weed control professionals, and growers. Nevertheless, ALS-inhibiting chemistries are among the most efficacious and widely used her-

bicides in the world. Resistance by a single weed species does not necessarily prevent a herbicide's use for the many other target species in any given cropping system. At the same time, target-site resistance provides opportunities for further economic gains, improvements to weed management tools, and advancement of the weed science discipline. In this section, we provide several examples of agricultural and scientific benefits afforded by ALS inhibitor resistance.

Development of Herbicide-Resistant Crops

A broad spectrum of weeds is controlled in most of the major crops using one or more ALS-inhibiting herbicides. Producers and chemical manufacturers would both benefit from expanded use of these chemicals in other crops and preservation of their current markets; however, crop selectivity often has been a problem with minor crops. Random herbicide-screening procedures are designed to identify herbicides with selectivity in one or more major crops, and selectivity in minor crops is of secondary importance. The design and development of herbicide resistance in various secondary crop species could impart the necessary margin of safety for the use of the target herbicide. Additionally, herbicide carryover injury could be avoided with crops resistant to ALS-inhibiting herbicides used for weed control in other crops grown in rotation.

Many researchers have reported on the intentional development of crops resistant to ALS-inhibiting herbicides. Although initial efforts to develop such crops began before the widespread occurrence of weed populations resistant to ALS-inhibiting herbicides, rapid and frequent occurrence of resistance in weed populations suggested that it would be relatively easy to develop R crops, encouraging several additional attempts. These attempts have been largely successful. Refer to Saari and Mauvais (1996) and Shaner et al. (1996) for a more thorough review.

A variety of crops, including corn (*Zea mays* L.), canola (*Brassica napus* L.), sugarbeet (*Beta vulgaris* L.), rice (*Oryza sativa* L.), and wheat, resistant to ALS-inhibiting herbicides have been developed by a variety of approaches, including somatic cell selection, mutation breeding, plant transformation, and interspecific crossing (Anderson and Georgeson 1989; Croughan 1996; D'Halluin et al. 1992; Mallory-Smith et al. 1990; McHughen 1989; Newhouse et al. 1992; Sebastian et al. 1989; Swanson et al. 1989; Wright and Penner 1998b). These herbicide-resistant crops will allow the expansion of selective weed control with currently registered, highly efficacious active ingredients into new crops and protect S rotational crops (e.g., sugarbeet) from possible carryover injury. Ironically, the development of crops resistant to ALS-inhibiting herbicides will result in even greater reliance on these herbicides, potentially exacerbating the problem of herbicide-resistant weed populations. Herbicide-resistant crops must be viewed simply as additional tools in weed management, and they do not displace the need for herbicide rotations and nonchemical weed control. It is unfortunate that herbicide resistance technology has not been more vigorously pursued for minor crops, for which the need of new weed management tools is much greater compared with the major crops.

Advancements in Molecular Modeling: Rational Design of R ALS

Of the nine amino acids that have been substituted in R ALSs from higher plants, four have been identified only from intentional selection experiments (Table 2). Three of the four were identified from biorational designing of R ALSs (Kakefuda et al. 1996; Ott et al. 1996). Specifically, a molecular model of the ALS enzyme was used to identify amino acids in ALS that, on substitution, would abolish the herbicide-binding site. Because the three-dimensional structure of ALS had not yet been determined, Ott et al. (1996) used the X-ray crystal structure of pyruvate oxidase (POX) (Muller and Schulz 1993) to model ALS.

Prokaryotic POX holoenzyme is a homotetramer and catalyzes the oxidative decarboxylation of pyruvate to yield acetate plus CO_2 (Grabau and Cronan 1986). ALS holoenzyme, in contrast, is a heteromeric protein consisting of large and small subunits (Duggleby 1997; Eoyang and Silverman 1984; Grimminger and Umbarger 1979; Hershey et al. 1999) and catalyzes the nonoxidative condensation of two pyruvate molecules to acetolactate with the concomitant release of CO_2 (or the analogous condensation of pyruvate and 2-ketobutyrate). Despite the differences between the two enzymes, POX and ALS are thought to have a common ancestral origin based on their biochemical and structural similarities (Chang and Cronan 1988). Both POX and ALS require TPP, FAD, and Mg^{+2} for full enzymatic activity, and both enzymes utilize a hydroxyethyl-thiamine pyrophosphate intermediate mechanism to decarboxylate pyruvate (Hawkes et al. 1989; Schloss 1990).

In addition to homology modeling based on POX, the model of the Arabidopsis ALS homodimer was derived from primary and computer-predicted secondary ALS structures and from structure-activity data from previous IMI analogue testing (Ott et al. 1996). The resultant ALS molecular model was particularly successful in accounting for much of the known herbicide resistance data (including cross-resistance patterns), so it was used to predict additional mutations within the herbicide-binding site that could potentially result in IMI-specific resistance. A trial and error iterative process was effective in producing a fully active mutant Arabidopsis ALS enzyme by site-directed mutagenesis that was resistant to IMI herbicides. R ALSs with substitutions at either Met_{124}, Arg_{199}, or Phe_{206} were identified (Table 2).

The elegant modeling work just described, other ALS modeling approaches (Akagi 1996; Ibdah et al. 1996), and the most recent report of the crystal structure of a yeast ALS (Pang et al. 2002) are improving our understanding of the molecular interactions between ALS and its substrates and cofactors. Much of this work was aided by information on specific ALS mutations that diminish herbicide sensitivity and driven by the desire to find new mutations with an eye toward the development of herbicide-resistant crops (Ott et al. 1996). Another driving force behind these studies was the desire to find novel chemistries that might inhibit ALS. Thus, just as triazine herbicides and triazine-resistant plants led to rapid advancements in our understanding of photosystem II, ALS-inhibiting herbicides and plants resistant to them are spurring advancements in our understanding of the biochemistry of ALS and the branched-chain amino acid pathway.

Target-Site Resistance to ALS-Inhibiting Herbicides as a Selectable Marker

Plant Transformation

Because of its dominant nature and its high magnitude of resistance, target-site resistance to ALS inhibitors provides a convenient selection system for plant transformation. For example, a resistance-conferring *ALS* gene and selection by either chlorsulfuron or imazapyr were used in conjunction in the development of protocols for producing transgenic rice and soybean [*Glycine max* (L.) Merr.] (Aragão et al. 2000; Li et al. 1992).

More recently, target-site resistance to ALS inhibitors has been used to evaluate a novel genetic engineering strategy (Beetham et al. 1999; Zhu et al. 2000). A technology that would greatly facilitate plant biology research and applications of plant biotechnology is targeted gene modification (Beetham et al. 1999). A potential approach to achieve this would be the use of chimeric RNA–DNA oligonucleotides. These oligonucleotides are designed to be self-complementary (i.e., they fold back on themselves) and are complementary to the targeted gene with the exception of one or few nucleotides comprising the desired mutation. The existence of known mutations in *ALS* that confer an easily selectable phenotype provides a good system to evaluate this technique. Targeted mutation of *ALS* has been obtained with both corn and tobacco using this technique (Beetham et al. 1999; Zhu et al. 2000). Because this technique does not involve the introduction of foreign transgenes, it avoids many of the problems (both real and perceived) that are associated with transgenic crops.

Although we are not aware of this being done, a resistance-conferring *ALS* allele could also be used in a weed science laboratory methods course to teach how to produce herbicide-resistant crops. One would first need to obtain a resistance-conferring *ALS* allele (including native or other suitable transit peptide and promoter). Once obtained, a clone of such a resistance gene could be provided to students, who would then be required to subclone it into a transformation vector (e.g., as described by Bergelson et al. 1996). Using a simple transformation protocol for Arabidopsis (Clough and Bent 1998), students could use their constructs to create herbicide-resistant Arabidopsis. Several techniques (such as plant transformation, herbicide efficacy evaluation, and segregation analysis) with relevance to contemporary weed science laboratory methods could be taught in a framework built upon this one project.

Weed Population Dynamics

In addition to its use as a selectable marker for plant transformation, target-site resistance to ALS inhibitors has been used as a selectable marker in the studies of plant population dynamics. Barrentine and Soigner (1995) used target-site resistance to ALS-inhibiting herbicides as a marker to estimate outcrossing rates in common cocklebur by determining the number of R progeny produced by S plants growing near R plants. Stallings et al. (1995) similarly used a field plot consisting of a mixture of S and R plants to model pollen movement in kochia. Guttieri et al. (1998) took advantage of target-site resistance to ALS inhibitors to estimate inbreeding coefficients in kochia. Unlike the previous two studies, however, in which R and S biotypes were planted in an arranged plot design, Guttieri et al. (1998) inferred genotypes of mother plants in natural (field) populations by testing their progeny for herbicide resistance–sensitivity.

Another way in which target-site resistance to ALS inhibitors has been used in weed biology is in the investigations of interspecific hybridization. *Amaranthus* weed species have long been suspected of hybridizing; lack of suitable markers, however, has made this difficult to verify. Recently, Tranel et al. (2002) and Wetzel et al. (1999) overcame this hurdle by using resistance-conferring *ALS* alleles as markers and were thereby able to confirm hybridization between waterhemp and Palmer amaranth (*Amaranthus palmeri* S. Wats.) and between waterhemp and smooth pigweed (*Amaranthus hybridus* L.). Whether investigating field populations or using R–S biotypes in controlled greenhouse or field experiments, target-site resistance to ALS inhibitors is a convenient marker that can be used to study herbicide resistance gene flow as well as general reproductive aspects of weed species.

Estimating Genetic Recombination

Some of the applications of target-site resistance to ALS inhibitors have been in very basic aspects of molecular biology. In a particularly clever study, Mourad et al. (1994) took advantage of resistance-conferring mutations within *ALS* to estimate gene recombination frequencies in Arabidopsis. Specifically, they used two Arabidopsis mutants, one (Csr1-1) contained a substitution at ALS Pro_{197} and the other (Csr1-2) contained a substitution at ALS Ser_{653}. Csr1-1 and Csr1-2 have SU- and IMI-specific resistance, respectively. Essentially, the approach was to first obtain plants heterozygous for the two mutations by crossing the two mutant lines. Heterozygous plants were then crossed with wild-type (S) plants, and the resultant progeny were selected with both an SU and IMI herbicide. Recombination between the two point mutations within *ALS* would result in an allele containing both point mutations. Only progeny that inherited such a recombinant allele should survive the double-herbicide selection. Out of 100,000 progeny analyzed, four double-mutant plants were recovered and verified to be recombinants. Thus, a recombination frequency of 0.008% was estimated between the 1,369 base pairs of the two point mutations (Mourad et al. 1994).

Weed Science Impacts of Resistance to ALS Inhibitors

Resistance to ALS-inhibiting herbicides has provided significant challenges to the weed science community. Growers must face the issue of a reduced number of weed control options if herbicides are no longer effective on their weed spectra. Measures to manage or prevent herbicide resistance can be costly, inconvenient, and difficult to implement. Chemical manufacturers are pressured to sell every hectare of product possible to ensure that stockholders are repaid for the expensive cost of discovering, developing, and registering a product. Managing the short-term need for financial results with the long-term need for product preservation is a difficult path to walk. Government and university experts attempt to influence the balance of economics and science; however, the success to date has been limited. Our

past and current successes of bringing new weed control chemicals to market have led many to a complacent attitude with regard to resistance management and prevention. As the herbicide industry has matured, industry consolidation and concomitant curtailing of research and development for novel herbicides have occurred. Discovering new modes of action and totally new chemistries has become increasingly more difficult.

Largely because of the widespread occurrence of resistance to ALS-inhibiting herbicides, herbicide resistance receives much more attention now than it did 10 yr ago in the marketing and development of new herbicides. For example, advertising campaigns for some herbicides have featured their ability to control ALS inhibitor–resistant weeds. Chemical manufacturers must make decisions to commercially develop or shelve new molecules increasingly early in the discovery process. Potential market share, competitors' products, commodity shifts, and R weed populations are all considerations in deciding whether or not to develop a new product. Manufacturers will consider now more than ever the lessons learned from ALS-inhibiting herbicide resistance.

In 1989 a consortium of agrochemical manufacturers founded the Herbicide Resistance Action Committee (HRAC) to foster the responsible use of herbicides and to support research to increase the general understanding of herbicide resistance. Resistance to ALS, ACCase, and photosystem II inhibitors was of primary concern. Information on resistance development and steps to manage and prevent resistance were developed and disseminated. As a mechanism to support research and understanding of herbicide resistance, HRAC supported a worldwide survey of R weeds and information clearinghouse at www.weedscience.com. In 2001 over 1 million pages were uploaded from this site to computers around the world (I. Heap, personal communication). The weed science community has been hugely successful in approaching herbicide resistance with scientific gusto.

In the past decade, weed scientists have greatly increased their scientific skills in basic chemistry and agronomy to include biochemistry, genetics, and molecular biology. Development of weed populations resistant to ALS inhibitors was accompanied by the application of these scientific disciplines to weed science research. This was probably at least somewhat coincidental because molecular biology in particular was becoming commonplace at this time in several fields of the study. Nevertheless, we feel that the widespread occurrence of resistance to ALS inhibitors encouraged the adoption of molecular techniques by weed scientists because of the significance of the resistance problem and the desire to understand the underlying molecular mechanisms. Additionally, determining target-site mutations conferring R ALSs is a relatively straightforward molecular biology process.

Now, there are numerous examples of *ALS* sequences (or at least partial sequences) from R weed biotypes (Table 1) that collectively indicate what to expect when sequencing *ALS* from a previously uncharacterized biotype. Additionally, the five mutations reported thus far group within two regions of the *ALS*, each of which can be conveniently amplified by polymerase chain reaction and then sequenced. Further simplifying *ALS* sequencing, to the best of our knowledge, all *ALS* genes reported to date from higher plants do not contain introns. (*ALS* genes from green algae, however, do contain introns [Funke et al. 1999]). Because of the relative simplicity of determining ALS mutations, such a project is an excellent way to introduce weed science students to molecular biology. We expect in the future that many young weed scientists will "cut their molecular biology teeth" by identifying an *ALS* mutation responsible for observed resistance in a particular weed biotype. In this way, a completely unexpected outcome of resistance to ALS inhibitors has been an infusion of molecular biology into the weed science discipline.

Resistance to ALS-inhibiting herbicides has provided difficult challenges to the weed science discipline but has also been the platform for growth in skills and general scientific principles. With the celebration of the 50th anniversary of *Weed Science,* we should not forget the gains our discipline has made as a result of herbicide resistance.

Acknowledgments

We thank the associate editor and anonymous reviewers for their valuable contributions to the manuscript.

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Received January 31, 2002, and approved April 24, 2002.