Herbicide Cross Resistance and Multiple Resistance in Plants

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I. Introduction

It is now well established that persistent herbicide application to a plant population is a strong selection pressure for individuals carrying genes conferring herbicide resistance. Plants expressing any genetically-endowed traits enabling survival in the presence of the herbicide have a strong advantage and may come to dominate the population.

The severity and time period over which resistance can develop varies dependent upon the herbicide(s) used and biological, agro-ecological, and managerial factors, but can be as short as three years from commencement of herbicide use (Tardif and Powles, 1993). For an overview of the herbicide resistance literature, the reader is referred to the published book proceedings from a number of international meetings (LeBaron and Gressel, 1982; Green et al., 1990; Caseley et al., 1991; Denholm et al., 1992), as well as a very recent book (Powles and Holtum, 1994).

This contribution does not seek to review herbicide resistance in general, but rather to concentrate on the more recent phenomena of herbicide cross resistance and multiple resistance.

II. Part A. Cross Resistance to Herbicides

Cross resistance is defined as the expression of a genetically-endowed mechanism conferring the ability to withstand herbicides from different chemical classes. Following Hall et al. (1994), we have chosen to use mechanism-based definitions for cross resistance as these have the advantage over herbicide history definitions in that herbicide histories may be incomplete, and do not allow for the introduction of resistance genes via seed or pollen. There is a disadvantage in that the mechanism(s) of resistance to herbicides must be known before an assignment can be made.

There are two broad cross resistance categories; target site cross resistance (considered in Section 1) and non target site cross resistance (considered in Section 2). The phenomenon of cross resistance is important from both a practical and scientific viewpoint. Agricultural producers and/or agrochemical manufacturers can experience substantial economic loss and other problems if cross resistance to a range of herbicides limits weed control options. Unravelling the biochemical and genetic basis of cross resistance, as well as implementing sustainable weed control programs, are important scientific challenges.

This review considers many examples of herbicide-resistant populations of the grass species *Lolium rigidum* and *Alopecurus myosuroides* because these species are the first to display widespread herbicide resistance across a range of chemical classes (see Hall et al., 1994). *L. rigidum* is an annual, diploid cross-pollinated species native to the Mediterranean and now widely dispersed in some regions of the world with a Mediterranean-type climate. *L. rigidum* is a widespread, abundant weed within the cropping regions of southern Australia where it decimates crop yield if not controlled. Herbicides have been widely employed to control *L. rigidum* and within a few years of use, herbicide-resistant biotypes became evident. Since the first report in 1982 (Heap and Knight, 1982), the occurrence of resistance has dramatically increased. What is striking about herbicide resistance

in *L. rigidum* in Australia is the complex resistance patterns which develop across many different herbicide groups. In some populations resistance exists to just one herbicide group, whereas in other populations resistance extends across many herbicide groups and modes of action. Resistance to many herbicides makes *L. rigidum* control in Australia a significant practical problem (Powles and Matthews, 1992).

A. myosuroides is also an annual, diploid, cross-pollinated species with high fecundity and is a major weed in parts of Northern Europe. Resistance to triazine herbicides in *A. myosuroides* was reported in Israel in 1982 (Yaacoby et al., 1986). Concurrently, or soon thereafter, populations resistant to substituted urea herbicides were reported in Germany (Niemann and Pestemer, 1984) and the U.K. (Moss and Cussans, 1985). Cross resistance has been documented in biotypes in England (Moss, 1992) and Spain (De Prado et al., 1991). In common with *L. rigidum*, many biotypes of *A. myosuroides* exhibit cross resistance to herbicides from a variety of herbicide classes (Moss, 1990; De Prado et al., 1991). However, the areas infested are not large and the number and severity of resistant populations are only a fraction of the resistant *L. rigidum* populations in Australia. Both *A. myosuroides* and *L. rigidum* exhibit many characteristics that favor the accumulation of herbicide resistance mechanisms. These characteristics include large populations of widespread distribution in cropping areas, high reproductive capacity, rapid seed bank turnover, allogamous reproduction, and genetic and phenotypic plasticity (Moss and Cussans, 1985, Powles and Matthews, 1992).

Numerous herbicide-resistant biotypes of both *L. rigidum* and *A. myosuroides* have been documented. Amongst these there are a wide range of resistant types and resistance patterns. Several biotypes of both species will be considered here, and to avoid confusion, the original published biotype names have been retained. These are listed in Tables 1 and 2 for *L. rigidum* and *A. myosuroides*, respectively, and give the resistance spectrum and types of resistance mechanisms, where known, for each biotype. The herbicide histories (not provided) of these biotypes range from simple to extremely varied. Salient features of the herbicide histories of these biotypes will be provided in the text.

1) Section 1: Target Site Cross Resistance

Target site cross resistance occurs when a change at the biochemical site of action of one herbicide also confers resistance to herbicides from a different chemical class that inhibit the same site of action in the plant. Target site cross resistance does not necessarily result in resistance to all herbicide classes with a similar mode of action or indeed all herbicides within a given herbicide class. While there are many examples of target site cross resistance, some of the most important examples are summarized below:

a. Target site cross resistance to acetolactate synthase (ALS)-inhibiting herbicides

Over the past decade, the most important area of herbicide chemistry has been the discovery of herbicides inhibiting acetolactate synthase (ALS). There are 15 classes of chemistry which have been described as inhibitors of ALS (Saari et al., 1994). Of these, the chemically dissimilar sulfonylurea, imidazolinone and triazolopyrimidine herbicides have been commercialized and are in widespread use. The large scale adoption and often persistent use of these herbicides has led to the appearance of weed biotypes resistant to the ALS-inhibiting herbicides. As reviewed by Saari et al. (1994), there are now many biotypes within at least 15 weed species (especially *Kochia scoparia* and *Lolium rigidum*) which have developed resistance to ALS-inhibiting herbicides, mainly through selection with sulfonylurea herbicides (presumably because they have been in commercial use for the longest period). In the vast majority of cases of resistance following selection with sulfonylurea herbicides, the resistance mechanism is a change in the target site enzyme ALS (reviewed by Saari et al., 1994). In most cases, the sulfonylurea-resistant biotypes with a resistant ALS enzyme exhibit varying levels of target site cross resistance to the chemically dissimilar, but ALS-inhibiting, imidazolinone and/or triazolopyrimidine herbicides (Table 3; Hall and Devine, 1990; Christopher et al., 1992; Saari et al., 1990; 1992; 1994).

The considerable variation in the level of resistance across and within various ALS-inhibiting herbicide chemistries (Table 3) is likely to be due to subtly different binding by particular herbicides on the ALS enzyme and different mutations of ALS. Evidence from competitive binding studies show that the three classes of ALS-inhibiting herbicides bind to the same, or closely overlapping sites on ALS (Durner et al., 1991; Landstein et al., 1993). The wide variation in target site cross resistance amongst biotypes with resistant ALS enzyme (Table 3) implies that there are a number of different functional mutations of the ALS gene. Knowledge of specific mutations of ALS providing resistance is now emerging. ALS gene sequences from a number of resistant biotypes of higher plants which have been examined show a substitution at a proline residue (173) in a highly conserved region of the enzyme, known as domain A. However, the proline substitutions vary in that substitutions of threonine, alanine, serine, histidine and glutamine for this proline have all been observed. Guttieri et al. (1992) examined ALS from three resistant weed species and observed Thr substitution in *Kochia scoparia* and a His substitution in *Lactuca serriola* at Pro 173. No alteration was observed in

domain A of ALS for a resistant biotype of *Salsola iberica*. Five other resistant biotypes of *K. scoparia* were examined and only three contained a substitution at Pro 173. In addition to changes at the Pro 173 of domain A, at least two other mutations have been observed to give sulfonylurea and/or imidazolinone resistance in higher plants; Ser 653 Asn in *Arabidopsis thaliana* (Sathasivan et al., 1991), and Trp 573 Leu in *Nicotiana tabacum* (Lee et al., 1988), and a number of other mutations providing resistance are known from yeast (Mazur and Falco, 1989). Significantly, in the only case so far published of resistance selected by an imidazolinone herbicide, a biotype of *Xanthium strumarium* resistant to imidazolinone herbicides at the whole plant and ALS enzyme level is not cross resistant to sulfonylurea or triazolopyrimidine herbicides and possesses an ALS enzyme susceptible to these herbicides (Schmitzer et al., 1993). Therefore, it is clear that there are several possible mutations of the ALS gene which will confer resistance to sulfonylurea and imidazolinone herbicides and yet retain enzyme function. It is likely, although not yet established, that these different mutations in the ALS gene provide different levels of target site cross resistance within and between ALS-inhibiting herbicide chemistries. The variations in target site cross resistance among herbicide-resistant mutants indicates that the binding domains for the various classes of ALS-inhibiting herbicides do not fully overlap. It is also clear from these studies that a number of different mutations can endow resistance to various ALS-inhibiting herbicides without any significant impairment of enzyme function *in vivo*. As discussed below, this is also likely to be the case for herbicide-resistant ACCase, but is not the case for herbicide-resistant PS2 in which very few mutations confer resistance and yet retain full enzyme functionality. Competitive fitness studies with ALS enzyme-based resistant biotypes of *Kochia scoparia* and *Lactuca serriola* indicate there is no fitness penalty to plants carrying a resistant ALS enzyme (Mallory-Smith et al., 1992).

b. Target site cross resistance to acetyl-CoA carboxylase (ACCase)-inhibiting herbicides

During the 1970s and 1980s, two chemically dissimilar herbicide groups, the aryloxyphenoxypropionic acid (APP) and cyclohexanedione (CHD) herbicides, which target the plastid enzyme ACCase, were commercially developed and widely adopted. These herbicides are lethal to many Graminaceae but are harmless to dicot species and have therefore become widely employed for grass weed control. Following widespread usage of ACCase-inhibiting herbicides, resistance to these modern generation graminicides has become extensive in *L. rigidum* in Australia and is developing rapidly in the closely related *L. multiflorum* in Oregon, in wild oats (*Avena* spp.) in Australia and N. America, and in other species (for a review of resistance to ACCase herbicides see Devine and Shimabukuro, 1994).

In *L. rigidum* in Australia, and *L. multiflorum* in North America, many ACCase target site-based resistant biotypes have appeared (Stanger and Appleby, 1989; Holtum and Powles, 1991; Gronwald et al., 1992; Tardif and Powles, 1993). In *L. rigidum*, selection either with an APP herbicide (Holtum and Powles, 1991), or a CHD herbicide (Tardif et al., 1993), has led to target site cross resistance to both the APP and CHD herbicides, however in both cases, the level of resistance to APPs is greater than that to CHDs (Table 4). It is evident from the data collated in Table 4 that different resistant *L. rigidum* biotypes possessing resistant ACCase exhibit different patterns of resistance at the whole plant level and in ACCase assays (Tardif and Powles, 1993). Many, but not all, *L. rigidum* biotypes exhibit target site cross resistance across the APP and CHD herbicide chemistries. In contrast, a biotype of *L. multiflorum* selected with diclofop-methyl and with an ACCase resistant to APP herbicides shows no target site cross resistance to the CHD herbicides (Gronwald et al., 1992). Two biotypes of *A. myosuroides* (Mason and Otmoor) have been documented as highly resistant to the APP herbicides as a result of resistant ACCase (Hall, Moss and Powles, unpublished). The ACCase from these biotypes is also resistant to CHD herbicides. Resistance to APP herbicides in several biotypes of the wild oat species *Avena fatua* and *Avena sterilis* is also endowed by resistant forms of the ACCase enzyme. In these cases, there are varying degrees of target site cross resistance to the CHD herbicides, ranging from none to moderate (Maneechote et al., 1994; Maneechote, Preston and Powles, unpublished). These levels of target site cross resistance to the CHD herbicides at the whole plant level correlate with the level of resistance displayed by ACCase from these biotypes (Maneechote, Preston and Powles, unpublished).

From the foregoing it is clear that target site-based resistance to ACCase herbicides does not always lead to cross resistance to other herbicides with the same site of action. This is the expected result where herbicides from different chemical classes bind to overlapping, but not identical sites on the target enzyme (see also (a) above and (c) below). This is likely, although not yet established at the molecular level, for APP and CHD herbicides interacting with ACCase. The patterns of resistance of ACCase to herbicides can be strikingly different even among resistant biotypes of the same species as can be seen from Table 4. For example, among biotypes of *L. rigidum*, resistance to haloxyfop can range from moderate to high, and resistance to sethoxydim can range from nonexistent to moderate. Therefore, we suggest the differences in target site cross resistance are the result of selection for different mutations of the ACCase gene in different resistant populations.

Evidence exists from maize cell lines that different alleles at the same locus encode different resistant forms of ACCase with different levels of target site cross resistance (Marshall et al., 1992). There remains a wealth of valuable information to be obtained from these various ACCase mutants. While the ACCase gene has recently been sequenced from a number of plant species (Roessler and Ohlrogge, 1993; Ashton et al., 1994; Ellborough et al., 1994; Shorrosh et al., 1994) there is, as yet, no specific knowledge of herbicide binding site(s) within the ACCase enzyme. The various different herbicide resistant ACCase mutants (Table 4) will be very useful in elucidating herbicide binding and the specific mutations which endow resistance while retaining enzyme functionality.

A second site of action has been proposed for APP and CHD herbicides. These herbicides cause a rapid depolarization of plant cell membrane potentials by allowing the influx of protons (Lucas et al., 1984; Shimabukuro, 1990). The maintenance of an electrogenic potential is vital to survival of the cells, however, the importance of the herbicide-induced depolarization of the membrane potential as a herbicidal mode of action has been questioned (DiTomaso et al., 1991). Also, the relevance of the herbicide-induced depolarization of the membrane potential to the field performance of these herbicides is entirely unknown. Cells from root tips and coleoptiles of some biotypes of *L. rigidum* resistant to APP and CHD herbicides are able to re-establish the membrane potential following removal of herbicide from the bathing solution (Häusler et al., 1991; Holtum et al., 1991; Shimabukuro and Hoffer, 1992). This ability to repolarize the membrane potential following removal of the herbicide is not observed with susceptible biotypes. Similar results have been obtained with a herbicide-resistant biotype of *Avena fatua* (Devine et al., 1993), however, in other resistant biotypes of *A. fatua* and *A. sterilis* repolarization of the membrane potential does not occur following removal of the herbicide (Maneechote et al., 1994; Maneechote, Preston and Powles, unpublished). Repolarization of the membrane potential occurred in resistant *L. rigidum* biotypes irrespective of the possession or absence of a resistant ACCase. Repolarization is pH dependent even in susceptible biotypes (DiTomaso, 1993; Holtum et al., 1994; Maneechote, Preston and Powles, unpublished). The biotypes of *L. rigidum* which show repolarization of the membrane potential following removal of the herbicide also displayed a reduced ability to acidify the external solution bathing roots or coleoptiles (Häusler et al., 1991; DiTomaso, 1993). DiTomaso (1993) claimed a direct connection between the differential abilities of the resistant *L. rigidum* biotypes to acidify the external medium and the repolarization of the membrane potential following removal of the herbicide. In contrast to the above, the biotype of *A. fatua* displaying the membrane repolarization phenomenon acidifies the external medium at the same rate as the susceptible biotype (Devine et al., 1993). There is still a myriad of unsolved questions regarding the repolarization of the membrane potential and its role, if any, in resistance to APP and CHD herbicides (see Holtum et al., 1994). What is clear is that there may be a fundamental difference in membrane properties of some resistant biotypes of *L. rigidum* compared to the susceptible biotypes (Häusler et al., 1991). What relevance this has to herbicide resistance is unclear.

c. Target site cross resistance to photosystem two (PS2)-inhibiting herbicides

Numerous chemically dissimilar herbicide classes act by inhibiting photosynthetic electron transfer at photosystem two (PS2). The extensively studied and widely used triazine and substituted urea herbicide groups are toxic to plants because they are potent and specific inhibitors of photosynthesis at PS2. These herbicides bind to the QB binding site on the D1 protein within the PS2 reaction center. Triazine herbicides have been persistently used for weed control in maize production in many parts of the world and this practice has led to widespread resistance in target weeds. The first report of herbicide resistance involved a triazine herbicide (Ryan, 1970), and since then triazine resistance has become the most prevalent and well characterized example of herbicide resistance world-wide, with resistance documented in biotypes of more than 60 species (LeBaron, 1991). For a review of resistance to PS2 herbicides see Gronwald (1994). With a few exceptions, triazine resistance is due to target site resistance endowed by a modification at the herbicide target site, the D1 protein of PS2 (reviewed by Gronwald, 1994).

It is noteworthy that biotypes highly resistant to triazine herbicides as a result of a modified D1 protein are not resistant to the chemically distinct substituted urea herbicides (Table 5), despite the fact that the substituted urea herbicides are also potent PS2 inhibitors (reviewed by Gronwald, 1994). The substituted urea and triazine herbicides bind to overlapping, but not identical, sites in PS2 (reviewed by Trebst, 1991). As a result, the mutation Ser 264 Gly providing resistance to triazine herbicides does not affect binding of substituted urea herbicides (Arntzen et al., 1982; Trebst, 1991). In contrast, as shown in Table 5, plants containing triazine-resistant PS2 are resistant to other PS2-inhibiting herbicide chemistries including the triazinones, uracils, and pyridazinones (Fuerst et al., 1986; Ducruet and De Prado, 1982; Oettmeier et al., 1982; De Prado et al., 1989). It is somewhat surprising that there are varying degrees of target site cross resistance to other PS2 inhibitors between species (Table 5), as all known triazine-resistant PS2 from higher plants contain the same Ser 264 to Gly substitution in the D1 protein (Trebst, 1991). The explanation for this variation

probably lies in the use of isolated thylakoids versus intact chloroplasts for measuring target site resistance, as the chloroplast envelope probably provides a differential barrier to these herbicides. Additionally, differences between species in the structure of the reaction center proteins surrounding the active site might contribute to greater or lesser sensitivity of the active site to different classes of herbicide.

A range of mutations within the QB binding site of the D1 protein providing resistance to triazine herbicides have been identified in unicellular algae such as Chlamydomonas, Euglena, Synechocystis, and Synechococcus (Trebst, 1991). Despite these varying mutations in lower plants, in higher plants only one mutation (Ser 264 Gly) has been identified in triazine-resistant weed species (Trebst, 1991). This mutation leads to a reduction in the capacity for photosynthetic electron transport between QA and QB (Bowes et al., 1980; Ort et al., 1983), which in turn leads to an increased susceptibility to photoinhibition in the resistant biotypes (Hart and Stemler, 1990a; Sundby et al., 1993). Such triazine-resistant individuals display a marked decrease in growth rate at normal light intensities (Hart and Stemler, 1990b) and a reduction in competitive fitness (reviewed in Holt and Thill, 1994). It appears likely that the other mutations within the QB binding site are even more detrimental to fitness and therefore, have not persisted in the wild.

It is therefore clear that for triazine resistance in higher plants a single mutation of Ser 264 Gly within the QB binding site on the D1 protein confers resistance, with no other target site mutations yet identified. Evidently, only this specific mutation can endow resistance while retaining enzyme functionality, despite selection of countless numbers of plants with triazine herbicides in many parts of the world. However, it is not wise to generalize from PS2 target site resistance to that which might occur with another herbicide target site enzyme. As discussed in (a) and (b) above, a different situation prevails for target site ALS or ACCase herbicide resistance in which there are likely to be several mutations which endow resistance while retaining enzyme functionality. In reality, for a particular enzyme targeted by herbicides, there could be from zero through to several potential mutations of the target enzyme which could endow herbicide resistance while retaining enzyme functionality. It is only after billions of plants have been exposed to herbicides across vast areas that the full array of potential for functional mutation of a herbicide target site becomes apparent. Following such widespread selection both ACCase and ALS exhibit several different mutations which endow herbicide resistance, whereas only one mutation has appeared in the D1 protein of PS2. Clearly, a variety of mutations providing resistance can be readily accommodated in some herbicide target sites while retaining enzyme functionality but few or no mutations providing resistance can be accommodated by other herbicide target sites.

d. Resistance to other modes of action

There have been few reports of target site resistance to herbicides with modes of action other than ALS, ACCase, or PS2. Where such reports are available, there are few cross resistance studies and relatively few studies with the target site in vitro. Two cases where target site cross resistance is evident are briefly described below:

i. Selection by dinitroanilines for biotypes of *Eleusine indica* which are resistant to dinitroaniline herbicides as a result of a herbicide-resistant microtubule assembly, are also resistant to amiprophosmethyl, a microtubule disrupting herbicide from a different chemical class (Vaughn et al., 1987; Vaughn and Vaughan, 1990). The exact basis of resistance in this biotype has not been established (Smeda and Vaughn, 1994).

ii. A biotype of *Sinapis arvensis* is resistant to a wide range of auxinic herbicides including dicamba, MCPA, mecoprop, 2,4-D, and picloram. The mechanism of resistance to these herbicides in this population has not been firmly established, but is probably the result of a modification of the auxin receptors (Peniuk et al., 1993).

2) Section 2: Non Target Site Cross Resistance

Non target site cross resistance is defined as cross resistance to dissimilar herbicide classes conferred by a mechanism(s) other than resistant enzyme target sites. Until recently documented for *L. rigidum* and *A. myosuroides*, non target site cross resistance was largely unknown in herbicide-resistant weeds but is well known in the insecticide resistance literature (Brattsten et al., 1986; Georghiou, 1986).
The evidence for non target site cross resistance in *L. rigidum* and *A. myosuroides* is presented below.

a. Non target site cross resistance to ALS-inhibiting herbicides

The study of Heap and Knight (1986) and widespread farmer experience in Australia has been that many (but not all) *L. rigidum* populations that developed

resistance following selection with the ACCase-inhibiting herbicide diclofop-methyl display resistance to cereal-selective ALS herbicides without any exposure to ALS herbicides (non target site cross resistance). Similarly, a laboratory experiment Matthews and Powles (unpublished data) showed that an initially susceptible *L. rigidum* population when selected for three generations with diclofop-methyl developed resistance to diclofop-methyl and simultaneously exhibited resistance to the ALS-inhibiting herbicide chlorsulfuron without any exposure to chlorsulfuron. This study and the field observations conclusively established that selection with an ACCase-inhibiting herbicide can lead to resistant populations that display non target site cross resistance to ALS-inhibiting herbicides without exposure to these herbicides.

The mechanistic basis of non target site cross resistance to ALS herbicides has been thoroughly investigated in *L. rigidum*. As expected, cross resistance to ALS herbicides from selection with ACCase herbicides is not due to resistance at the ALS target enzyme (Matthews et al., 1990). Instead these biotypes of *L. rigidum* are resistant as a result of an enhanced rate of herbicide metabolism, which endows resistance to certain ALS-inhibiting herbicides (Figures 1 and 2). It is likely that the increased metabolism in these *L. rigidum* biotypes is catalyzed by the same Cyt P450 enzyme-based mechanism operating in wheat (Christopher et al., 1991; 1992). Wheat is resistant to many ALS-inhibiting herbicides as a result of rapid metabolism of these herbicides by aryl-hydroxylation (Sweetser et al., 1992), catalyzed by a Cyt P450 mono-oxygenase. Some chlorsulfuron-resistant *L. rigidum* biotypes with sensitive ALS and a resistance profile to ALS-inhibiting herbicides similar to wheat can oxidatively metabolize chlorsulfuron more rapidly than the susceptible biotype (Figures 1 and 2; Christopher et al., 1991; Cotterman and Saari, 1992; Burnet et al., 1994a). The products of metabolism of chlorsulfuron in *L. rigidum* and wheat are also similar (Christopher et al., 1991; Cotterman and Saari, 1992), with the major metabolite identified as glucose-conjugated hydroxy-chlorsulfuron (Cotterman and Saari, 1992). Malathion which has been shown to inhibit the Cyt P450-dependent detoxification of primisulfuron, a sulfonylurea herbicide, in microsome preparations from maize (Kreuz and Fonné-Pfister, 1992) can inhibit chlorsulfuron metabolism and reduce chlorsulfuron resistance in the cross-resistant biotype SLR31 if applied in conjunction with chlorsulfuron (Christopher et al., 1994). This reversal of resistance in SLR31 by malathion confirms that detoxification plays a major role in chlorsulfuron resistance in this biotype. Taken together, these studies clearly establish that enhanced metabolism is the basis of non target site cross resistance of *L. rigidum* to ALS herbicides. Cyt P450s are clearly implicated in enhanced metabolism of chlorsulfuron in resistant *L. rigidum*, however, the in vitro demonstration of Cyt P450-dependent chlorsulfuron metabolism in isolated microsomes has to date proved elusive (Preston and Powles, unpublished).

b. Non target site cross resistance to ACCase-inhibiting herbicides

Over the past decade in Australia, the ACCase-inhibiting herbicide diclofop-methyl has been annually applied to millions of hectares of cereal crop to control *L. rigidum* and wild *Avena* species. Since the first reports of *L. rigidum* resistant to diclofop-methyl (Heap and Knight, 1982; 1986; 1990), at least two thousand field populations have developed resistance. Similarly, in laboratory experiments, (Matthews and Powles, unpublished) resistance to diclofop-methyl was selected in as little as three generations from an initially susceptible population following application of diclofop-methyl at agriculturally-relevant rates.

Many of the *L. rigidum* biotypes selected with and resistant to diclofop-methyl do not contain a resistant ACCase (Matthews et al., 1990; Holtum et al., 1991). Extensive studies have been conducted with one such biotype (SLR31) to identify the basis of non target site resistance. This biotype exhibits a modest increase in the rate of diclofop-methyl metabolism (Holtum et al., 1991). The rate of metabolism of diclofop-acid, the herbicidally-active form, occurs at about 1.5 times the rate observed in a susceptible biotype (Figure 1A). An increase in the rate of metabolism of this order should provide, at least, low-level resistance to diclofop-methyl – however, the overall contribution that metabolism makes to diclofop-methyl resistance in SLR31 is difficult to assess. A considerable proportion of the diclofop acid, about 20 percent in SLR31 and 30 percent in susceptible biotypes, remains un-metabolized even 192 h after treatment (Holtum et al., 1991).
The location of this remaining herbicide is not known, however, we speculate that it has been sequestered away from the metabolizing enzymes, and the active site (Holtum et al., 1991; Holtum et al., 1994). Not all of the metabolism products of diclofop-methyl in *L. rigidum* have been identified, however, glucose conjugates of both arylhydroxy diclofop and diclofop acid have been observed (Shimabukuro and Hoffer, 1991; Preston, unpublished). SLR31 produced more glucose conjugates of arylhydroxy diclofop than did the susceptible biotype (Preston, unpublished), suggesting the involvement of a Cyt P450 in the enhanced metabolism of diclofop in this biotype. Despite these observations, in pot experiments the level of diclofop-methyl resistance in SLR31 is not altered by the addition of the cytochrome P450 inhibitors 1-aminobenzotriazole (ABT), piperonyl butoxide (PBO), or tetcyclasis (Tardif, Preston and Powles, unpublished). Differences in diclofop metabolism between SLR31 and susceptible biotypes

do not appear to be due to secondary differences between herbicide affected and unaffected plants as other *L. rigidum* biotypes (SLR3 and WLR96) with ACCase enzyme-based resistance to diclofop, show no increase in diclofop metabolism (Tardif et al., 1993; Tardif, Preston, Holtum and Powles, unpublished). In addition, this biotype also displays a membrane recovery response whose relationship to resistance is uncertain (Häusler et al., 1991; Shimabukuro and Hoffer, 1992). Studies to identify the precise nature of non target site cross resistance in this biotype are continuing in our laboratory.

A number of biotypes of *A. myosuroides* exhibit varying levels of resistance to diclofop-methyl and fenoxaprop-ethyl (Moss, 1992). Two biotypes, Peldon A1 and Lincs. E1, from the U.K. have been examined and are resistant to the APP herbicides diclofop-methyl and fenoxaprop-ethyl, and the CHD herbicide tralkoxydim (Moss, 1990; Hall, Moss and Powles, unpublished). Both resistant biotypes show enhanced metabolism of diclofop-methyl and fenoxaprop-ethyl (Figure 3A). Rates of diclofop acid detoxification in the resistant biotypes (Peldon A1 and Lincs. E1) are 1.6 times faster than in the susceptible biotype (Hall, Moss and Powles, unpublished). Similarly, the rate of metabolism of fenoxaprop acid is about two times faster in these two resistant biotypes compared to the susceptible (Hall, Moss and Powles, unpublished). These biotypes also show increased metabolism of the substituted urea herbicides chlorotoluron (Figure 3B) and isoproturon (Kemp and Caseley, 1987; Kemp et al., 1990). It appears likely that enhanced metabolism is the common mechanism of herbicide resistance operating in the Peldon A1 biotype (Kemp et al., 1990).

c. Non target site cross resistance to PS2-inhibiting herbicides

As discussed in Section 1, the vast majority of cases of herbicide resistance to the PS2-inhibiting herbicides are the result of a change at the PS2 target site, which confers resistance to the triazine and some other PS2-inhibiting herbicides, but not to the substituted urea herbicides (Table 5). Conversely, biotypes of *L. rigidum* in Australia have developed resistance to PS2-inhibiting herbicides following selection with either triazine or urea herbicides. A decade of selection with atrazine (in a mixture with the 1-4 triazole herbicide amitrole) resulted in a biotype (WLR2) resistant to atrazine and a wide range of other triazine herbicides (Burnet et al., 1992). Significantly, this biotype exhibits cross resistance to a wide range of substituted urea herbicides (Burnet et al., 1992). Similarly, a *L. rigidum* biotype (VLR69) selected for a decade with a substituted urea herbicide (diuron) displays resistance to diuron which also extends to a range of other urea herbicides and exhibits cross resistance to triazine herbicides (Burnet et al., 1994b). The mechanism endowing triazine and substituted urea herbicide resistance has been identified in these *L. rigidum* biotypes as due to enhanced rates of herbicide metabolism (Burnet et al., 1993a; b). In the resistant biotypes, the triazine herbicide simazine is metabolized via *N*-dealkylation to de-ethylsimazine and di-de-ethylsimazine at two to three times the rate of metabolism attained by the susceptible biotype (Figure 2A; Burnet et al., 1993a). Lesser amounts of other metabolites are also detected suggesting other degradation pathways are present. Similarly, the substituted urea herbicide chlorotoluron is also metabolized at an enhanced rate (Figure 2B; Burnet et al., 1993b). Although the first metabolite of chlorotoluron to appear is *N*-monodemethylated chlorotoluron, the major metabolite has been identified as a glucose conjugate of ring-hydroxylated chlorotoluron (Preston, unpublished). The resistant biotypes display increased metabolism of chlorotoluron through both of these pathways suggesting the involvement of more than one herbicide-detoxifying mechanism in these biotypes. Broad cross resistance to substituted urea herbicides which have *N*-alkyl groups in common but differ in phenyl substituents can be explained by increased activity of an *N*-demethylating enzyme. The ring-hydroxylating enzyme might then provide increased resistance to some, but not all, substituted ureas. Significantly, these resistant biotypes show much greater resistance to chlorotoluron, 8- to 10-fold, than to other substituted urea herbicides, 2- to 3-fold (Burnet et al., 1992; 1994b). ABT, PBO and tetcyclasis, three potent, broad-spectrum inhibitors of Cyt P450 enzymes, inhibit metabolism of chlorotoluron and antagonize resistance in these two biotypes (Burnet et al., 1993b; Preston and Powles, unpublished). ABT also inhibits simazine metabolism and reduces the level of simazine resistance in these biotypes (Burnet et al., 1993a). Therefore, the enzymic basis for the enhanced metabolism resistance mechanism in these biotypes is likely to be due to increased activity of Cyt P450 monooxygenase enzymes which have the capacity to either de-alkylate or ring-hydroxylate these herbicides. However, despite intensive effort, it has not yet been possible to isolate from these biotypes active Cyt P450 enzymes capable of metabolizing herbicides *in vitro* (Preston and Powles, unpublished).

In Europe, biotypes of *A. myosuroides* have developed resistance following selection with substituted urea herbicides, particularly chlorotoluron. As for *L. rigidum*, in all examined biotypes of *A. myosuroides* resistant to substituted ureas, resistance is not due to a resistant PS2 target site (De Prado et al., 1991; Hall, Moss and Powles, unpublished). As with *L. rigidum*, resistance in *A. myosuroides* is due to an enhanced rate of metabolism of chlorotoluron and isoproturon (Figure 3B; Kemp et al., 1990; Hall, Moss and Powles, unpublished), which is probably endowed by increased activity of Cyt P450 catalyzed metabolism.

The level of resistance to chlorotoluron can be reduced by adding a variety of Cyt P450 inhibitors including ABT, triadimefon, and tridiphane (Kemp and Caseley, 1987; Kemp et al., 1990). Of these, ABT, at least, can inhibit metabolism of chlorotoluron and isoproturon (Kemp and Caseley, 1991; Kemp et al., 1990). Direct evidence that a Cyt P450 enzyme is responsible for resistance to chlorotoluron has recently been obtained (J. Caseley, pers. comm.). Microsomal membrane preparations isolated from Peldon A1 and a susceptible population displayed low intrinsic rates of chlorotoluron metabolism. Following exposure of young seedlings to a low concentration of chlorotoluron, the rates of metabolism in isolated microsomes were increased, a process known as induction. The rate of chlorotoluron metabolism by isolated microsomes was greater for the resistant Peldon A1 biotype than for the susceptible.

It is clear from the abovementioned studies with *A. myosuroides* and *L. rigidum* that a number of biotypes have developed non target site cross resistance across many herbicide groups. The basis of non target site cross resistance is enhanced rates of herbicide metabolism involving the Cyt P450 enzyme family. Control of such non target site cross resistant weed populations can be difficult with herbicides because Cyt P450 enzymes are able to detoxify a wide range of herbicidal compounds *in vitro* (Moreland et al., 1993). Hence, any crop-selective herbicide where selectivity is Cyt P450-based is a likely candidate for non target site cross resistance. This means that existing metabolism-based resistant weed biotypes of *L. rigidum* and *A. myosuroides* are potentially resistant to yet-to-be discovered herbicides that can be metabolized by Cyt P450. While at the moment the only Cyt P450-endowed non target site cross resistance reported has been in *L. rigidum* and *A. myosuroides*, it is likely that this phenomenon will appear in other weed species.

III. Part B: Multiple Resistance to Herbicides

The most intractable problems of herbicide resistance now and for the future will involve weeds which exhibit multiple herbicide resistance. Unknown in plants until recently the phenomenon of multiple resistance is defined as the expression (within individuals or populations) of more than one resistance mechanism. Multiple resistant plants may possess from two to many distinct resistance mechanisms and may exhibit resistance to a few or many herbicides. The simplest cases are where an individual plant (or population) possesses two or more different resistance mechanisms which provide resistance to a single herbicide, or class of herbicides. More complicated are situations where two or more distinct resistance mechanisms have been selected either sequentially or concurrently by different herbicides and endow resistance to the classes of herbicide to which they had been exposed. The most complicated and difficult to control situations are where a number of resistance mechanisms, involving both target site and non target site resistance mechanisms, are present within the same individual. Simple cases of multiple resistance have been documented for a small number of weed species, however, the majority of cases and the most complicated situations have been reported for biotypes of *L. rigidum*.

There are a small number of documented cases where a weed biotype has resistance to a single class of herbicides but possesses two different resistance mechanisms. A triazine-resistant biotype of *Brachypodium distachyon* with a resistant PS2 target site also displayed increased metabolism of atrazine (Gressel et al., 1983). A biotype of *L. rigidum* (WLR1) selected only with chlorsulfuron is resistant to ALS-inhibiting herbicides and has a resistant ALS enzyme as well as enhanced metabolism of chlorsulfuron (Christopher et al., 1992). Although both target site and non target site cross resistance mechanisms are present in this biotype, resistance only extends to the ALS-inhibiting herbicides. In both of these cases, the modified target site is the most powerful resistance mechanism. As researchers frequently examine for target site based resistance mechanisms early in a study, we believe it likely that there have been many cases reported as target site mechanisms without examination for the presence of other resistance mechanisms. This is understandable in that target site-based resistance is often more efficacious than non target site mechanisms and tends to obscure the latter when present in the same individual.

A somewhat more complicated case of multiple herbicide resistance occurs in a biotype of *A. myosuroides* (Lincs. E1). This biotype has widespread non target site cross resistance endowed by increased metabolism to a range of herbicide classes following selection with chlorotoluron (Hall, Moss and Powles, unpublished). Following additional selection with an ACCase herbicide, in addition to enhanced herbicide metabolism, this biotype has individuals (approximately 15 percent of the population) with resistant ACCase (Hall, Moss and Powles, unpublished). Similarly, multiple herbicide resistance has been reported on a number of occasions when herbicides of different chemical classes have been applied to a weed population either as a mixture, or sequentially, following the development of resistance to the first herbicide. At least one biotype of *Conyza canadensis* from Hungary displays multiple mechanisms of resistance. This biotype has a selection history involving atrazine and paraquat and is resistant to both triazine and bipyridyl herbicides (Pölös et al., 1988). Resistance to the triazine herbicides, as in most cases of triazine resistance, is conferred by a change at the PS2 active site (Pölös et al., 1987). Resistance to paraquat is due to a non-

target site mechanism, which has not yet been identified (Lehoczki et al., 1992). Similarly, a biotype of *Amaranthus retroflexus* developed target site resistance to triazine herbicides following many years of application. Diuron was then applied to this resistant population and resistance developed to diuron through another, as yet unknown, mechanism (Lehoczki et al., 1991). In this case the accumulation of resistance mechanisms was sequential. A biotype of *Phalaris paradoxa* with PS2 target site-based resistance to triazine herbicides was also reported to be resistant to diclofop-methyl (Yaacoby et al., 1986). In this case, no history of exposure to diclofop-methyl was reported and the mechanism of cross resistance to diclofop-methyl has not been examined. From these few studies it is clear that resistance can occur to herbicide mixtures, and that in such cases, multiple mechanisms of resistance may appear.

The most complicated and intractable cases of multiple resistance to herbicides have been reported in *L. rigidum* in Australia. As presented in Table 1, many *L. rigidum* populations possess multiple resistance mechanisms and individuals within any population may differ in their component resistance genes. Studies with *L. rigidum* biotype SLR31 present the best documented case of resistance conferred by multiple mechanisms. SLR31 has a complex history of applications of many different herbicides and is resistant to herbicides from many different classes (Table 1). This biotype exhibits multiple resistance due to the following resistance mechanisms:

1) a 1.5-fold enhanced metabolism of the ACCase-inhibiting herbicide diclofop-methyl (Figure 1A; Holtum et al., 1991)

2) the membrane recovery response correlated with resistance to ACCase-inhibiting herbicides (Häusler et al., 1991)

3) 12 percent of the population possess herbicide-resistant ACCase enzyme (Tardif and Powles, 1994), with the remainder of the resistant population containing a herbicide-sensitive ACCase (Matthews et al., 1990)

4) a twofold enhanced metabolism of the ALS-inhibiting herbicide chlorsulfuron (Figure 1B; Christopher et al., 1991; 1992)

Another *L. rigidum* biotype, VLR69, has also been exposed to a wide variety of herbicides over a 20-year period and has similarly developed multiple herbicide resistance (Table 1) and possesses multiple resistance mechanisms:

1) a 1.5-fold enhanced metabolism of the ACCase-inhibiting herbicide diclofop-methyl (Preston, Tardif, Christopher and Powles, unpublished)

2) all, or the vast majority of individuals possess a resistant form of ACCase enzyme (Preston, Tardif, Christopher and Powles, unpublished)

3) a twofold enhanced metabolism of the ALS-inhibiting herbicide chlorsulfuron (Figure 2C; Burnet et al., 1994a)

4) 5 percent of the population exhibits an ALS enzyme resistant to ALS-inhibiting herbicides with the remainder of the population possessing a susceptible ALS (Burnet et al., 1994a)

5) the membrane-recovery phenomenon (Häusler et al., 1991)

6) enhanced metabolism of the PS2-inhibiting herbicides simazine and chlorotoluron (Figure 2A and 2B; Burnet et al., 1993a; b)

Therefore, biotype VLR69 contains a number of resistance mechanisms, including resistant ALS, resistant ACCase, and enhanced metabolism. The enhanced metabolism evident for ACCase-, ALS- and PS2-inhibiting herbicides is unlikely to be endowed by one enzyme as recent evidence based on the effects of Cyt P450 inhibitors on metabolism of a variety of herbicides suggests that several Cyt P450 enzymes are responsible for metabolism-based cross resistance in this biotype (Preston, Tardif, Christopher and Powles, unpublished).

One conclusion that can be drawn from the studies on multiple resistance in *L. rigidum* is that biotypes with extremely varied and persistent histories of application of selective herbicides have developed widespread multiple resistance as the result of the accumulation of many resistance mechanisms. Biotypes with less varied herbicide histories typically have only one or two resistance mechanisms. A likely scenario is that multiple resistance can develop if alternative selective herbicides are employed as the

sole means of control of already resistant populations. Therefore, integrated weed management (IWM) strategies are required. For Southern Australian agriculture we are in the middle of a 6-year agronomic research project to quantify IWM practices for the control of herbicide resistant *Avena* spp. and *L. rigidum* populations (Matthews, Lwellewyn, Nietschke, Reeves and Powles, unpublished). While outside the scope of this review it is clear that there are a range of weed control techniques which can be integrated with herbicide use to deliver IWM programs for *L. rigidum* control that are economically and environmentally sustainable. As reviewed by Matthews (1994), crop and pasture rotation to reduce *L. rigidum* seedbank reserves, together with manipulation of agronomic factors and judicious herbicide usage can produce a workable IWM package. In the case of *L. rigidum*, the mature seed remains rigidly attached to the plant at maturity and therefore innovations involving modification of crop harvesting machinery enables substantial *L. rigidum* seed to be retained and removed in the harvest operation (Matthews et al., 1994). This practice can greatly reduce *L. rigidum* seed return to fields and contribute to a successful IWM strategy (Matthews, 1994).

IV. Conclusions and Future Directions

As discussed in Part A of this review, by far the most common forms of cross resistance to herbicides are conferred by target site cross resistance mechanisms. Target site changes only endow resistance to herbicides affecting a target site. As detailed in Tables 3-5, there can be quite different patterns and degree of target site cross resistance across chemical groups affecting a target site. From a practical viewpoint, control of target site-based resistant weed populations can often easily be achieved by the use of herbicides with a different mode of action. This has been the most widely used method for combating target site based herbicide resistance. The success with which target site-based resistance has been controlled by alternative herbicides has led to a certain complacency as to the ease with which herbicide-resistant populations can be managed. However, the appearance of non target site-based cross resistant weed populations, with wide ranging herbicide resistance spectra, should thoroughly dispel the notion that herbicide rotation alone will manage resistance. For example, as discussed in Section 2, resistance due to increased metabolism in many biotypes of *L. rigidum* and *A. myosuroides* means resistance across numerous herbicide classes giving widespread cross resistance (Tables 1 & 2). In these cases of non target site cross resistance endowed by metabolism, the Cyt P450 enzyme family have been implicated. To date, Cyt P450-based metabolism is the only mechanism documented to give widespread cross resistance in weeds and control of such populations can be difficult as Cyt P450 enzymes are able to detoxify a wide range of herbicidal compounds. In *L. rigidum*, the enhanced metabolism Cyt P450 resistance mechanism is often combined with other resistance mechanisms resulting in biotypes with multiple resistance mechanisms conferring resistance across many herbicide chemistries (Part B).

While *L. rigidum* in Australia is currently unique in the range of multiple resistance mechanisms accumulated, herbicide resistance in *A. myosuroides* and other species illustrates that non target site cross resistance and the accumulation of resistance mechanisms within populations will occur in other species. One lesson learned from *L. rigidum* in Australia is that it is those populations with the most intense and varied herbicide selection pressure that are most likely to exhibit multiple resistance mechanisms. We should not be surprised that a species such as *L. rigidum* possesses multiple resistance mechanisms (Powles and Matthews, 1992). This cross-pollinated, highly abundant and genetically variable annual species is present in Australia over vast areas where it is regularly exposed to herbicides. This selection pressure has led to the accumulation of a diversity of resistance mechanisms, both target site and non target site, resulting in a formidable array of resistance mechanisms. Hence, multiple resistance has first occurred in *L. rigidum* because of the confluence of the biology of *Lolium* and its abundance and role in the Australian agro-ecosystem (Powles and Matthews, 1992).

The lessons to be learned from the Australian experience with *L. rigidum* are salient; with current herbicide use patterns, other weed species in various parts of the world will inevitably exhibit multiple resistance. Once multiple herbicide resistance is manifest, especially where one of the resistance mechanisms is Cyt P450-endowed non target site cross resistance, herbicide control can be difficult and even new herbicide chemistries may be unsuccessful on existing multiple resistant biotypes. As weed control is essential to agricultural productivity to sustain a burgeoning world population, it is vital that there not be large scale development of multiple herbicide-resistant weed populations in major food producing areas. To delay, avoid or combat widespread herbicide resistance, all sectors of the agricultural industry must learn to advocate and use herbicides with restraint within IWM strategies which minimize the selection pressures for resistance. Biological and evolutionary realities dictate that this is the only sensible way forward. We must accept that modern herbicides are scarce resources of great utility in aiding food and fiber production and that they should be used wisely so as to ensure that they are not driven into redundancy by resistance. Given economic realities, at both the manufacturer and producer level, there are considerable challenges in changing current practice. It is hoped that this review

stimulates thought and action towards the essential changes needed.

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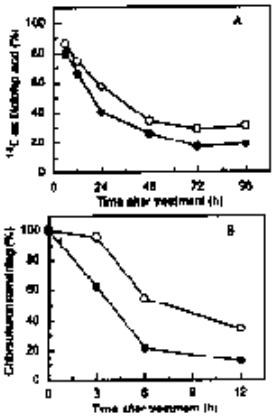

Figure 1. Enhanced metabolism of diclofop (A) and chlorsulfuron (B) in *L. rigidum* biotype SLR31 (J) compared to a susceptible biotype (E). Data are modified from Holtum et al., 1991 and Christopher et al., 1992

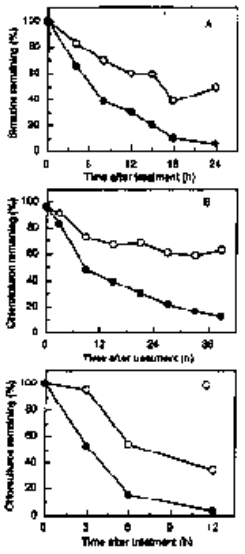

Figure 2. Enhanced metabolism of simazine (A), chlorotoluron (B), and chlorsulfuron (C) in *L. rigidum* biotype VLR69 (J) compared to a susceptible biotype (E). Data are modified from Burnet et al., 1993a; 1993b; 1994a.

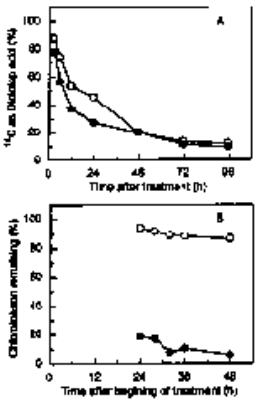

Figure 3. Enhanced metabolism of diclofop (A) and chlorotoluron (B) in *A. myosuroides* biotype Peldon A1 (J) compared to a susceptible biotype (E). Data are modified from Hall, Moss and Powles, unpublished.

Tables

Table 1. Herbicide-Resistant Biotypes of *L. rigidum* Mentioned in the Text: Resistance Status and Mechanisms.

Biotype	Resistance Status (chemical classes)	Resistance Mechanisms Identified	References
SLR3	Aryloxyphenoxypropionate Cyclohexanedione	Resistant ACCase	Tardit et al., 1993
SLR31	Aryloxyphenoxypropionate Cyclohexanedione Sulfonylurea Imidazolinone Dinitroanaline Chloracetamide Isoxazolidinone Carbamate	Resistant ACCase Metabolism Membrane repolarisation	Holtum et al., 1991 Häusler et al., 1991 Tardif & Powles, 1994 Christopher et al., 1991
VLR69	Aryloxyphenoxypropionate Cyclohexanedione Sulfonylurea Imidazolinone Triazine Substituted urea Triazinone Chloroacetamide	Resistant ACCase Resistant ALS Metabolism Membrane repolarisation	Burnet et al., 1993a Burnet et al., 1993b Burnet et al., 1994a Häusler et al., 1991 Preston, Tardif, Christopher & Powles, unpublished
WLR1	Sulfonylurea Imidazolinone	Resistant ALS Metabolism	Christopher et al., 1992
WLR2	Triazine Substituted urea Triazinone Aminotriazole	Metabolism	Burnet et al., 1993a Burnet et al., 1993b
WLR96	Aryloxyphenoxypropionate Cyclohexanedione	Resistant ACCase Membrane repolarisation	Häusler et al., 1991 Holtum & Powles, unpublished

a: Biotypes are not necessarily resistant to all members of each herbicide class.
b: Mechanisms indicated may give resistance to one or more herbicide classes. See text for further details.

Table 2. Herbicide-Resistant Biotypes of *A. myosuroides* Mentioned in the Text: Resistance Status and Mechanisms.

Biotype	Resistance Status (chemical classes)	Resistance Mechanisms Identified	References
Lincs. E1	Aryloxyphenoxypropionate Cyclohexanedione Substituted urea Dinitroanaline	Resistant ACCase Metabolism	Hall, Moss & Powles, unpublished
Mason	Aryloxyphenoxypropionate Cyclohexanedione	Resistant ACCase	Hall, Moss & Powles, unpublished
Otmoor	Aryloxyphenoxypropionate Cyclohexanedione	Resistant ACCase	Hall, Moss & Powles, unpublished
Peldon A1	Aryloxyphenoxypropionate Cyclohexanedione Substituted urea Triazine Triazinone Sulfonylurea Imidazolinone Dinitroanaline Thiocarbamate Carbamate	Metabolism	Kemp & Caseley, 1987 Kemp et al., 1990 Hall, Moss & Powles, unpublished

a: Biotypes are not necessarily resistant to all members of each herbicide class.

Table 3: Target Site Cross Resistance Patterns of ALS from Weed Species Resistant to ALS-inhibiting Herbicides

Species - biotype	Herbicide			Reference
	Sulfonylurea (Chlorsulfuron)	Imidazolinone (Imazapyr)	Triazolopyrimidine (2,6-Dichloro-sulfonanilide)	
	Resistance ratio (I50 R / I50 S)			
Brassica tournefortii	>95	0.8	>8 (Flumetsulam)	Boutsalis & Powles, unpublished
Kochia scoparia	18	6	20	Saari et al., 1990
Lolium perenne	35	7	>24	Saari et al., 1992
Lolium rigidum - WLR1	>32	8	-	Christopher et al., 1992
Salsola iberica	8	4	8	Saari et al., 1992
Sisymbrium orientale	>190	75	>14 (Flumetsulam)	Boutsalis & Powles, unpublished
Sonchus oleraceus	14	3	3 (Flumetsulam)	Boutsalis & Powles, unpublished
Stelleria media	13	2	9 (Flumetsulam)	Saari et al., 1992
Stelleria media	>54	7 (Imazamethabenz)	>100	Hall & Devine, 1990
Xanthium strumarium	1.1 (Chlorimuron)	>324 (Imazaquin)	1.4 (Flumetsulam)	Schmitzer et al., 1993

Table 4: Target Site Cross Resistance Patterns of ACCase from Weed Species Resistant to ACCase-inhibiting Herbicides

	Aryloxyphenoxypropionate		Cyclohexanedione	
	(Diclofop)	(Haloxyfop)	(Sethoxydim)	
	Resistance ratio (I50 R / I50 S)			
Alopecurus myosuroides - Mason	11	>27 (Fenoxaprop)	>12	Hall, Moss & Powles, unpublished
Alopecurus myosuroides - Otmoor	14	>36 (Fenoxaprop)	>12	Hall, Moss & Powles, unpublished
Avena fatua	10	7	14	Maneechote, Preston & Powles, unpublished
Avena sterilis	52	25	8	Maneechote et al., 1994
Lolium multiflorum	28	9	0.9	Gronwald et al.,1992
Lolium rigidum – SLR3	>35	>10	7.8	Tardif et al., 1993
Lolium rigidum – WLR96	85	216	2.8	Holtum & Powles, unpublished
Lolium rigidum – VLR69	30	20	1	Preston, Tardif, Christopher & Prowles, unpublished
Setaria viridis	>47	60 (Quizalofop)	50	Marles, et al., 1993, unpublished

Table 5: Target Site Cross Resistance Patterns of PS2 from Weed Species Resistant to PS2-inhibiting Herbicides

Species	Herbicide					Reference
	Triazine (Atrazine)	Triazinone (Metribuzin)	Uracil (Bromacil)	Pyridazinone (Pyrazon)	Substituted Urea (Diuron)	
	Resistance ratio (I50 R / I50 S)					
Amaranthus hybridus	830	260	20	290	1.4	Fuerst et al., 1986
Amaranthus retroflexus	~1000	260	20	~63	1.4	Pfister & Arntzen, 1979
Amaranthus retroflexus	251	>1500	>2000	-	4	Oettmeier et al., 1982
Ambrosia artemisiifolia	189	21	-	-	1.9	Arntzen et al., 1982
Brassica campestris	1000	89	9	-	1.7	Ducruet & De Prado, 1982
Chenopodium album	1300	33	88	330	-	Fuerst et al., 1986
Chenopodium album	542	167	-	-	1.2	De Prado et al., 1989
Conyza bonariensis	407	91	-	-	1.1	De Prado et al., 1989
Senecio vulgaris	>200	-	125	-	1.6	Radosevich et al., 1979
Senecio vulgaris	890	-	114	16	1.6	Fuerst et al., 1986

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