

ACCCase-inhibiting herbicides: mechanism of action, resistance evolution and stewardship

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ABSTRACT: Herbicides play an important role in preventing crop yield losses due to both their weed interference ability and their capacity for increasing soil conservation in no-till systems. Group A herbicides or acetyl-CoA carboxylase (ACCase) are essential tools for the selective management of glyphosate resistance in grass weed species. In this review, we describe important aspects of ACCase biology and herbicides targeting this enzyme, along with a discussion on stewardship programs to delay the evolution of herbicide resistance which can evolve either through target site and/or non-target site mechanisms. Sixteen-point mutations have been reported to confer resistance to ACCase inhibitors. Each mutation confers cross resistance to a different group of herbicides. Metabolic resistance can result in resistance to multiple herbicides with different mechanisms of action (MoA), and herbicide detoxification is often conferred by cytochrome P450 monooxygenases and glutathione-S-transferases. Regardless of whether resistance mechanisms are target or non-target site, using herbicides with the same MoA will result in resistance evolution. Therefore, while field surveys and resistance mechanism studies are crucial for designing reactive management strategies, integrated weed management plays a central role in both reactive and proactive mitigation of herbicide resistance evolution.

Keywords: herbicide resistance, integrated weed management, aryloxyphenoxypropionates, cyclohexanediones, phenylpyrazoline

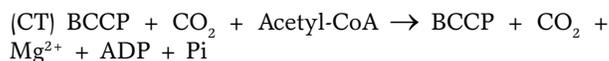
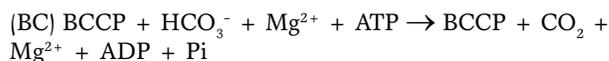
Introduction

The world population has grown over the past few decades and is estimated to reach 9.7 billion people in 2050 (Gerland et al., 2014). As the population continues to grow, agriculture technologies need to increase crop yields to meet the ever-increasing demand for food (Tester and Langridge, 2010). South America is a major food producer in the global agriculture chain, encompassing approximately 25 % of the world's total cultivated area with cotton, corn, and soybean, representing 1.7, 23.0, and 62.1 million ha, respectively (USDA, 2018). Weeds are one of the greatest challenges to modern agriculture causing, on average, a 35 % reduction in crop yield (Oerke, 2006). Herbicides are extremely efficient tools for weed management and have been a key component to maintain no-till systems in agriculture (Naylor, 2008).

Group A herbicides or acetyl-CoA carboxylase (ACCase) inhibitors were first introduced into the market in 1978 (Kaundun, 2014) with the appearance of diclofop-methyl. These herbicides provide selective grass weed control in dicot crops and a limited number of active ingredients for use in monocot crops with an estimated treated area of 120 million ha per year (Busi et al., 2018). ACCase-inhibiting herbicides play a key role in managing glyphosate-resistant (GR) grasses, one of the greatest weed management challenges facing South America (Lopez Ovejero et al., 2017). This manuscript covers a detailed review of important aspects related to ACCase inhibitors along with best stewardship practices for herbicide resistance management.

ACCase and its physiological function

Fatty acids are carboxylic acids with long aliphatic chains that perform important physiological functions (e.g. energy storage, cell/organelle membrane structure composition, hormonal regulation) in living organisms. The ubiquitous, biotin-dependent ACCase enzyme catalyzes two irreversible reactions that determine commitment to the fatty acid synthesis pathway (Dayan et al., 2019). The enzyme consists of three functional domains: biotin-carboxyl carrier protein (BCCP), biotin carboxylase (BC), and carboxyltransferase (CT, with subunits α and β) (Figure 1). The BC and CT domains shoulder the catalytic activities that are dependent upon ATP, Mg^{2+} , and HCO_3^- , which result in acetyl-CoA carboxylation and the formation of malonyl-CoA. The two reactions catalyzed by the BC and CT subunits are presented, respectively, below (Nikolau et al., 2003; Sasaki and Nagano, 2004; Shorrosh et al., 1994):



While malonyl-CoA is necessary for *de novo* synthesis of fatty acids in plastids, cytosolic malonyl-CoA is required for the elongation of very long chain fatty acids (VLCFAs) and secondary metabolites such as flavonoids and suberins (Harwood, 1988). Plants express plastidic and cytoplasmic ACCase isoforms. The plastidic isoform is responsible for more than 80 % of total ACCase

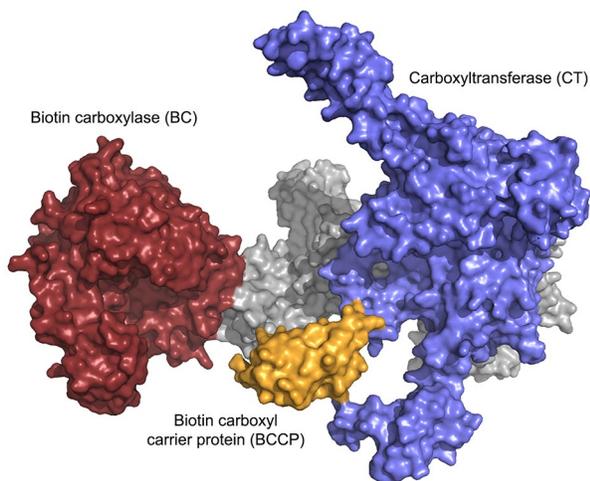


Figure 1 – A tertiary structure view of wheat (*T. aestivum*) eukaryotic ACCase and its domains: biotin carboxylase (BC), biotin carboxyl carrier protein (BCCP), and carboxyltransferase (CT).

activity in leaves (Egli et al., 1993; Ashton et al., 1994; De Prado et al., 2004). Plants belonging to the Poaceae family (grasses), possess a homomeric (or eukaryotic) plastidic ACCase in which the BCCP, BC, and CT domains are localized within a single polypeptide chain (Inclendon and Hall, 1997). Both plastidic and cytoplasmic ACCase in Poaceae become active when homodimerized (Egli et al., 1993; Zhang et al., 2003). Dicotyledonous plants have homomeric form in the cytoplasm and heteromeric (or prokaryotic) form in the plastids, where each domain is encoded by different genes expressed in a coordinated fashion (Sasaki and Nagano, 2004).

ACCase-inhibiting (Group A) herbicides Classification and general characteristics

ACCase-inhibiting or Group A herbicides are divided into three chemical families: aryloxyphenoxypropionates (FOPs), cyclohexanodiones (DIMs), and phenylpyrazole (DENs). While FOPs and DIMs were introduced over 45 years ago, DEN was launched in 2006 and consists of a single herbicide, pinoxaden (Hofer, 2006; Dayan et al., 2019). All molecules belonging to these chemical groups consist of a carbon skeleton with polar substituents, but structures presenting distinct characteristics (Délye, 2005). Most FOPs are in the form of formulated methyl, butyl or ester, providing more lipophilicity and increased capacity to cross cellular membranes by acid trapping (Takano et al., 2019b). These herbicides have a molecular weight of between 327 and 400 g mol⁻¹, pKa of 3.5-4.1 in their weak acid form and Log K_{ow} of 3.6-4.2 in the formulated form (Shaner, 2014).

The three classes of ACCase-inhibiting herbicides have limited residual activity in the soil. This is attributed to their high values of solid-liquid partition (K_d) and adsorption potential (K_{oc}), resulting in herbicide molecules becoming tightly bound to soil particles.

However, once in the soil, these herbicides can be converted to their acid form, and be absorbed by plant roots and cause damage. The potential for carryover varies from one species to another, soil characteristics, and herbicide dosage, but residual activity was not observed for more than 14 days (Lancaster et al., 2018).

Mechanism of action (MoA)

ACCase-inhibiting herbicides have specific activity on grasses due to their selective inhibition of homomeric plastidic ACCase which is only found in monocots, with exceptions. Neither heteromeric plastidic nor homomeric cytosolic forms are inhibited by ACCase inhibitors, making dicots tolerant to them (Kukorelli et al., 2013). Exceptions include susceptible Geraniaceae species and a few *Brassica* and *Arabidopsis* species (Kaundun, 2014) expressing the homomeric ACCase in their chloroplasts.

These herbicides halt ACCase activity by blocking fatty acid biosynthesis, preventing the formation of lipid and secondary metabolites in susceptible plants. This results in a loss of cell membrane integrity, metabolite leakage, and ultimately cell death (Délye, 2005; Kaundun, 2014). This process begins when the herbicide is absorbed by the leaves and translocates to proliferating meristematic tissues through the phloem where it damages the cell membrane structure, inhibits meristematic activity, and restricts the growth of new leaves (Kukorelli et al., 2013). Necrotic symptoms can be observed in growing tissues after one week of application, with initial chlorosis and subsequent disintegration of the leaves (Dayan et al., 2019). The efficacy of these herbicides is positively correlated with higher relative air humidity due to an increase in molecule uptake and translocation in the plant (Cieslik et al., 2013). Studies of enzyme kinetics have shown that FOPs and DIMs are non-competitive inhibitors of ATP, Mg²⁺, and HCO₃⁻, but are competitive inhibitors of acetyl-CoA substrate. This suggests they act by inhibiting the transcarboxylation step (CT domain) rather than the biotin carboxylation step (BC domain) despite binding to the same catalytic site in the CT domain (Rendina et al., 1990; Burton et al., 1991; Burton, 1997; Devine, 2002).

Molecular and biochemical data have clearly established that the CT domain in the homomeric ACCase bears the target binding site of FOPs, DIMs, and DEN (Délye, 2005; Xia et al., 2016) even though they bind in distinct regions of the homodimer interface. Crystal structure analyses of *Staphylococcus aureus* CT domain in complex with at least one herbicide from each group showed that the molecules shared two common anchoring points (Ile1735 and Ala1627) with the yeast CT domain regardless of discrepancies in their chemical structures (Xia et al., 2016) (Figure 2A and B).

Results from a computational simulation of *Setaria italica* CT domain in complex with ACCase inhibitors suggested that these herbicides can also form a hydrogen bond with binding site at residue Ser698 (Zhu et al., 2006). For one specific FOP (metanifop) residue

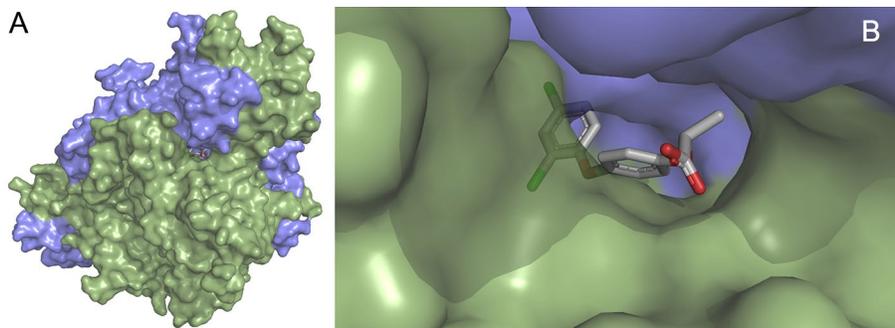


Figure 2 – Crystal structure of the carboxyltransferase (CT) domain of yeast ACCase in complex with the herbicide diclofop (A). A closer view of diclofop within the binding domain formed at the interface of the dimerized CT structure (B). Adapted from 1UYR (Zhang et al., 2004).

Thr194 was essential to the interacting and binding to the CT domain (Xia et al., 2016). Furthermore, kinetic analyses suggested FOPs and DIMs present double inhibition, *i.e.* the binding of one of these herbicide classes prevents the binding of molecules from the other (Rendina et al., 1990). Finally, studies with pinoxaden showed this molecule has a very similar binding site to tepraloxymid, a DIM herbicide, despite considerable differences in their chemical structures (Yu et al., 2010; Kaundun, 2014). Not only do these findings suggest the wide variety of molecular mechanisms that underlie CT domain inhibition, but also shed light on the importance of elucidating the molecular basis for target and cross-resistance among ACCase-inhibiting herbicides (Xia et al., 2016).

Mechanisms of weed resistance to ACCase inhibitors

Weeds resistance to ACCase inhibitors have significant economic relevance especially due to the limited number of herbicides with alternative MoAs, and their role in managing GR monocot weeds in post-emergence. Resistant biotypes may evolve after six to ten years of selective pressure by ACCase inhibitors, particularly in crop systems in which the application of these herbicides is used as the only form of grass weed management tool (Devine, 2002). The high initial frequency (6×10^{-10} plants) of resistant biotypes also significantly affects resistance evolution (Vidal and Fleck, 1997). The first case of resistance to ACCase inhibitors was reported in 1982, only four years after their introduction into the market, in *Lolium rigidum* from a wheat field in Australia (Heap and Knight, 1982). To date, 48 resistant species have been reported worldwide (Heap, 2019). In Australia, resistance to pinoxaden was reported for *L. rigidum* populations even before the herbicide was launched in 2006 as shown in studies from 2003 and 2005 (Boutsalis et al., 2012). Likewise, target site mutations were found in herbarium specimens of the grass weed *Alopecurus myosuroides*, which were collected between 1788 and 1975, prior to the commercial release of herbicides inhibiting ACCase

(Délye et al., 2013). This evidence suggests that point mutations causing resistance to ACCase inhibitors evolve from standing genetic variation in weed populations, rather than *de novo* mutations in wild-type genotypes.

In South America, populations of eight weed species have been reported with resistance to ACCase inhibitors: *Sorghum halepense* (Johnsongrass – also resistant to glyphosate), *Urochloa plantaginea* (alexandergrass), *Digitaria ciliaris* (southern crabgrass), *Eleusine indica* (indian goosegrass – also resistant to glyphosate), *Avena fatua* (wild oat), *Lolium multiflorum* (ryegrass – also resistant to glyphosate or ALS inhibitors), *Echinochloa crus-galli* (barnyardgrass) and *Digitaria insularis* (sourgrass – also resistant to glyphosate) (Heap, 2019). As is the case for other herbicides and MoAs, weed biotypes resistant to ACCase inhibitors can evolve from target site resistance or non-target site resistance.

Target site resistance (TSR)

Resistance cases directly associated with the ACCase enzyme can emerge from mutations or increased enzyme expression levels (Figure 3). The affinity of herbicides to enzymes is one of the properties that determine herbicide efficacy (Dayan et al., 2010; Dayan et al., 2015). Physicochemical interactions are among the main factors determining the affinity for a ligand (e.g. herbicide) to an enzyme. In the case of ACCase-inhibiting herbicides, the interactions between the active ingredient (FOPs, DIMs, or DEN) and the amino acids in specific positions of the polypeptide chain on ACCase CT domain define affinity and inhibitor efficacy (Figure 2A and B). Thus, a single nucleotide polymorphism (mutation) in the ACCase gene can result in amino acid substitutions imparting resistance to herbicides.

The genetic determinants and associated fitness costs are well known for weeds resistant to ACCase-inhibiting herbicides (Colbach et al., 2016). Mutations in the plastidic ACCase gene resulting in enzyme primary sequence modifications have been the subject of research for over a decade and are well characterized (Délye, 2005). Sixteen such alterations have been described so far and most notably observed at amino

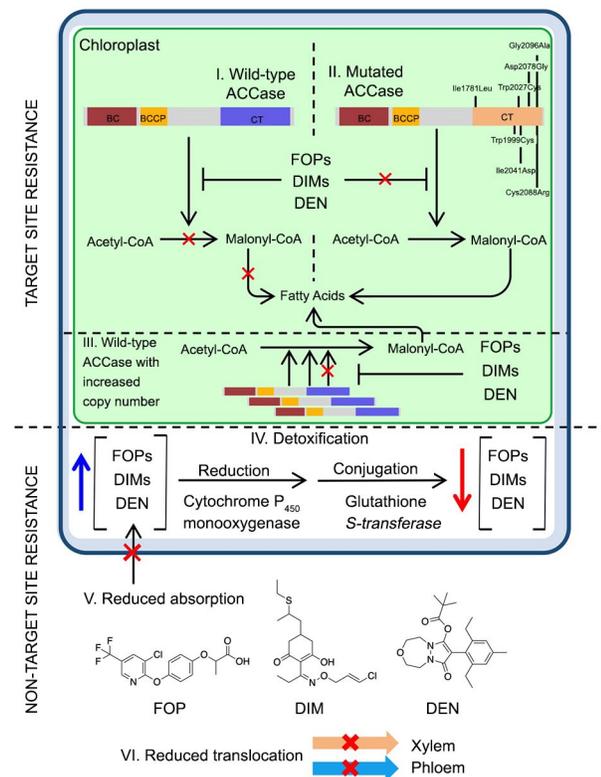


Figure 3 – Main aspects of acetyl-coenzyme A carboxylase (ACCase)-inhibiting herbicide resistance in grasses and different ways by which resistance can evolve. (I) interaction between ACCase inhibitors and a wild type enzyme; (II) resistance by ACCase mutations or (III) wild type ACCase increased copy number; (IV) metabolic resistance by herbicide detoxification, (V) reduced absorption, or (VI) reduced translocation. BC = biotin carboxylase, BCCP = biotin carboxyl carrier protein; CT = carboxyltransferase; FOP = aryloxyphenoxypropionates; DIM = cyclohexanedione; DEN = phenylpyrazolin.

acid positions 1781, 2027, 2041, 2078, and 2096 of the polypeptide chain, but also occur at positions 1999 and 2088 (Heckart et al., 2008; Kaundun, 2010; Beckie et al., 2012; Kaundun et al., 2012; Kaundun et al., 2013). Target site mutation in grass species commonly present in South America have been reported in other parts of the world (Table 1). Unfortunately, only a very limited number of weeds resistant to ACCase inhibitors in South America have had the resistance mechanism elucidated such as *E. indica* (Osuna et al., 2012).

Cross-resistance to herbicides that act under the same MoA is usually caused by TSR mechanisms (Beckie et al., 2012; Chen et al., 2017), even though recent evidence indicates the importance of NTSR in conferring cross-resistance (Iwakami et al., 2019). Several authors have reported weeds manifesting cross-resistance to different ACCase-inhibiting herbicides, including those arising from mutations Ile1781Leu,

Ile2041Asn, and Trp2027Cys (Chen et al., 2017). In addition to the mutations Asp2078Gly and Cys2088Arg conferring broad spectrum of resistance on all classes of ACCase-inhibiting herbicides (Yu et al., 2007; Délye et al., 2008; Kaundun, 2010; Scarabel et al., 2011; Cruz-Hipolito et al., 2011; Gherekhloo et al., 2012; Osuna et al., 2012; Kaundun et al., 2012), resistance levels are not solely dependent upon amino acid substitutions. Allele number and initial frequency, recessive and dominant allele interactions, weed species, plant growth stage, herbicide recommended dose, and other factors also influence herbicide resistance levels (Kaundun, 2014).

This implies that the same mutation may result in contrasting herbicide sensitivity phenotypes when different species are compared. This is the case of Ile2041Asn, a mutation that results in a cycloxydim-resistant biotype in *Phalaris paradoxa* but not in *Alopecurus myosuroides* (Délye et al., 2008; Hochberg et al., 2009). Homozygosity levels determined *L. rigidum* control with clethodim in a field in Australia where the recommended doses were efficient against heterozygous Ile1781Leu plants but not homozygous plants (Yu et al., 2007). Furthermore, ACCase gene mutation frequencies naturally vary with species, site, and the geography of herbicide selection pressure (Délye et al., 2010). Pleiotropy also affects resistance dynamics in a population and should be considered for establishing prediction models and recommendations towards best management practices aimed at delaying eventual mutation-related resistance cases (Colbach et al., 2016).

Selection pressure imposed by ACCase-inhibiting herbicides can lead to increased enzyme-specific activity (higher [enzyme activity: total protein mass] ratio) due to a higher protein expression rate. ACCase overexpression allows for sustained fatty acid synthesis rates under the same herbicide concentrations that would normally inhibit catalysis as the active ingredient no longer blocks the enzyme physiological role at rates incompatible with cellular metabolism. Reported cases include *Sorghum halepense* in the US (Bradley et al., 2001), *Leptochloa chinensis* in Thailand (Pornprom et al., 2006), and *E. indica* in Malaysia (San Cha et al., 2014). Importantly, increased protein expression rates may be associated with ACCase mutations (San Cha et al., 2014) and should be considered in the context of an integrated weed management approach.

Non target site resistance (NTSR)

Non target site resistance has gained attention as an emerging resistance mechanism to ACCase-inhibiting herbicides (Kaundun, 2014). This type of resistance encompasses a range of processes, including enhanced metabolism, herbicide detoxification, and reduced uptake and translocation (Powles and Yu, 2010; Kukorelli et al., 2013; Kaundun, 2014). Resistance levels resulting from these processes are relatively low when compared to TSR and plants may be controlled if treated at early growth stages. In addition, NTSR is often present in

Table 1 – Reported mutations in ACCase associated with resistance to different classes of Group A herbicides in grass species commonly present in South American fields.

Substitution	Species	Resistance to	Reference
Ile1781Leu	<i>Lolium multiflorum</i>	Clodinafop Haloxifop Sethoxydim Pinoxaden Clethodim (low level)	(Powles and Yu, 2010; Scarabel et al., 2011; Kukorelli et al., 2013)
Trp1999Cys	<i>Lolium perenne</i>	Fenoxaprop only	(Powles and Yu, 2010; Kukorelli et al., 2013; Xu et al., 2014)
Trp2027Cys	<i>Eleusine indica</i>	Fenoxaprop Clodinafop Pinoxaden	(Powles and Yu, 2010; Kukorelli et al., 2013; San Cha et al., 2014)
Trp2027Cys	<i>Digitaria insularis</i>	Haloxifop Quizalofop Fenoxaprop Pinoxaden	(Takano et al., 2020)
Ile2041Asn/Val	<i>Lolium rigidum</i>	Clodinafop Haloxifop Pinoxaden (low level)	(Powles and Yu, 2010; Scarabel et al., 2011; Kukorelli et al., 2013)
Ile2041Asn	<i>Sorghum halepense</i>	Fluazifop Propaquizafop Quizalofop Haloxifop	(Powles and Yu, 2010; Kukorelli et al., 2013; Scarabel et al., 2014)
Asp2078Gly	<i>Lolium multiflorum</i>	Diclofop Sethoxydim Clethodim Pinoxaden	(Kaundun, 2010; Powles and Yu, 2010; Kukorelli et al., 2013)
Asp2078Gly	<i>Avena fatua</i>	Diclofop Fenoxaprop Cyhalofop Propaquizafop Clethodim Cycloxydim Pinoxaden	(Powles and Yu, 2010; Cruz-Hipolito et al., 2011; Kukorelli et al., 2013)
Asp2078Gly	<i>Eleusine indica</i>	Fluazifop Haloxifop Cyhalofop Sethoxydim Clethodim Tepraloxymidim	(Powles and Yu, 2010; Osuna et al., 2012; Kukorelli et al., 2013)
Cys2088Arg	<i>Lolium rigidum</i>	Clodinafop Haloxifop Sethoxydim Clethodim Pinoxaden	(Powles and Yu, 2010; Scarabel et al., 2011; Kukorelli et al., 2013)
Gly2096Ala	<i>Avena fatua</i>	Clodinafop Fenoxaprop Diclofop Haloxifop Sethoxydim (low level)	(Délye, 2005; Powles and Yu, 2010; Beckie et al., 2012; Kukorelli et al., 2013)

populations that already contain one of the TSR alleles, such as in *Lolium rigidum* (Han et al., 2016).

Detoxification occurs when herbicide metabolism rates increase, and the active ingredient is modified into a non-toxic molecule by oxidation, hydrolysis, or reduction (phase 1). Subsequently, metabolites are combined with a glutathione tripeptide, a sugar molecule, or an amino acid (phase 2) (Délye, 2005). Therefore, toxic component concentration decreases to an extent that is no longer capable of inhibiting vital metabolic pathways. Resistant biotypes are characterized by increased expression levels of enzymes involved in herbicide metabolism, in particular, those of cytochrome P450 monooxygenase enzymes (phase 1) and glutathione-S-transferase (phase 2) (Brazier et al., 2002; Kaundun, 2014). Glucosyl-S-

transferase causes herbicide conjugation and its gene is typically upregulated in herbicide-resistant weeds (Yu and Powles, 2014). Cases associated with cytochrome P450-mediated enhanced metabolism have been widely reported (Fernández et al., 2016) and confirmed in different weed species such as *Avena* spp., *E. phyllopogon* and *L. rigidum* (Menendez and De Prado, 1996; De Prado et al., 2005; Bakkali, 2007; Ahmad-Hamdani et al., 2012). Moreover, a recent report found the existence of temperature-dependent pinoxaden resistance in *Brachypodium hybridum*, proposing that the oxidation and glucose conjugation biochemical pathways are significantly increased under the combination of pinoxaden application and high temperatures (Matzrafi et al., 2017).

A large number of genes are clearly involved in the mechanisms that relate to NTSR and in many weed species, cytochrome P450 monooxygenase, glutathione-S-transferase and glucosyl transferase enzymatic activities are associated with multiple resistance (Délye, 2005; Powles and Yu, 2010). It is noteworthy that cross- and multiple-resistance patterns associated with NTSR are often unpredictable, considering that resistance is conferred by metabolization rates of specific herbicides by those enzymes, regardless of their MoA. Consequently, weed management strategies based on the herbicide rotation with different MoAs becomes an inappropriate approach to mitigate resistance (Yu and Powles, 2014; Fernández et al., 2016). For example, an *L. rigidum* population with cytochrome P450-related increased metabolism is resistant to herbicides with distinct MoAs, including photosystem II, ALS, ACCase, and microtubule inhibitors (Preston and Powles, 2002; Powles and Yu, 2010).

Most cross-resistance studies in grass weeds to FOPs/DIMs/DEN report TSR and consequent reduction in ACCase sensitivity to these herbicides as the underlying cause (Yu et al., 2007; Kaundun, 2014; Chen et al., 2017). A number of reports have emphasized the need to better understand and elucidate the mechanisms of NTSR-based cross-resistance, considering that it is a threat to global crop production (Yu and Powles, 2014; Shergill et al., 2017; Iwakami et al., 2019). A recent study with a multiple resistant *E. phyllopogon* biotype on the three classes of ACCase inhibitors suggests the existence of a single *trans* element responsible for the overexpression of two genetically unlinked cytochrome P450 genes, CYP81A12 and CYP81A21. This finding supports the idea that NTSR can lead to cross-resistance to multiple herbicides due to the activation of P450s that can even metabolize different classes of herbicides, such as ACCase and ALS inhibitors (Iwakami et al., 2019). Nonetheless, NTSR mechanisms still require additional investigation as their molecular basis remains, as yet, unknown.

Stewardship and herbicide resistance management

Since 2012, over 96 % of soybean cultivated in South America has been genetically engineered for glyphosate-resistance (Peterson et al., 2018). The overreliance on a single MoA and the absence of herbicide rotation and mixtures have contributed to the evolution of GR weeds (Takano et al., 2019a). Glyphosate resistance has now spread across most soybean fields from South America and the magnitude of infestation is even greater for grasses. The estimated infested area with GR *D. insularis*, for instance, is estimated to exceed 20 million ha in Brazil (Lopez Ovejero et al., 2017). ACCase inhibitors are the main tools deployed to manage GR grass weeds such as *D. insularis*, *L. multiflorum* and *E. indica* (Yu et al., 2007; Gemelli et al., 2013; Takano et al., 2018). To date, 48 species have been reported as resistant to ACCase inhibitors in the world (Figure 4), and eight of them are in South America (Heap, 2019).

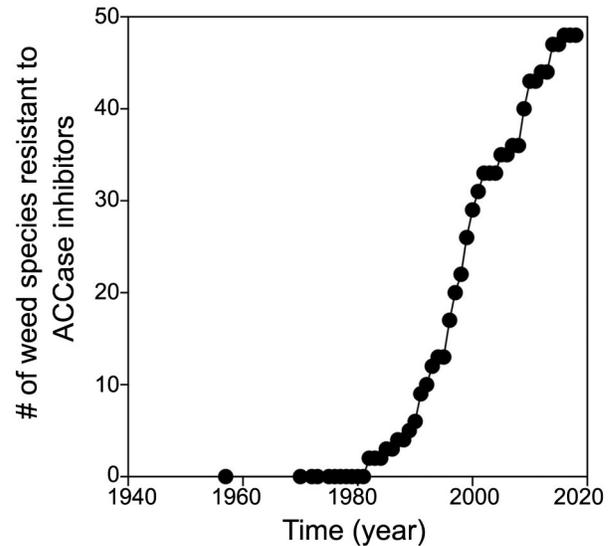


Figure 4 – Number of weed species with resistance to ACCase-inhibiting herbicides from 1970 to present. Adapted from <http://www.weedscience.org> (Heap, 2019).

Clethodim is currently the most used ACCase herbicide in Brazil. This is because it generally provides better control over glyphosate-resistant *D. insularis*, compared to other ACCase-inhibiting herbicides (Gemelli et al., 2013). There is a very limited number of alternative herbicides to selectively control grasses in post-emergence. The upcoming traits for herbicide resistance in crops providing selective post-emergence grass control are Liberty Link soybean (glufosinate-resistance) and Enlist corn (haloxyfop-resistance). This will probably increase the usage of FOP herbicides to control *D. insularis* in corn post-emergence. Therefore, it is crucial to establish stewardship strategies to avoid the evolution and spread of ACCase resistant populations.

Integrated weed management (IWM) is the combination of multiple weed control methods in order to reduce weed interference below the economic threshold level (Thill et al., 1991). IWM is becoming more and more critical for both reactive and proactive weed resistance management (Figure 5). Survey studies are critical to designing resistance management strategies through a more reactive approach (Beckie et al., 2000). Similarly, understanding herbicide resistance mechanisms is a key component in designing management strategies. For instance, as seen in Table 1, certain mutations in ACCase confer resistance on one chemical family of herbicides but not on others. Therefore, even though rotating herbicides from different groups (FOP, DIM or DEN) could still be effective in the short term (depending on which mutation is involved), it cannot be recommended due to the rapid selection of cross resistance. For example, the mutation Trp2027Cys in *Digitaria insularis* (Takano et al., 2020) confers resistance to FOPs but not on DIMs. Therefore,

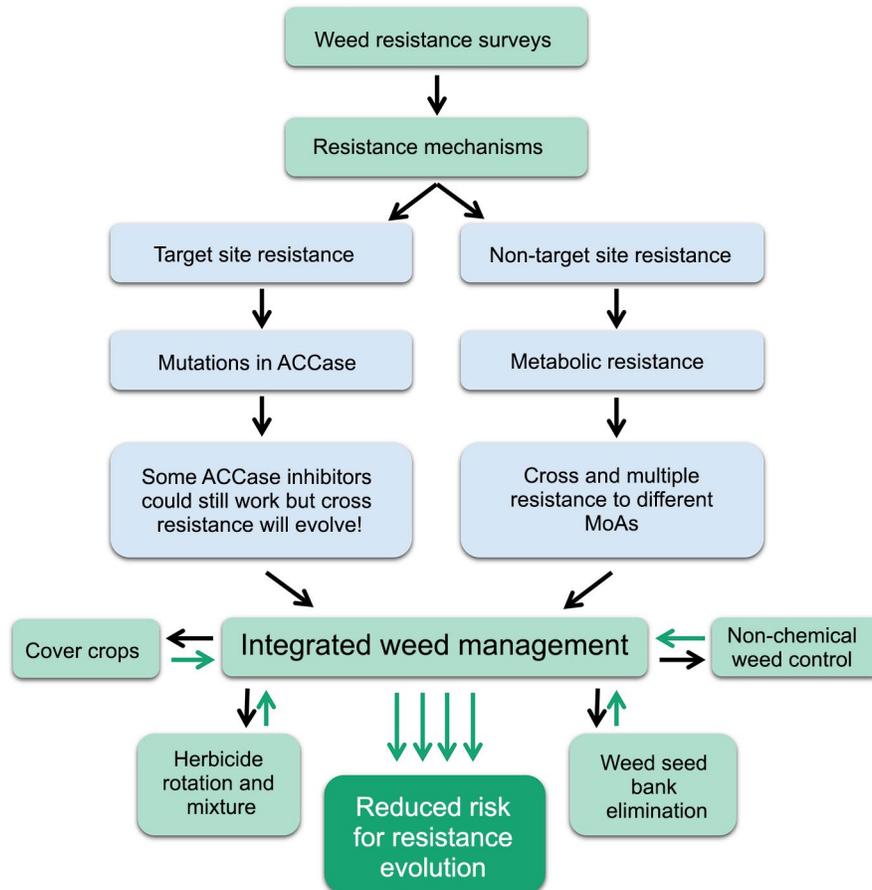


Figure 5 – The central role of integrated weed management (IWM) in avoiding or delaying herbicide resistance evolution. In a more reactive situation, IWM works as the only alternative to control weeds that have already evolved resistance (black arrows). In this case, weed resistance surveys and resistance mechanisms studies are crucial to design a management approach. On the other hand, an ideal situation, farmers can be more proactive avoiding or delaying the evolution of resistant weeds through IWM practices (green arrows).

using DIMs would still be an effective treatment but these herbicides should be used rationally and take into account other IWM practices. The inheritance mode of a resistance trait is also important in the designing of weed management strategies (Neve, 2007). If resistance is conferred by one single gene, resistant biotypes would be selected faster under high doses of herbicides (Ng et al., 2004). On the other hand, when resistance is inherited by multiple genes (e.g. metabolic resistance), low doses of herbicides allow the accumulation of resistance genes over generations (Neve and Powles, 2005). Unfortunately, there are still considerable gaps between research-based evidence and how weeds can be managed more efficiently to overcome herbicide resistance (Lamichhane et al., 2017).

When weeds evolve resistance to ACCase inhibitors, their management becomes more challenging due to the lack of alternative MoAs available for selective grass control in post-emergence. In addition, when resistance mechanisms involve herbicide metabolism, they can confer resistance to multiple herbicide MoAs (Busi et

al., 2012). Therefore, herbicide resistance management should definitely not focus only on herbicides, but on a more proactive approach as part of the IWM program (Beckie et al., 2012). One of the most efficient goals within IWM is to focus on lowering the weed seed bank density as close as possible to zero (Norsworthy et al., 2012). The harvest weed seed control is a promising tool to destroy weed seeds at crop harvest, lowering the soil seed bank and adding one additional diversity level in weed control (Walsh et al., 2018). Likewise, the integration of herbicide rotation and mixture with cover crops such as *Brachiaria ruziziensis* is a successful example of integrated weed management to mitigate herbicide resistance (Marochi et al., 2018).

Best agronomic practices significantly contribute to integrated weed management. For instance, spraying herbicides under recommended doses and appropriate conditions (e.g. luminosity, relative humidity and temperature) are important to delay resistance evolution (Norsworthy et al., 2012). Likewise, application technology principles (e.g. appropriate nozzles, tractor

speed, tank pressure, droplet size, use of surfactants, and spray volume) are essential to maximize efficacy and avoid NTSR selection by sub-doses (Busi et al., 2013). Mixing ACCase inhibitors with glyphosate generally enhances grass weed control even for glyphosate resistant species (Takano et al., 2018).

Resistance to ACCase inhibitors is still an emerging issue in South America; immediate attention and efforts are needed from several levels of the agricultural production chain (e.g. academia, industry, and government) (Powles and Gaines, 2016). All of these stakeholders collaborating with each other could provide efficient stewardship strategies to avoid losing efficacy of this important herbicide class. All existing tools for weed control, including both chemical and non-chemical approaches, should be considered by stewardship programs to preserve the efficacy of the technology. In addition, robust programs should fundamentally focus on educating growers to understand the importance of key practices and highlight the opportunity for greater crop yields in the long term.

Final remarks

A holistic strategy towards managing herbicide-resistant weeds is crucial for agricultural sustainability and rising crop yield rates that will provide food, fibers, and energy to a growing population. ACCase-inhibiting herbicides are one of the most important tools to control GR grass species and prevent yield losses due to weed interference. Acquiring additional knowledge on the mechanisms behind both TSR and NTSR is key to designing mitigation strategies. Alternating or combining herbicides with different MoAs is valid provided that IWM tactics are well established and do not rule out other approaches that consider additional practices (e.g. no-till farming). Whichever tools are developed, they ought to be diverse enough to guarantee complementarity and assure that weeds not controlled by one single method will be targeted by the other(s). The future of agriculture is dependent on the synergy that needs to be created in the intersection of IWM, biotechnology, and stewardship.

Authors' Contributions

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