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Review

Emerging Challenges for Weed Management in Herbicide-Resistant Crops

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Abstract: Since weed management is such a critical component of agronomic crop production systems, herbicides are widely used to provide weed control to ensure that yields are maximized. In the last few years, herbicide-resistant (HR) crops, particularly those that are glyphosate-resistant, and more recently, those with dicamba (3,6-dichloro-2-methoxybenzoic acid) and 2,4-D (2,4-dichlorophenoxyacetic acid) resistance are changing the way many growers manage weeds. However, past reliance on glyphosate and mistakes made in stewardship of the glyphosate-resistant cropping system have directly led to the current weed resistance problems that now occur in many agronomic cropping systems, and new technologies must be well-stewarded. New herbicide-resistant trait technologies in soybean, such as dicamba-, 2,4-D-, and isoxaflutole- ((5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone) resistance, are being combined with glyphosate- and glufosinate-resistance traits to manage herbicide-resistant weed populations. In cropping systems with glyphosate-resistant weed species, these new trait options may provide effective weed management tools, although there may be increased risk of off-target movement and susceptible plant damage with the use of some of these technologies. The use of diverse weed management practices to reduce the selection pressure for herbicide-resistant weed evolution is essential to preserve the utility of new traits. The use of herbicides with differing sites of action (SOAs), ideally in combination as mixtures, but also in rotation as part of a weed management program may slow the evolution of resistance in some cases. Increased selection pressure from the effects of some herbicide mixtures may lead to more cases of metabolic herbicide resistance. The most effective long-term approach for weed resistance management is the use of Integrated Weed Management (IWM) which may build the ecological complexity of the cropping system. Given the challenges in management of herbicide-resistant weeds, IWM will likely play a critical role in enhancing future food security for a growing global population.

Keywords: agronomic practices; dicamba; glyphosate; glufosinate; isoxaflutole; herbicide resistance; herbicide-resistant crops; mesotrione; non-target site resistance (NTSR); plant growth regulators (PGR); target site resistance (TSR); 2,4-D

1. Introduction

Weed management is a critical component of crop production systems throughout the world. Herbicides are the primary tool used for weed control in modern agricultural crop production systems, although their misuse and overuse has led to rapid evolution of herbicide-resistant weeds [1]. Genetically-modified glyphosate-resistant crops have enabled farmers to use glyphosate in broadcast post-emergence applications in soybean (*Glycine max* (L.) Merr.), corn (*Zea mays* L.), cotton (*Gossypium hirsutum* L.), canola (*Brassica napus* L.), sugar beet (*Beta vulgaris* L.), and alfalfa (*Medicago sativa* L.) to control problematic weeds without damaging the crop [2]. The wide availability of glyphosate-resistant crops has made glyphosate the most widely used herbicide in the world; however, due to the widespread use of glyphosate, numerous cases of weed resistance have been reported in many different countries [3]. This evolution of weed resistance to glyphosate has imposed new challenges in many agronomic cropping systems, and new technologies have been developed to deal with this resistance. Biotechnology-driven herbicide-resistance traits (e.g., 2,4-D- and dicamba-resistant soybean) are technologies that have led to striking advancements in agricultural crop weed management systems [4], although both herbicides have potential to provide injury to sensitive broadleaf plants in close proximity from off-target movement [5,6]. There have been numerous reports of off-target movement for dicamba from its use in dicamba-resistant soybean [7], and there is concern that greater adoption of 2,4-D-resistant crops may lead to more off-target movement of this herbicide as well [8]. This review provides an overview of the reliance on herbicide-resistant (HR) crops, the weed resistance issues that resulted from their mismanagement, the new herbicide trait technologies developed to better manage weed resistance, and some issues resulting from the field implementation of these new technologies.

2. Reliance on Herbicide-Resistant Crops

The reliance on glyphosate has directly led to the current weed resistance problems that now occur in many agronomic cropping systems. Glyphosate-resistant agronomic crops have transformed the way most growers manage weeds since the technology allowed a new weed control practice that was very effective, easy-to-use, highly economical, and relatively safe [5]. Agronomic crop growers were attracted to the flexibility and simplicity of the glyphosate and glyphosate-resistant crop technology package and adopted the technology at an unprecedented rate [9]. The technology is effective and easy to use, and farmers have often responded by exclusively planting glyphosate-resistant cultivars and applying glyphosate herbicide in the same fields, year after year [2]. Thus, many soybean growers relied only on glyphosate for weed control which directly led to a reduction in the use of other herbicide options [10]. The absence of soil residual herbicide applications by many growers directly led to multiple in-crop applications of glyphosate, with as many as four or more per growing season [5]. Additionally, the timing of burndown applications shifted, with these applications being made at planting or many weeks following planting; the advantage to the grower was control of multiple species, winter and summer annuals, with one application. Moreover, delaying the post-emergence application of glyphosate allowed growers to control weeds that would emerge following the burndown application, yet weeds might be 76 cm tall if the post-emergence application was delayed [10]. This resulted in widespread overuse and misuse of this herbicide in glyphosate-resistant crops. Although glyphosate-resistant crops have generally been thought of as successful, the evolution of weeds resistant to glyphosate developed faster and was more widespread than many expected.

Glyphosate has been, by far, the most widely adopted HR crop trait, yet there are several other crop traits which confer resistance to other herbicides. Crops that have been modified for glyphosate resistance using predominantly the cp4 epsps (*Agrobacterium tumefaciens* strain CP4), but also gat4621 (*Bacillus licheniformis*), goxv247 (*Orchobactrum anthropi* strain LBAA), mepsps (*Zea mays*), or 2mepsps (*Zea mays*) genes include alfalfa, canola, corn, cotton, potato (*Solanum tuberosum* L.), soybean, sugar beet, and wheat (*Triticum aestivum* L.). Several crop species have also been modified for glufosinate resistance, including canola, chicory (*Chicorium intybus* L.), corn, cotton, rice (*Oryza sativa* L.), soybean, and sugar beet, using the bar (*Streptomyces hygroscopicus*) and pat (*S. viridochromogenes*) genes [11]. Glyphosate-resistant crops have historically been preferred by growers for many reasons, including pre-emption of the market share before glufosinate-resistant crops arrived on the market and lower cost and increased flexibility compared to glufosinate-resistant crops; for example, since glufosinate is a contact herbicide and requires proper coverage, more carrier volume (140 to 187 L ha^{-1}) is required for mixing glufosinate than glyphosate (94 L ha^{-1}). Additionally, target weed height for glufosinate application is less than 10 cm; glufosinate controls 110 fewer species, can only be applied up to R1 in soybeans (compared to R3 for glyphosate), and has a rainfast period of 4 h compared to 30 min for some formulations of glyphosate. Additionally, glyphosate provides better control of perennials than glufosinate; this provides an advantage in no-till cropping systems, which may allow the establishment of perennials in the absence of tillage [12,13]. Within a few years following introduction, the adoption of glyphosate-resistant cotton eclipsed the use of genetically-modified bromoxynil-resistant cotton. Acetolactate synthase- (ALS-) inhibiting herbicide resistant crops have been developed through genetic modification, with corn an example that has been modified with the zm-hra gene (*Zea mays*) for resistance to sulfonylurea and imidazolinone herbicides. Traits for sulfonylurea resistance have also been inserted into other crops: Cotton with S4-HrA (*Nicotiana tabacum* cv. Xanthi), flax (*Linum usitatissiumum* L.) with als (*Arabidopsis thaliana*), and soybeans with gm-hra (*Glycine max*) and most recently, csr1-2 (*Arabidopsis thaliana*). Other traits, resulting from somaclonal variation and conventional breeding include sethoxydim-resistant corn [14], imidazolinone-resistant corn, wheat, rice, canola, and sunflower [15], and nicosulfuron-resistant sorghum [16].

Next-generation HR crops have been engineered for resistance to additional herbicide groups and active ingredients; resistance traits for glufosinate and glyphosate are being combined with resistances to acetyl CoA carboxylase inhibitors (chemical family: arloxyphenoxypropionates (FOPs)), plant growth regulators (active ingredients: dicamba and 2,4-D), acetolactate synthase inhibitors (chemical families: sulfonureas and imidazolinones), hydroxyphenylpyruvyldioxygenase inhibitors (active ingredients: isoxaflutole and mesotrione). These stacked traits may slow the evolution of resistance if stewarded appropriately and certain conditions are met; transgenes must target the same weed species, which is susceptible to two or more stacked herbicide active ingredients; target weeds must not be cross resistant to herbicides, and both herbicides must be used and must have relatively equal residual effects [17]. However, this is the first time that all traits introduced on the market will already have resistant weed species present somewhere in the US [3]. The development of new herbicide-resistant crops coincides with the grower expectation that new technology will solve herbicide resistance issues [18]. These new trait technologies will require proper stewardship, which includes implementing an Integrated Weed Management (IWM) strategy, using cultural, mechanical, biological, and chemical methods at the appropriate timing [19], and implementing Best Management Practices (BMPs), which are recommendations which may or may not include IWM strategies, to slow the evolution and spread of herbicide-resistant weeds [20]. Studies have documented the reluctance of growers to use non-chemical methods for weed control, due to issues of convenience, complexity, and cost [21], and there is the ever-present risk of repeating the same mistakes which were made in the management of glyphosate-resistant crops.

One of the major changes in the approach to chemical weed control as a result of increased occurrence of glyphosate-resistance weeds is the recent grower shift to increased use of pre-emergence herbicides and overlapping soil residual herbicide programs [22]. Research has shown that the use of pre-plant and pre-emergence herbicides has increased from 25% to 70% of US soybean acreage between 2000 and 2015 [23]. The use of pre-emergence, soil applied herbicides is an important part of an IWM program and may slow the evolution to post-emergence products by providing early control of weeds. Resistance to pre-emergence herbicides has not evolved as quickly as with post-emergence selection pressure [24], and soil-applied herbicide mixtures may further slow the evolution of resistance in pre-emergence use [25]. Simplified rotations or lack of rotation of soil-applied herbicides may result in resistance evolution [25]; as the rate of pre-emergence herbicide dissipates in the soil over time, declining concentrations of single SOA applications may allow herbicide-resistant weeds to emerge [26]. Therefore, other tactics used in combination with pre- and post-emergence herbicides remain important for resistance management. From collective, historical experience in selection for herbicide-resistant weeds, it is now known that evolution of herbicide resistance is inevitable if herbicides provide the only weed control solution [27]. Once herbicide resistance evolves, these resistant biotypes may spread through natural or mechanical means and may impact management beyond HT cropping systems.

3. Herbicide Resistance

The overreliance on glyphosate herbicide in glyphosate-resistant agronomic cropping systems has selected for weeds resistant to this herbicide [2]. Although the use of herbicide-resistant crop traits is changing due to new availability, until very recently, single-trait glyphosate-resistant crops dominated the market. Between 2009 and 2011, US herbicide use increased by 239 million kg, compared to non-herbicide-resistant hectares, with glyphosate use accounting for a majority of the increase [28]. Many weed scientists predicted the evolution of glyphosate-resistant weed species due to the over-application of glyphosate by primarily utilizing this herbicide alone for weed management [29,30]. Glyphosate-resistant weeds have been confirmed in almost 300 cases, and include almost 40 species in 28 countries [3]. The most documented glyphosate-resistant weed species include *Amaranthus palmeri* S. Watson, *Amaranthus tuberculatus* (Moq.) Sauer (syn. *A. rudis* Saur), *Ambrosia artemisiifolia* L., *Ambrosia trifida* L., *Conyza canadensis* (L.) Cronquist, and *Lolium perenne* L. Many of these have been documented in various areas of the world; thus, several broadleaf weed species, such *A. artemisifolia*, *A. trifida*, *A. palmeri*, *A. tuberculatus*, and *C. canadensis*, pose great danger to the sustainability of agronomic agricultural production systems [31]. The consequences of glyphosate-resistant weeds have led to changes in the way agricultural systems are managed. It is estimated that the management of glyphosate-resistant weeds has led to an increase in the number and amounts of herbicides applied [28]. Additionally, the cost of managing glyphosate-resistant weeds is estimated to have increased by 50% to 100% [32].

The rapid rise in glyphosate-resistant weeds demonstrates that HR crops are sustainable only as a component of more broadly integrated and ecologically-based weed management systems [9]. Although current glyphosate-based weed management systems are in jeopardy as evidenced by the speed at which weed populations are developing resistance, glyphosate has not lost all utility as it still controls a greater number of weeds more effectively than most other herbicides [5]. Since the evolution of weeds resistant to glyphosate has threatened the continued success and sustainability of crops resistant to glyphosate applications, new technologies have been developed to manage these glyphosate-resistant weed species. These are new transgenic crops now resistant to existing herbicide active ingredients, either released on the market or in development (2,4-D, dicamba, isoxaflutole, mesotrione). While these may offer some solutions to widespread resistances and multiple-resistant populations, there are already resistances to these chemistries present in the US [3]. For example, globally, there are 17 unique cases of herbicide resistance to dicamba; nine of these cases are the same species, *Bassia scoparia* (L.) A.J. Scott (syn. *Kochia scoparia* (L.) Schrad.), which is a driver weed (weed which determines management decisions) in some regions of the US. Between 2009 and 2018, there have been 2 populations of *A. tuberculatus* (Illinois, Nebraska) and 2 populations of *A. palmeri* (Kansas) identified as resistant to 2,4-D. All but one of these populations have multiple-resistances to other active ingredients, including ALS-inhibiting herbicides, 4-hydroxyphenylpyruvate dioxygenase-(HPPD-) inhibiting herbicides, including mesotrione, and the active ingredients atrazine (photosystem II-inhibiting herbicide) and glyphosate [3]. There is one case of isoxaflutole-resistant *A. tuberculatus* in Iowa, which is also resistant to ALS-inhibiting herbicides, atrazine, glyphosate, and mesotrione [3]. While these cases do not represent common occurrences of resistance, they suggest the likelihood of resistance evolution with increased selection pressure.

Herbicide resistance cases can be classified as target-site resistance (TSR) or non-target-site resistance (NTSR). TSR mechanisms involve a mutation in the genetic code for an herbicide binding site or overproduction of the targeted enzyme. Plants may also evolve the ability to detoxify foreign compounds, including herbicides, through metabolic resistance. Metabolic resistance is a non-target-site resistance (NTSR), similar to reduced absorption or translocation or herbicide sequestration in that the herbicide does not reach the target site in a concentration sufficient to cause plant death. Use of lower-than-recommended herbicide rates has been associated with the rapid evolution of NTSR [33]. Studies have shown that TSR evolution can also happen relatively quickly when populations are under intense selection pressure, depending upon the mutation rate for alleles conferring resistance.

For example, if the mutation rate is 5 individuals per one billion, then only 4000 plants yielding 250,000 seeds per plant would be needed to produce 5 resistant individuals [34,35]. It is predicted that if the rate of herbicide evolution continues, with the lack of new herbicide mechanisms of action, growers will not have available herbicide tools by the year 2050 [36]. For about 30 years, up until the 1980s, there was approximately one new MOA introduced every 2.5 to 3 years; however, there have been no new MOA's for agricultural production systems since the 1980s [37]. The selection of weed resistance to HPPD-inhibiting (e.g., mesotrione-resistant *A. palmeri*) and plant growth regulator (PGR) (e.g., 2,4-D-resistant *A. tuberculatus*) herbicides has been linked to NTSR, where weeds have the ability to rapidly metabolize herbicides through processes involving cytochrome P450 monooxygenases, glucosyl transferases, glutathione S-transferases, and other enzyme systems such as aryl acylamidase [38–40].

To complicate matters, resistant populations may be a mix of both TSR and NTSR [40]. Mechanisms of metabolic resistance can confer cross-resistance to herbicides that have not yet been developed [40]. Previous work has been focused on TSR mechanisms, and researchers may not have been looking for NTSR mechanisms in herbicide-resistant populations if TSR mechanisms were discovered first. Herbicide SOA tank mixtures are a foundational practice for diversifying weed management programs [41], and tank mixes and rotations are predicted to have reduced effectiveness in the case of NTSR (Tranel, personal communication). For example, rotation between HPPD-inhibiting and PGR herbicides could select for a detoxifying cytochrome p450 monooxengenase in theory, which would lead to cross-resistance [42]. Therefore, the occurrence of NTSR has the potential to change current agronomic practices.

Many growers are still reluctant to diversify weed management practices since they perceive alternative tactics as being less-cost effective despite growing evidence that such tactics can improve profitability as well as mitigate weed resistance issues [21,43]. The current economic situation in the US does not support grower adoption of alternative weed control methodologies due to the perceived risk associated with alternative tactics; financial and social incentives to adopt diversified weed management systems, as in an IWM approach, may improve adoption rate [18]. Grower networks, operating at relevant geographic scales, could encourage proactive change through sharing of knowledge and equipment [44,45]. IWM would require complex, detailed knowledge of weed biology and ecology to understand the impact of management on seed banks, alternative weed control strategies, the critical period of weed interference, and how to create optimal conditions for the crop to increase crop competitiveness [19,46]. Weed-competitive crop cultivars are often promoted as part of an IWM strategy, and this is becoming a focus of crop breeding programs, as plant traits that promote weed competitiveness are discovered [22]. Additionally, knowledge of mechanical practices, such as conservation tillage or harvest weed seed destruct (HWSD), and knowledge of cultural practices, such as diversified crop rotations and the use of cover crops, are also valuable in IWM strategies. Typically, if adopted, IWM is used as a reactive, rather than proactive, approach to weed management, and generally, there is a focus on diversifying weed management through herbicide SOA mixtures [47]. While mixtures may slow the evolution of TSR, they may increase the selection for NTSR, which may lead to cross-resistance to multiple SOA groups [40].

4. New Herbicide Trait Technologies and Developing Environmental Issues

New genetically-modified cultivars of soybean, cotton, corn and canola with resistance to additional herbicide chemistries, including dicamba and 2,4-D in soybean, are being offered as a solution for glyphosate-resistant weeds [9], but there may be inherent challenges in the use of these new crop trait technologies. In cropping systems where glyphosate-resistant weeds species are a major problem, combinations of mesotrione, isoxaflutole, glufosinate, dicamba and 2,4-D may provide an effective weed management tool [4,34,48]. However, there is potential for off-target movement that may result in damage to other adjacent, sensitive broadleaf plants. Although injury from low rates or simulated drift rates of several herbicides has been reported in many crops, dicamba and 2,4-D drift are of particular concern due to great potential of crop injury [49–52]. Plant response to these PGR herbicides is easily recognized as leaf cupping and crinkling and/or epinasty, and very low rates of herbicide may cause injury in susceptible plants [53]. Injury to soybean has been documented in the literature at the lowest published non-zero rate of 0.03 g ha^{-1} [54]. While low rates of PGR herbicides may not cause yield loss in soybeans, chemical trespass is illegal and may have other unintended consequences. Soybeans are the most sensitive species tested in response to dicamba and, therefore, were used to set the standard for dicamba drift studies. Soybean sensitivity standards may not reflect the sensitivity of native or non-cultivated species since these plants may vary dramatically in their response to dicamba due to genetic non-uniformity [55]. While soybean is able to metabolize vapor and particle drift levels of 2,4-D [6], other species may not. Tomato (*Lycopersicon esculentum* Mill. 'Marglobe") and lettuce (*Latuca sativa* L.) crops may be injured with as little as 0.001% of the labeled rate of 2,4-D butyl ester [56]. Besides susceptible agronomic crops, vegetable and fruit crops, orchards, vineyards, and homeowner gardens/landscapes are commonly grown in some areas in close proximity to herbicide-treated agronomic fields, all of which are concerns for off-target movement since they are generally highly sensitive to 2,4-D and dicamba [57].

Herbicide formulations differ in their ability to move off-target, and new formulations for use in HR crops have been developed for low volatility. There are two forms of dicamba, which are approved for use in HR crops: Dicamba DGA salt (diglycolamine salt of 3,6-dichloro-2-methoxybenzoic acid) with VaporGrip® technology and dicamba BAPMA salt (N,N-Bis-(3-aminopropyl) methylamine salt of 3,6-dichloro-2-methoxybenzoic acid). Dicamba acid is highly volatile, with a vapor pressure of 4.32×10^{-5} mm Hg [58]. Newer formulations attach a larger, heavier salt to dicamba, and therefore, volatize at a lower rate than the older form of dicamba, DMA salt (dimethylamine salt of 3,6-dichloro-2-methoxybenzoic acid) [59]. There is a choline salt formulation of dicamba, which is being used in herbicide volatility studies [60], but plans to bring this non-volatile formulation to market have not been announced. The herbicide 2,4-D has also undergone a formulation change for its new use in HR crops; historically, the amine formulation or the more volatile ester formulation were used. The current formulation for use in HR crops is the choline salt of 2,4-D (ethanaminium, 2-hydroxy-N,N,N-trimethyl-, 2-(2,4-dichlorophenoxy)acetic acid hydroxide), with a vapor pressure of 1.4×10^{-7} at 25C is considered non-volatile, similar to 2,4-D dimethylamine (vapor pressure 1.0×10^{-9}) [61], and much less volatile than 2-ethylhexyl ester of 2,4-D (vapor pressure 2.92×10^{-4}) [62].

Herbicides applied to crops may move off-target when environmental conditions are favorable for particle and vapor drift, which can result in adjacent agronomic or horticultural crop injury. There are many variables which determine the risk to sensitive plants, such as the herbicide formulation; tank additives; herbicide rate; nozzle type; droplet size; spray pressure; sprayer type (shielded/unshielded); boom height; timing of application; and prevailing environmental conditions, such as wind speed, stability and turbulence of the atmosphere, temperature and humidity [63,64]. For example, dicamba volatility can be reduced if temperature is decreased or relative humidity is increased [65,66]. The interaction of herbicide vapor or particle drift with atmospheric conditions is not well-investigated [64] but is gaining attention with the increasing use of PGR herbicides in HR crops. Temperature inversions have been suggested as the cause of some cases of dicamba off-target movement [7]. An inversion is formed when a layer of cool air is present at the soil surface, with a layer of warm air above it and often forms during sunset, sunrise, and in calm wind conditions. Fine particles may be trapped and may move with wind currents or down drafts [63]. Analysis of National Climate Reference Network measurements from 2012 to 2017 indicates that inversions develop most evenings between 15 May and 30 June, with little difference across the US soybean growing region. This analysis confirmed that inversions can form before sunset, after sunrise, and in winds in excess of 4.8 km h^{-1}; all are conditions in which an inversion might not be anticipated [7]. Furthermore, depending on the susceptibility of plants to a specific herbicide, off-target injury can occur a considerable distance from point of application [67]. Thus, as these herbicide resistance traits become more widely utilized in agronomic crops, the potential for off-target movement also increases [57].

Numerous drift issues with dicamba, including damage to adjacent horticultural crops and native flora, have already been realized after only a couple of years in the marketplace. There were numerous cases of dicamba off-target movement in 2016 in illegal applications since no registrations for in-crop use had been granted [68]. In 2017, there were more than 2700 reported cases of off-target movement of dicamba to susceptible crops, with estimated impact to over 3.6 million acres of soybeans [68,69]. These acreage estimates did not encompass the damage to other crops and other broadleaf plants in the proximity of agricultural fields. After modification of the product labels and application requirements for the 2018 growing season, there were still over 1400 reported cases of off-target movement in 2018. There is debate as to whether this figure was under- or over-reported [68]. These occurrences have posed severe challenges to the implementation of this new technology, and in 2018, new label language was standardized across all dicamba products and training for all dicamba applicators became mandatory in order to reduce the occurrence of off-target movement [68]. Dicamba off-target movement has brought high-profile attention from the media and public [70–75], which threatens to extend to all pesticides and HR crops, especially with the ongoing debate surrounding the human health impacts of glyphosate [76,77]. The impact of new HR crop traits and associated herbicide use patterns on biodiversity is not understood and is predicted to have negative consequences to native flora and fauna in and surrounding agricultural fields [78].

5. Conclusions

Due to rapidly evolving glyphosate-resistant weed populations, it is essential that other weed management alternatives be identified and implemented quickly [5]. Although recent research has also demonstrated that various integrated weed management strategies can be effective in managing glyphosate-resistant weeds [79,80], dicamba and 2,4-D applications may provide an effective weed management tool in cropping systems with glyphosate-resistant weeds [9,34]. These new technologies may fill efficacy gaps for weed control and diversify weed management practices in a short-term timescale. However, the rapid increase of glyphosate-resistant weeds demonstrates that herbicide-resistant crop biotechnology is sustainable only as a component of broader integrated and ecologically based weed management systems [9]. By using diverse weed management practices, growers will preserve the utility of herbicide resistant traits and new technologies in crops with less potential for weeds to evolve herbicide resistance [5]. While data support that herbicide mixtures, as would be used in new stacked HR trait packages in HR crops are more successful in slowing the evolution of herbicide resistance than rotations of herbicides [41], this practice is still seen as only delaying the inevitable when herbicides are the sole weed control tactic used [81]. Therefore, the effectiveness of stacking multiple herbicide resistance traits into crops will depend upon the efficacy of each herbicide on the target weed species and may not slow resistance if a target weed is already resistant to one or more of the stacked traits [17]. Moreover, the combination of selective forces imparted by multiple herbicide active ingredients in stacked trait packages may select for multiple herbicide resistance and NTSR [9,47].

The integration of multiple SOAs along with IWM in an agroecological approach is important for improving sustainability of weed management systems. IWM encourages a multi-faceted approach to weed management, which includes a combination of strategies such as prevention, seedbank management, new technologies in robotics and remote sensing, tillage, diverse crop rotations, cover crops and intercropping, biological controls, and the use of diverse and effective herbicide SOAs. IWM must be adopted proactively by growers in order to effectively steward new technologies. Therefore, growers, academics, and industry scientists must work together to overcome the barriers for adoption of IWM. Until the field of weed science changes the way that weeds and weed control are approached, through true integration of biology and ecology, there will be a continued drive to address the issues that continue to arise as a result of each new technological solution [82], perpetuating the evolutionary arms race between new herbicide technologies and herbicide-resistant weeds.

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