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Review

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Managing herbicide resistance in China

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Abstract

Since its initial introduction in the late 1950s, chemical control has dominated weed management practices in China. Not surprisingly, the development of herbicide resistance has become the biggest threat to long-term, sustainable weed management in China. Given that China has followed the same laissez-faire approach toward resistance management that has been practiced in developed countries such as the United States, herbicide resistance has evolved rapidly and increased steadily over the years. Previously, we carried out a systematic review to quantitatively assess herbicide-resistance issues in China. In this review, our main objective is to focus on mechanistic studies and management practices to document the (1) history of herbicide application in China; (2) resistance mechanisms governing the eight most resistance-prone herbicide groups, including acetolactate synthase inhibitors, acetyl-CoA carboxylase inhibitors, synthetic auxin herbicides, 5-enolpyruvylshikimate-3-phosphate synthase inhibitors, protoporphyrinogen oxidase inhibitors, photosystem I electron diverters, photosystem II inhibitors, and long-chain fatty-acid inhibitors; and (3) herbicide-resistance management strategies commonly used in China, including chemical, cultural, biological, physical, and integrated approaches. At the end, perspectives and future research are discussed to address the pressing need for the development of integrated herbicide-resistance management in China.

Introduction

Pesticide resistance has always been a global concern, and in May 2018, *Science* published a special issue focusing on the rise of resistance (Ash 2018; Atashgahi et al. 2018; Baker et al. 2018; Fisher et al. 2018; Gould et al. 2018). Herbicide resistance causes substantial yield loss, agroecosystem imbalance, and food safety issues. Since their initial introduction in the late 1950s, herbicides have dominated weed control practices in China. Herbicide resistance, inevitably, has become the biggest threat to the sustainability of chemical-based weed management in China. Given that China has followed the same laissez-faire approach toward resistance management that has been practiced in developed countries, which emphasizes private incentives and voluntary actions (Davis and Frisvold 2017), herbicide resistance has constantly/rapidly evolved and steadily increased over the past decade. According to the International Herbicide-Resistant Weed Database (Heap 2019), cases of herbicide resistance have increased remarkably in China between 2009 and 2019. There were only 15 resistance cases documented before 2009, but 45 were recorded by 2019 (Figure 1). A total of 27 weed species (13 dicots and 14 monocots) have evolved resistance to 13 different herbicide modes of action (MOAs) in 10 major crops in China (Liu et al. 2019). These resistant weeds pose a serious threat to chemical control in China and have therefore caught Chinese researchers' attention. Many studies seek to monitor levels of resistance or decipher the causes of resistance. However, the general understanding of herbicide resistance in China is still in its early stages (Liu et al. 2019). Previously, we carried out a systematic review to quantitatively assess herbicide-resistance issues in China (Liu et al. 2019). In this review, however, we focus on mechanistic studies and management practices to document the (1) history of herbicide application in China; (2) resistance mechanisms of major herbicide groups; and (3) herbicide-resistance management strategies currently practiced in China.

History of Herbicide Application in China

Before the introduction of herbicides, weed control in China was generally limited to manual weeding, which is labor-intensive and not suitable for modernized agriculture (Zhang 2003). China began to study chemical weed control in the mid-1950s (Zhang 1997). The first introduced herbicide was 2,4-D, used to control broadleaf weeds in wheat (*Triticum aestivum* L.)

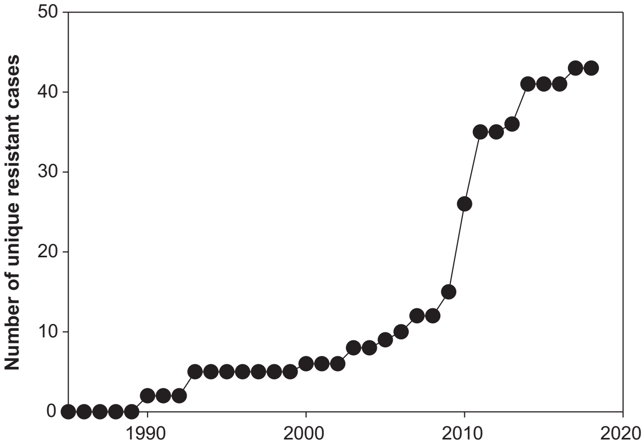

Figure 1. The development of herbicide-resistant cases in China. Data from 1985 to 2019 were provided from the International Survey of Herbicide-Resistant Weeds (Heap 2019).

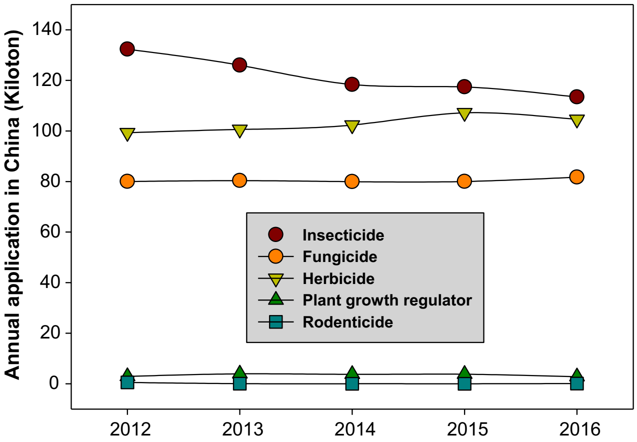

Figure 2. Pesticide application between 2012 and 2016 in China. Each data point represents the amount of active ingredient in pesticides. Data were collected from the Institute for the Control of Agrochemicals, Ministry of Agriculture, China.

(Zhang 1997). Subsequently, nitrofen and sodium pentachlorophenate were tested for barnyardgrass [*Echinochloa crus-galli* (L.) P. Beauv.] control in rice (*Oryza sativa* L.) in the early 1960s (Zhang 1997). In the 1970s, herbicide field trials and field demonstrations were carried out. Several herbicides, including thiobencarb, molinate, butachlor, chlortoluron, trifluralin, alachlor, and linuron, were applied in rice, wheat, soybean [*Glycine max* (L.) Merr.], cotton (*Gossypium hirsutum* L.), and other major crops (Zhang 2003). Use of herbicides steadily increased, becoming an important and attractive form of weed control for farmers (Zhang 1997, 2003). At the end of the 1990s, herbicides were employed extensively to control weeds in China, and by 2015 China had become one of the most important herbicide-producing and herbicide-consuming nations in the world (GACC 2015). Figure 2 presents the annual Chinese usage of insecticides, fungicides, herbicides, plant growth regulators, and rodenticides between 2012 and 2016. Herbicides were the second most used class of pesticides, only surpassed by insecticides. The amount of herbicides applied increased continuously, while insecticide applications decreased, even during the implementation of the Action Plan for Zero Increase in Pesticide Use by 2020 (Zhang et al. 2018c) released by the Chinese government to limit pesticide consumption without decreasing crop yields. There are several factors that influence the current situation in China. One major factor is the development of domestic herbicide production capacity, which allows herbicide prices to be reduced by more than 50%. Another factor is the shortage of workers to hand weed fields due to the spontaneous migration of rural labor to cities in pursuit of employment opportunities and increased wages (Gianessi 2013; Haggblade et al. 2017; Huang et al. 2017). As a result, herbicides are in high demand and are viewed as the most reliable form of weed control in China.

Resistance Mechanisms of Major Herbicide Groups in China

Herbicide resistance commonly refers to the inherited ability of a weed population to survive and reproduce at regularly applied herbicide doses, with the final result being weed control failure (Norsworthy et al. 2012). It is widely recognized that exposure to herbicides causes changes in weed populations over time via natural selection and the adaptive evolution of weeds (Beckie et al. 2012; Powles and Yu 2010). Several factors influence herbicide-resistance evolution: (1) genetic factors, including frequency, number, dominance, and fitness cost of resistance genes; (2) biology of weed species, including cross-pollination versus self-pollination, seed production capacity, seed longevity in the soil seedbank and seed/pollen movement capacity; (3) herbicides used, including chemical structure, MOAs, and residual activity; and (4) operational factors, including herbicide dose, agroecosystem factors (nonchemical weed controls, such as crop rotation), and skills of the operator (treatment machinery, timing, and environmental conditions) (Powles and Yu 2010). To effectively manage herbicide resistance, it is important to understand possible resistance mechanisms. Two major resistance mechanisms, non–target-site–based resistance (NTSR) and target-site–based resistance (TSR), are broadly grouped to explain the ability of herbicide-resistant (HR) weeds to survive herbicide treatments. TSR mechanisms focus on gene amplification of target enzymes or mutations that change enzyme or protein conformation and herbicide binding. NTSR mechanisms typically focus on reduced translocation in vascular tissue, sequestration in cell walls or vacuoles, reduced penetration, and enhanced metabolism (Délye et al. 2013).

Currently, at least 11 weed species in China have evolved NTSR associated with changes in cytochrome P450 monooxygenase (P450) (Li et al. 2017c), glutathione-*S*-transferase (GST) (Li et al. 2013), glycosyltransferases (GTs) (Zhao et al. 2017b), ethylene biosynthesis (EB) (Xu et al. 2013b), ATP-binding cassette (ABC) transporters (Yang et al. 2016), polyamines (An et al. 2014), micro-RNAs (miRNAs), and several typical antioxidant enzymes (Pan et al. 2016, 2017) (Table 1). NTSR endowing herbicide resistance is less often reported, and its resistance mechanisms are poorly understood because of its more complexity and diversity compared with TSR mechanisms. However, it poses a greater challenge to HR weed management because of the potential for cross/multiple resistance to develop. GST- and P450-mediated metabolic resistance have been recognized as the primary NTSR mechanisms. In China, evolved P450-mediated resistance has been reported in several weeds, including American sloughgrass [*Beckmannia syzigachne* (Steud.) Fernald] (Li et al. 2017c), shortawn foxtail (*Alopecurus aequalis* Sobol.) (Zhao et al. 2017b), water chickweed [*Myosoton aquaticum* (L.) Moench] (Liu et al. 2015b), flixweed [*Descurainia sophia* (L.) Webb ex Prantl] (Yang et al. 2016), perennial ryegrass (*Lolium perenne* L.) (Zhang et al. 2017b), rice

Table 1. Weeds with a non–target site based resistance mechanism(s) in China.[a]

Crop	Weed species	Herbicide	Mode of action (HRAC)	Resistance mechanism	Reference
Wheat	*Beckmannia syzigachne*	Fenoxaprop-P-ethyl Mesosulfuron-methyl	ACCase inhibitors ALS inhibitors	P450	Li et al. 2017c
	Alopecurus aequalis	Mesosulfuron-methyl	ALS inhibitors	P450, GST, GT, ABC transporter	Zhao et al. 2017b
	Myosoton aquaticum	Tribenuron-methyl	ALS inhibitors	GST, P450	Liu et al. 2015b
	Descurainia sophia	Thifensulfuron-methyl	ALS inhibitors	P450, ABC transporter	Yang et al. 2016
	Lolium perenne	Fenoxaprop-P-ethyl	ACCase inhibitors	P450	Zhang et al. 2017b
Rice	*Echinochloa crus-galli* (L.) P. Beauv. var. *zelayensis* (Kunth) Hitchc.	Quinclorac	Synthetic auxins	Ethylene biosynthetic pathway	Xu et al. 2013b
	Echinochloa crus-galli	Quinclorac	Synthetic auxins	GST	Li et al. 2013
	Echinochloa phyllopogon	Metamifop	ACCase inhibitors	P450	Zuo et al. 2016
	Sagittaria trifolia	Bensulfuron-methyl, penoxsulam, bispyribac-sodium	ALS inhibitors	P450	Zhao et al. 2017a
Soybean	*Amaranthus retroflexus*	Thifensulfuron-methyl	ALS inhibitors	P450	Wang et al. 2017
	E. crus-galli	Quizalofop-p-ethyl	ACCase inhibitors	Peroxidase, GST	Huan et al. 2011b
Maize	*Digitaria sanguinalis*	Nicosulfuron	ALS inhibitors	P450	Mei et al. 2017
Canola	*Poa annua*, *A. aequalis*	Fenoxaprop-P-ethyl	ACCase inhibitors	P450	Wang et al. 2013
Papaya and banana	*Eleusine indica*	Paraquat	PSI electron diverter	Polyamines, ABC transporter	An et al. 2014
Not specified	*E. indica*	Glyphosate	EPSPS inhibitors	GST	Chen et al. 2017b
	Pennisetum americanum (L.) Leeke	Atrazine	PSII inhibitors	Enzymatic defense	Jiang et al. 2016
	B. syzigachne	Fenoxaprop-P-ethyl	ACCase inhibitors	P450	Pan et al. 2015
	B. syzigachne	Fenoxaprop-P-ethyl	ACCase inhibitors	miRNAs, Laccase	Pan et al. 2016, 2017

[a]Abbreviations: HRAC, Herbicide Resistance Action Committee; ABC, ATP-binding cassette; ACCase, acetyl-CoA carboxylase; ALS, acetolactate synthase; EPSPS, 5-enolpyruvylshikimate-3-phosphate synthase; GST, glutathione-*S*-transferase; GT, glycosyltransferases; miRNAs, micro-RNAs; PSI, photosystem I; PSII, photosystem II; P450, cytochrome P450 monooxygenase.

barnyardgrass [*Echinochloa phyllopogon* (Stapf) Koso-Pol.] (Zuo et al. 2016), threeleaf arrowhead (*Sagittaria trifolia* L.) (Zhao et al. 2017a), redroot pigweed (*Amaranthus retroflexus* L.) (Wang et al. 2017), large crabgrass [*Digitaria sanguinalis* (L.) Scop.] (Mei et al. 2017), and annual bluegrass (*Poa annua* L.) (Wang et al. 2013). Enhanced activity of GST and/or P450 alongside target-site gene mutations often contribute to herbicide resistance, as in *M. aquaticum* resistance to tribenuron-methyl (Liu et al. 2015b).

A recent review on herbicide resistance in China indicated that acetolactate synthase (ALS) inhibitors, acetyl-CoA carboxylase (ACCase) inhibitors, synthetic auxin herbicides, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) inhibitors, protoporphyrinogen oxidase (PPO) (also known as protoporphyrinogen IX oxidase) inhibitors, photosystem I (PSI) electron diverters, photosystem II (PSII) inhibitors, and long-chain fatty-acid (LCFA) inhibitors are the herbicide groups most prone to developing resistance, accounting for 97% of developed resistance in China (Liu et al. 2019). To manage HR weeds in farmland, it is very important to understand the mechanisms of these eight herbicide groups.

ALS Inhibitors

ALS-inhibiting herbicides include five groups based on molecular structure: sulfonylureas (SUs), imidazolinones (IMIs), pyrimidinylthiobenzoates (PTBs), triazolopyrimidines (TPs), and sulfonylaminocarbonyltriazolinone (SCT). These herbicides control weeds by inhibiting ALS, which is a key enzyme for biosynthesis of branch-chained amino acids. Almost all studies on the mechanisms of ALS inhibitor resistance focus on modifications of the ALS enzyme. A total of 160 weed species (62 monocots and 98 dicots) have evolved resistance to ALS inhibitors globally due to eight mutations and 29 distinct amino acid substitutions located in the *ALS* gene: Ala-122-Thr/Val/Tyr/Ser/Asn, Pro-197-Thr/His/Arg/Leu/Gln/Ser/Ala/Ile/Asn/Glu/Tyr, Ala-205-Val/Phe, Asp-376-Glu, Arg-377-His, Trp-574-Leu/Gly/Met/Arg, Ser-653-Thr/Asn/Ile, and Gly-654-Val/Asp (Heap 2019). Generally, ALS inhibitors of different groups are associated with different amino acid substitutions in resistant weeds. Substitutions of Ala-122 or Ser-653 result in IMI but not in SU resistance, whereas substitutions of Pro-197 usually result in SU but not in IMI resistance. In some cases, low to moderate levels of IMI resistance have also been found in biotypes with the Pro-197 substitution. Substitutions of Trp-574 result in high levels of both IMI and SU resistance. Substitutions of Pro-197 and Ala-205 usually lead to cross-resistance (Tranel and Wright 2002). In China, there are five mutations with 13 amino acid substitutions in 10 weed species that provide known TSR to ALS inhibitors. The most common amino acid substitutions providing TSR to ALS inhibitors are found at residue Pro-197 in pickerelweed [*Monochoria vaginalis* (Burm. f.) C. Presl. ex Kunth] (Pro-197-Ser) (Wang et al. 2004), *D. sophia* (Pro-197-Ser/Leu/Ala/Thr/His/Tyr) (Cui et al. 2011; Deng et al. 2015), shepherd's purse [*Capsella bursa-pastoris* (L.) Medik.] (Pro-197-Ser/Leu/Thr/His/Tyr/Arg/Ala) (Zhang et al. 2017a), *M. aquaticum* (Pro-197-Ser/Glu) (Liu et al. 2013, 2015a), and *A. aequalis* (Pro-197-Thr/Arg) (Guo et al. 2016; Xia et al. 2015). The Trp-574-Leu mutation is also linked in several weed species to TSR to ALS inhibitors, including *A. aequalis* (Guo et al. 2015), *D. sophia* (Deng et al. 2017), *A. retroflexus* (Chen et al. 2015b), and Japanese foxtail (*Alopecurus japonicus* Steudel) (Bi et al. 2016) (Table 2). These mutations at different sites or domains render ALS inhibitors unable to bind at the catalytic site of the target enzyme, resulting in increased resistance to ALS-inhibiting herbicides (Powles and Yu 2010). In many resistance cases, however, NTSR and TSR can coexist. For

Table 2. Mutations in weeds resistant to acetolactate synthase inhibitors in China.

Amino acid[a]	Substitute residue	Herbicide	Weed species	Reference
Pro-197	Ser	Bensulfuron-methyl, pyrazosulfuronethyl	*Monochoria vaginalis*	Wang et al. 2004
	His	Bensulfuron-methyl	*Monochoria korsakowii* Regel et Maack	Lu et al. 2009
	Leu	Bensulfuron-methyl	*Rotala indica* (Willd.) Koehne	Kim 2012
	Ser	Mesosulfuron-methyl	*Beckmannia syzigachne*	Li et al. 2015a
	Leu, Ser, Ala	Tribenuron-methyl	*Descurainia sophia*	Cui et al. 2011
	Leu, Thr	Tribenuron-methyl	*D. sophia*	Cui et al. 2008
	Leu, Ser, Thr, His	Tribenuron-methyl	*Capsella bursa-pastoris*	Cui et al. 2012
	Ser	Tribenuron-methyl	*C. bursa-pastoris*	Jin et al. 2011
	Tyr, His, Leu, Ser, Arg, Ala, Thr	Tribenuron-methyl	*C. bursa-pastoris*	Zhang et al. 2017a
	Ser	Tribenuron-methyl	*Myosoton aquaticum*	Liu et al. 2013
	Glu	Tribenuron-methyl	*M. aquaticum*	Liu et al. 2015a
	Leu, Ser, His, Thr, Tyr	Tribenuron-methyl	*D. sophia*	Deng et al. 2015
	Thr	Mesosulfuron-methyl	*Alopecurus aequalis*	Xia et al. 2015
	Ser	Tribenuron-methyl	*D. sophia*	Xu et al. 2015
	Ser	Pyrazosulfuron-ethyl, bensulfuron-methyl metsulfuron-ethyl, tribenuron-methyl pyroxsulam, penoxsulam, bispyribac-sodium,imazethapyr, imazapic	*Eclipta prostrata* L.	Li et al. 2017a
	Arg	Mesosulfuron-methyl	*A. aequalis*	Guo et al. 2016
	Ser, Thr, Leu	Bensulfuron-methyl	*Sagittaria trifolia*	Fu et al. 2017; Wei et al. 2015
Trp-574	Leu	Mesosulfuron-methyl	*A. aequalis*	Xia et al. 2015
	Leu	Tribenuron-methyl	*D. sophia*	Deng et al. 2017
	Gly	Tribenuron-methyl	*Galium aparine*	Sun et al. 2011
	Arg	Nicosulfuron	*Digitaria sanguinalis*	Li et al. 2017b
	Leu	Imazethapyr, thifensulfuron-methyl	*Amaranthus retroflexus*	Chen et al. 2015b; Wang et al. 2017
	Leu	Mesosulfuron-methyl	*Alopecurus japonicus*	Bi et al. 2016
	Leu	Mesosulfuron-methyl, pyroxsulam, flucarbazone-sodium	*A. aequalis*	Guo et al. 2015
	Trp, Leu	Tribenuron-methyl	*C. bursa-pastoris*	Zhang et al. 2017a
Ser-653	Thr	Imazethapyr	*A. retroflexus*	Chen et al. 2015b
Ala-205	Val	Imazethapyr, thifensulfuron-methyl	*A. retroflexus*	Chen et al. 2015b; Wang et al. 2017
Asp-376	Glu	Tribenuron-methyl	*D. sophia*	Xu et al. 2015
	Glu	Pyroxsulam, mesosulfuron-methyl, rimsulfuron, nicosulfuron, sulfosulfuron, imazapic, penoxsulam, pyribenzoxim, flucarbazone-sodium	*A. japonicus*	Feng et al. 2016

[a]Amino acid followed by the location/site of substitution.

example, the *ALS* gene mutation Pro-197-Thr in combination with two non–target site based genes, *CYP96A13* and *ABCC1*, confers resistance to tribenuron-methyl, an ALS inhibitor, in *D. sophia* (Yang et al. 2016). In *M. aquaticum*, GST/P450-mediated metabolic resistance combined with a Pro-197-Ser mutation is involved in herbicide resistance to ALS inhibitors (Liu et al. 2015b).

ACCase Inhibitors

ACCase-inhibiting herbicides can be divided into three classes based on chemical structure: aryloxyphenoxypropionates (APPs, also known as FOPs), cyclohexanediones (CHDs, also known as DIMs), and phenylpyrazolins (PPZs, also known as DENs) (Kaundun 2014). ACCase inhibitors are used to control Poaceae weeds by inhibiting ACCase, which is a critical enzyme in fatty-acid synthesis. Likewise, the resistance mechanisms of ACCase inhibitors generally belong to TSR. A total of 10 mutations at codon positions 1734, 1738, 1739, 1781, 1999, 2027, 2041, 2078, 2088, and 2096 are determined by dominant alleles and confer resistance to ACCase inhibitors. The most common mutations are located at residue 1781 (Powles and Yu 2010). Seventeen distinct amino acid substitutions located in the carboxyl transferase (CT)domain of the plastidic *ACCase* gene have been reported worldwide: Arg-1734-Gly (Tang et al. 2012); Met-1738-Leu (Tang et al. 2012); Thr-1739-Ser (Tang et al. 2012); Ile-1781-Leu (Xia et al. 2015), -Val (Collavo et al. 2011), -Thr (Kaundun et al. 2013); Trp-1999-Cys (Xu et al. 2014), -Leu (Xu et al. 2014), -Ser (Yuan et al. 2015); Trp-2027-Cys (Du et al. 2016; Li et al. 2014; Yu et al. 2017); Ile-2041-Asn (Tang et al. 2015), -Val (Délye et al. 2003), -Thr (Guo et al. 2017); Asp-2078-Gly (Guo et al. 2015); Cys-2088-Arg (Yu et al. 2007); and Gly-2096-Ala (Du et al. 2016), -Ser (Beckie et al. 2012). These different amino acid substitutions can confer diverse cross-resistance to different ACCase-inhibiting herbicides. In Chinese cropping systems, at least seven weed species have evolved target-site ACCase resistance: *A. japonicus* (Tang et al. 2012), *A. aequalis* (Xia et al. 2015), *B. syzigachne* (Du et al. 2016), keng stiffgrass [*Pseudosclerochloa kengiana* (Ohwi) Tzvelev] (Yuan et al. 2015), Chinese sprangletop [*Leptochloa chinensis* (L.) Nees] (Yu et al. 2017), Asia minor bluegrass (*Polypogon fugax* Nees ex Steud.) (Tang et al. 2014), and *E. crus-galli* (Huan et al. 2011a). Table 3 shows that a total of nine mutations at codon positions and 11

Table 3. Mutations in weeds resistant to acetyl-CoA carboxylase inhibitors in China.

Amino acid[a]	Substitute residue	Herbicide	Weed species	Reference
Arg-1734	Gly	Haloxyfop-R-methyl	*Alopecurus japonicus*	Tang et al. 2012
Met-1738	Leu	Haloxyfop-R-methyl	*A. japonicus*	Tang et al. 2012
Thr-1739	Ser	Haloxyfop-R-methyl	*A. japonicus*	Tang et al. 2012
Ile-1781	Leu	Mesosulfuron-methyl	*Alopecurus aequalis*	Xia et al. 2015
	Leu	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-p-methyl, sethoxydim, clethodim, pinoxaden	*Beckmannia syzigachne*	Du et al. 2016
	Leu	Fenoxaprop-P-ethyl	*A. japonicus*	Bi et al. 2016
	Leu	Fenoxaprop-P-ethyl, clodinafop-propargyl, sethoxydim, pinoxaden	*B. syzigachne*	Tang et al. 2015
	Leu	Fenoxaprop-P-ethyl, clodinafop-propargyl, pinoxaden	*A. aequalis*	Xia et al. 2015
	Leu	Quizalofop-P-ethyl	*Echinochloa crus-galli*	Huan et al. 2011a
Trp-1999	Ser	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, sethoxydim, pinoxaden	*Pseudosclerochloa kengiana*	Yuan et al. 2015
	Cys, Leu	Fenoxaprop-P-ethyl,	*A. japonicus*	Xu et al. 2014
Trp-2027	Cys	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-p-methyl, sethoxydim, clethodim, pinoxaden	*B. syzigachne*	Du et al. 2016
	Cys	Fenoxaprop-P-ethyl, pinoxaden, clodinafop-propargyl, sethoxydim, clethodim	*B. syzigachne*	Li et al. 2014
	Cys	Cyhalofop-butyl	*Leptochloa chinensis*	Yu et al. 2017
	Cys	Fenoxaprop-P-ethyl	*A. japonicus*	Xu et al. 2013a
Ile-2041	Asn	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-p-methyl, sethoxydim, clethodim, pinoxaden	*B. syzigachne*	Du et al. 2016
	Asn	Fenoxaprop-P-ethyl, clodinafop-propargyl, sethoxydim, pinoxaden	*B. syzigachne*	Tang et al. 2015
	Asn	Clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-R-methyl, quizalofop-p-ethyl, fenoxaprop-P-ethyl	*Polypogon fugax*	Tang et al. 2014
	Asn	Haloxyfop-R-methyl	*A. japonicus*	Tang et al. 2012
	Asn	Fenoxaprop-P-ethyl	*A. aequalis*	Guo et al. 2016
	Thr	Fenoxaprop	*A. aequalis*	Guo et al. 2017
	Asn	Fenoxaprop-p-ethyl, clodinafop-propargyl, pinoxaden, clethodim	*A. japonicus*	Feng et al. 2016
Asp-2078	Gly	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-p-methyl, sethoxydim, clethodim, pinoxaden	*B. syzigachne*	Du et al. 2016
	Gly	Fenoxaprop-P-ethyl, clodinafop-propargyl, sethoxydim, pinoxaden.	*B. syzigachne*	Tang et al. 2015
	Gly	Quizalofop-P-ethyl, clethodim, sethoxydim, pinoxaden, fenoxaprop-P-ethyl, clodinafop-propargyl	*A. aequalis*	Guo et al. 2015
Gly-2096	Ala	Fenoxaprop-P-ethyl, clodinafop-propargyl, fluazifop-P-butyl, haloxyfop-p-methyl, sethoxydim, clethodim, pinoxaden	*B. syzigachne*	Du et al. 2016

[a] Amino acid followed by the location/site of substitution.

distinct amino acid substitutions confer resistance to ACCase inhibitors in China.

In addition to amino acid substitutions, various forms of NTSR can also confer resistance to ALS and ACCase inhibitors. These NTSR mechanisms include increases in metabolism, reductions in herbicide absorption, and impaired translocation of herbicide molecules. P450s, ABC transporters, GT, and protective enzymes, such as superoxide dismutase, catalase, and peroxidase, could play important roles in conferring NTSR to weed species in China (Table 1). Mechanisms of both TSR and NTSR to mesosulfuron-methyl and fenoxaprop-P-ethyl were identified in an *A. aequalis* population (Zhao et al. 2017b). These concurrent forms of resistance pose significant challenges to the management of resistance. Additionally, in comparison to TSR, mechanisms of NTSR to ACCase and ALS inhibitors are much less well known, because they can confer resistance to herbicides with different target sites. As a result, resistance to ACCase- and ALS-inhibiting herbicides has major impacts on agriculture in China.

Synthetic Auxin Herbicides

In contrast to resistance to ACCase and ALS inhibitors, the incidence of weed resistance to synthetic auxin herbicides is much lower, although these herbicides have been in use for more than 30 yr in China. There have been relatively few research advances involving molecular resistance mechanisms of weeds to synthetic auxins, because elucidating the mechanisms of resistance to this class of herbicides is particularly difficult (Powles and Yu 2010). In China, 12 weed species have developed resistance to synthetic auxins such as quinclorac, MCPA (4-chloro-2-ethyphenoxyacetate), 2,4-D butylate, and fluroxypyr (Liu et al. 2019). Quinclorac is widely used for weed control during rice production in China and is the most resistance-prone synthetic auxin herbicide used. Its intensive use has selected for herbicide resistance to quinclorac in eight *Echinochloa* species (Peng et al. 2019). The mechanisms of resistance to quinclorac center on components of the ethylene biosynthesis pathway, including 1-aminocyclopropane-1-carboxylic acid synthase, 1-aminocyclopropane-1-carboxylic acid oxidase, as well as those of the cyanide detoxification pathway via β-cyanoalanine synthase (Gao et al. 2017, 2018; Xu et al. 2013b). There are few known mechanisms of resistance to MCPA, 2,4-D butylate, and fluroxypyr. Resistance to MCPA generally involves changes in translocation or metabolism (Busi et al. 2018). It is hoped that the mechanistic biochemical and molecular basis of evolved resistance to synthetic auxin herbicides will be deciphered in the next few years.

EPSPS Inhibitors

Of the commonly used EPSPS inhibitors, glyphosate is the only member of the group for which resistance has been observed. Worldwide, a total of 47 weed species have evolved resistance to glyphosate (Heap 2019; Liu et al. 2019). In China, a total of eight weed species have developed resistance to glyphosate within three crops: goosegrass [*Eleusine indica* (L.) Gaertn.], *D. sanguinalis*, *L. chinensis*, *A. retroflexus*, and common purslane (*Portulaca oleracea* L.) in cotton; *E. indica*, horseweed [*Conyza canadensis* (L.) Cronquist], Asian copperleaf (*Acalypha australis* L.), and *C. canadensis* in orchard crops; and *C. canadensis* in ramie (Liu et al. 2019). Both TSR and NTSR to glyphosate have been confirmed. Overexpression of EPSPS, a target enzyme, and mutations at amino acid positions Thr-102 and Pro-106 confer glyphosate TSR in *E. indica*, coatbuttons (*Tridax procumbens* L.), and *C. canadensis* in Chinese crop fields (Chen et al. 2015a; Gherekhloo et al. 2017; Mei et al. 2018; Yu et al. 2015). Glyphosate NTSR is endowed by restricted glyphosate translocation and sequestration to vacuoles in addition to glyphosate metabolization, controlled by the aldo-keto reductase (*AKR*) gene (Ge et al. 2010; Lorraine-Colwill et al. 2002; Pan et al. 2019). It has been demonstrated that the *AKR* gene *EcAKR4-1* from jungle rice [*Echinochloa colona* (L.) Link] confers glyphosate resistance (Pan et al. 2019).

PPO Inhibitors

Currently, PPO-inhibiting herbicides include nine groups based on molecular structure: *N*-phenylphthalimides, diphenylethers, phenylpyrazoles, pyrimidindiones, oxadiazoles, oxazolidinediones, thiadiazoles, triazinones, and triazolinones. These herbicides control weeds by inhibiting PPO, a crucial enzyme in the biosynthesis of heme and chlorophyll, and catalyzing the oxidation of protoporphyrinogen to protoporphyrin IX. Some PPO inhibitors have been used for many years, but there has been little observed evolution of resistance to these herbicides. The possible reason for the slow evolution of weeds resistant to PPO inhibitors is the two target sites (*PPO1* and *PPO2*) used by PPO inhibitors, compared with the single target site used by other enzyme-inhibiting herbicides (e.g., ALS inhibitors, ACCase inhibitors).To date, only 14 weed species have evolved resistance to PPO inhibitors globally (Heap 2019). Deletion of amino acid Gly-210 in waterhemp [*Amaranthus tuberculatus* (Moq.) Sauer] (Lee et al. 2008; Patzoldt et al. 2006) and amino acid substitutions Arg-98-Leu in common ragweed (*Ambrosia artemisiifolia* L.) (Rousonelos et al. 2012), Arg-98-Gly and Arg-98-Met in Palmer amaranth (*Amaranthus palmeri* S. Watson) (Giacomini et al. 2017), Gly-399-Ala in *A. palmeri* (Rangani et al. 2019), and Ala-212-Thr in *E. indica* (Bi et al. 2020) contribute to TSR to PPO-inhibiting herbicides. There are few reported cases of evolved NTSR to PPO inhibitors (Dayan et al. 2014). In China, seven weed species, including *E. crus-galli*, barnyardgrass (*Echinochloa glabrescens* Munro ex Hook. f.), rough barnyardgrass [*Echinochloa crus-galli* var. *mitis* (Pursh) Peterm.], Chinese arrowhead [*Sagittaria trifolia* var. *sinensis* (Sims) Makino], *D. sophia*, Chinese melon [*Cucumis melo* var. *agrestis* (L.) Naudin], Asiatic dayflower (*Commelina communis* L.), and *A. retroflexus*, have evolved resistance to five PPO-inhibiting herbicides, including oxadiazon, oxyfluorfen, carfentrazone-ethyl, fluoroglycofen, and fomesafen (Liu et al. 2019). These cases of resistance to PPO inhibitors are brief reports without deciphered information on the resistance mechanisms. Although natural resistance to PPO-inhibiting herbicides has evolved slowly (Powles and Yu 2010), it may occur more frequently in weed species with large populations under continuous and extensive herbicide use (Jasieniuk et al. 1996).

Photosystem I Electron Diverters

PSI electron diverters are primarily non-translocated herbicides. These herbicides control weeds by accepting electrons from the PSI protein complex and subsequently transferring them to molecular oxygen to generate herbicide radicals. These radicals promote the formation of dangerous molecules such as reactive oxygen species (ROS), which can destroy membrane lipids, damage chlorophyll, and induce cell death (UCIPM 2020). Globally, 73 unique cases (species by site of action) of resistance to PSI electron diverters have been reported (Heap 2019). Almost all of these cases involve paraquat resistance (Heap 2019). In China, a total of six weed species, including *A. japonicus*, tall fleabane [*Conyza sumatrensis* (Retz.) E. Walker], *E. indica*, Asian mazus [*Mazus fauriei* Bonati], common hardgrass [*Sclerochloa dura* (L.) P. Beauv.], and Oriental false hawkbear [*Youngia japonica* (L.) DC], have developed resistance to paraquat (Dong et al. 2015). At least five NTSR mechanisms have been proposed for paraquat resistance in plant cells, including uptake, efflux, sequestration, detoxification, and catabolism of the ROS produced by the herbicide (Xi et al. 2012). Vacuolar sequestration has been recognized and extensively reported as the major mechanism of paraquat resistance in weeds (Brunharo and Hanson 2017; Hawkes 2014). Several functional genes that play important roles in sequestering paraquat away from chloroplasts and into the vacuole have been identified, but further research is required to understand how these genes are regulated (Fujita and Shinozaki 2014; Luo et al. 2019). Regarding the possibility of TSR to paraquat, it is debatable whether paraquat has any specific binding site from which it accepts electrons (Hawkes 2014). To date, a binding site mutation-based mechanism for paraquat resistance has not been identified (Hawkes 2014; Luo et al. 2019; Powles and Yu 2010).

Photosystem II Inhibitors

PSII inhibitors control weeds by inhibiting photosynthesis. This is accomplished by the herbicide binding to D1 proteins located in the photosystem II complex (UCIPM 2020). The binding occurs at three different attachment sites. Based on their attachment sites, PSII-inhibiting herbicides are classified into three groups by the Herbicide Resistance Action Committee (HRAC). Group C1 includes pyridazinone, triazine, triazinone, and uracil herbicides; group C2 includes ureas and amides; and group C3 includes benzothiadiazinone, nitrile, and phenylpyridazine herbicides. To date, there have been 107 unique cases (species by site of action) of resistance to PSII-inhibiting herbicides globally (Heap 2019). In China, a total of five weed species (manyflower redstem [*Ammannia multiflora* Roxb.], common chickweed [*Stellaria media* (L.) Vill.], catchweed bedstraw (*Galium aparine* L.), *A. japonicus*, *B. syzigachne*) have developed resistance to PSII-inhibiting herbicides (Liu et al. 2019). TSR to PSII-inhibiting herbicides is mainly due to seven mutations within the *psbA* gene encoding the D1 protein that results in nine distinct amino acid substitutions in resistant plants: Phe-274-Val, Ser-264-Gly/Thr, Asn-266-Thr, Phe-255-Ile, Ala-251-Val/Thr, Val-219-Ile, and Leu-218-Val (Lu et al. 2019b; McMurray et al. 2019; Powles and Yu 2010; Thiel and Varrelmann 2014). The most common amino acid substitution providing TSR to PSII inhibitors is Ser-264-Gly. NTSR to PSII-inhibiting herbicides is due to enhanced metabolism mediated by P450s and/or GSTs (Anderson and Gronwald 1991; Busi et al. 2011). Commonly, TSR along with NTSR induces resistance in many weed species to PSII-inhibiting herbicides, such as *P. annua* resistance to atrazine, amicarbazone, and diuron (Svyantek et al. 2016) and wild radish (*Raphanus raphanistrum* L.) resistance to metribuzin (Lu et al. 2019a).

Long-Chain Fatty-Acid Inhibitors

LCFA inhibitors include acetamide, chloroacetamide, oxyacetamide, and tetrazolinone herbicides. These herbicides control weeds by inhibiting LCFA synthesis. Cases of resistance to LCFA-inhibiting herbicides have been reported in many countries (Heap 2019). In China, a total of eight weed species are currently resistant to LCFA-inhibiting herbicides, including pretilachlor and butachlor (Liu et al. 2019). Pretilachlor resistance is attributed to high cytochrome P450 activity in some perennial weeds (Shim et al. 2002), but there are no reports on the exact mechanisms of resistance to pretilachlor. However, several mechanisms conferring resistance to butachlor have been elucidated. Butachlor resistance can be caused by α-amylase activation (Huang et al. 1995), increased hydrolase activity (Huang and Lin 1993), and increased protease activity (Kumar and Prakash 1994) in resistant plants. Another possible resistance mechanism may be related to the accumulation of phytoalexins, which is considered a defense mechanism in higher plants. After treatment with pretilachlor and butachlor, the phytoalexin momilactone was greatly increased in rice. The accumulation of momilactone may be required for rice protection and growth regulation. However, the mechanism of resistance of pretilachlor/butachlor-resistant *E. crus-galli* has not yet been determined (Tamogami et al. 1995).

Resistance Mechanisms of Major Herbicide Groups in China

Overall, for the herbicide groups most prone to resistance in China presented here, more research has focused on mechanisms of TSR than on those of NTSR. The possible reason is that NTSR mechanisms are more complex than those of TSR. Generally, target-site mutations provide high-level resistance and can be identified rapidly by molecular markers. NTSR is often ignored, because it generally confers lower resistance levels and is often linked with TSR (Liu et al. 2015b; Pan et al. 2015; Wang et al. 2017; Zhang et al. 2017b; Zhao et al. 2017b). In addition, due to the limited genomic information available for weeds, fewer NTSR mechanisms have been elucidated at the molecular level. Only a few *CytP450* genes have been identified as contributing to resistance in weeds such as *B. syzigachne*, *D. sophia*, and *A. aequalis* (Yang et al. 2016; Zhao et al. 2017b). However, NTSR could be more concerning, because it could confer resistance to multiple classes of herbicides. Farmers will face a reduced number of herbicide alternatives, because weeds will gradually evolve resistance to existing, new, or yet-to-be-discovered herbicides (Powles and Yu 2010). Therefore, NTSR is currently unpredictable and a troublesome problem for weed control. In the near future, herbicide-resistance research should center on the evolution and management of NTSR.

Herbicide-Resistance Management in China

Based on the occurrence of HR weeds and advances in resistance mechanisms, weed researchers in China have made great efforts in developing resistance management strategies during the last few decades. We searched through literature published from 1980 to 2018 using the China National Knowledge Infrastructure (CNKI) and Web of Science databases, then manually screened for resistance management strategies. A total of 158 records were retrieved from the two databases; among those records, strategies generally involved a combination of early preventative measures and one or more major management strategies once resistance was detected. Major management strategies include chemical, cultural, biological, and physical practices; of those resistance management strategies, approximately 46.4% were chemical, 25.0% were cultural, 17.9% were biological, 5.4% were early preventative, and 5.3% were physical (Figure 3). Based on these results, chemical strategies are the mainstay for managing herbicide resistance in China.

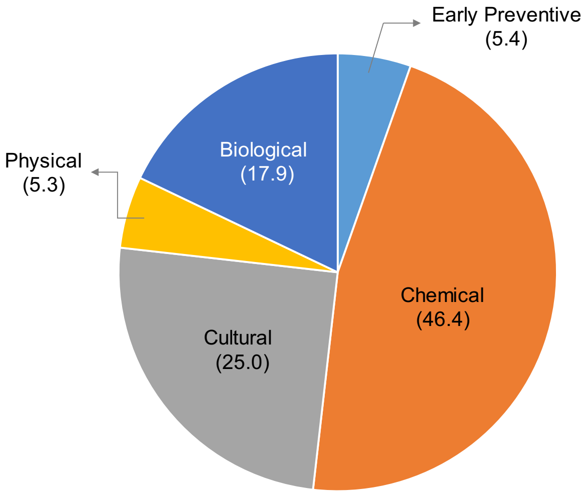

Figure 3. Major herbicide-resistance management practices in China. The current management practices used to combat herbicide-resistance issues in China include early preventative, chemical, cultural, biological, and physical strategies. Based on percentages (in parentheses), synthetic herbicides (~50%) have dominated control practices.

Early Preventative Measures

Early preventative measures include resistance detection, risk assessment, and government policy, which can provide important scouting information for resistance management. Currently, a series of rapid and simple resistance-detection technologies have been developed. Resistance of *E. crus-galli* to quinclorac can be rapidly identified using label cards in combination with a water-culture method for growing plants without soil (Li et al. 2015b) or with DNA technologies coupled with sequencing information (Chen et al. 2017a). Computational models are often used in the development of novel herbicides (Choe et al. 2015; Qu et al. 2017b; Zhu et al. 2011). In a simulation of the evolution of ALS inhibitor resistance associated with the *ALS* Pro-197-Leu mutation, a series of novel derivatives of 2-benzoyloxy-6-pyrimidinyl salicylic acid were designed and displayed strong inhibitory activity against highly-resistant *D. sophia* (Qu et al. 2017a). However, modeling is only a preliminary tool used to compare the theoretical advantages of management practices. It is also necessary that researchers implement long-term field trials to evaluate novel strategies, such as studies on the population dynamics and possible future populations of weeds (Jones and Medd 2000) or on the potential and capacity for soil mineralization after anti-resistance herbicide application (Cheyns et al. 2012; Jones and Medd 2005; Neve et al. 2011a, 2011b). In addition, government policies such as exotic pest and weed quarantine policies contribute to the prevention of herbicide resistance and limit the spread of invasive resistant species (Davis and Frisvold 2017). Furthermore, to delay or relieve the development of herbicide resistance, diverse management strategies, including chemical, cultural, biological, and physical practices, as well as the use of HR crops, have been established (Norsworthy et al. 2012; Vencill et al. 2012).

Chemical Management

Chemical management mainly includes herbicide sequence; herbicide rotation; development of novel herbicides and herbicide mixtures; use of synergists, new formulations, or new adjuvants; and use of full herbicide rates. When a resistance mechanism endows TSR, herbicide sequences, herbicide rotations, and herbicide mixtures have generally played a key role in delaying resistance (Gressel and Segel 1990). Herbicide sequence refers to more than one application of herbicides with different MOAs within one cropping system during a single growing season, whereas herbicide rotation refers to the application of herbicides with different MOAs to multiple crops over multiple growing seasons in a field (Beckie 2006). In recent years, adoption of herbicide sequences and rotations has increased markedly in China. However, the two tactics urgently require different herbicides with new MOAs. Disappointingly, no commercial herbicides with new MOAs have been released over the past 30 yr (Davis and Frisvold 2017), prompting growers and herbicide companies to shift from new herbicides to herbicide mixtures, which are more effective at managing resistance than herbicide rotations (Beckie and Harker 2017). According to the website of the China Pesticide Information Network (www.icama.org.cn), Chinese agricultural chemical industries have developed a series of mixtures, such as penoxsulam mixed with mesotrione/fenoxaprop-P-ethyl/fluroxypyr-meptyl, cyhalofop-butyl with bispyribac-sodium/metamifop/pyribenzoxim, and mesotrione with pyrazosulfuron-ethyl/pretilachlor/simetryn, that are used to control resistant populations of *E. crus-galli*, *L. chinensis*, *M. vaginalis*, and smallflower umbrella sedge (*Cyperus difformis* L.) in rice. Additionally, the mixture of bentazone with fomesafen is used to delay or prevent the development of ALS and/or PPO resistance in weeds. Although herbicide mixtures are less costly, there are no effective tank mixes for contact and systemic herbicides because of antagonism. It is worth noting that cross-resistance and multiple resistance would be delayed or relieved when herbicide sequence, rotation, and/or mixture are used concurrently. When weeds develop NTSR, synergist application, formulation changes, and the use of new adjuvants also aid in managing herbicide resistance by increasing the concentration of herbicidal ingredients at the target site. In China, a series of new formulations (microcapsules, ionic liquids, etc.) (Tang et al. 2020; Zhang et al. 2018a) and adjuvants (adjuvant methylated seed oil, KAO® adjuvants A-134 [Kao Corporation, Tokyo, Japan] and A-178 [Kao Corporation, Shanghai, China], etc.) (Hao et al. 2019a, 2019b; Zhang et al. 2013) have been applied to combat herbicide resistance. In addition, herbicide application at the full recommended rate is key to preventing weeds from rapidly evolving resistance. Research has demonstrated that lower than recommended dose selection favors the rapid evolution of polygenic resistance (Lagator et al. 2013; Manalil et al. 2011; Neve and Powles 2005; Yu et al. 2013). Neve and Powles (2005) demonstrated that susceptible annual ryegrass (*Lolium rigidum* Gaudin) can evolve resistance to diclofop-methyl after only three recurrent rounds of selection.

Herbicide-Resistant Crop Management

Another chemical strategy is the introduction and adoption of HR crops, which can theoretically reduce the use of herbicides and achieve better yields than conventional crops. However, existing data suggest that this is not the case, and in fact HR crops may negatively affect agronomy, agricultural practices, and weed management, as well as lead to biodiversity loss (Schütte et al. 2017). During continuous glyphosate/glufosinate-resistant crop cultivation, weed scientists recommend that farmers apply other herbicides (e.g., synthetic auxins) in tank mixtures with glyphosate/glufosinate rather than simply using higher rates of glyphosate/glufosinate for increased control efficiency (Schütte et al. 2017). It is also noted that gene flow by pollen or seed dispersal from HR crops to weeds may cause the rise of HR superweeds, greatly jeopardizing the potential benefits of HR crops (Bain et al. 2017). In China, glyphosate-resistant soybean, cotton, and maize (Fan et al. 2017; Ren et al. 2015; Zhang et al. 2017c) and glufosinate-resistant rice and canola (*Brassica napus* L.) (Cai et al. 2008; Cui et al. 2016), have been extensively studied. However, no commercial HR crops are currently approved for cultivation by the Chinese government.

Cultural Management

To increase crop competitiveness, maximize the growth of crops, and diminish weed germination and emergence, diverse cultural management is applied through crop rotation and intercropping, cultivar selection, water and fertilizer use practices, mulching, optimization of timing and density of crop planting, and use of allelopathic and cover crops. These cultural practices disrupt the life cycles of weeds and change the surrounding weed community based on the growth characteristics of each crop (Buhler 2002). In Chinese agricultural production, crop rotation is usually adopted by rotation of a grass crop (e.g., corn, wheat, rice) with a broadleaf crop (e.g., soybean, cotton, canola), or rotation of a wetland crop (e.g., rice) with a dryland crop (e.g., wheat) (Liu et al. 2018; Zhang 2003). In addition, growers often attempt to enhance crop competitiveness through the use of mulching (Yang et al. 2018), allelopathy (Li et al. 2019), cover crops, and full-season cultivars combined with suitable planting timing and planting density (Deng et al. 2010). These methods aid in inhibiting the emergence and growth of HR weeds, thus reducing seed yield of the weeds and decreasing the soil seedbank. These cultural tactics are important for resistance management in China. However, cultural management tactics utilizing suppression, competition, and shading do not provide complete weed control.

Biological Management

Biological management is achieved by using living organisms or their products to reduce population, growth, and reproduction of weeds (Charudattan 2005). Classical biological methods making use of a natural enemy of weeds, such as herbivorous animals, insects, and pathogenic microorganisms, have proven to be practical and effective strategies for HR weed control in China. In Chinese rice production, considerable success has been observed by raising fish, ducks, geese, and other herbivorous animals in paddy fields. The use of the leaf beetle *Agasicles hygrophila*, to control alligatorweed [*Alternanthera philoxeroides* (Mart.) Griseb.], is another successful case of biological control in China (Ma et al. 2003). In addition, the use of microbial herbicides to control weeds has a long history in China (Li et al. 2003). The first microbial herbicide in China was 'Lubao No. 1', used against Peruvian dodder (*Cuscuta australis* R. Br.) in the 1960s (Li et al. 2003). Subsequently, considerable research has been conducted on the development of bioherbicides from microorganisms, including bacterial, fungal, and actinomycete-derived products (Li et al. 2003). However, these biological agents have not been accepted for mass production because of their action conditions and potentially insignificant

Table 4. Risk level associated with the current herbicide-resistance management practices.

Management strategy	Risk level of developing herbicide resistance		
	Low	Medium	High
Chemical			
Herbicide modes of action (MOAs)	>2	2	1
Number of applications[a]	1	>1[b]	>>1
Cultural	Often	Sometimes	Never
Physical	Often	Sometimes	Never
Biological	Often	Sometimes	Never
Integrated	All practices	Chemical paired with others[c]	Chemical

[a] Number of applications of the same MOA herbicides within one cropping season.

[b] The number of applications per year required for weeds to develop resistance to herbicides with different MOAs varies. For resistance-prone herbicides (e.g., acetolactate synthase/acetyl-CoA carboxylase inhibitors), however, weeds only need two to three applications per year.

[c] Chemical paired with cultural, biological, and physical practices (Liu et al. 2015c).

economic profit. Our research team produced a novel bioorganic fertilizer composed of kitchen garbage, maize straw, wood-destroying fungi dregs, rice straw, tobacco straw, plant ash, and chicken and sheep manure that not only provides biological control of HR weeds but also supplies nutrients to the crop. Scientific data indicated the fertilizer can effectively control grass (*E. crus-galli*) and broadleaf weeds (*M. vaginalis*) in rice fields with an average rate of more than 80% weed suppression, while increasing rice yield by 16.3% to 29.8% relative to controls (Li et al. 2018). Biological management is an active research area pursued by weed scientists but is generally not used as a broad part of resistance management, depending rather on local agricultural environments. Therefore, effective use of biological management is context dependent.

Physical Management

Physical management of HR weeds includes deep plowing in winter, cleaning crop seeds before planting, tillage during the growth process of crops, damaging weed seeds at crop harvest (achieved by chaff carts), hay baling, windrow collection, and cleaning mechanical harvesters using mechanical equipment or manual labor. Physical management is beneficial, increasing output of seedbanks by stimulating weed seed germination, leading to rapid loss of weed seeds from the soil (Buhler 1995; Yenish et al. 1992), and decreasing input to seedbanks by preventing weed seeds from entering the soil. It is documented that physical practices can prevent more than 95% of weed seeds from entering the soil and thus dramatically reduce weed seedling emergence in following crops (Harrington and Powles 2012; Walsh et al. 2018; Walsh and Powles 2007).

Generally, physical practices focus on tillage, which buries small weeds and disrupts or severely damages weeds through harrowing, moldboard plowing, or some other technique at the early stage of weed development, resulting in weed mortality (Mohler et al. 1997; Rasmussen 2004; Van der Weide et al. 2008). For example, winter plowing to a depth of 15 to 20 cm can expose overwintering underground parts (e.g., tubers) of HR perennial weeds (e.g., *S. trifolia*) to cold air, freezing them to death or inactivating them. However, as a major mechanical control method, tillage may not be desirable, because it is labor-intensive with high labor costs, in addition to causing soil erosion, especially when plowing is used. Moreover, although hoeing can be effective on younger weeds, it becomes difficult after weeds reach the cotyledon stage (Kurstjens and Perdok 2000).

Integrated Herbicide-Resistance Management

Current herbicide-resistance management strategies are beneficial for preventing or at least delaying the development of herbicide resistance, but each has its respective limitations. Therefore, the establishment of integrated herbicide-resistance management systems combining chemical, cultural, biological, and physical strategies is a pressing need. In this review, "integrated herbicide-resistance management systems" refers to combinations of more than one strategy of HR weed management (chemical, cultural, biological, or physical) during or surrounding a crop life cycle in a given field. In China, integrated herbicide-resistance management systems may include several different combinations of management practices, representing low to medium levels of risk for the development of herbicide resistance (Table 4). Many integrated herbicide-resistance management systems are helpful to farming systems (Llewellyn et al. 2007). However, these integrated practices for managing herbicide resistance are not widely adopted by Chinese farmers for several reasons. First, management of HR weeds is still in the preliminary stage in China (Liu et al. 2019). Current knowledge of most management systems is still at the nascent stage and is incomplete. Second, chemical management offers significant advantages in the short term. Most integrated herbicide-resistance management systems are based on use of herbicides in combination with agricultural measures, which increases agricultural production costs compared with chemical management only. These economic constraints directly influence farmers' decisions of whether and when to implement integrated herbicide-resistance management systems. Third, chemical management is more popular for weed control because herbicides are considered to be easier to use, relatively cheaper, more effective, and less labor-intensive. In addition, most Chinese farmers are less aware of the evolution of resistance promoted by continuous and extensive use of herbicides. Many farmers even believe that alternative herbicides with novel MOAs exist for control of HR weeds if and when herbicide resistance occurs. For these reasons, integrated management systems are rarely adopted in China. Therefore, the first step is to modify integrated herbicide-resistance management systems to better fit the diverse local ecological regions of China. Then, area-wide field demonstrations should be conducted to increase farmers' confidence that integrated herbicide-resistance management systems can be successful. Additionally, integrated management programs should be developed to enhance farmers' awareness of herbicide resistance, to educate farmers effectively on the purposes of integrated management, and to cover the measures necessary to prevent or delay herbicide-resistance evolution.

Case Study: Integrated Herbicide-Resistance Management in Rice and in Wheat

The heaviest infestation of HR weeds in China is *E. crus-galli* in rice, followed by *G. aparine* and *D. sophia* in wheat (Liu et al. 2019). For managing *E. crus-galli* multi-resistant to penoxsulam, bispyribac-sodium, and quinclorac, an integrated herbicide-resistance management is adopted as follows. Before rice planting, growers make use of high-quality weed-free seeds, clean out weeds on field margins, consider rotation with wheat/canola/cotton, and then optimize planting timing and planting density of rice. After transplanting, a 10- to 20-cm-deep water layer is maintained for a long time, which is beneficial in reducing infestation of annual grass resistant weeds (e.g., *E. crus-galli*). Next, a three-step herbicide application strategy is employed. Specifically, the first step is to use different MOA PRE herbicides (e.g., pretilachlor) before weed-seed germination. The second step is to apply different MOA POST herbicides (e.g., metamifop) or herbicide mixtures to control *E. crus-galli* at the 3-leaf stage. Whether the third step should proceed or not depends on the density of *E. crus-galli* in the field after the previous two treatment steps. If necessary, foliar-applied herbicides will be used to control *E. crus-galli* at the 4- to 5-leaf stage. After chemical control, the remaining multi-resistant *E. crus-galli* might start to produce seeds, at which point a physical practice such as pulling weeds by hand will be utilized to prevent the seeds from spreading. Furthermore, seeds will be removed at harvest through the cleaning of mechanical harvesters. Using this integrated system, control efficacy for multi-resistant *E. crus-galli* is often greater than 85% (Ma et al. 2012; Zhang et al. 2018b).

Similarly, another integrated management system can be established to manage tribenuron-resistant *G. aparine* and *D. sophia*, which are prevalent in wheat. Such a system could involve replacement of herbicides at high resistance risk with different MOA herbicides, mixtures with no cross-resistant herbicides, rotation with highly effective herbicides, and ancillary measures involving cultural practices. This means that different effective commercial herbicide products, including fluroxypyr, pyraflufen-ethyl, florasulam, carfentrazone-ethyl, and mixtures of florasulam with fluroxypy/carfentrazone-ethyl/clodinafop-propargyl, which do not share cross-resistance with tribenuron, are applied to control tribenuron-resistant *G. aparine* and *D. sophia*. These chemical practices, combined with rice–wheat crop rotation and 30- to 35-cm-deep tillage before wheat planting, can effectively control tribenuron-resistant weeds.

Summary and Perspectives

Herbicides alone cannot create resistant weeds. Resistance to herbicides is an outcome of natural selection in the presence of selection pressure exerted by herbicides. Resistance is bound to happen if an herbicide is in continuous use without proper levels of risk assessment in place, as shown in Table 4. In China, ALS inhibitors, ACCase inhibitors, synthetic auxin herbicides, EPSPS inhibitors, PPO inhibitors, PSI electron diverters, PSII inhibitors, and LCFA inhibitors are the eight herbicide groups most prone to developing resistance. Based on the underlying resistance mechanisms (reviewed here), China has established diverse strategies, including chemical, cultural, biological, physical, and most recently, integrated tactics to manage HR weeds. To develop more effective integrated management systems against herbicide resistance, future work should focus on (1) understanding the biology and ecology of crop–weed interactions; (2) elucidating herbicide-resistance mechanisms, especially for the grossly understudied NTSR; (3) strengthening research on preventive measures; and (4) developing new resistance management strategies, specifically for non-chemical approaches, through continued and collaborative efforts among scientists, farmers, manufacturers, and policy makers both in China and worldwide.

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