Weed Technology

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4-Hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicides: past, present, and future

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Abstract

The herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD) are primarily used for weed control in corn, barley, oat, rice, sorghum, sugarcane, and wheat production fields in the United States. The objectives of this review were to summarize 1) the history of HPPD-inhibitor herbicides and their use in the United States; 2) HPPD-inhibitor resistant weeds, their mechanism of resistance, and management; 3) interaction of HPPD-inhibitor herbicides with other herbicides; and 4) the future of HPPD-inhibitor-resistant crops. As of 2022, three broadleaf weeds (Palmer amaranth, waterhemp, and wild radish) have evolved resistance to the HPPD inhibitor. The predominance of metabolic resistance to HPPD inhibitor was found in aforementioned three weed species. Management of HPPD-inhibitor-resistant weeds can be accomplished using alternate herbicides such as glyphosate, glufosinate, 2,4-D, or dicamba; however, metabolic resistance poses a serious challenge, because the weeds may be cross-resistant to other herbicide sites of action, leading to limited herbicide options. An HPPD-inhibitor herbicide is commonly applied with a photosystem II (PS II) inhibitor to increase efficacy and weed control spectrum. The synergism with an HPPD inhibitor arises from depletion of plastoquinones, which allows increased binding of a PS II inhibitor to the D1 protein. New HPPD inhibitors from the azole carboxamides class are in development and expected to be available in the near future. HPPD-inhibitor-resistant crops have been developed through overexpression of a resistant bacterial HPPD enzyme in plants and the overexpression of transgenes for HPPD and a microbial gene that enhances the production of the HPPD substrate. Isoxaflutole-resistant soybean is commercially available, and it is expected that soybean resistant to other HPPD inhibitor herbicides such as mesotrione, stacked with resistance to other herbicides, will be available in the near future.

Review

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Nomenclature:
Bicyclopyrone; bipyrazone; isoxaflutole; mesotrione; pyroxasulfotole; tembotrione; tolpyralate; topramezone; Palmer amaranth, *Amaranthus palmeri* L.; waterhemp, *Amaranthus tuberculatus* L.; wild radish, *Raphanus raphanistrum* L.; barley, *Hordeum vulgare* L.; corn, *Zea mays* L.; oat, *Avena sativa* L.; rice, *Oryza sativa* L.; sorghum, *Sorghum bicolor* (L.) Moench; sugarcane, *Saccharum officinarum* L.; wheat, *Triticum aestivum* L.

Keywords:
Azole carboxamides; integrated weed management; herbicide interaction; pyrazolone; resistant crops; resistant weeds; synergism; triketone

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Introduction

Herbicides are used for managing weeds in diverse cropping systems in many countries (Jhala et al. 2014a). The 4-hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicides represent one of the latest discoveries of a new herbicide site of action that was introduced in the late 1990s (Mitchell et al. 2001). Based on the site of action, HPPD inhibitor has been classified as Group 27 herbicides by the Weed Science Society of America and Herbicide Resistance Action Committee (Mallory-Smith and Retzinger 2017). The HPPD-inhibiting herbicides are broadly classified into chemical families: isoxazole (e.g., isoxaflutole), pyrazolone (e.g., pyrasulfotole, tolpyralate, topramezone), triketone (e.g., bicyclopyrone, mesotrione, and tembotrione; Figure 1), and isoxazolidinone (e.g., clomazone; Lee et al. 1997). An additional class, azole carboxamides, has emerged in the patent literature, but these molecules have not been commercialized as of 2022 (Figure 1).

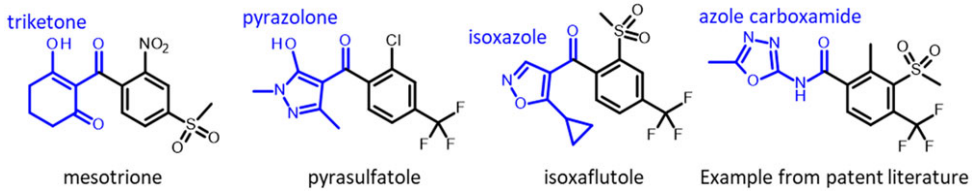

Figure 1. Chemical structures of some herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD).

These herbicides inhibit the HPPD enzyme found in plants and animals that is essential for the synthesis of plastoquinone and tocopherols (Liu and Lu 2016). The plastoquinone is in turn a co-factor in the formation of carotenoids, which protect chlorophyll in plants. Because of the lack of plastoquinone, tocopherols and carotenoid synthesis due to HPPD inhibition, sensitive plants suffer oxidative damage and chlorophyll destruction, turn white without deformation, and eventually die (Mitchell et al. 2001). The HPPD-inhibiting herbicides are mainly used to control annual grass and broadleaf weeds, including herbicide-resistant biotypes primarily in grass crops such as sugarcane and corn (Grossman and Ehrhardt 2007; Pallett et al. 2001). After the evolution and widespread occurrence of weeds that became resistant to the acetolactate synthase (ALS) inhibitor, atrazine and glyphosate, the HPPD-inhibiting herbicides, played a key role for their management in agronomic crops, primarily in corn (Ganie and Jhala 2017).

The HPPD-inhibitor herbicides are used primarily for selective preemergence (PRE) and postemergence (POST) use as a weed control mechanism primarily in corn, barley, oat, rice, sorghum, sugarcane, and wheat. Mesotrione is labeled for PRE use in weed control in sorghum and sugarcane. The HPPD- and photosystem (PS) II-inhibiting herbicides are applied in a mixture, because certain herbicides belonging to both sites of action interact synergistically and provide higher efficacy compared with being applied alone (Fluttert et al. 2022). For example, field experiments conducted in Nebraska reported that Palmer amaranth (*Amaranthus palmeri* L.) that was resistant to atrazine and an HPPD inhibitor was effectively controlled by their mix, even applied at labeled rates (Chahal and Jhala 2018a).

The scientific literature is not available to cover the past, present, and future of the HPPD inhibitor. Therefore, the objectives of this review were to 1) summarize the history of HPPD-inhibitor herbicides and their use in the United States; 2) summarize HPPD-inhibitor resistant weeds, their mechanism of resistance, and management; 3) highlight the interactions of HPPD-inhibitor herbicides with other herbicides; and 4) summarize the future of HPPD-inhibitor herbicides, including products in the pipeline and HPPD-inhibitor-resistant crops.

History of HPPD-Inhibiting Herbicides

Inhibitors of HPPD (HPPD, EC 1.13.11.27) were the results of several concurrent industry research programs. Pyrazolones were first commercialized by the Sankyo company in 1980 with pyrazolynate in the United States (Figure 2). Pyrazoxyfen by Ishihara followed in 1985, benzofenap by Mitsubishi and Rhône-Poulenc in 1987, topramezone by BASF in 2006, and pyrasulfotole by Bayer Crop Science in 2007 (Figure 3). The Ishihara company has commercialized its corn herbicide tolpyralate, which was first registered in 2017 (Tsukamoto et al. 2021).

KingAgroot launched four new pyrazolone herbicides in China in 2020: cyprafluone, bipyrazone, fenpyrozone, and tripyrasulfone. Cyprafluone became KingAgroot's first active ingredient to launch outside of China when granted registration in Pakistan in 2021 (KingAgroot 2021), with a plan for registration in other countries. Cyprafluone controls grass weeds such as Japanese foxtail (*Alopecurus japonicus* Steud.) and littleseed canarygrass (*Phalaris minor* Retz.) in wheat (*Triticum aestivum* L.). Wang et al. (2020) reported that bipyrazone applied POST has a potential for broadleaf weed control in wheat in China.

Concurrently, a research group at Stauffer, a legacy company of ICI and now Syngenta, discovered the triketone-type HPPD inhibitor in 1982 through a chemical ecology approach. Researchers at Reed Gray observed that few weeds grew under crimson bottlebrush [*Callistemon citrinus* (Curtis) Skeels] in the California chaparral. Bioassay-guided isolation of crimson bottlebrush extracts led to the identification of fractions that can induce bleaching in developing seedlings. The active fractions contained the natural product leptospermone, a natural inhibitor of HPPD (Dayan et al. 2007; Owens et al. 2013). The herbicidal activity of leptospermone and a series of synthetic triketone analogues were patented in 1980 (Figure 4). Structure-activity relationship studies characterized the chemical toxophore that is responsible for inhibiting HPPD (Ahrens et al. 2013).

Triketones were first introduced to growers in 1991 by Zeneca (now Syngenta) with sulcotrione. Since then, a steady stream of triketones have been launched: benzobicyclon (by SDS Biotech in 2001), mesotrione (by Syngenta in 2002), tembotrione (by Bayer Crop Science in 2007), tefuryltrione (by Bayer in 2009), and bicyclopyrone (by Syngenta in 2015; Beaudegnies et al. 2009). Kumiai Chemical registered fenquinotrione (Figure 4), trademarked as Effeeda, to control broadleaf weeds and sedges in rice in Japan. The molecule's 4-methoxyphenyl group confers resistance to rice while maintaining weed control efficacy via selective metabolism (Yamamoto et al. 2021). Kumiai collaborated with Certis to register fenquinotrione in the European Union for weed control in cereals and rice. Certis submitted a registration package in 2021. If successful, it is expected that the product will be available around 2025. Ishihara launched lancotrione-sodium in 2019 for control of broadleaf weeds and sedges in rice, including weeds that are resistant to sulfonylurea herbicides. Originally invented at Central China Normal University, benquitrione is the first in a series of quinazoline-2,4-diones triketone herbicides from Guang-Fu Yang's laboratory, co-developed with Shandong Cynda (Figure 4; Wang et al. 2015).

The first HPPD inhibitor was discovered serendipitously by Japanese companies, with pyrazolynate discovered by Sankyo and commercialized in 1980, and pyrazoxyfen discovered by Ishihara in 1985 (Figure 4). Both were commercialized for weed control in rice before their site of action was understood. It is now known that these compounds were pro-herbicides that are bio-activated into free hydroxypyrazole active pharmacophore, which inhibits HPPD.

Studies carried out by Rhone-Poulenc (now Bayer Crop Science) in the late 1980s led to the discovery of isofluxatole, an

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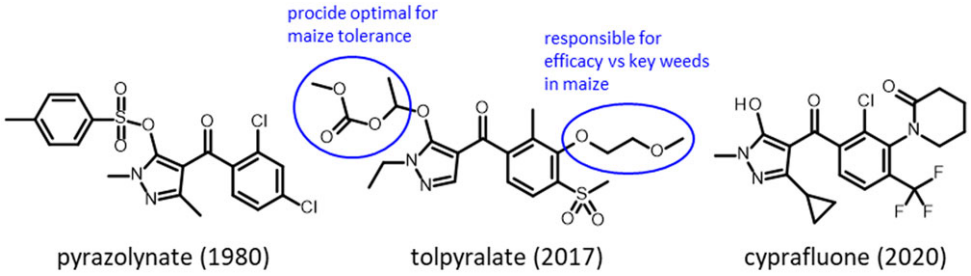

Figure 2. Chemical structures of pyrazolone herbicides, a chemical family of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD).

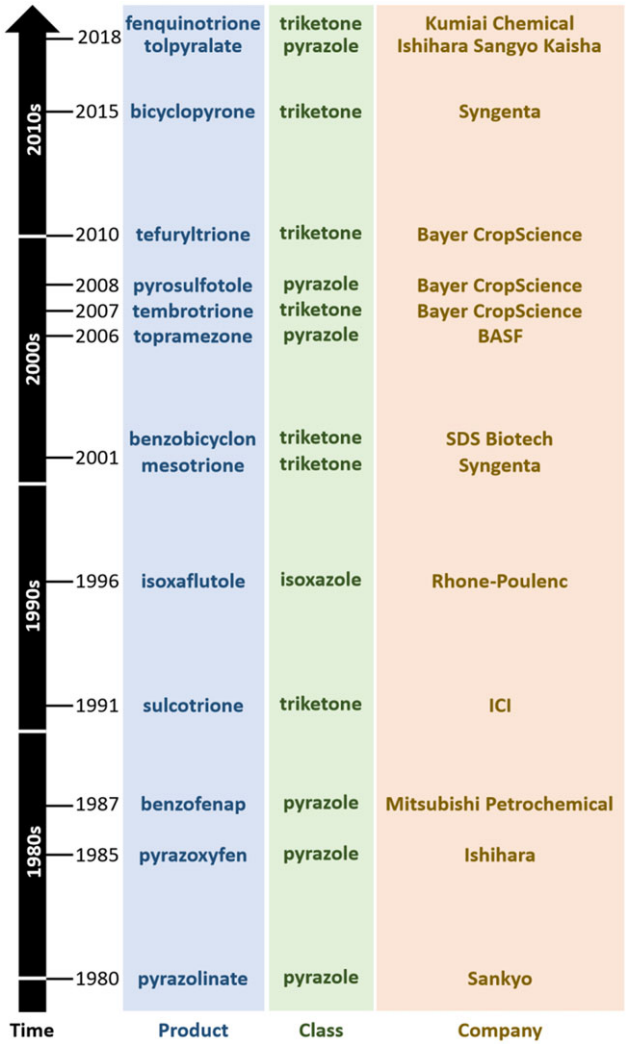

Figure 3. Timeline of commercialization of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD), their respective chemical classes, and manufacturer.

isoxazole heterocyclic proherbicide that is bio-activated to a diketonitrile by soil and plant enzymes (Pallett et al. 2001; Figure 4). The bleaching caused by the HPPD inhibitor is similar to that observed with an inhibitor of phytoene desaturase (PDS), but the mechanism by which this bleaching occurred eluded researchers. The link between triketone molecules and their inhibition of HPPD was first elucidated using mammalian systems related to tyrosine metabolism. Subsequent investigations in plant systems established that HPPD catalyzes a key step in plastoquinone and tocopherol synthesis (Schultz et al. 1985), and further studies demonstrated that plastoquinone was an essential co-factor for phytoene desaturase (Norris et al. 1995). This established the link between inhibition of HPPD and the bleaching symptoms that can be observed in the foliage of treated plants. In brief, plants treated with an HPPD inhibitor accumulate tyrosine and are depleted in plastoquinone. Without plastoquinone, PDS cannot function, which halts carotenoid biosynthesis, resulting in bleaching of the new growth, which is known as the "triketone effect" (Lee et al. 1997).

Use of HPPD Inhibitor in the United States

In a survey conducted by the United States Department of Agriculture–National Agricultural Statistics Service (USDA-NASS) in 2018, the use of HPPD-inhibiting herbicides, including isoxaflutole, tembotrione, mesotrione, bicyclopyrone, and topramezone, was estimated at about 193,000, 214,000, 1,898,000, 102,000, and 41,000 kg, respectively (Figure 5).

Mesotrione. Mesotrione belongs to the triketone family of HPPD-inhibitor herbicides and represents one of the most used active ingredients in corn (applied to about 42% of planted corn in 2018) with an average of one application (75 to 150 g ha^{-1}) per year (Figure 6; USDA-NASS 2018). The Midwestern states, including Iowa, Illinois, Kansas, Minnesota, and Nebraska, led the use of mesotrione with an average annual use of >10,000 kg in 2018 at the rate of >1.27 kg mesotrione per square mile in each state (Figure 6). Increased use of mesotrione in recent years is primarily attributed to increasing demand for controlling glyphosate-resistant weeds (Chahal and Jhala 2018b; Ganie et al. 2015; Ganie and Jhala 2017). Mesotrione is a systemic herbicide applied alone or in mixture for selective PRE and POST control of grass and broadleaf weeds in field corn, seed corn, yellow popcorn, sweet corn, and grain sorghum (Abit et al. 2010; Armel et al. 2003; Currie and Geier 2018; Janak and Grichar 2016; Stephenson et al. 2004; Williams et al. 2005).

Mesotrione in a pre-mixture or tank-mixture with other herbicides can provide effective control of ALS-, PS II-, and glyphosate-resistant weeds (Chahal and Jhala 2018a; Ganie et al. 2015). In addition to corn and grain sorghum, the use of mesotrione applied PRE in spring cereals, including barley (*Hordeum vulgare* L.), durum wheat, oats (*Avena sativa* L.), and spring wheat, has been found to be safe and provides adequate selective control of broadleaf weeds, including common lambsquarters (*Chenopodium album* L.), common ragweed (*Ambrosia artemisiifolia* L.), and wild buckwheat (*Polygonum convolvulus* L.) in a study conducted in Ontario, Canada (Soltani et al. 2011, 2014); however, mesotrione use in those crops is limited (Walsh et al. 2021).

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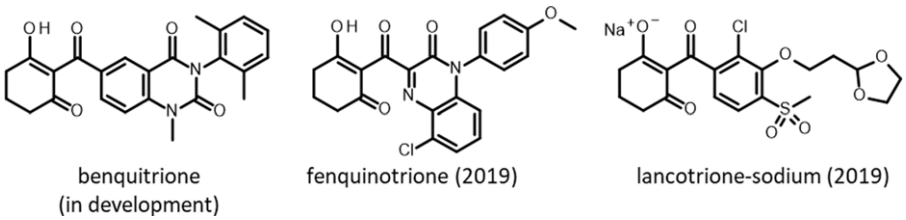

Figure 4. Chemical structures of triketone herbicides, a chemical family of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD).

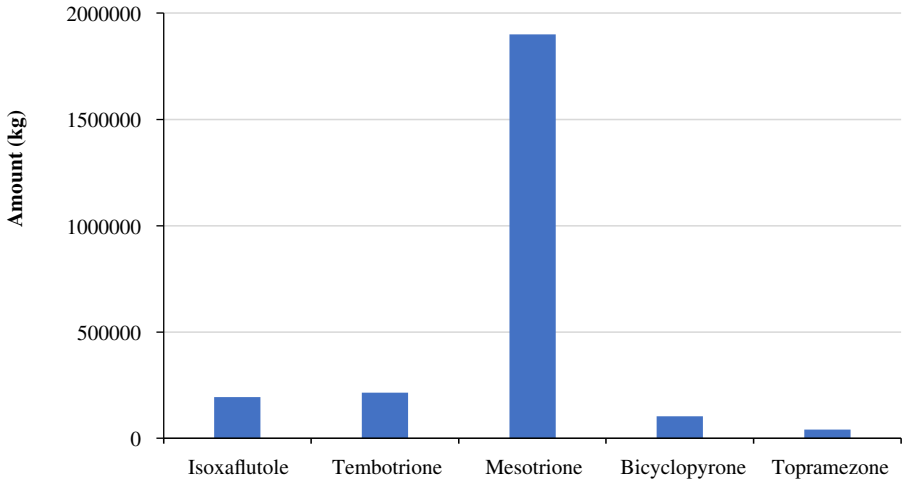

Figure 5. Annual use of major herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD) in corn production in the United States in 2018 (Source: USDA-NASS 2018).

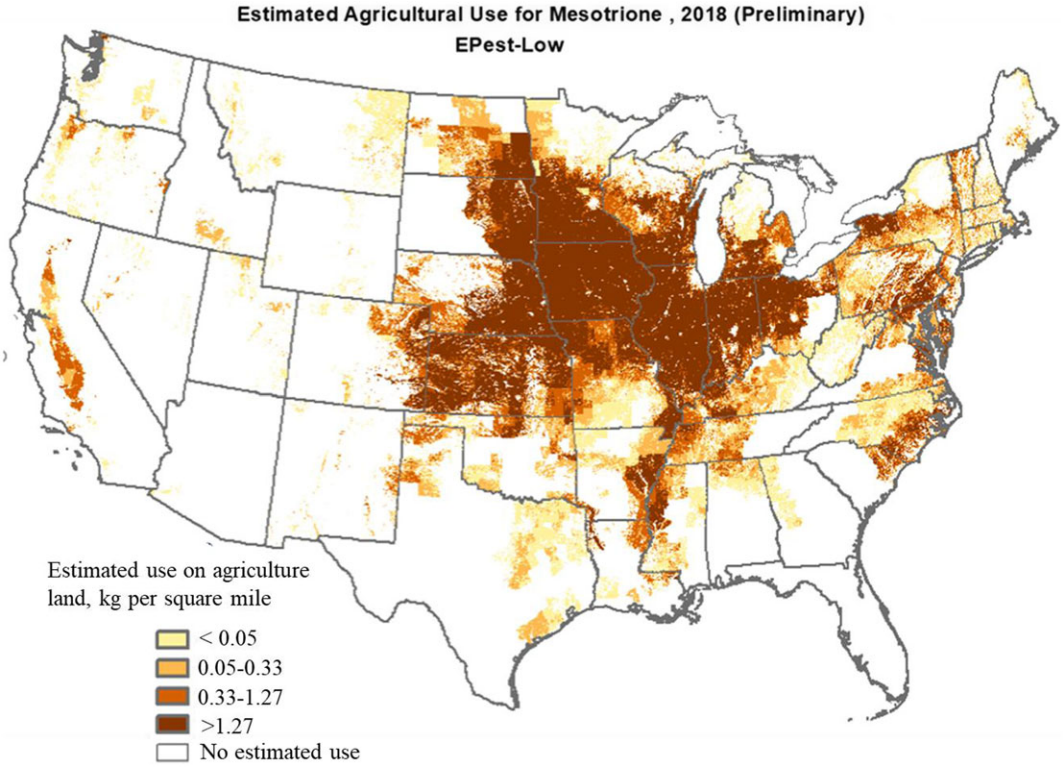

Figure 6. Mesotrione use in agricultural land across the United States in 2018 (adapted from the U.S. Geological Survey by the U.S. Department of the Interior).

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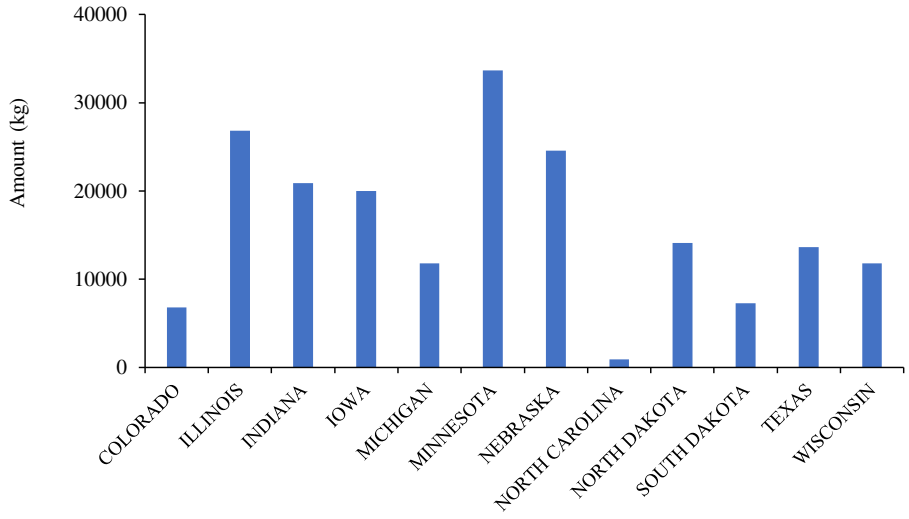

Figure 7. Tembotrione use in various corn-producing states in the United States (Source: USDA-NASS 2018).

Tembotrione

Tembotrione is a member of the triketone family of HPPD inhibitors that is used for selective POST control of grass and broadleaf weeds in corn (Stephenson et al. 2015). Tembotrione is the second-highest used HPPD inhibitor in the United States, with an annual use rate of >200,000 kg (Figure 7; USDA-NASS 2018). Minnesota, Illinois, Nebraska, Indiana, and Iowa were leading states for annual use (>20,000 kg) of tembotrione in corn production in 2018 (Figure 7). Tembotrione (Laudis; Bayer Crop Science, St Louis, MO) is applied alone or in a mixture from field corn emergence to the V8 growth stage or V7 (sweet corn). More recently, metabolic-based resistance (CYP-mediated metabolism) to tembotrione has been identified in several grain sorghum lines (Pandian et al. 2020), indicating a future increase in tembotrione use in other crops.

Isoxaflutole

Isoxaflutole was the first member of the isoxazole class of HPPD inhibitor. Common brand names include Balance Flexx™ and Corvus™, and were the first HPPD-inhibiting herbicides introduced in North America in 1996 (Figure 1; Pallett et al. 1998). It is a selective herbicide primarily used for PRE control of grass and broadleaf weeds in corn, and recently in isoxaflutole-resistant soybean (Mausbach et al. 2021). Isoxaflutole is commonly mixed with PS II-inhibiting herbicides (e.g., atrazine) to improve weed control efficacy and spectrum (Benoit et al. 2019; Chahal and Jhala 2018a; Fluttert et al. 2022). According to the survey conducted by the USDA-NASS (2018), isoxaflutole was the third-most used HPPD inhibitor in corn (used in about 8% of planted corn) with an average of one application (72 g ha^{-1}) per year (Figure 8). Iowa, Illinois, and Nebraska were the leading states for isoxaflutole use among various corn-producing states in 2018 (Figure 8). Isoxaflutole has been widely used as a part of herbicide-resistant weed management strategies (including ALS-, PS II-, and glyphosate-resistant) in corn (Benoit et al. 2019; Chahal et al. 2015; Stephenson and Bond 2012).

Isoxaflutole can also be used for weed control in fallow fields depending on the subsequent rotational crop (Currie and Geier 2016; Kumar and Jha 2015). In this context, isoxaflutole-resistant soybean has recently been developed in which isoxaflutole can be used as a part of an herbicide strategy to control ALS- and glyphosate-resistant weeds, including Palmer amaranth, waterhemp, and Canada fleabane (*Erigeron canadensis* L.; Ditschun et al. 2016; Mausbach et al. 2021; Smith et al. 2019a).

Bicyclopyrone and Topramezone

Bicyclopyrone and topramezone are two other HPPD-inhibitor herbicides (via an active ingredient of an individual product or various premixtures) that are commonly used for grass and broadleaf weed control in field corn, seed corn, silage corn, yellow popcorn, sweet popcorn, and sugarcane (Sarangi and Jhala 2018). Topramezone belongs to the pyrazolone family with an annual use of >41,000 kg, whereas bicyclopyrone belongs to the triketone family with an annual use of >100,000 kg in corn production (Figure 9).

According to the USDA-NASS (2018) survey, Illinois, Iowa, Kansas, Missouri, Nebraska, and Wisconsin were the leading states for annual use of bicyclopyrone with an estimate of >5,000 kg in corn crops, whereas Illinois and Iowa were the top states in annual use of topramezone (>5,000 kg) for weed control in corn (Figure 9). In addition to corn, topramezone and bicyclopyrone are known to provide effective weed control in other crops, including turf, sweet potato [*Ipomoea batatas* (L.) Lam.], wheat, chickpea (*Cicer arietinum* L.), and rice (Brosnan and Breeden 2013; Lindley et al. 2020; Moore 2019).

Pyrasulfotole and Tolpyralate

Pyrasulfotole is a member of the pyrazolone family of HPPD inhibitors and is registered for use on cereal grains, including wheat, barley, rye, triticale, and grain sorghum (Kumar et al. 2014; Reddy et al. 2013; Torbiak et al. 2021). Pyrasulfotole is an active ingredient of Huskie™ (a premixture of pyrasulfotole and bromoxynil; Bayer Crop Science, Saint Louis, MO) that is used for broadleaf weed control in sorghum. In contrast, tolpyralate is a new HPPD inhibitor that came to the market in 2020 and controls several annual grass and broadleaf weed species with a low use rate (30 to 50 g ha^{-1}) in corn (Tsukamoto et al. 2021; Willemse et al. 2021c).

Benzobicyclon

Benzobicyclon, a pro-herbicide, is a member of the triketone family of HPPD inhibitors. It was first registered for use in rice crops in 2021 under the tradename Rogue® (Gowan Company, Yuma, AZ),

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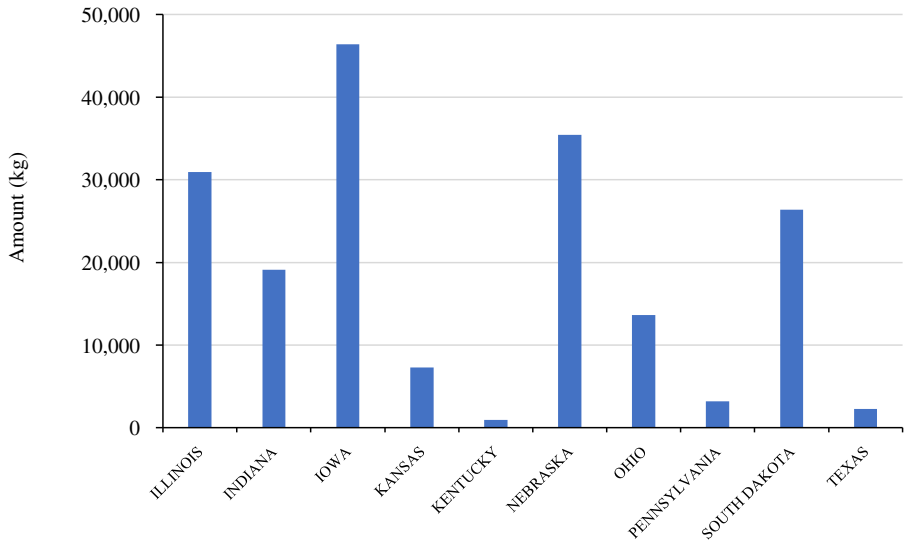

Figure 8. Isoxaflutole use in major corn-producing states in the United States (Source: USDA-NASS 2018).

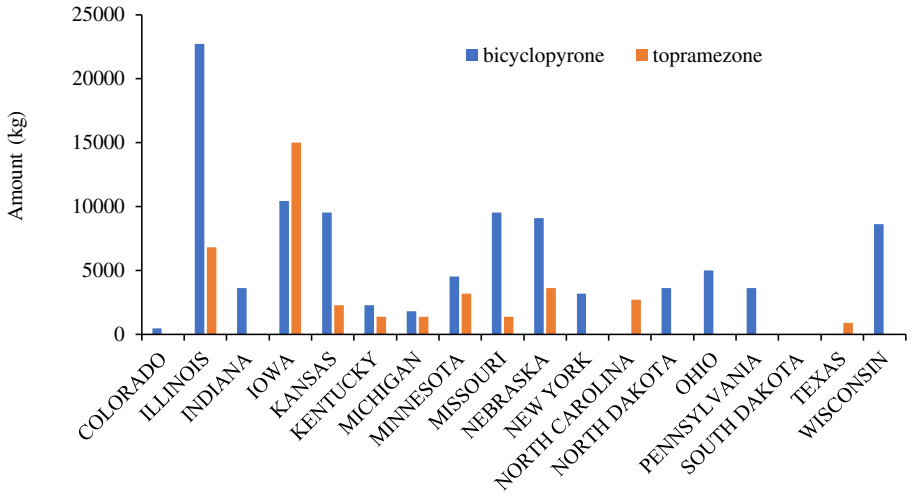

Figure 9. Bicyclopyrone and topramezone use in various corn-producing states in the United States (Source: USDA-NASS 2018).

mainly for control of aquatic weeds, sprangletop species (*Leptochloa* spp.), and suppression of weedy rice biotypes when applied post-flood. This is the only HPPD-inhibiting herbicide available for use rice production in the United States.

HPPD-Inhibitor-Resistant Weeds and Their Mechanisms of Resistance

Although HPPD-inhibitor herbicides have been in use for more than two decades, the evolution of HPPD-inhibitor-resistant weeds is relatively less widespread and slower than some other herbicide sites of action (Jhala et al. 2014b; Kaundun 2021). As of 2022, three broadleaf weeds (Palmer amaranth, waterhemp, and wild radish) have evolved resistance to HPPD-inhibitor herbicides across the globe (Heap 2022). Several populations of HPPD-inhibitor-resistant Palmer amaranth and waterhemp have evolved across the Midwestern United States (Jhala et al. 2014b; Hausman et al. 2011), while HPPD-inhibitor-resistant wild radish has been documented in Western Australia. The first case of resistance to these herbicides was reported in a population of waterhemp from a corn field in Illinois that had a history of repeated HPPD-inhibitor use (Hausman et al. 2011). The resistance in Palmer amaranth (Thompson et al. 2012) and wild radish (Lu et al. 2020) were not selected with HPPD-inhibitor herbicides; rather, these populations exhibited cross-resistance with the mechanisms that bestow resistance to different herbicide sites of action (Lu et al. 2020; Nakka et al. 2017).

Mechanisms of Resistance to HPPD Inhibitors

Palmer Amaranth

The first case of Palmer amaranth resistance to the HPPD inhibitor (also found to be resistant to PS II- and ALS-inhibitor formulas) was confirmed in a field in central Kansas where there was no history of HPPD inhibitor use, though there was a long history of use of herbicides that PS II and ALS (Jhala et al. 2014b; Thompson et al. 2012). This population was originally found to be resistant to Huskie®, a premix of pyrasulfotole (an HPPD inhibitor) and bromoxynil (a PS II inhibitor). Furthermore, this Palmer amaranth biotype was resistant to several HPPD inhibitor herbicides,

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including mesotrione, tembotrione, and topramezone (Thompson et al. 2012). Later, a Palmer amaranth population from a corn field in Nebraska that had a history of HPPD inhibitor use was found to be resistant to these herbicides (Jhala et al. 2014b). Populations of Palmer amaranth in Kansas and Nebraska exhibited up to 18-fold resistance to mesotrione, tembotrione, or topramezone (Jhala et al. 2014b; Nakka et al. 2017; Thompson et al. 2012). In both populations, the mechanism of resistance to the HPPD inhibitor was due to neither differential herbicide uptake/translocation nor mutations or amplification of the *HPPD* gene (Küpper et al. 2018; Nakka et al. 2017). The Kansas Palmer amaranth biotype metabolized more than 90% of mesotrione at 24 h after treatment compared with sensitive plants (Nakka et al. 2017). Additionally, a 4-fold to 14-fold higher *HPPD* gene expression was found in this population (Nakka et al. 2017). Similarly, the rapid metabolism of tembotrione was attributed to the resistance in Palmer amaranth population from Nebraska (Küpper et al. 2018). Although 4-hydroxylation of tembotrione followed by glycosylation was identified in both resistant and sensitive plants, the time taken to form metabolites was shorter in resistant plants compared with sensitive plants (Küpper et al. 2018). More recently, a population of Palmer amaranth from Kansas (Riley County) was resistant to mesotrione and tembotrione (Shyam et al. 2021). The mechanism of resistance in this population is being investigated.

Waterhemp

Resistance to HPPD inhibitor herbicides has been documented in several populations of waterhemp across the Midwestern United States, including Illinois, Iowa, and Nebraska (Heap 2022). A biotype of waterhemp known as MCR (for McLean County resistant) from Illinois was the first reported case of resistance to an HPPD inhibitor (Hausman et al. 2011). This biotype was previously confirmed to be resistant to atrazine and ALS-inhibiting herbicides. MCR waterhemp had 10-fold and 35-fold resistance to mesotrione compared with two susceptible populations from Illinois (Hausman et al. 2011). The mechanism of mesotrione resistance in MCR waterhemp was not due to reduced herbicide absorption/translocation nor because of alterations in the *HPPD* gene sequence or expression. However, compared with sensitive plants, MCR waterhemp rapidly metabolized mesotrione via hydroxylation of the cyclohexanedione ring of mesotrione (Ma et al. 2013). Importantly, the time required to metabolize 50% of the absorbed mesotrione was ~11.7 h in MCR compared with 25.4 to 27.8 h in the susceptible plants. Application of the cytochrome P450 inhibitor (malathion) increased the susceptibility of MCR plants to mesotrione, suggesting that the metabolism of mesotrione was mediated via P450 activity in this population (Ma et al. 2013).

The HPPD-inhibitor-resistant waterhemp from Nebraska known as NEB showed a 2.4-fold and 45-fold level of resistance to mesotrione applied PRE and POST, respectively, compared with a known susceptible population (Kaundun et al. 2017). Similar to MCR waterhemp, mesotrione resistance in the Nebraska population was primarily due to higher levels of mesotrione metabolism via 4-hydroxylation (Kaundan et al., 2017). Furthermore, the metabolites of mesotrione were identified as 4-hydroxymesotrione and AMBA [2-amino-4-(methylsulfonyl) benzoic acid; (Kaundan et al. 2017)]. No duplication, alteration, or over-expression of the *HPPD* gene that can confer resistance was found in this population (Kaundan et al. 2017). Moreover, mesotrione-resistant waterhemp population from Illinois and Nebraska were also resistant to topramezone, which belongs to the pyrazolone subfamily of HPPD inhibitors. Both populations rapidly metabolized topramezone, and the metabolic profiles indicated two different putative hydroxylated forms of topramezone (hydroxytopramezone-1 and hydroxytopramezone-2), although hydroxytopramezone-1 was more abundant in the Illinois waterhemp population (Lygin et al. 2018). When metabolic profiles at 48 h after treatment were compared with naturally tolerant corn, the waterhemp population from Illinois had more hydroxylated metabolites, whereas corn plants produced desmethyl and benzoic acid metabolites of topramezone, suggesting that waterhemp initially metabolizes topramezone differently than corn (Lygin et al. 2018).

More recently, the mechanism of resistance to syncarpic acid-3, a nonselective, noncommercial HPPD inhibitor, was investigated in an Illinois population of waterhemp (Concepcion et al. 2021). Although the Phase I metabolite, likely produced due to P450-mediated hydroxylation was detected in this population, this metabolite was not found to be responsible for resistance; rather, the glutathione-syncarpic acid conjugate that formed as a result of Phase II metabolism was associated with resistance to syncarpic acid in the waterhemp population (Concepcion et al. 2021).

Wild Radish. A population of wild radish from a Western Australian grain field with no prior history of HPPD inhibitor use is resistant to these herbicides (Lu et al. 2020). This population is also resistant to other herbicides such as PS II inhibitor, ALS inhibitor, and synthetic auxin (Lu et al. 2020). This wild radish population exhibited 4-fold to 6.5-fold resistance to mesotrione, tembotrione, and isoxaflutole (Lu et al. 2020). The resistant plants were able to metabolize mesotrione approximately 8-fold faster than the sensitive plants (Lu et al. 2020). It was also confirmed that the resistance was not due to reduced uptake/translocation of mesotrione, and no target site alterations were detected (Lu et al. 2020).

Although resistance to HPPD inhibitor herbicides has currently been reported in three weed species across the globe, if selection pressure continues, new cases of resistance evolution to HPPD inhibitor will increase. More importantly, the predominance of metabolic resistance to HPPD inhibitor herbicides, was found in all three weed species (Jugulam and Shyam 2019; Yu and Powles 2014). Therefore, prudent strategies, including integration of nonchemical methods, need to be designed for sustainable weed management.

Management of HPPD-Inhibitor-Resistant Weeds

As of 2022, Palmer amaranth and waterhemp are the only two weed species in the United States that have evolved resistance to HPPD-inhibitor herbicides (Heap 2022; Jhala et al. 2014b). Therefore, strategies described here focus on the management of HPPD-inhibitor-resistant Palmer amaranth and waterhemp primarily in corn and soybean production systems. Although the evolution of herbicide resistance in weed species cannot be completely averted, it can possibly be delayed by implementing diversified weed management practices (Norsworthy et al. 2012). Mixing herbicides that have different sites of action is often recommended to delay the evolution of herbicide-resistant weeds (Diggle et al. 2003; Evans et al. 2016). In corn, HPPD-inhibiting herbicides are mixed with PS II-inhibiting herbicides due to their synergistic activity for controlling triazine-resistant weeds (Chahal et al. 2019; Hugie et al. 2008; Woodyard et al. 2009c). However, continued use of this mixture to control atrazine-resistant weeds in corn has resulted in the evolution and widespread occurrence of Palmer amaranth and waterhemp populations resistant to PS II and HPPD inhibitors (Jhala et al. 2014b).

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Herbicide options to control Palmer amaranth and waterhemp in corn and soybean crops include inhibitors of ALS, PS II, HPPD, protoporphyrinogen oxidase (PPO), very long chain fatty acid (VLCFA), glyphosate, glufosinate, and synthetic auxins. However, Palmer amaranth and waterhemp populations with multiple resistance to ALS, PS II, HPPD, and PPO inhibitors, and glyphosate are increasingly common in the Midwestern United States (Heap 2022; Jhala et al. 2014b; Schultz et al. 2015; Shyam et al. 2021; Varanasi et al. 2018). This has reduced herbicide options to control weeds in corn and soybean production systems (Sarangi et al. 2019). Therefore, herbicide programs containing diverse herbicide sites of action and detoxification pathways are required to manage HPPD-inhibitor-resistant Palmer amaranth and waterhemp.

Fortunately, waterhemp biotypes with metabolic resistance to atrazine, a resistance mechanism present in a majority of populations in the Midwest (Tranel 2021), are sensitive to other PS II-inhibitor herbicides such as metribuzin (Jacobs et al. 2020). Therefore, metribuzin mixed with an HPPD-inhibitor can control populations that are resistant to an HPPD inhibitor and atrazine. For example, atrazine at 4.48 kg ha^{-1} applied PRE provided 26% control of PS II-inhibitor-resistant and HPPD-inhibitor-resistant waterhemp at 4 wk after treatment (WAT), whereas metribuzin 560 g ha^{-1} provided 95% control of the same population (Evans et al. 2019). Similarly, in a greenhouse study, waterhemp that was resistant to PS II and HPPD inhibitors exhibited a synergistic response to metribuzin at 191 g ha^{-1} + mesotrione at 53 g ha^{-1} applied POST, indicating that this may be a viable option for controlling atrazine- and HPPD-inhibitor-resistant waterhemp in corn (O'Brien et al. 2018).

PRE herbicides serve as a foundation for herbicide-resistant weed management; however, using a PRE and a POST herbicide from the same site of action is not a recommended strategy because it can potentially lead to an increase in the frequency of resistance over time (Hausman et al. 2013; Wuerffel et al. 2015). Therefore, herbicides from alternative sites of action should be included in herbicide programs when HPPD-inhibitor-resistant weeds are present in the field (Chahal and Jhala 2018b). For example, a PRE application of isoxaflutole at 105 g ha^{-1} plus mesotrione 210 g ha^{-1} provided <65% control of HPPD-inhibitor-resistant waterhemp at 4 WAT compared with >85% control by using acetochlor 1,680 g ha^{-1} applied PRE in corn (Hausman et al. 2013). In a similar study conducted in soybean, flumioxazin at 70 g ha^{-1}, sulfentrazone 280 g ha^{-1}, metribuzin 420 g ha^{-1}, or pyroxasulfone 210 g ha^{-1} applied PRE provided >85% control of HPPD-inhibitor-resistant waterhemp (Hausman et al. 2013). This strategy would potentially reduce the number of survivors, thereby delaying the selection of resistance alleles in the population (Wuerffel et al. 2015).

Relatively fewer POST herbicide options are available to control HPPD-inhibitor-resistant Palmer amaranth and waterhemp in corn and soybean crops (Jhala et al. 2014a). Glufosinate, 2,4-D, or dicamba are among the few POST herbicides that provide more than 80% control; for example, Jhala et al. (2014b) reported that glufosinate (450 g ha^{-1}), 2,4-D ester (560 g ha^{-1}), or dicamba (560 g ha^{-1}) provided >80% control of HPPD-inhibitor-resistant Palmer amaranth 3 WAT. Similarly, 740 g ha^{-1} of glufosinate or 280 g ha^{-1} of dicamba provided >90% control of HPPD inhibitor-resistant waterhemp at 3 WAT (Sarangi et al. 2019). Glufosinate used at 595 g ha^{-1} applied alone or mixed with dicamba at 280 g ha^{-1} provided ≥79% control of HPPD-inhibitor-resistant Palmer amaranth 4 WAT in corn (Chahal and Jhala 2018a). Additionally, Oliveira et al. (2017) reported that mixing metribuzin (210 g ha^{-1}) to a premix of mesotrione + atrazine (650 g ha^{-1}) applied POST in corn, controlled HPPD-inhibitor-resistant waterhemp by >90% at 3 WAT.

Although herbicides such as metribuzin, pyroxasulfone, glufosinate, or dicamba applied alone can control early- to mid-season cohorts of Palmer amaranth and waterhemp, a season-long control of these weed species is rarely achieved due to their extended period of emergence (Hager et al. 1997; Keeley et al. 1987). Therefore, multiple herbicide applications (PRE followed by POST), specifically overlapping residual herbicides, are recommended to achieve a season-long control of HPPD-inhibitor-resistant weeds. For example, a premix of acetochlor + clopyralid + flumetsulam (1,190 g ha^{-1}), or saflufenacil + dimethenamid-*P* (780 g ha^{-1}) applied PRE provided >90% control of HPPD-inhibitor-resistant Palmer amaranth for 3 wk; however, control was reduced to <70% later in the season (Chahal and Jhala 2018b). In the same study, glyphosate (870 g ha^{-1}) + dicamba (280 g ha^{-1}) was needed to obtain >96% control. Similarly, overlapping residual herbicide programs, including pyroxasulfone (110 g ha^{-1}) + saflufenacil (75 g ha^{-1}), or saflufenacil + dimethenamid-*P* (586 g ha^{-1}) applied PRE followed by glyphosate (870 g ha^{-1}) + diflufenzopyr + dicamba (157 g ha^{-1}) + pyroxasulfone (91 g ha^{-1}), or glyphosate + dicamba + diflufenzopyr (157 g ha^{-1}) + pendimethalin (1,060 g ha^{-1}) applied POST controlled HPPD-inhibitor-resistant Palmer amaranth >95% at corn harvest (Chahal et al. 2018a). In a study conducted in a conventional corn crop, herbicide programs including acetochlor (2,130 g ha^{-1}), or mesotrione + *S*-metolachlor + atrazine (2,780 g ha^{-1}) applied PRE, followed by dicamba + diflufenzopyr (196 g ha^{-1}) applied POST, controlled HPPD-inhibitor-resistant Palmer amaranth >95% (Chahal et al. 2018b). Similarly, dicamba + thiencarbazone-methyl + atrazine or dicamba + ABMS (acetochlor + bicyclopyrone + mesotrione + *S*-metolachlor) applied PRE followed by ABMS alone or in a mixture with atrazine, *S*-metolachlor, or mesotrione applied early POST provided 85% to 6% control of glyphosate and mesotrione-resistant Palmer amaranth at 2 wk after early POST and 2 and 7 wk after late POST in glyphosate/glufosinate-resistant corn in central Kansas (Liu et al. 2021).

While sequential applications of PRE followed by POST herbicides with multiple sites of action can control HPPD-inhibitor-resistant Palmer amaranth and waterhemp, relying on a single control tactic would potentially enhance selection pressure for the evolution of multiple-herbicide-resistant weeds. Therefore, diversified weed management strategies, including cultural, biological, mechanical, and chemical weed management (with multiple sites of action), are needed to manage herbicide-resistant weed seed banks. More specifically, multi-tactic strategies that target multiple life stages of the weed, including understanding reproductive biology and potential for pollen-mediated gene flow, are required (Jhala et al. 2021a, 2021b). This can be accomplished by using an effective multiple-sites-of-action herbicide program, using cover crops, planting corn or soybean in narrow rows, using a harvest weed seed control method, and adopting diversified crop rotations (Mohler et al. 2021; Striegel and Jhala 2022). The increasing use of HPPD-inhibitor herbicides in agronomic crops requires research on herbicide interactions and alternative herbicides or methods for controlling multiple herbicide-resistant weeds.

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Interactions of HPPD-Inhibitor Herbicides with Other Herbicides

The HPPD-inhibiting herbicides are commonly mixed with other herbicides, particularly PS II-inhibiting herbicides, to increase weed control and spectrum. The assumption of an herbicide combination is that each herbicide acts independently when applied together (i.e., additive); however, that is not always the case. Weed control from a mixture of two herbicides may be greater (synergistic) or less than (antagonistic) the combined effect of the herbicides applied alone (Colby 1967; Hatzios and Penner 1985).

Efficacy

The HPPD-inhibiting herbicides applied PRE with a PS II-inhibitor herbicide can have both additive and synergistic effects. In greenhouse studies, atrazine + mesotrione applied PRE were additive for control of velvetleaf (*Abutilon theophrasti* Medik.) and ivyleaf morningglory (*Ipomoea hederacea* Jacq.); however, several rate combinations indicated synergistic control (Bollman et al. 2006). In field experiments, isoxaflutole + metribuzin applied PRE exhibited additive or synergistic control of Canada fleabane, common lambsquarters, *Amaranthus* spp., common ragweed, velvetleaf, *Setaria* spp., barnyardgrass [*Echinochloa crus-galli* (L.) Beauv.], and fall panicum (*Panicum dichotomiflorum* Michx.; Ditschun et al. 2016; Smith et al. 2019b). In contrast, control of a population of HPPD-inhibitor-resistant and PS II-inhibitor-resistant Palmer amaranth with mesotrione or topramezone applied PRE with atrazine was additive (Chahal and Jhala 2018a).

The literature is replete with observations of additive or synergistic weed control when HPPD-inhibiting herbicides are applied POST with a PS II inhibitor. Mesotrione + atrazine (Abendroth et al. 2006; Armel et al. 2005; Creech et al. 2004), mesotrione + bromoxynil or metribuzin (Abendroth et al. 2006) were consistent for controlling several annual weeds as well as Canada thistle [*Cirsium arvense* (L.) Scop.] compared to mesotrione applied alone. Mixing atrazine with tolpyralate improved control (Metzger et al. 2018) or reduced the biologically effective dose of tolpyralate for control of weeds commonly found in corn production fields in Nebraska (Osipitan et al. 2018). In research plots throughout North America, mixing atrazine with tembotrione reduced variability in weed control and sweet corn yield variation (Williams et al. 2011a, 2011b). Similar findings were observed with atrazine + isoxaflutole, mesotrione, topramezone, tembotrione, or tolpyralate for waterhemp control in field corn (Willemse et al. 2021a). Furthermore, atrazine improved the efficacy of pyrasulfotole + bromoxynil for weed control in grain sorghum (Reddy et al. 2013).

Synergism between an HPPD inhibitor and a PS II inhibitor applied POST can be observed in herbicide-resistant weed populations. Synergistic control with mesotrione + atrazine has been observed in PS II-inhibitor-resistant redroot pigweed (*Amaranthus retroflexus* L.) (Hugie et al. 2008; Sutton et al. 2002) and PS II-inhibitor-resistant wild radish (Walsh et al. 2012), including temporally separated herbicide applications (e.g., atrazine PRE followed by mesotrione POST; Woodyard et al. 2009a). Palmer amaranth, including a PS II-inhibitor-resistant population, exhibited synergistic control with atrazine + mesotrione or tembotrione, but not atrazine with tolpyralate or topramezone (Kohrt and Sprague 2017). Synergistic control of multiple-herbicide-resistant waterhemp was observed with mesotrione + bromoxynil or bentazon; and tolpyralate + bromoxynil (Willemse et al. 2021b). In contrast, activity of isoxaflutole or mesotrione applied POST with metribuzin on waterhemp populations varying in herbicide resistance traits was mostly additive (O'Brien et al. 2018).

Mixing an HPPD inhibitor with a PS II inhibitor does not always result in synergistic weed control. Volunteer potato (*Solanum tuberosum* L.) control with mesotrione, tembotrione, or topramezone applied POST was not improved when mixed with atrazine, bentazon, or bromoxynil (Koepke-Hill et al. 2010). Advances have been made in understanding the mechanisms that account for synergistic weed control from mixing HPPD and PS II inhibitors. Armel et al. (2005) reported that uptake, translocation, and metabolism of mesotrione did not account for improved control of Canada thistle with mesotrione + atrazine. Mesotrione absorption in Palmer amaranth increased when it was mixed with atrazine, partially accounting for observed synergism (Chahal et al. 2019). PS II inhibitors compete with plastoquinones for the D1 protein binding site, disrupting electron transfer in PS II. The inability to transfer electrons creates triplet chlorophyll and singlet oxygen that destroy plant membranes (Hess 2000). Armel et al. (2007) showed that carotenoid biosynthesis inhibitor increased the binding efficiency and efficacy of PS II inhibitor by reducing the reformation of the D1 protein following initiation of photo inhibition.

Several factors influence the synergism of an HPPD inhibitor applied in a mixture with a PS II inhibitor. For both PRE and POST applications, the herbicide rate influences the extent of synergistic weed control (Bollman et al. 2006; Hugie et al. 2008). In addition to the application rate of the HPPD inhibitor, synergistic weed control was observed more frequently with triketone herbicides (mesotrione and tembotrione) compared to pyrazolone herbicides (topramezone and tolpyralate; Kohrt and Sprague 2017). Adverse environmental conditions (e.g., inadequate rainfall) influence plant response to a mixture of HPPD and PS II inhibitors applied PRE (Smith et al. 2019b) and POST (Woodyard et al. 2009b). Moreover, the time of POST herbicide application can influence the plant response to HPPD and PS II inhibitors (O'Brien et al. 2018).

HPPD-inhibitor herbicides can interact with herbicides other than PS II inhibitors. The synthetic auxin triclopyr improved foliar uptake of mesotrione and control of smooth crabgrass (Yu and McCullough 2016). Conversely, a mixture of an HPPD inhibitor and an ALS inhibitor can be antagonistic. For example, reduced efficacy of sulfonylurea herbicides applied with mesotrione + atrazine for control of *Setaria* spp. (Schuster et al. 2008) was due to decreased absorption, and in some cases reduced translocation of nicosulfuron (Schuster et al. 2007). Not only can an HPPD inhibitor antagonize an ALS inhibitor for annual grass control, but an ALS inhibitor can also antagonize the HPPD inhibitor (Kaastra et al. 2008).

Crop Tolerance

Field corn production systems rely extensively on a mixture of HPPD and PS II inhibitors. Considerable field research demonstrates excellent crop tolerance with their mixtures (Johnson et al. 2002; Osipitan et al. 2018; Stephenson et al. 2004; Whaley et al. 2006; Willemse et al. 2021a). Additional research shows that the synergistic effect of HPPD and PS II inhibitors for weed control was not observed on sweet corn response (Choe et al. 2014). Sweet corn injury from tembotrione was influenced by the safener isoxadifen and the genotypic class at a P450 locus (*Nsf1*; Williams and

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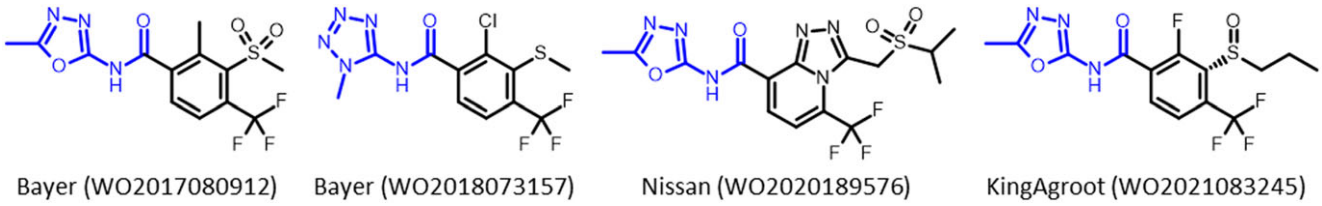

Figure 10. Examples of recently submitted patents for herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD) from Bayer Crop Science, Nissan, and KingAgroot.

Pataky 2010). The extent to which crops other than corn respond to a mixture of HPPD inhibitor and other herbicides has been studied. In an herbicide carryover study, a mixture of atrazine and mesotrione accentuated crop injury and yield losses in broccoli (*Brassica oleracea* var. *italica*), carrot (*Daucus carota* L.), cucumber (*Cucumis sativus* L.), and onion (*Alium cepa* L.; Robinson 2008). Grain sorghum was not injured by pyrasulfotole + bromoxynil applied alone or with synthetic auxin; however, the mixing of carfentrazone, a PPO inhibitor, increased phytotoxicity (Besançon et al. 2016). Isoxaflutole + metribuzin applied PRE on isoxaflutole-resistant soybean injured the crop in environments with the most rainfall, and injury was often synergistic (Smith et al. 2019b). Sugarcane displayed transient injury symptoms when topramezone was mixed with ametryn or metribuzin compared with topramezone applied alone (Negrisoli et al. 2020).

Future of HPPD-Inhibiting Herbicides

HPPD-inhibitor herbicides continue to be researched, patented, and commercialized by agrochemical companies. Benquitrione is currently in development for use in sorghum. A new class of HPPD inhibitor, azole carboxamides, were first disclosed by Bayer Crop Science in 2011 (Koehn et al. 2011). While no molecules have yet been commercialized, azole carboxamides have come to dominate the HPPD-inhibitor patent literature, with contributions from Syngenta, BASF, Nissan, KingAgroot, Nippon Soda, and SSARD, in addition to follow-up inventions from Bayer Crop Science. There have been more than 120 international patent applications for azole carboxamides, which represent applications of more than 50% of all HPPD-inhibiting herbicides since 2012. Herbicides from this class are in development that are expected to be available commercially around 2030. Azole carboxamides have different physical properties compared to the previously described classes with a different metabolism, which could potentially overcome non-target-site resistance (Jugulam and Shyam 2019). Patent applications that describe new herbicidal active ingredients will typically include thousands of compounds. However, companies will typically include a low number, often one, of these molecules in additional patent applications for use in mixtures with other active ingredients, for use in herbicide-resistant crops, or for inventions in the synthetic process. These additional patents hint to these specific molecules being of particular interest and likely candidates for further development (Figure 10).

Future of HPPD-Inhibitor-Resistant Crops

Research and development of HPPD-inhibitor-resistant crop traits began in the early 2000s. Traits were initially created that were useful in PRE weed control programs. Due to the commercial success of glyphosate-resistant crops, the impact of the early HPPD-inhibitor-resistant crop traits were not as large as anticipated. In the last decade, however, interest in developing HPPD-inhibitor-resistant crop traits has re-emerged and is being driven by the impact of wide-scale occurrence of glyphosate-resistant weeds. This has led to the need for alternatives, and new HPPD-inhibitor crop traits are actively being developed across the crop protection industry, primarily for use in soybean and cotton.

Certain grass crop species such as corn are resistant to most HPPD-inhibitor herbicides (Mitchell et al. 2001); therefore, HPPD inhibitors such as mesotrione can be applied PRE and POST in corn, POST in oats and sugarcane, but it is labeled only for PRE weed control in sorghum. Nonetheless, HPPD-inhibitor-resistant lines in dicot species [e.g., tobacco (*Nicotiana tabacum* L.) and soybean that would be otherwise highly sensitive to these herbicides] have been developed. Tobacco transformed with an *HPPD* gene from wheat showed resistance to mesotrione (Hawkes et al. 2001, 2019). Siehl et al. (2014) developed transgenic soybean that is resistant to isoxaflutole, mesotrione, and tembotrione with increased selectivity and a wide spectrum of weed control. In addition, isoxaflutole-resistant soybean has been developed and is available for commercial cultivation in the United States; however, its adoption is limited due to restriction in use of isoxaflutole (Alite 27) in certain counties in states such as Nebraska (Mausbach et al. 2021).

Bayer Crop Science has a long history of involvement in the development of HPPD-inhibitor-resistant crop traits, with efforts mainly focused on the expression of an herbicide-insensitive bacterial HPPD enzyme from *Pseudomonas fluorescens*. A mutated form of the gene that carries a mutation at amino acid position G336W had increased tolerance to isoxaflutole. This gene is used in the FG72 soybean in commercial use (Matringe et al. 2005). Work initiated by the former Monsanto business (now part of Bayer Crop Science) also focused on development of an HPPD trait and a planned launch of this trait (HT4) in soybean is expected in the late 2020s. Details of the trait gene used are unknown at the time of writing. This trait is expected to be stacked with 2,4-D, glyphosate, glufosinate, and dicamba. A further development known as HT5 is expected to launch later, adding resistance to PPO-inhibiting herbicides (Reither 2021).

BASF acquired much of Bayer Crop Science's HPPD-inhibitor-resistant crop technology during the crop protection industry consolidation period in the mid-2010s. As such, BASF is now bringing to market products containing the HPPD trait from FG72 soybean into other crops such as cotton (Steadman 2021). A further development is the HPPD trait known as pfHPPD-4, which is expressed in the GMB151 soybean line. This is a *Pseudomonas HPPD* gene that carries four mutations compared to a single mutation that occurs in the FG72 trait (Olson and Weeks 2020).

Syngenta's involvement with HPPD inhibitor-resistant crop traits dates to 2000, when several HPPD target genes, including the wild oat (*Avena sativa* L.) gene were characterized. The *Avena sativa HPPD* gene was later used to develop a soybean (SYT-0H2) that is resistant to mesotrione applied PRE (Hawkes et al. 2019). Syngenta has recently disclosed the invention of a

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series of further evolved *Avena* HPPD target site genes that have much enhanced resistance to a broad range of HPPD inhibitors including mesotrione and bicyclopyrone (Hawkes et al. 2019). These genes are capable of providing resistance to POST applications of these herbicides (Hawkes et al. 2019). Plant Arc Bio has applied for an exemption for an HPPD-inhibitor trait based on a fungal (*Trichoderma harzianum* spp.) *HPPD* gene. The target crops are soybean and cotton (PlantArcBio 2022; Shatlin 2021), although the spectrum of herbicide resistance of this trait is unknown as of 2022. An alternative technology has been described by the NARO Institute in Japan, which involves the metabolic degradation of certain HPPD-inhibitor formulas such as mesotrione. The *His-1* gene was discovered as a part of a project to study the differences in herbicide sensitivity among rice cultivars. The metabolic nature of the gene means that this trait is likely to be narrower in the resistance spectrum compared with target-site-based approaches (Maeda et al. 2019). Given the renewed investment in the development of HPPD-inhibitor-resistant crops, it is expected that HPPD-inhibiting herbicides will play an important role in weed control programs in soybean and cotton from the late 2020s onward. If such traits can be combined with the next generation of HPPD-inhibitors, their usefulness will likely be extended into the future. Management of multiple herbicide–resistant crop volunteers might be challenging, and future research should focus on this topic (Jhala et al. 2021c).

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References

Abendroth JA, Martin AR, Roeth FW (2006) Plant response to combinations of mesotrione and photosystem II inhibitors. Weed Technol 20:267–274

Abit MJ, Al-Khatib K, Currie RS, Stahlman PW, Geier PW, Gordon BW, Olson BL, Claassen MM, Regehr DL (2010) Effect of postemergence mesotrione application timing on grain sorghum. Weed Technol 24:85–90

Ahrens H, Lange G, Müller T, Rosinger C, Willms L, van Almsick A (2013) 4-Hydroxyphenylpyruvate dioxygenase inhibitors in combination with safeners: Solutions for modern and sustainable agriculture. Angew Chem Int Ed 52:9388–9398

Armel GR, Wilson HP, Richardson RJ, Hines TE (2003) Mesotrione combinations in no-till corn (*Zea mays*). Weed Technol 17:111–116

Armel GR, Hall GJ, Wilson HP, Cullen N (2005) Mesotrione plus atrazine mixtures for control of Canada thistle (*Cirsium arvense*). Weed Sci 53:202–211

Armel GR, Rardon PL, McComrick MC, Ferry NM (2007) Differential response of several carotenoid biosynthesis inhibitors in mixtures with atrazine. Weed Technol 21:947–953

Beaudegnies R, Edmunds AJ, Fraser TE, Hall RG, Hawkes TR, Mitchell G, Schaetzer J, Wendeborn S, Wibley J. (2009) Herbicidal 4-hydroxyphenylpyruvate dioxygenase inhibitors—a review of the triketone chemistry story from a Syngenta perspective. Bioorg Med Chem 17:4134–4152

Benoit L, Soltani N, Hooker DC, Robinson DE, Sikkema PH (2019) Efficacy of HPPD-inhibiting herbicides applied preemergence or postemergence for control of multiple herbicide resistant waterhemp [*Amaranthus tuberculatus* (Moq.) Sauer]. Can J Plant Sci 99:379–383

Besançon TE, Riar R, Heiniger RW, Weisz R, Everman WJ (2016) Weed control and crop tolerance with pyrasulfotole plus bromoxynil combinations in grain sorghum. Int J Agron Crop Sci 1:14–27

Bollman SL, Kells JJ, Penner D (2006). Weed response to mesotrione and atrazine applied alone and in combination preemergence. Weed Technol 20:903–907

Brosnan JT, Breeden GK (2013) Bermudagrass (*Cynodon dactylon*) control with topramezone and triclopyr. Weed Technol 27:138–142

Chahal PS, Aulakh JS, Jugulam M, Jhala AJ (2015) Herbicide resistant Palmer amaranth (*Amaranthus palmeri* S. Wats.) in the United States—Mechanisms of resistance, impact, and management. *In* Price A, ed., Herbicides, agronomic crops, and weed biology. Rijeka, Croatia: In Tech

Chahal PS, Ganie ZA, Jhala AJ (2018a) Overlapping residual herbicides for control of photosystem (PS) II- and 4-hydroxyphenylpyruvate dioxygenase (HPPD)-inhibitor-resistant Palmer amaranth (*Amaranthus palmeri* S. Watson) in glyphosate-resistant maize. Front Plant Sci 8: 2231

Chahal PS, Irmak S, Gaines T, Amundsen K, Jugulam M, Jha P, Travlos IS, Jhala AJ (2018b) Control of photosystem II–and 4-hydroxyphenylpyruvate dioxygenase inhibitor–resistant Palmer amaranth (*Amaranthus palmeri*) in conventional corn. Weed Technol 32:326–335

Chahal PS, Jhala AJ (2018a) Interaction of PS II- and HPPD-inhibiting herbicides for control of Palmer amaranth resistant to both herbicide sites of action. Agron J 110:2496–2506

Chahal PS, Jhala AJ (2018b) Economics of management of photosystem II and HPPD inhibitor-resistant Palmer amaranth in corn. Agron J 110:1905–1914

Chahal PS, Jugulam M, Jhala AJ (2019) Basis of atrazine and mesotrione synergism for controlling atrazine- and HPPD inhibitor-resistant Palmer amaranth. Agron J 111:3265–3273

Choe E, Williams MM II, Boydston RA, Huber JL, Huber SC, Pataky JK (2014) Photosystem II-inhibitors play a limited role in sweet corn response to 4-hydroxyphenyl pyruvate dioxygenase-inhibiting herbicides. Agron J 106: 1317–1323

Colby SR (1967) Calculating synergistic and antagonistic responses of herbicide combinations. Weeds 15:20–22

Concepcion JC, Kaundun SS, Morris JA, Hutchings S-J, Strom SA, Lygin AV, Riechers DE (2021) Resistance to a nonselective 4-hydroxyphenylpyruvate dioxygenase-inhibiting herbicide *via* novel reduction–dehydration–glutathione conjugation in *Amaranthus tuberculatus*. New Phytol 232:2089–2105

Creech JE, Monaco TA, Evans JO (2004) Photosynthetic and growth responses of *Zea mays* L and four weed species following post-emergence treatments with mesotrione and atrazine. Pest Manag Sci 60:1079–1084

Currie RS, Geier P (2016) Fallow weed control with preemergence applications of Balance Pro, Corvus, Banvel, Atrazine, and Authority MTZ. Kansas Agricultural Experiment Station Research Reports, Vol 2(7). DOI: 0.4148/2378-5977.1263

Currie RS, Geier P (2018) Efficacy of mesotrione-based tank mixtures and application timings compared to standards in irrigated corn. Kansas Agricultural Experiment Station Research Reports: Vol 4(8). DOI: 10.4148/2378-5977.7640

Dayan FE, Duke SO, Sauldubois A, Singh N, McCurdy CR, Cantrell CL (2007) p-Hydroxyphenylpyruvate dioxygenase is a herbicidal target site for β-triketones from *Leptospermum scoparium*. Phytochemistry 68:2004–2014

Diggle AJ, Neve PB, Smith FP (2003) Herbicides used in combination can reduce the probability of herbicide resistance in finite weed populations. Weed Res 43:371–382

Ditschun S, Soltani N, Robinson DE, Tardif FJ, Kaastra AC, Sikkema PH (2016) Control of glyphosate-resistant Canada fleabane (*Conyza canadensis* L. Cronq.) with isoxaflutole and metribuzin tank mix. Can J Plant Sci 96:72–80

Evans CM, Strom SA, Riechers DE, Davis AS, Tranel PJ, Hager AG (2019) Characterization of a waterhemp (*Amaranthus tuberculatus*) population from Illinois resistant to herbicides from five site-of-action groups. Weed Technol 33: 400–410

Evans JA, Tranel PJ, Hager AG, Schutte B, Wu C, Chatham LA, Davis AS (2016) Managing the evolution of herbicide resistance. Pest Manag Sci 72:74–80

Fluttert JC, Soltani N, Galla M, Hooker DC, Robinson DE, Sikkema PH (2022) Additive and synergistic interactions of 4-hydroxyphenylpyruvate dioxygenase (HPPD)- and photosystem II (PSII)-inhibitors for the control of glyphosate-resistant horseweed (*Conyza canadensis*) in corn. Weed Sci 70:319–327

Ganie ZA, Jhala AJ (2017) Confirmation of glyphosate-resistant common ragweed (*Ambrosia artemisiifolia*) in Nebraska and response to postemergence corn and soybean herbicides. Weed Technol 31:225–237

Ganie ZA, Stratman G, Jhala AJ (2015) Response of selected glyphosate-resistant broadleaved weeds to premix of fluthiacet-methyl and mesotrione (Solstice™) applied at two growth stages. Can J Plant Sci 95:861–869

Grossmann K, Ehrhardt T (2007) On the mechanism of action and selectivity of the corn herbicide topramezone: a new inhibitor of 4-hydroxyphenylpyruvate dioxygenase. Pest Manag Sci 63:429–439

Hager AG, Wax LM, Simmons FW, Stoller EW (1997) Waterhemp management in agronomic crops. Champaign: University of Illinois Bulletin, X855. 12 p

Hatzios KK, Penner D (1985) Interactions of herbicides with other agrochemicals in higher plants. Rev Weed Sci 1:1–63

Hausman NE, Singh S, Tranel PJ, Riechers DE, Kaundun SS, Polge ND, Thomas DA, Hager AG (2011) Resistance to HPPD-inhibiting herbicides in a population of waterhemp (*Amaranthus tuberculatus*) from Illinois, United States. Pest Manag Sci 67:258–261

Hausman NE, Tranel PJ, Riechers DE, Maxwell DJ, Gonzini LC, Hager AG (2013) Responses of an HPPD inhibitor-resistant waterhemp (*Amaranthus tuberculatus*) population to soil residual herbicides. Weed Technol 27:704–711

Hawkes TR, Langford MP, Viner R, Blain RE, Callaghan FM, Mackay EA, Hogg BV, Singh S, Dale RP (2019) Characterization of 4-hydroxyphenylpyruvate dioxygenases, inhibition by herbicides and engineering for herbicide tolerance in crops. Pestic Biochem Physiol 156:9–28

Hawkes TR, Holt DC, Andrews CJ, Thomas PG, Langford MP, Hollingworth S, Mitchell G (2001) Mesotrione: mechanism of herbicidal activity and selectivity in corn. Vol 2, pages 563–568 *in* The BCPC Proceedings - Weeds, British Crop Protection Council. Brighton, UK, November 12–15, 2001

Heap I (2022) The International Herbicide-Resistant Weed Database. http://www.weedscience.org. Accessed: March 11, 2022

Hess FD (2000) Light-dependent herbicides: an overview. Weed Sci 48:160–170

Hugie JA, Bollero GA, Tranel PJ, Riechers DE (2008) Defining the rate requirements for synergism between mesotrione and atrazine in redroot pigweed (*Amaranthus retroflexus*). Weed Sci 56:265–270

Jacobs KE Jr, Butts-Wilmsmeyer CJ, Ma R, O'Brien SR, Riechers DE (2020) Association between metabolic resistances to atrazine and mesotrione in a multiple-resistant waterhemp (*Amaranthus tuberculatus*) population. Weed Sci 68:358–366

Janak TW, Grichar WJ (2016) Weed control in corn (*Zea mays* L.) as influenced by preemergence herbicides. Int J Agron https://doi.org/10.1155/2016/2607671. Accessed: May 2, 2022

Jhala AJ, Beckie HJ, Mallory-Smith C, Jasieniuk M, Busi R, Norsworthy JK, Bagavathiannan MV, Tidemann BD, Geddes CM (2021a) Transfer of resistance alleles from herbicide-resistant to susceptible grass weeds via pollen-mediated gene flow. Weed Technol 35:869–885

Jhala AJ, Beckie HJ, Peters T, Culpepper S, Norsworthy J (2021c) Interference and management of herbicide-resistant crop volunteers. Weed Sci 69:257–273

Jhala AJ, Knezevic SZ, Ganie ZA, Singh M (2014a) Integrated weed management in corn (*Zea mays* L.). Pages 177–196 *in* Chauhan B, Mahajan G, eds. Recent Advances in Weed Management. New York: Springer

Jhala AJ, Norsworthy JK, Ganie ZA, Sosnoskie LM, Beckie HJ, Mallory-Smith CA, Liu J, Wei W, Wang J, Stoltenberg DE (2021b) Pollen-mediated gene flow and transfer of resistance alleles from herbicide-resistant broadleaf weeds. Weed Technol 35:173–187

Jhala AJ, Sandell LD, Rana N, Kruger GR, Knezevic SZ (2014b) Confirmation and control of triazine and 4-hydroxyphenylpyruvate dioxygenase-inhibiting herbicide-resistant Palmer amaranth (*Amaranthus palmeri*) in Nebraska. Weed Technol 28:28–38

Johnson BC, Young BG, Matthews JL (2002) Effect of postemergence application rate and timing of mesotrione on corn (*Zea mays*) response and weed control. Weed Technol 16:414–420

Jugulam M, Shyam C (2019) Non-target site resistance to herbicides: Recent developments. Plants 8:417. https://doi.org/10.3390/plants8100417 Accessed: June 04, 2022

Kaastra AC, Swanton CJ, Tardif FJ, Sikkema PH (2008) Two-way performance interactions among ρ-hydroxyphenylpyruvate dioxygenase- and acetolactate synthase-inhibiting herbicides. Weed Sci 56:841–851

Kaundun SS (2021) Syngenta's contribution to herbicide resistance research and management. Pest Manag Sci 77:1564–1571

Kaundun SS, Hutchings S-J, Dale RP, Howell A, Morris JA, Kramer VC, Shivrain VK, McIndoe E (2017) Mechanism of resistance to mesotrione in an *Amaranthus tuberculatus* population from Nebraska, USA. PLOS ONE 12(6): e0180095

Keeley PE, Carter CH, Thullen RJ (1987) Influence of planting date on growth of Palmer amaranth (*Amaranthus palmeri*). Weed Sci 35:199–204

KingAgroot (2021) Cypyrafluone was approved and registered by Pakistan, KingAgroot officially entered the overseas market. https://www.kingagroot.com/En/html/news-21Dec07.html. Accessed: March 3, 2022

Koepke-Hill RM, Armel GR, Wilson HP, Hines TE, Vargas JJ (2010) Herbicide combinations for control of volunteer potato. Weed Technol 24:91–94

Kohrt JR, Sprague CL (2017) Response of a multiple-resistant Palmer amaranth (*Amaranthus palmeri*) population to four HPPD-inhibiting herbicides applied alone and with atrazine. Weed Sci 65:534–545

Kumar V, Jha P, Reichard N (2014) Occurrence and characterization of kochia (*Kochia scoparia*) accessions with resistance to glyphosate in Montana. Weed Technol 28:122–130

Kumar V, Jha P (2015) Effective preemergence and postemergence herbicide programs for kochia control. Weed Technol 29:24–34

Koehn A, Tiebes J, Van Almsick A, Ahrens H, Heinemann I, Braun R, Schmitt MH, Willms L, Feucht D, Rosinger CH (2011) Preparation of N-(1,2,5-oxadiazol-3-yl) benzamides as herbicides. World Intellectual Property Organization. International Patent Application # WO2011035874. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011035874&_cid=P20-L3ZT1G-82733-1. Accessed: June 4, 2022

Küpper A, Peter F, Zöllner P, Lorentz L, Tranel PJ, Beffa R, Gaines TA (2018) Tembotrione detoxification in 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor-resistant Palmer amaranth (*Amaranthus palmeri* S. Wats.). Pest Manag Sci 74: 2325–2334

Lee DL, Prisbylla MP, Cromartie TH, Dagarin DP, Howard SW, Provan WM, Ellis MK, Fraser T, Mutter LC (1997) The discovery and structural requirements of inhibitors of p-hydroxyphenylpyruvate dioxygenase. Weed Sci 45:601–609

Lindley JJ, Jennings KM, Monks DW, Chaudhari S, Schultheis JR, Waldschmidt M, Brownie C (2020) Effect of bicyclopyrone herbicide on sweetpotato and Palmer amaranth (*Amaranthus palmeri*). Weed Technol 34:552–559

Liu M, Lu S (2016) Plastoquinone and ubiquinone in plants: Biosynthesis, physiological function, and metabolic engineering. Front Plant Sci 7:1898

Liu R, Kumar V, Jhala A, Jha P, Stahlman PW (2021) Control of glyphosate- and mesotrione-resistant Palmer amaranth in glyphosate- and glufosinate-resistant corn. Agron J 113:5362–5372

Lu H, Yu Q, Han H, Owen MJ, Powles SB (2020) Evolution of resistance to HPPD-inhibiting herbicides in a wild radish population via enhanced herbicide metabolism. Pest Manag Sci 76:1929–1937

Lygin AV, Kaundun SS, Morris JA, Mcindoe E, Hamilton AR, Riechers DE (2018) Metabolic pathway of topramezone in multiple-resistant waterhemp (*Amaranthus tuberculatus*) differs from naturally tolerant maize. Front Plant Sci 9:1644

Ma R, Kaundun SS, Tranel PJ, Riggins CW, McGinness DL, Hager AG, Hawkes T, McIndoe E, Riechers DE (2013) Distinct detoxification mechanisms confer resistance to mesotrione and atrazine in a population of waterhemp. Plant Physiol 163:363–377

Maeda H, Murata K, Sakuma N, Takei S, Yamazaki A, Karim MR, Kawata M, Hirose S, Kawagishi-Kobayashi M, Taniguchi Y, Suzuki S, Sekino K, Ohshima M, Kato H, Yoshida H, Tozawa Y (2019) A rice gene that confers broad-spectrum resistance to β-triketone herbicides. Science 365:393–396

Mallory-Smith C, Retzinger EJ (2017) Revised classification of herbicides by site of action for weed resistance management strategies. Weed Technol 17:605–619

Matringe M, Sailland A, Pelissier B, Rolland A, Zink O (2005) Hydroxyphenylpyruvate dioxygenase inhibitor-resistant plants. Pest Manag Sci 61:269–276

Mausbach J, Irmak S, Sarangi D, Lindquist J, Jhala AJ (2021) Control of acetolactate synthase inhibitor/glyphosate-resistant Palmer amaranth (*Amaranthus palmeri*) in isoxaflutole/glufosinate/glyphosate-resistant soybean. Weed Technol 35:779–785

Metzger BA, Soltani N, Raeder AJ, Hooker DC, Robinson DE, Sikkema PH (2018) Tolpyralate efficacy: Part 1. Biologically effective dose of tolpyralate for control of annual grass and broadleaf weeds in corn. Weed Technol 32:698–706

https://doi.org/10.1017/wet.2022.79 Published online by Cambridge University Press

Mitchell G, Bartlett DW, Fraser TE, Hawkes TR, Holt DC, Townson JK, Wichert RA (2001) Mesotrione: a new selective herbicide for use in maize. Pest Manag Sci 57:120–128

Mohler CL, Teasdale JR, DiTommaso A (2021) Manage weed on your farm- A guide to ecological strategies. SARE handbook series # 16. https://www.sare.org/resources/manage-weeds-on-your-farm/. Accessed: April 4, 2022

Moore (2019) Evaluation of topramezone for use in rice (*Oryza sativa* L.) production. Master's thesis. Fayetteville: University of Arkansas. https://scholarworks.uark.edu/etd/3436 Accessed: April 14, 2022

Nakka S, Godar AS, Wani PS, Thompson CR, Peterson DE, Roelofs J, Jugulam M (2017) Physiological and molecular characterization of hydroxyphenylpyruvate dioxygenase (HPPD)-inhibitor resistance in Palmer amaranth (*Amaranthus palmeri* S. Wats.). Frontiers Plant Sci 8:555

Negrisoli RM, Odero DC, MacDonald GE, Sellers BA, Laughinghouse HD (2020) Sugarcane response and fall panicum (*Panicum dichotomiflorum*) control with topramezone and triazine herbicides. Weed Technol 34: 241–249

Norris SR, Barrette TR, DellaPenna D (1995) Genetic dissection of carotenoid synthesis in Arabidopsis defines plastoquinone as an essential component of phytoene desaturation. Plant Cell 7:2139–2149

Norsworthy JK, Ward SM, Shaw DR, Llewellyn RS, Nichols RL, Webster TM, Bradley KW, Frisvold G, Powles SB, Burgos NR, Witt WW, Barrett M (2012) Reducing the risks of herbicide resistance: Best management practices and recommendations. Weed Sci 60(SPI):31–62

O'Brien SR, Davis AS, Riechers DE (2018) Quantifying resistance to isoxaflutole and mesotrione and investigating their interactions with metribuzin POST in waterhemp (*Amaranthus tuberculatus*). Weed Sci 66:586–594

Oliveira MC, Jhala AJ, Gaines T, Irmak S, Amundsen K, Scott JE, Knezevic SZ (2017) Confirmation and control of HPPD-inhibiting herbicide–resistant waterhemp (*Amaranthus tuberculatus*) in Nebraska. Weed Technol 31:67–79

Olson A, Weeks M (2020) Petition for a determination of nonregulated status for a plant-parasitic nematode-protected and herbicide tolerant GMB151 soybean. https://www.aphis.usda.gov/brs/aphisdocs/19_31701p.pdf Accessed: May 18, 2022

Osipitan OA, Scott JE, Knezevic SZ (2018) Tolpyralate applied alone and with atrazine for weed control in corn. J Agric Sci 10:32–39

Owens DK, Nanayakkara NPD, Dayan FE (2013) In planta mechanism of action of leptospermone: Impact of its physico-chemical properties on uptake, translocation, and metabolism. J Chem Ecol 39:262–270

Pallett KE, Cramp SM, Little JP, Veerasekaran P, Crudace AJ, Slater AE (2001) Isoxaflutole: the background to its discovery and the basis of its herbicidal properties. Pest Manag Sci 57:133–142

Pallett KE, Little JP, Sheekey M, Veerasekaran P (1998) The mode of action of isoxaflutole: I. physiological effects, metabolism, and selectivity. Pest Biochem Physiol 62:113–124

Pandian BA, Varanasi A, Vannapusa AR, Sathishraj R, Lin G, Zhao M, Tunnell M, Tesso T, Liu S, Prasad PV, Jugulam M (2020) Characterization, genetic analyses, and identification of QTLs conferring metabolic resistance to a 4-hydroxyphenylpyruvate dioxygenase inhibitor in sorghum (*Sorghum bicolor*). Front Plant Sci 11:596581

PlantArcBio (2022) PlantArcBio Receives USDA/APHIS Regulatory Exemption in the US for its Proprietary HPPD Herbicide-Tolerant Gene for Soybean and Cotton. CISION PR Newswire. https://www.prnewswire.com/il/news-releases/plantarcbio-receives-usdaaphis-regulatory-exemption-in-the-us-for-its-proprietary-hppd-herbicide-tolerant-gene-for-soybean-and-cotton-301454516.html. Accessed: July 20, 2022

Reddy SS, Stahlman PW, Geier PW, Thompson CR, Currie RS, Schlegel AJ, Olson BL, Lally NG (2013) Weed control and crop safety with premixed pyrasulfotole and bromoxynil in grain sorghum. Weed Technol 27:664–670

Reither B (2021) R&D pipeline update: The beginning of what's next. https://www.bayer.com/sites/default/files/BayerCMD2021_CropScience_RandD_Presentation.pdf. Accessed: July 20, 2022

Robinson DE (2008) Atrazine accentuates carryover injury from mesotrione in vegetable crops. Weed Technol 22:641–645

Sarangi D, Jhala AJ (2018) Comparison of a premix of atrazine, bicyclopyrone, mesotrione, and s-metolachlor with other preemergence herbicides for weed control and corn yield in no-tillage and reduced-tillage production systems in Nebraska, USA. Soil Tillage Res 178:82–91

Sarangi D, Stephens T, Barker AL, Patterson EL, Gaines TA, Jhala AJ (2019) Protoporphyrinogen oxidase (PPO) inhibitor–resistant waterhemp (*Amaranthus tuberculatus*) from Nebraska is multiple herbicide resistant: confirmation, mechanism of resistance, and management. Weed Sci 67: 510–520

Schultz JL, Chatham LA, Riggins CW, Tranel PJ, Bradley KW (2015) Distribution of herbicide resistances and molecular mechanisms confer-ring resistance in Missouri waterhemp (*Amaranthus rudis* Sauer) populations. Weed Sci 63:336–345

Schuster CL, Al-Khatib K, Dille JA (2007) Mechanism of antagonism of mesotrione on sulfonylurea herbicides. Weed Sci 55:429–434

Schuster CL, Al-Khatib K, Dille JA (2008) Efficacy of sulfonylurea herbicides when tank mixed with mesotrione. Weed Technol 22:222–230

Schultz C, Soll J, Fiedler E, Schultze-Siebert D (1985) Synthesis of prenylquinones in chloroplasts. Physiol Plantarum 64:123–129

Shatlin D (2021) Request 21-264-01cr: 7 CFR § 340.1(e) Request for confirmation that PlantArcBio's HPPD herbicide tolerant soy is exempt from regulation under §340.1(c)(2). https://www.aphis.usda.gov/biotechnology/downloads/confirmation-response/21-264-01cr-a1.pdf. Accessed: July 20, 2022

Shyam C, Borgato EA, Peterson DE, Dille JA, Jugulam M (2021) Predominance of metabolic resistance in a six-way-resistant Palmer amaranth (*Amaranthus palmeri*) population. Front Plant Sci 11:614618

Siehl DL, Tao Y, Albert H, Dong Y, Heckert M, Madrigal A, Lincoln-Cabatu B, Lu J, Fenwick T, Bermudez E, Sandoval M, Horn C, Green JM, Hale T, Pagano P, Clark J, Udranszky IA, Rizzo N, Bourett T, Howard RJ, Johnson DH, Vogt M, Akinsola G, Castle LA (2014) Broad 4-hydroxyphenylpyruvate dioxygenase inhibitor herbicide tolerance in soybean with an optimized enzyme and expression cassette. Plant Physiol 166:1162–1176

Smith A, Soltani N, Kaastra AJ, Hooker DC, Robinson DE, Sikkema PH (2019a) Annual weed management in isoxaflutole-resistant soybean using a two-pass weed control strategy. Weed Technol 33:411–425

Smith A, Soltani N, Kaastra AC, Hooker DC, Robinson DE, Sikkema PH (2019b) Isoxaflutole and metribuzin interactions in isoxaflutole-resistant soybean. Weed Sci 67:485–496

Soltani N, Shropshire C, Sikkema PH (2011) Response of spring planted barley (*Hordeum vulgare* L.), oats (*Avena sativa* L.) and wheat (*Triticum aestivum* L.) to mesotrione. Crop Prot 30:849–853

Soltani N, Shropshire C, Cowan T, Sikkema PH (2014) Weed management in spring planted cereals with mesotrione. Am J Plant Sci DOI: 10.4236/ajps.2014.51020

Steadman J (2021) Inside cotton's pipeline: What's coming from BASF. Cotton Grower. https://www.cottongrower.com/crop-inputs/inside-cottons-pipeline-whats-coming-from-basf/. Accessed: July 20, 2022

Stephenson DO, Bond JA, Walker ER, Bararpour MT, Oliver LR (2004) Evaluation of mesotrione in Mississippi Delta corn production. Weed Technol 18:1111–1116

Stephenson DO, Bond JA (2012) Evaluation of thiencarbazone-methyl– and isoxaflutole-based herbicide programs in corn. Weed Technol 26:37–42

Stephenson DO, Bond JA, Landry RL, Edwards HM (2015) Weed management in corn with postemergence applications of tembotrione or thiencarbazone: tembotrione. Weed Technol 29:350–358

Striegel A, Jhala AJ (2022) Economics of reducing Palmer amaranth (*Amaranthus palmeri* S. Watson) seed production in dicamba/glufosinate/glyphosate-resistant soybean. Agron J 114:2518–2540

Sutton P, Richards C, Buren L, Glasgow L (2002) Activity of mesotrione on resistant weeds in maize. Pest Manag Sci 58:981–984

Thompson CR, Peterson ED, Nathan GL (2012) Characterization of HPPD-resistant Palmer amaranth. Abstract No. 413 in Proceedings of the Weed Science Society of America annual meeting. Waikoloa, Hawaii, February 6–9, 2012

Torbiak AT, Blackshaw RE, Brandt RN, Hamman B, Geddes CM (2021) Herbicide strategies for managing glyphosate-resistant and -susceptible kochia (*Bassia scoparia*) in spring wheat. Can J Plant Sci 101:607–620

Tranel PJ (2021) Herbicide resistance in *Amaranthus tuberculatus*. Pest Manag Sci 77:43–54

Tsukamoto M, Kikugawa H, Nagayama S, Suganuma T, Okita T, Miyamoto H (2021) Discovery and structure optimization of a novel corn herbicide, tolpyralate. J Pestic Sci 46:152–159

https://doi.org/10.1017/wet.2022.79 Published online by Cambridge University Press

[USDA-NASS] United States Department of Agriculture–National Agricultural Statistics Service (2018) Agricultural chemical use. https://quickstats.nass.usda.gov. Accessed: June 13, 2022

Varanasi VK, Brabham C, Norsworthy JK, Nie H, Young BG, Houston M, Barber T, Scott RC (2018) A statewide survey of PPO-inhibitor resistance and the prevalent target-site mechanisms in Palmer amaranth (*Amaranthus palmeri*) accessions from Arkansas. Weed Sci 66:149–158

Walsh MJ, Stratford K, Stone K, Powles SB (2012) Synergistic effects of atrazine and mesotrione on susceptible and resistant wild radish (*Raphanus raphanistrum*) populations and the potential for overcoming resistance to triazine herbicides. Weed Technol 26:341–347

Walsh MJ, Newman P, Chatfield P (2021) Mesotrione: a new preemergence herbicide option for wild radish (*Raphanus raphanistrum*) control in wheat. Weed Technol 35:924–931

Wang DW, Lin HY, Cao RJ, Ming ZZ, Chen T, Hao GF, Yang WC, Yang GF (2015) Design, synthesis and herbicidal activity of novel quinazoline-2,4-diones as 4-hydroxyphenylpyruvate dioxygenase inhibitors. Pest Manag Sci 71:1122–1132

Wang H, Liu W, Jin T, Peng X, Zhang L, Wang J (2020) Bipyrazone: a new HPPD inhibiting herbicide in wheat. Sci Rep 10:5521

Whaley CM, Armel GR, Wilson HP, Hines TE (2006) Comparison of mesotrione combinations with standard weed control programs in corn. Weed Technol 20:605–611

Willemse C, Soltani N, Benoit L, Jhala AJ, Hooker DC, Robinson DE, Sikkema PH (2021a) Is there a benefit of adding atrazine to HPPD-inhibiting herbicides for control of multiple-herbicide-resistant, including group 5-resistant, waterhemp in corn? J Agr Sci 13:21–31

Willemse C, Soltani N, David CH, Jhala AJ, Robinson DE, Sikkema PH (2021b) Interaction of 4-hydroxyphenylpyruvate dioxygenase (HPPD) and atrazine alternative photosystem II (PS II) inhibitors for control of multiple herbicide–resistant waterhemp (*Amaranthus tuberculatus*) in corn. Weed Sci 69:492–503

Willemse C, Soltani N, Metzger B, Hooker DC, Jhala AJ, Robinson DE, Sikkema PH (2021c) Biologically-effective-dose of tolpyralate and tolpyralate plus atrazine for control of multiple-herbicide-resistant waterhemp [*Amaranthus tuberculatus* (Moq.) J. D. Sauer] in corn. Agr Sci 12:424–443

Williams MM II, Pataky JK, Nordby JN, Riechers DE, Sprague CL, Masiunas JB (2005) Cross-sensitivity in sweet corn to nicosulfuron and mesotrione applied postemergence. HortScience 40:1801–1805

Williams MM II, Pataky JK (2010) Factors affecting differential sensitivity of sweet corn to HPPD-inhibiting herbicides. Weed Sci 58:289–294

Williams MM II, Boydston RA, Peachey RE, Robinson D (2011a) Performance consistency of reduced atrazine use in sweet corn. Field Crops Res 121: 96–104

Williams MM II, Boydston RA, Peachey RE, Robinson D (2011b) Significance of atrazine as a tank-mix partner with tembotrione. Weed Technol 25:299–302

Woodyard AJ, Hugie JA, Riechers DE (2009a) Interactions of mesotrione and atrazine in two weed species with different mechanisms for atrazine resistance. Weed Sci 57:369–378

Woodyard AJ, Bollero GA, Riechers DE (2009b) Broadleaf weed management in corn utilizing synergistic postemergence herbicide combinations. Weed Technol 23:513–518

Woodyard AJ, Hugie JA, Riechers DE (2009c) Interactions of mesotrione and atrazine in two weed species with different mechanisms for atrazine resistance. Weed Sci 57:369–378

Wuerffel RJ, Young JM, Tranel PJ, Young BG (2015) Soil-residual protoporphyrinogen oxidase-inhibiting herbicides influence the frequency of associated resistance in waterhemp (*Amaranthus tuberculatus*). Weed Sci 63:529–538

Yamamoto S, Tanetani Y, Uchiyama C, Nagamatsu A, Kobayashi M, Ikeda M, Kawai K (2021) Mechanism of action and selectivity of a novel herbicide, fenquinotrione. J Pestic Sci 46:249–257

Yu J, McCullough PE (2016) Triclopyr reduces foliar bleaching from mesotrione and enhances efficacy for smooth crabgrass control by altering uptake and translocation. Weed Technol 30:516–523

Yu Q, Powles S (2014) Metabolism-based herbicide resistance and cross resistance in crop weeds: A threat to herbicide sustainability and global crop production. Plant Physiol 166:1106–1118

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