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Is there a place for new herbicides targeting photosynthetic electron transport?

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Review

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Abstract

Due to increased food demand, the use of herbicides is both necessary and on the rise. Several herbicide classes target photosynthetic electron transport: Herbicide Resistance Action Committee (HRAC) Groups 5, 6, and 22. These herbicides are used in large amounts in many different cropping systems to control several species of broadleaf and grass weeds. This article provides a comprehensive review of what these photosynthesis inhibitors are, how they are used, and their modes of action. Presently, commercial herbicides only inhibit electron flow at two different sites: photosystem II (PSII) and photosystem I (PSI). Herbicides that inhibit electron flow at PSII block the movement of electrons down the electron transport chain, while those that inhibit electron flow at PSI accept electrons. Necrosis developing on the leaves of plants treated with PSII and PSI inhibitors is due to the accumulation of reactive oxygen species. Evolution of resistance, toxicity concerns, and other limitations of these herbicides call for the exploration of new chemistries that can be used to target this pathway.

Introduction

As global food demand continues to rise, there is an increased need for new agricultural practices that maintain and sustain the current levels of food production and trade. Among practices pivotal to these current production levels is the use of herbicides (Gianessi and Reigner 2017). Conventional agriculture employs a variety of herbicides with different modes of action to control weeds that threaten the yield of agricultural crops (Gianessi 2013). However, the management of weeds with the herbicides that are currently available is facing some challenges due to several factors, such as evolution of resistance, environmental risks associated with certain herbicides, and mammalian toxicity. Currently, there are more than 500 cases of unique herbicide resistance reported globally (Heap 2024). Additionally, many herbicides have restricted-use labels or have been banned in various places around the world due to their perceived risks (Kniss 2017).

Several herbicide classes inhibit photosynthesis, the core physiological process all plants rely on to generate their own chemical energy in the form of carbohydrates using light energy, CO_2, and H_2O (Youvan and Marrs 1987). Photosynthesis is one of the most-studied and well-understood biological processes, and herbicides have been instrumental in dissecting this complex pathway (Dayan et al. 2010; Draber et al. 1991). However, the current commercial herbicides that target photosynthesis pose issues due to many weed species evolving resistance to them, limited use due to the toxic nature of some of these compounds, and their lasting impacts on the environment (Gianessi 2013). To assess the need for new photosynthetic inhibitors for agricultural use, it is important to understand their current relevance to food production, how these herbicides work, how resistance evolves, and the factors limiting their use.

There are many herbicide groups affecting photosynthesis. This review focuses only on those directly affecting photosynthetic electron transports (Groups 5, 6, and 22). Readers interested in herbicides affecting photosynthesis indirectly, such as bleaching herbicides (Groups 12, 13, 27, 32, and 33), inhibitors of porphyrin synthesis (Group 14), and inhibitors disrupting photorespiration (Group 10) are referred to other reviews.

What Are Photosynthetic Inhibitors?

Most photosynthetic inhibitors cause necrosis in plant tissue by disrupting the photosynthetic electron transport chain. There are currently two modes of action for commercial herbicides targeting photosynthesis: namely, blocking electron transport at the D1 protein of photosystem II (PSII) and electron diversion from photosystem I (PSI) (Fuerst and Norman 1991). Despite there being multiple other possible targets in the light reactions of photosynthesis, only these two modes of action, PSII and PSI, are used in agriculture as herbicides. More than 80 commercial herbicides targeting PSII have been classified in either Group 5 or 6 by the Herbicide Resistance Action Committee (HRAC) (Figure 1). While both groups block electron transport in the photosynthetic electron transport chain by competing for the binding site of

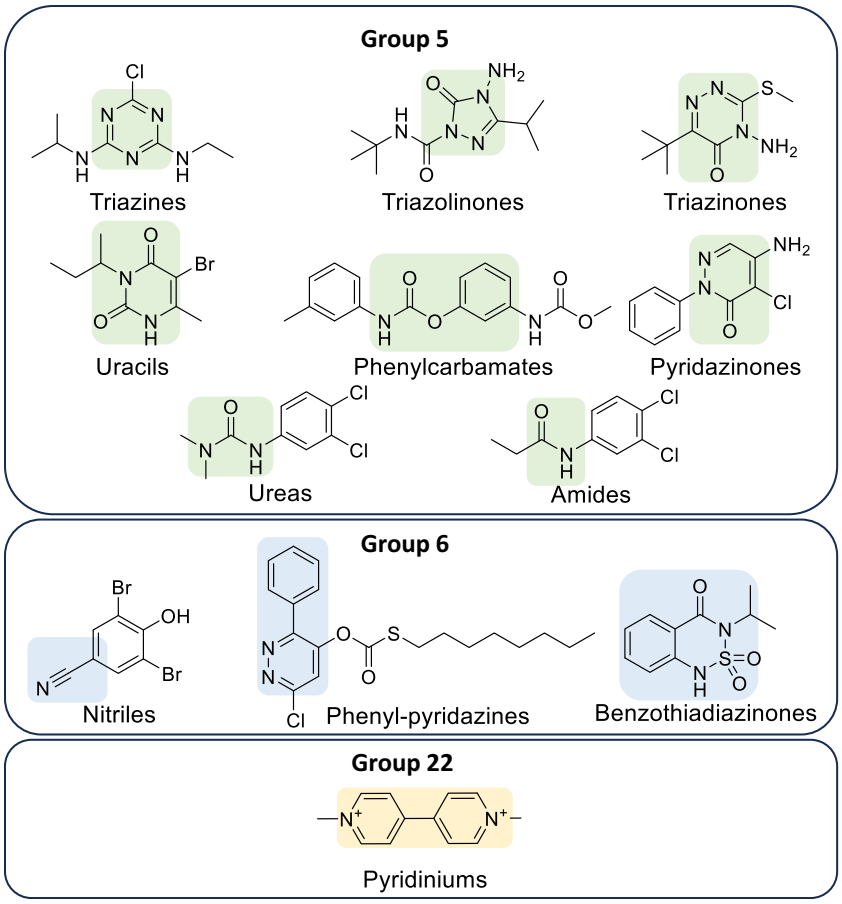

Figure 1. Structural characteristics of commercial herbicides targeting photosynthesis. Examples of Group 5 herbicides: atrazine (triazines), diuron (ureas), amicarbazone (triazolinones), metribuzin (triazinones), bromacil (uracils), phenmedipham (phenylcarbamates), chloridazon (pyridazinones), and propanil (amides). Examples of Group 6 herbicides: bromoxynil (nitriles), pyridate (phenyl-pyridazines), and bentazon (benzothiadiazinones). Example of Group 22 herbicides: paraquat (pyridiniums).

plastoquinone (PQ) on the D1 protein, sensitivity to Group 5 PSII-inhibiting herbicides is reduced by mutations at Ser-264, whereas sensitivity to Group 6 herbicides is reduced by mutations at His-215 (Fuerst and Norman 1991). Group 5 consists of eight different chemical classes, while Group 6 consists of three chemical classes (Figure 1). PSI herbicides are classified by the HRAC as Group 22 herbicides, otherwise known as pyridiniums (Figure 1). The two most common pyridinium herbicides are paraquat and diquat (Fuerst and Norman 1991). These herbicides divert electrons from PSI and generate free radical intermediates that produce large amounts of reactive oxygen species (ROS) to cause phytotoxicity (Krieger-Liszkay et al. 2011).

Photosynthetic inhibitors control mainly broadleaf weeds but can also be used to manage some varieties of grass weeds. Group 5 contains the most chemical classes (e.g., triazines, triazolinones, triazinones, uracils, amides, ureas, pyridazinones, and phenyl carbamates) (Heap 2024; Figure 1). The two largest classes within Group 5 are the triazines and ureas, with 27 individual herbicides in each (Figure 2). Group 6 consists of the nitrile, phenyl-pyridazine, and benzothiadiazinone chemical classes. Group 22 is limited to four pyridiniums (Figures 1 and 2); however, only two are used as commercial products. It is important to note that only 22 of the more than 80 registered herbicides in Groups 5, 6, and 22 are commercially available in the United States. This is because many of the Group 5 and 6 herbicides have limited spectra of activity, and only a few of them are used for their broad spectra of activity (Martin 1987). The remaining chemical classes utilize only one or two unique compounds for commercial agriculture (Figure 2).

How Are Commercial Herbicides Targeting Photosynthesis Used?

Group 5 and 6 herbicides are widely used for the control of a variety of weed species. The triazine atrazine is by far the most-used Group 5 herbicide and is applied primarily on corn (*Zea mays* L.), with more than 32 million kg yr^{-1} applied in the United States (Figure 3). Other than atrazine (and simazine), the other relevant Group 5 herbicides are used in a variety of cropping systems. For example, the triazinone metribuzin is used in soybean [*Glycine max* (L.) Merr.]-cropping systems, whereas the urea herbicide diuron is used primarily in cotton (*Gossypium hirsutum* L.) systems, and the amide propanil is used almost exclusively in rice (*Oryza sativa* L.) systems (Figure 3). Group 6 herbicides are generally used either in soybean or wheat (*Triticum aestivum* L.) systems (Figure 3). Paraquat is the most-used Group 22 herbicide, with almost seven times the amount applied in comparison to diquat. Paraquat is used as a nonselective herbicide or defoliant in a variety of cropping systems, including soybean, corn, cotton, orchards, and wheat, with most being applied to soybean (Figure 3).

With the dominance of atrazine, most of the photosynthesis-inhibiting herbicides are applied in the Corn Belt region of the Unites States. As of 2018, the states with the greatest use were

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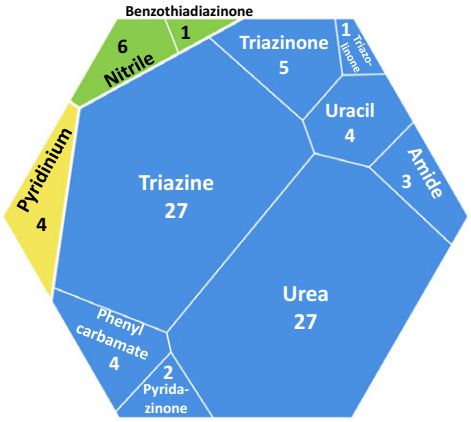

Figure 2. Relative size of each chemical class within Herbicide Resistance Action Committee (HRAC) Groups 5 (blue), 6 (green), and 22 (yellow) herbicides. Of the 81 registered herbicides used to generate this figure, only 5 triazines, 2 triazinones, 2 uracils, 2 phenylcarbamates, 1 pyridazinone, 5 ureas, 1 amide, 1 nitrile, 1 benzothiadiazinone, and 2 pyridiniums were used in the United States in 2018. Data from USGS Pesticide National Synthesis Project (USGS 2024).

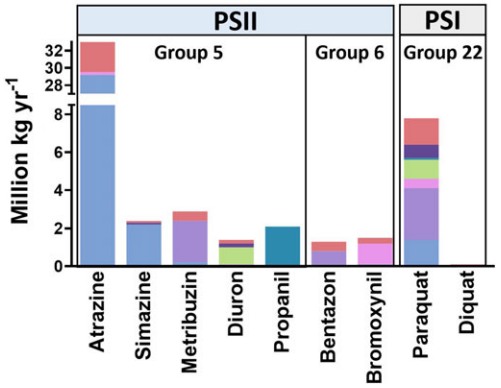

Figure 3. Most-used herbicides targeting photosynthesis in the United States. Herbicides are organized by Herbicide Resistance Action Committee (HRAC) Groups 5 and 6 targeting photosystem II (PSII) and HRAC Group 22 targeting photosystem I (PSI). Atrazine and simazine are triazines, metribuzin is a triazinone, diuron is a urea, and propanil is an amide, bentazon is a benzothiadiazinone, bromoxynil is a nitrile, and paraquat and diquat are pyridiniums. = corn; = soybean; = wheat; = cotton; = rice; = orchards and grapes; = other crops. Most recent complete data available are for 2018, obtained from USGS Pesticide National Synthesis Project (USGS 2024).

Kansas and Illinois, which each use more than 5 million kg yr^{-1} of these herbicides, closely followed by Nebraska and Iowa, which each use approximately 3 to 5 million kg yr^{-1}. Other states that use notable amounts of these photosynthetic inhibitors are Texas, Arkansas, Missouri, Indiana, and Ohio, each using about 2 to 3 million kg yr^{-1} per state (Figure 4).

Group 5 herbicides have a market value of nearly US$2.2 billion yr^{-1} (Figure 5). This is primarily accounted for by atrazine (US $800 million yr^{-1}), which is the most-used photosynthesis-inhibiting herbicide in the United States by a large margin. Group 22 herbicides amount to US$935 million yr^{-1}, consisting mostly of paraquat at US$560 million yr^{-1}, which is consistent with its lower use (Figure 5). Bentazon leads the market value for the Group 6 herbicides and accounts for US$217 million yr^{-1} out of a total US$227 million yr^{-1}, amounting to the lowest market value of all three herbicide groups targeting photosynthesis (Figure 5). Nonetheless, the market trends between 2017 and 2022 reflect a 17% increase in market value for Group 5 herbicides, an 8% increase for Group 6, and a 23% increase for Group 22.

Overview of the Light Reaction of Photosynthesis

The process of photosynthesis in plants is split into two phases: the light or Hill reactions and the dark reactions or Calvin cycle (Niyogi et al. 2015). For the purpose of this review, we will only briefly describe the light reactions. The light reactions of photosynthesis are localized within the thylakoid membranes residing in chloroplasts, the specialized photosynthetic organelles that arose from an ancient endosymbiotic event (Niyogi et al. 2015). Light, CO_2, and water are the three components required to synthesize sugar in plants, while O_2 is a by-product of these reactions (Whitmarsh and Govindjee 1999). First, water is split into O_2, protons, and electrons at the water-splitting complex (Figure 6). These electrons enter the photosynthetic electron transport chain, while the protons accumulate within the lumen and drive photophosphorylation of ADP into ATP via the chloroplast ATP synthase (Youvan and Marrs 1987). The electrons enter the photosynthetic electron transport chain on the lumen side of PSII following the oxidation of P680, the first checkpoint in the photosynthetic electron transport chain. These electrons are excited by light energy from a redox potential of approximately +100 mV to a redox potential of approximately −500 mV. Once on the stroma side of PSII, these electrons exit PSII and are transferred to PQ (Whitmarsh and Govindjee 1999). PQ accepts two electrons from PSII and two protons from the stroma to form plastoquinol (PQH_2) and transfers these electrons with a redox potential of approximately +200 mV to the cytochrome b6/f complex (Herbert 1975; Figure 6). The cytochrome b6/f complex then shuttles these electrons to the blue copper protein plastocyanin inside the lumen, which has a redox potential of approximately +400 mV (Gross 1993). Plastocyanin then transfers these electrons to P700 in PSI, where light energy excites them from the redox potential of approximately +400 mV to approximately −500 mV. From here, the redox potential of these electrons slowly decreases until they are used by ferredoxin/ferredoxin/NADP reductase (FNR) to convert $NADP^+$ to NADPH (Dai et al. 2004). The protons from the water-splitting reaction travel to ATP synthase, where they are used in the photophosphorylation of ADP to form ATP.

How Herbicides Targeting Photosynthesis Work

All Group 5 and 6 herbicides are selective. They control the desired weed species without injuring the crops on which they are used. The main mechanism of selectivity relies on differential metabolism of the herbicides. For example, atrazine is very safe to corn, because corn rapidly detoxifies this herbicide via the action of glutathione *S*-transferases. Sensitive weeds are not able to metabolize atrazine fast enough (Davis et al. 1964; Shimabukuro 1967; Shimabukuro et al. 1971). On the other hand, Group 22 herbicides, like paraquat, are not considered selective, because they are not rapidly metabolized by any plants (Kim and Kim 2020; Sagar 1987).

With respect to their mechanism of action, PSII herbicides inhibit photosynthesis by binding at the D1 protein on the reducing side of PSII. Here, they competitively bind to the PQ binding site and halt electron flow after they have been initially excited by light energy in the P680 reaction center and have traveled through PSII (Shipman 1981; Trebst et al. 1983). These herbicides bind competitively at the Q_B site due to their higher

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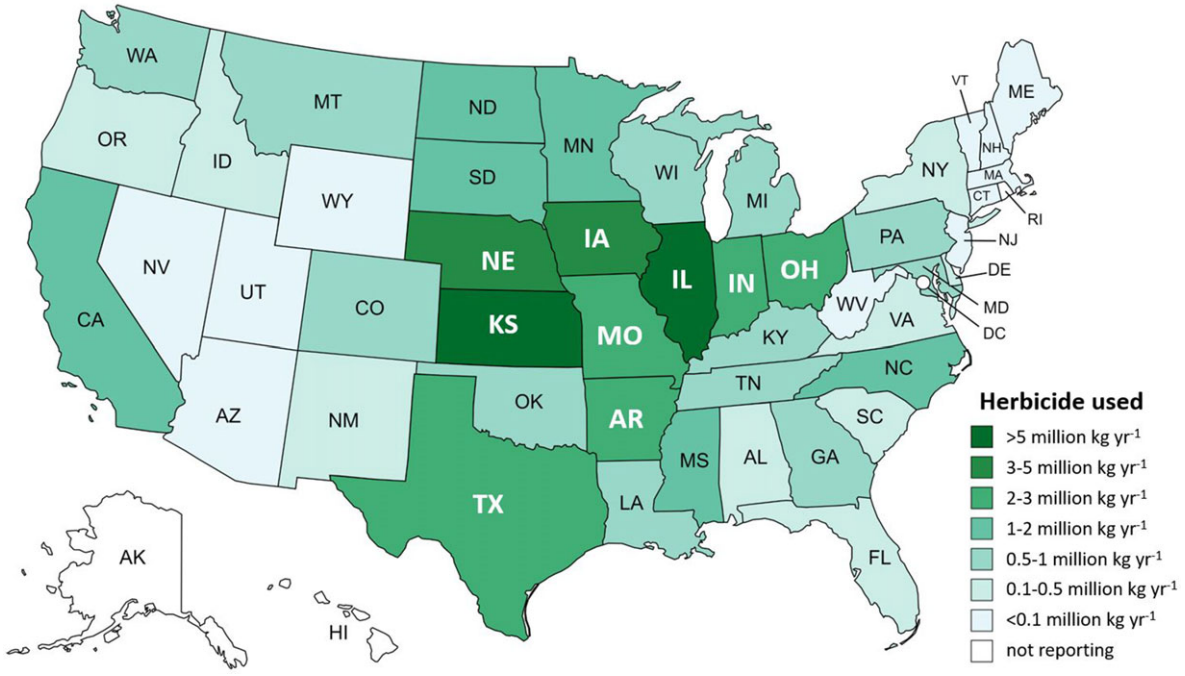

Figure 4. Total amount of groups 5, 6, and 22 herbicides used per year in each state in 2018. Data from USGS Pesticide National Synthesis. Project (USGS 2024). Map was generated with MapChart (https://www.mapchart.net/usa.html).

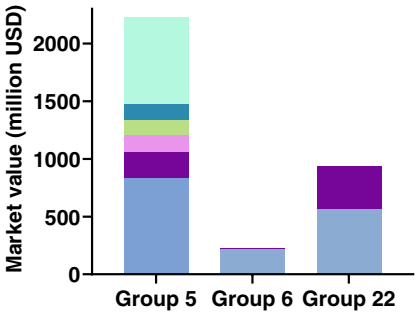

Figure 5. 2022 Worldwide market value of herbicides targeting photosynthesis. Group 5 herbicides included: = atrazine; = metribuzin; = diuron; = tebuthiuron; = metamitron; = 19 other herbicides. Group 6 herbicides included: = bentazon; = pyridate. Group 22 herbicides included: = paraquat; = diquat. Data kindly provided by AgbioInvestor.com.

affinity to the site than that of the PQ itself (Oettmeier 1999; Figure 7). Because electron transport is inhibited at this point, electrons can no longer be shuttled through the rest of the photosynthetic electron transport system, and photosynthesis is subsequently halted. Thus, treated plants are no longer able to produce ATP or NADPH, both of which are required for sustaining plant life (Droppa et al. 1981). Because the H bonding of Group 5 herbicides interacts with Ser-264 and Group 6 herbicides interact with His-215, they are sensitive to mutation in these respective residues to which they bind (Figure 7B). These sites are where the PQ in PSII binds, and when herbicidal compounds bind there, they block the photosynthetic electron transfer process (Amesz 1973). This blockage of electrons causes the production of singlet oxygen, a type of ROS, and other free radicals. The chlorotic damage observed in treated plants is a result of the photo-oxidative damage caused by these ROS (Hess 2000; Pallett and Dodge 1980; Rutherford and Krieger-Liszkay 2001; Traxler et al. 2023). In some types of plants that exhibit resistance to PSII inhibitors, the active ingredient can be broken down into mobile, nontoxic metabolites, thus becoming no longer phytotoxic (Rigon et al. 2020). In contrast, there are no known cases of metabolism-based resistance to PSI inhibitors.

Group 22 herbicides such as paraquat and diquat disrupt the photosynthetic electron transport chain at PSI (Dodge and Harris 1970). With redox potentials approximately −450 mV, these herbicides act as electron acceptors as they emerge from PSI and form reactive radical intermediates that react with free oxygen to generate ROS, causing lipid peroxidation and rapid necrosis of photosynthetically active tissue (Krieger-Liszkay et al. 2011). These compounds cause the accumulation of both hydrogen peroxide and superoxide in levels higher than those that can be quenched by the plants, resulting in tissue necrosis. This accumulation of ROS occurs via a series of reactions known as the Fenton reaction and the Haber-Weiss reaction. The Fenton reaction yields hydroxide (OH^-) and hydroxyl radical ($OH^•$) with the reactants Fe^{2+} and hydrogen peroxide (H_2O_2). Hydroxyl radicals produced by the Fenton reaction are highly unstable and the most toxic of the ROS as the initiator of lipid peroxidation (Traxler et al. 2023). The hydroxyl radical can also be produced through the Haber-Weiss reaction, in which hydrogen peroxide and superoxide radical are catalyzed by Fe^{2+}. This reaction yields not only the hydroxyl radical, but hydroxide as well (Traxler et al. 2023). In plants, the overproduction of ROS may cause DNA, protein, and lipid damage, which ultimately causes cell death (Plaza et al. 2021). Additionally, this inhibits the production of NADPH, because electron transport is diverted at a point likely before the ferredoxin and before it is used to produce NADPH.

PSI-inhibiting compounds are contact herbicides, meaning that they act on contact with plant tissue exposed to light and do not readily translocate (Funderburk and Lawrence 1964). This also means that plants are mostly unable to metabolize PSI herbicides,

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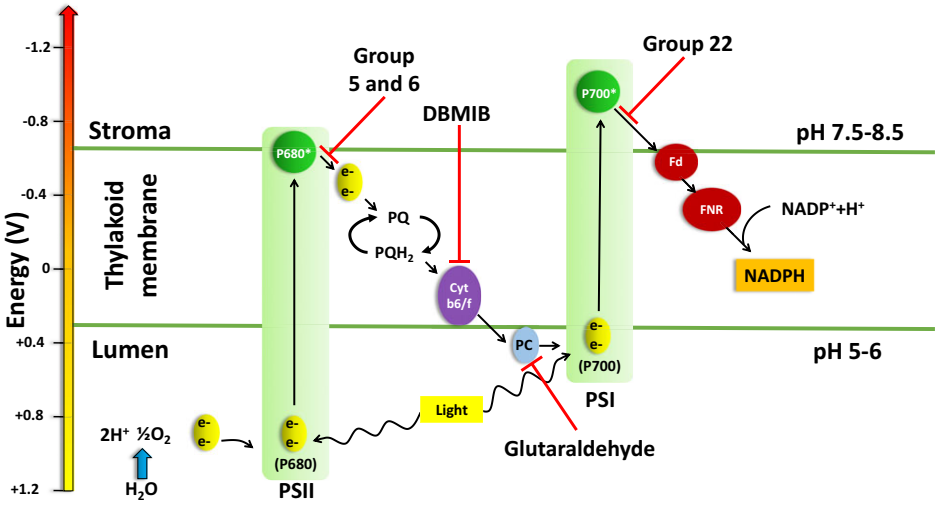

Figure 6. Z-scheme of photosynthetic electron transport chain and points where inhibitors act along this chain. Photosystem II (PSII), photosystem I (PSI), plastoquinone (PQ), plastoquinol (PQH_2), 2,5-dibromo-6-isopropyl-3-methyl-1,4- benzoquinone (DBMIB), plastocyanin (PC), ferredoxin (Fd), and ferredoxin/NADP reductase (FNR).

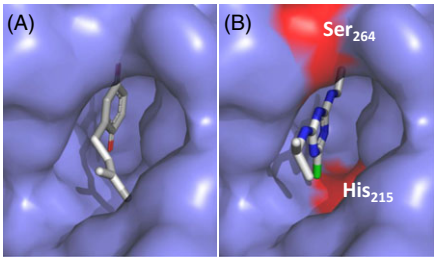

Figure 7. Crystal structure of the D1 protein of *Arabidopsis thaliana* (PDB: 7OUI) showing the plastoquinone (PQ) binding pocket with either (A) pentyl benzoquinone (analog of PQ) or (B) atrazine. Reduced sensitivity to Group 5 herbicides is caused by mutations in Ser-264, whereas reduced sensitivity to Group 6 herbicides is caused by mutations in His-215 (shown in red in B). The coordinates of atrazine binding were obtained from the crystal structure of the *Rhodopseudomonas viridis* reaction center (PDB: 5PRC).

because they kill tissues so rapidly. Because these herbicides do not bind to a specific site and the compounds themselves cause the phytotoxic effect, it has been difficult for plants to evolve resistance to Group 22 herbicides (discussed later).

As an aside, it should be noted that PSII is a highly promiscuous target, meaning that thousands of molecules have been identified to inhibit PSII in high-throughput screens carried by the ag-chem industry. On the other hand, PSI inhibitors are much less common.

Resistance to Inhibitors of Photosynthesis

Repeated use of the same herbicide has driven evolution of resistance in weeds (Rigon et al. 2020). Resistance can result from target-site mutations and/or overexpression (TSR) or via other non–target site (NTSR) mechanisms that alter the way plants detoxify, move, or compartmentalize the herbicides (Gaines et al. 2020). Because inhibitors of photosynthesis have been widely used in agriculture for many years, many weed species have evolved resistance to herbicides targeting the photosynthetic electron transport chain (Gronwald 1997). Resistance to inhibitors of PSII has evolved in 92 weed species such as common ragweed (*Ambrosia artemisiifolia* L.), redroot pigweed (*Amaranthus retroflexus* L.), annual bluegrass (*Poa annua* L), and knotweed species (*Polygonum* spp.) and has been reported widely across the globe, but primarily in the United States, Canada, and France (Heap 2024; Pfister and Arntzen 1979; Figures 8 and 9). Resistance to Group 5 herbicides is reported in 87 species, while resistance to Group 6 herbicides is only reported in 5 species as of 2024 (Heap 2024). Many species have evolved resistance to triazines, a Group 5 class of herbicides. Because reduced sensitivity to triazines is linked to mutations at Ser-264 on the D1 protein of the PSII complex, most of the triazine resistance cases involve mutations at that site (Battaglino et al. 2021; Gronwald 1997; Oettmeier 1999; Pfister and Arntzen 1979). In Group 5 herbicides, a Ser-264 to Gly mutation is responsible for resistance to triazines in the D1 protein (Funderburk and Lawrence 1964; Oettmeier 1999). This Ser-264 to Gly mutation has been found in more than 50 independent species across more than 20 different nations (Oettmeier 1999). However, biotypes that exhibit resistance to triazines due to this mutation are not resistant to urea-type herbicides, which are chemically distinct (Powles and Preston 1995). Several varieties of double and triple mutants also exist with mutations at two or three different sites, respectively. These mutations cause resistance to more than one herbicide in the same plant (cross-resistance). Some resistance to PSII herbicides has been found that does not involve TSR mutations. Instead, these plants evolved metabolism-based NTSR that detoxifies the Group 5 herbicides via the activity of glutathione *S*-transferases (Oettmeier 1999).

In some instances, species exhibit negative cross-resistance. Negative cross-resistance is described as a mutation that causes resistance at a class of herbicides but also causes hypersensitivity to another class of herbicide. Some weeds present resistance to triazines while remaining sensitive to ureas. Weeds that are resistant to triazines have greater sensitivity to herbicides from Groups 1, 30, and 6 (Fuerst et al. 1986; Gadamski et al. 2000).

Though it is less common, PSI resistance has been confirmed. However, it should be noted that resistance to PSI herbicides has evolved more recently than the resistance to PSII-inhibiting herbicides, which is likely attributable to the higher use rates and higher frequency of use of PSII herbicides. Paraquat resistance has been reported in 28 weed species across 14 different countries (Hawkes 2014). Both grass weeds (such as goosegrass [*Eleusine*

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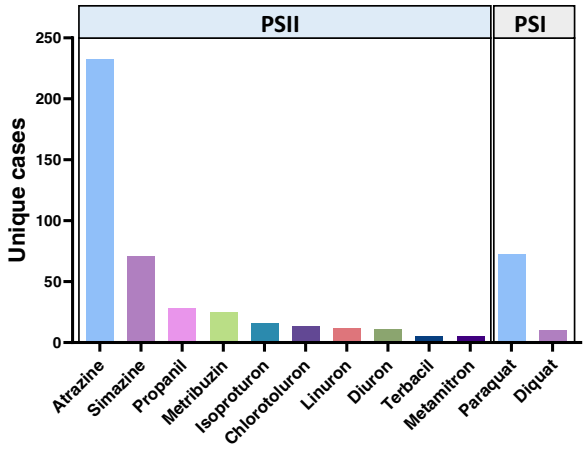

Figure 8. Unique cases of herbicide resistance in photosynthetic inhibitors grouped by active compound. PSI, photosystem I; PSII, photosystem II.

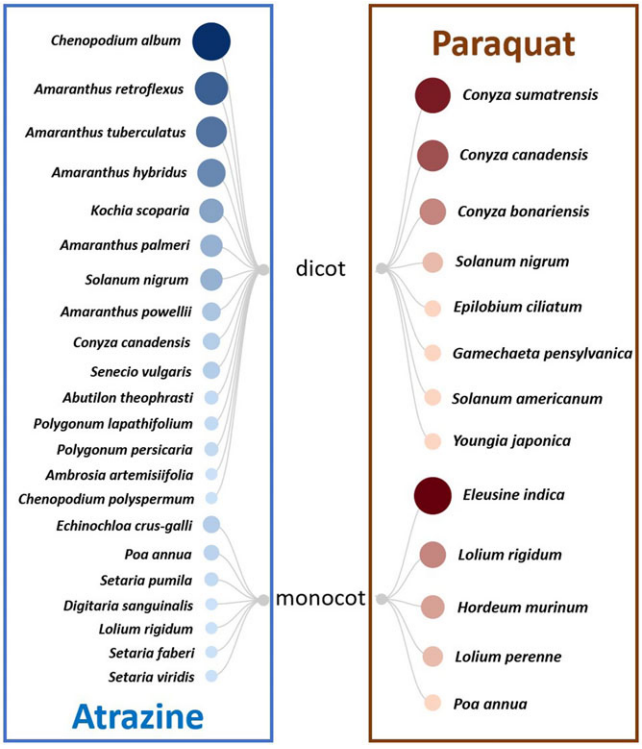

Figure 9. Most common monocot and dicot weed species with resistance to the photosystem II (PSII) herbicide atrazine (blue) and photosystem I (PSI) herbicide paraquat (brown).

indica (L.) Gaertn.] and rigid ryegrass [*Lolium rigidum* Gaudin]) and broadleaf weed species (*Conyza* spp. and others) have evolved resistance to PSI inhibitors, as they have to PSII inhibitors. However, resistance to PSI inhibitors seems more difficult to evolve, because these herbicides do not bind to a specific protein. The lack of ligand/protein interaction in this type of inhibition is not likely to result in a target-site mutation imparting resistance to PSI inhibitors. Additionally, PSI herbicides are fast acting, so plants have difficulty evolving mechanisms of NTSR to them. The compounds themselves accept electrons to generate ROS and cause oxidative stress. It is currently hypothesized that plants resistant to ROS-generating herbicides may have an increased antioxidant system that rapidly quenches excessive superoxide and hydrogen peroxide (Amorim et al. 2022). Plants overexpressing two or more enzymes in the Halliwell-Asada cycle (i.e., CuZnSOD, MnSOD, stromal ascorbate peroxidase, or dehydroascorbate reductase) have higher tolerance to PSI herbicide application. Overexpressing these enzymes causes the rapid inactivation of peroxide to reduce ROS and its effects. Similar effects are also seen in plants that overexpress catalase. Some studies also suggest that resistance to PSI herbicides can be caused by mutations that cause the sequestration of these herbicides into plant cell vacuoles (Hawkes 2014).

Limitations of Inhibitors of Photosynthesis

Despite their effectiveness, herbicides targeting photosynthesis have certain drawbacks. PSII inhibitors, particularly triazines, persist in ecosystems for extended amounts of time. They may damage ecosystems that exist in natural bodies of water (Muller et al. 2008). Additionally, these compounds are highly mobile in soil, allowing for high levels of soil translocation and leaching into waterbodies. This leaching is caused by the relatively high polarity of such compounds (Bottoni et al. 1996; Rodgers 1968). These herbicides are also suspected to be endocrine disruptors, meaning that exposure to these compounds causes interference with the endocrine system, the system in animals that is responsible for the synthesis and regulation of hormones (Moore and Waring 1998). Effects of endocrine disruption include increased risk of certain cancers, interference with reproduction and development, and defects in other bodily systems such as the nervous or immune systems (Casals-Casas and Desvergne 2011). In certain species, this can produce hermaphroditic individuals (Evans 2022). In humans, the primary means of exposure to such compounds is through drinking water, which is generally sourced from the ground water these herbicides leach into. Due to these health and environmental concerns, atrazine has been banned in Uruguay (Camargo et al. 2020).

The primary limitation of the use of PSI inhibitors like paraquat and diquat is their high relative toxicity. Paraquat is the most abundantly used PSI herbicide, with over 8 million kg yr^{-1} applied in the United States. This pyridinium is considered a dangerous substance. Paraquat can be fatal even in small amounts when swallowed or inhaled or even when in contact with skin, with oral and dermal LD_{50} values in rat of about 80 mg kg^{-1}. Prolonged and repeated exposure to paraquat can cause extreme organ damage, primarily to its target organs of the respiratory system (USEPA 2024). Paraquat disrupts mitochondrial electron transport and exposure also causes heart, kidney, and liver failure. Additionally, there is no known cure or antidote for paraquat poisoning. Paraquat exposure has also been linked to Parkinson's disease (Tangamornsuksan et al. 2019).

Like PSII herbicides, PSI herbicides may also be toxic to aquatic ecosystems, having large toxic effects on algae, bacteria, fish, and aquatic invertebrates (Tsai 2013). Paraquat is water soluble and can move quickly in these aquatic environments, although it is not mobile in soils. Paraquat persists in the environment for extended periods of time and can have a half-life of more than 6 yr (Donaher and Van den Hurk 2023).

Although paraquat continues to be used in the United States, its use is highly regulated and even banned in several other parts of the world, including several South American countries (Camargo et al. 2020). In Uruguay, paraquat requires a professional prescription to be used and is the only herbicide with this requirement. In 2020,

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paraquat was permanently banned in Brazil. In Colombia, only two herbicide prohibitions are in effect, one of which being the aerial application of paraquat (Camargo et al. 2020). In each of these nations and several others, paraquat is frequently put under review time and time again due to its known human health and environmental effects.

Additionally, a limitation presented by the herbicides that we currently use commercially is the lack of sites targeted. While Groups 5, 6, and 22 target either PSII or PSI, other compounds can target other aspects of photosynthesis. For example, 2,5-dibromo-6-isopropyl-3-methyl-1,4-benzoquinone (DBMIB) blocks the photosynthetic electron transport chain at the cytochrome b6/f complex (Bauer and Wijnands 1974; Trebst et al. 1970). Although the mode of action of DBMIB was identified before the 1980s and its relative toxicity is low, DBMIB is not used as a commercial herbicide, likely because it can inhibit the respiratory process when handled or used incorrectly. Furthermore, glutaraldehyde inhibits electron transport at the level of plastocyanin (Hardt and Kok 1977), but has toxicity effects similar to those of paraquat. However, glutaraldehyde is a very toxic reagent used to stabilize proteins in microscopy. Consequently, this compound has never been developed as a herbicide targeting this site of action.

Is There a Need for New Herbicides Targeting Photosynthesis?

Herbicides targeting photosynthesis have been used in agriculture since the 1960s (Ross and Kreiger 1980). Even though there are many cases of herbicide resistance (Gronwald 1997; Rigon et al. 2020) and some concerns over the environmental toxicity of these compounds, they remain popular. Herbicide discovery is a long and difficult process, but an important one to pursue to address pressing issues currently faced by farmers. Despite the 21.1% increase in cost of herbicide development since 1995 (AgbioInvestor 2024), photosynthesis is one of the best-understood biological processes, and it has been a successful source of valuable herbicides. Consequently, research on new photosynthesis-inhibiting herbicides aiming to identify molecules with modes of action outside known PSII and PSI targets or targeting known modes of action but with novel interactions within these sites should be pursued. However, while the combined market value of herbicides targeting photosynthesis is US$3.4 billion yr^{-1}, nearly 50% of that value rests in one active ingredient from each group (atrazine for Group 5, bentazon for Group 6, and paraquat for Group 22). Therefore, potential new herbicides targeting photosynthesis will have to perform better, cost less, overcome resistance, and have better environmental and toxicological profiles than the three leading active ingredients.

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