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An overreliance on herbicides in several important grain- and cotton-producing regions of the world has led to the widespread evolution of herbicide-resistant weed populations. Of particular concern are weed populations that exhibit simultaneous resistance to multiple herbicides (MHR). Too often, herbicides are the only tool used for weed control. We use the term herbicide-only syndrome (HOS) for this quasi-addiction to herbicides. Growers and their advisers focus on herbicide technology, unaware of or ignoring basic evolutionary principles or the necessary diversity provided by other methods of weed control. Diversity in weed control practices disrupts resistance evolution. Significant challenges exist to implementing diversity, including how to address information so that producers choose to alter existing behaviors (HOS) and take calculated risks by attempting new and more complex strategies. Herbicide resistance management in the long term will require creativity in many sectors, including roles for growers, industry, researchers, consultants, retailers, and regulators. There can be creativity in herbicide registration and regulation, as exemplified by the recent U.S. Environmental Protection Agency program that encourages herbicide registrants to register products in minor crops. We propose one idea for a regulatory incentive to enable herbicide registrants in jurisdictions such as the United States to receive an extended data exclusivity period in exchange for not developing one new herbicide in multiple crops used together in rotation, or for implementing stewardship practices such as robust mixtures or limitations on application frequency. This incentive would provide a mechanism to register herbicides in ways that help to ensure herbicide longevity. Approaches based only on market or financial incentives have contributed to the current situation of widespread MHR. Our suggestion for regulatory creativity is one way to provide both financial and biological benefits to the registering company and to the overall stakeholder community by incentivizing good resistance management.

Key words: Herbicide-only syndrome; multiple herbicide resistance; regulation.

The burgeoning global human population is highly dependent on the world's great crops of wheat, rice, corn, and soybean. In the face of many biological, environmental, and economic challenges, production of these vital crops must be substantially increased to meet future global food needs. Challenging global crop productivity every year are crop-infesting weeds, which if uncontrolled will devastate crop yield and quality. For decades, herbicides have reliably and efficiently controlled crop-infesting weeds, providing positive impacts on crop productivity and thus global food supply. However, an overreliance on herbicides for weed control in several important grain- and cotton-producing regions of the world has led to the widespread evolution of herbicide-resistant weed populations (Heap 2015). Of particular concern are weed populations that exhibit MHR. Our purpose here is to highlight that MHR is a major threat to agriculture and to emphasize that herbicides can be sustainable only if change occurs in current use practices. Herbicide sustainability requires many changes, including changes in governmental herbicide regulation to encourage diversity.

Herbicide-Only Syndrome

In the great crop-producing U.S. Midwest and South (known as the Corn Belt and the Cotton Belt, respectively) there were in 2014 a massive 32 million hectares on which growers reported weeds (*Amaranthus* spp., *Conyza* spp., *Kochia scoparia*, and other damaging species) resistant to the world's most important herbicide, glyphosate (Stratus Ag Research 2015). In addition to glyphosate resis-

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tance, many of these resistant weeds display MHR (Bell et al. 2013; Davis et al. 2009; Legleiter and Bradley 2008; Varanasi et al. 2015), including a waterhemp [*Amaranthus tuberculatus* (Moq.) J.D. Sauer] population resistant to five herbicide mode-of-action groups (Schultz et al. 2015). In Australia, MHR in the grass weed *Lolium* spp. extends across 20 million hectares (Boutsalis et al. 2012; Broster and Pratley 2006; Owen et al. 2014; Preston and Powles 2002), and MHR is also evident across significant areas in the dicot crop weed wild radish (*Raphanus raphanistrum* L.) (Owen et al. 2015; Walsh et al. 2007). In Western Europe there are at least 5 million hectares of MHR blackgrass (*Alopecurus myosuroides* Huds.) in 12 countries (Délye et al. 2010; Heap 2015; Moss et al. 2007). Herbicide control of MHR weeds can be very difficult as resistance can extend across many if not most of the herbicide options.

Too often, herbicides are the only tool used for weed control. We use the term HOS for this quasi-addiction to herbicides. Growers and their advisers focus on herbicide technology, unaware of or ignoring basic evolutionary principles or the necessary diversity provided by other methods of weed control. In short, for most field crop situations, a herbicide is chosen for short-term control of crop-infesting weeds. By comparison, other methods of weed control (biological or physical control, mechanical control, crop and pasture rotations, etc.) are viewed as long-term methods, often problematic to implement for practical and economic reasons, and giving variable results, which are often less visually efficient than evident with herbicides. All of these factors contribute to growers, and those that advise and supply them, focusing on herbicide technology and displaying HOS. The issue is that HOS ignores the potent evolutionary forces at work from strong herbicide selection with the outcome of resistance evolution and, increasingly, MHR.

MHR weeds would be less of an immediate threat if there were a continued pipeline of new herbicides effective on existing resistant weed populations. However, the discovery of a truly new, effective herbicide that meets stringent toxicological and environmental standards is a very rare event (Duke 2012). No new herbicides with novel modes of action for large-scale use in broad-acre agriculture have been introduced in the past 30 yr, and the number of all herbicides registered and introduced to the market has dropped precipitously. The combination of HOS with a lack of new herbicides and continued decline in available active ingredients due to regulatory exclusions generates the current, substantial problem of insufficient diversity in weed control.

HOS Must Change to Diversity

With MHR weed populations in many parts of the world it is abundantly evident that weed control programs relying exclusively on herbicides used without sufficient diversity are unsustainable. MHR in weed species is just another manifestation that weed species are potent survivors. Weeds have demonstrated, in some cases over millennia, the capacity to adapt and persist despite humans' best attempts to eradicate them (Barrett 1983; Vigueira et al. 2013). Yet, with creativity and diversity it is very possible to control weeds, even MHR weeds. Diversity in weed management disrupts resistance evolution and is essential for the sustainability of all weed control measures. Significant challenges exist to implementing diversity, including how to address information so that producers choose to alter existing behaviors (HOS) and take risks by attempting new and more complex strategies. Diversity can take many forms, and of course will differ from region to region and between different farm enterprises. Clearly, solutions to herbicide resistance on large crop fields in nations such as Argentina, Australia, Brazil, Canada, and the United States will include some different approaches than those used on smaller, more intensive crop fields in some other parts of the world. Solutions must be tailored to specific regions, farms, and even fields. However, we believe that to help herbicide sustainability in all cropping regions there must be nonchemical strategies that disrupt the selection pressures driving resistance evolution (Walsh et al. 2012, 2013). The harvest weed seed control (HWSC) strategies developed in Australia to introduce diversity for MHR *Lolium* spp. control are now in early stages of research in North America and elsewhere. We expect that HWSC strategies will develop in North America and elsewhere using available resources and amenable to local conditions and will probably be different from those that have developed in Australia. Such innovative research is necessary to address HOS and protect yields of vital crops globally.

Incentivizing Stewardship for More-Sustainable Management: A Role for Regulation

We conclude that HOS must be replaced with herbicides and diversity (HAD). HAD will be different in different parts of the world. HAD can involve many types of management practices (Norsworthy et al. 2012) and to achieve HAD will require creativity in many sectors, with roles for growers, industry, researchers, consultants, retailers, and government regulators. For example, the development of HWSC systems is an example of farmer and researcher creativity. Here we propose a possible creative role for government in contributing to HAD to help extend the longevity of new herbicides introduced in the United States or elsewhere.

In a world of MHR weeds, stewardship must aim to increase herbicide longevity. Resistance management and herbicide longevity is all about HAD. There can be creativity in herbicide registration and regulation, as exemplified by the recent U.S. Environmental Protection Agency (EPA) program titled "Exclusive Use Data Protection for Minor Use Registrations" (EPA 2014), which encourages herbicide registrants in the United States to register products in minor crops. This program provides a new option to address a longstanding problem of limited pest management options in minor crops that do not have a large enough market to justify the expense of pesticide registration. A company registering a new herbicide active ingredient for use in a major crop may receive an extension of exclusive use of 1 yr for each three minor crop registrations up to a maximum of three additional years, in addition to the 10 yr of exclusive use currently provided by the U.S. Federal Insecticide, Fungicide, and Rodenticide Act (EPA 2014). The exclusivity is extended by the EPA keeping the registration data package confidential for an extended period of time. Normally, competing companies wishing to obtain a registration for a previously registered active ingredient after the expiration of patents will forego the substantial burden of producing an identical data package themselves and wait for the registration data package to become public information. Under the minor crops program, competing companies may not access the registration data package for additional time and therefore must wait longer to use the data package to support their own registration of the active ingredient. Additionally, the U.S. EPA Minor Crop Pest Management Program (known as IR-4) supports development of research data that back new EPA tolerances and labeled uses for products already registered in other crops, making this available to registrants (at no cost) who register their products in minor crops. These regulatory programs provide incentives to herbicide registrants to pursue actions that may not otherwise provide sufficient financial return. Similar incentives from regulatory agencies could be used to protect both economic and biological benefits of herbicides.

We propose a regulatory change using the existing and creative minor crops registration example to provide an extension in data registration exclusivity in return for actions by the herbicide registrant to register herbicides and promote their use in ways that help to ensure herbicide longevity. The exclusive-use extension provides much value to the original herbicide registrant, in return for an action that they otherwise would likely not do. This mechanism could be used to provide economic incentive to extend the useful life of new herbicides or new and existing herbicides made selective in crops through biotechnology, by reducing the application frequency from what it would likely be if regulated only by the prevailing attitude of HOS. The economic incentive would be provided in return for reducing the potential use of the new herbicide and thereby reducing selection pressure for resistance.

To illustrate the potential effects of this regulatory change, consider the following scenario. A unique new herbicide is discovered and registered for use in soybean. The new herbicide provides effective control of several weed species, including MHR biotypes resistant to multiple current herbicides previously effective in soybean. Under current regulations, the new herbicide would likely be very popular and be used widely in intensive soybean production areas. The application frequency would be close to 1.0 ha^{-1} yr^{-1} in soybean. Under our proposed regulatory change, the registering company could instead choose to include a limit on application frequency on their label such that the herbicide could only be legally used once every other year, an application frequency of 0.5 ha^{-1} yr^{-1}. The herbicide registrant would exchange current sales for future sales in return for extension of registration data exclusivity, and the useful life of the new product would be extended due to a reduction in selection pressure provided by a reduction in application frequency.

Another example of how the proposed regulation could reduce selection pressure for resistance involves crops grown in rotation. Crop rotation is a typically recommended best management practice for herbicide resistance because it usually results in a more diverse herbicide program that can slow resistance evolution. The diversity in herbicides is enforced because herbicide modes of action that are selective in one crop are often not selective in other crops in the rotation and therefore different modes of action are used in the rotational partner crop. Consider if a herbicide registrant identified a new corn-selective herbicide, the new herbicide could, with biotechnology or through chemistry alteration or with a safener, also be made selective in soybean and therefore be used continuously in a corn–soybean rotation with the resultant higher herbicide resistance risk than if the herbicide was confined only to one crop. Here we suggest that the existing and creative minor crops registration mechanism could be modified so that, for example, a company could introduce a new herbicide in corn, and voluntarily choose to not introduce it in soybean (or vice versa), reducing the risk of resistance evolution. The higher resistance risk is due to increased selection pressure, because the application frequency of the new herbicide would increase from 0.5 ha^{-1} yr^{-1} (used only in corn) to 1.0 ha^{-1} yr^{-1} (used in both corn and soybean on the same field). In this scenario, a company could receive an extra time period (to be determined) for their new herbicide in corn, and no competitors could introduce the same herbicide in corn or soybean. This mechanism would provide financial reward and incentive for not introducing the new herbicide in soybean, with the objective of obtaining a longer useful life for a precious new herbicide resource.

Herbicide registrants must recoup their large discovery and development costs during the period of exclusive registration and therefore, understandably, seek to maximize sales. Because of the time limit on data exclusivity, competitors will eventually enter the market and there is economic pressure to maximize sales without regard to resistance evolution risks. For the initial herbicide registrant there is no point in preserving their herbicide technology only to see later-entering competitors promote actions that may increase the selection pressure for resistance. The business reality to maximize herbicide sales is evident but does not recognize the biological reality of resistance evolution. Use of the same herbicide in multiple crops in rotation can lead to eventual loss of the herbicide in all crops due to resistance evolution. Using the same herbicide repeatedly in a continuous cropping system also leads to resistance evolution. An incentivized label restriction to reduce the application frequency of a new herbicide, whether in a continuous cropping system or a crop rotation, could be feasible through an exclusive-use extension. The voluntary reduction in market share by the herbicide registrant would reduce the frequency of applications and the total area treated, thereby reducing the selection pressure for resistance and delaying in time the loss of the new herbicide due to resistance. The same argument prevails for additional potential voluntary measures from industry, such as stewardship programs that include robust herbicide mixtures with demonstrated activity on the same species or sequential use of multiple modes of action during the growing season (e.g., PRE and POST herbicides with different modes of action).

Several issues need consideration for such a regulation to be developed. The regulatory agency would need legislative authorization to grant an extension of data-use exclusivity to registrants. The minor crops program provides additional sales for a herbicide registrant, while the proposed resistance regulation would reduce current sales in exchange for future sales. Therefore the financial incentives for the registrants would need to be carefully calculated to determine the necessary return from the extra years of data exclusivity to compensate for the potential loss of sales due to reduced application frequency, and how many extra years would be needed to constitute a break-even point. Biotechnology traits have value and the loss of that value from not capitalizing on opportunities in additional crops would need to be determined. Methods to determine whether a registrant is eligible for the incentive would need to be established, such as deciding whether a new herbicide could be made selective in potential rotational crops through chemical safeners or biotechnology or both. Multiple registrants may have the same mode of action and register at different times, and to achieve the goals of this program may require coordination to keep a new mode of action out of alternative crops. A potential consequence of this regulation would be a restriction of access to new technology. If a new corn-selective herbicide could be introduced in soybean and it was not introduced as a result of this regulation, soybean producers would not benefit from the new technology. Such economic benefits and consequences would need to be carefully considered in the implementation of this proposed regulatory change, but of course resistance evolution dynamics are blind to these economic factors.

In a world of MHR and HOS, longer utility of new herbicide resources is imperative, because there is not a continuous stream of new herbicides exacerbated by continued losses of older herbicides, and therefore concerted actions must occur to keep herbicides working. Recently U.S. President Obama announced a 5-yr plan and $1.2 billion per annum budget to combat antibiotic-resistant bacteria (Sun 2015). President Obama's statement that "we should do everything in our power to ensure that antibiotics remain effective" applies equally to herbicides and resistance. We propose that herbicides are no less important in safeguarding our food supply than antibiotics are in safeguarding our health. Approaches based only on financial incentives arising from market forces without consideration of evolutionary realities have contributed to the current situation of widespread MHR. Our suggestion of a specific regulatory incentive provides both financial and biological benefits to the registering company and to the overall stakeholder community by incentivizing a reduced market share for a new herbicide, reduced total applications within a given time frame, and a longer potential useful life span of a new herbicide by reducing selection pressure. This regulatory incentive does not replace good resistance management by growers and advisers, and indeed must be complemented by good resistance management practices in order to have utility. Our proposal provides a mechanism to reconcile economic objectives with sound resistance management to prolong the life of precious herbicide resources and herbicide-resistance genetic traits. While the specific proposal applies to the U.S. EPA, creative regulatory practices could be implemented by pesticide regulatory authorities in any country desiring to provide incentives in return for voluntary action. Such regulatory creativity has been demonstrated in incentivizing herbicide registrants to register a new herbicide for use in minor crops. This creativity can be applied to minimize herbicide resistance evolution, helping move HOS to HAD.

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