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SPECIAL ISSUE

OPINION

Seventy-five years of synthetic herbicide use in agriculture: Will there be 100?

Herbicide discovery through innovation and diversity

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Abstract: Nowadays only five global corporations operate herbicide discovery programs. In response to this industry consolidation, few new herbicide discoveries and global evolution of herbicide resistant weed populations there has been the very recent emergence of currently nineteen small start-up companies focused on herbicide discovery. This diversity and focus in start-ups is hoped to result in innovative new herbicide discovery that is needed to counter major herbicide resistance evolution in global weed species.

Keywords: Crops, Herbicides And Resistance, Innovation, Precision Agriculture, Start-ups, Weeds

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Around 75 years ago, dichlorophenoxyacetic acid (2,4-D) was the first synthetic, crop-selective herbicide introduced for use in global agriculture. Indeed, 2,4-D was independently discovered during World War II UK and USA war research efforts and then developed post-war as a herbicide (Peterson, 1967). The success of 2,4-D in removing weeds from crops catalyzed the creation of herbicide discovery programs within existing and new chemical companies. Soon there were many corporations with activities in the chemicals area with herbicide discovery programs. Table 1 shows by around 1975 in Western Europe/USA at least nineteen corporations operated significant herbicide discovery programs (and potentially others). In total, these corporations employed many hundreds of herbicide discovery chemists and associated specialists.

In addition to the corporations listed in Table 1, some Japanese corporations have operated herbicide discovery programs, albeit much smaller programs (Table 2). Adding to this effort, some herbicide discovery efforts occurred (and continue) in university and other public sector research organisations (Dayan, Duke, 2022).

Table 1 - WesternEurope/USA corporations in 1975 with herbicide discovery programs

American Cyanamid	USA
BASF	Germany
Bayer	Germany
Ciba-Geigy	Switzerland
Dow	USA
Dr R Maag	Switzerland
DuPont	USA
Eli Lilly	USA
Hoechst	Germany
I.C.I.	UK
Monsanto	USA
Rhone-Poulenc	France
Rohm & Haas	USA
Roussel UCLAF	France
Schering	Germany
Shell	UK
Stauffer	USA
Velsicol	USA
Zoecon	USA

Table 2 - Japanese corporations with herbicide discovery programs (2022)
Ishihara Sangyo
Hokko Chem
Kumiai Chem
Kyoyu Agri
Mitsui Chem Agro
Nihon Nohyaku
Nippon Soda
Nissan Chem
OAT Agrio
SDS Biotech
Sumitomo Chemical Company

The herbicide discovery R & D efforts by the companies listed in Tables 1 and 2, and others, yielded a steady stream of new herbicides. Between 1970-1990, many herbicides were discovered and became widely adopted by farmers in many parts of the world. Crops, especially the major global field crops such as rice, wheat, maize, soybean, canola, cotton etc. were relieved of their previously yield-limiting weed infestations and could express their yield potential. Thus, herbicides made and continue to make major contributions to lifting global agricultural productivity and feeding a burgeoning world human population. However, many factors drove major consolidation among the corporations listed in Table 1, including the rising cost of discovering and developing crop protection chemistries (Phillips, 2020). Remarkably, there are now only five truly global corporations that operate herbicide discovery programs – BASF, Bayer, Corteva, FMC, Syngenta (hereinafter referred to as the Ag majors). The result of this industry consolidation has been far less herbicide discovery effort than existed in earlier decades. Of course, the five Ag majors have innovated and operate sophisticated herbicide discovery programs. However, the fact is that industry consolidation has resulted in less herbicide discovery staff and less diversity than in earlier decades (Table 1). While there are many contributing factors this industry consolidation correlates with few new herbicide discoveries.

Another major factor contributing to the decline in effort and innovation in herbicide discovery was the introduction of crops genetically engineered to tolerate herbicides. Roundup Ready® soybeans were commercialized in 1996 followed by other field crops that were rapidly and widely adopted in N and S America ushering in an era where the effectiveness and convenience of herbicide tolerant crops eliminated large markets for crop selective herbicides. Herbicide tolerant crops are now grown on more than 150 million hectares of the global soybean, corn, cotton, canola and sugarbeet crops (www.agbioinvestor.com). Ag majors responded by shifting investment from the discovery of novel herbicides to more attractive opportunities in crop protection chemistry and seeds and traits.

Adding to the reality of few new herbicide discoveries (Dayan, Duke, 2022) has been the loss of herbicide efficacy due to widespread evolution of herbicide resistance in prominent weed species infesting crop fields worldwide. The great success of herbicides in world agriculture resulted in herbicide over-reliance and this inevitably led to the evolution and a global explosion of herbicide resistant weed biotypes (Powles, Yu, 2010). There are now widespread resistant weed populations to most herbicides (www.weedscience.com), including to glyphosate, the world's most used herbicide (Duke, Powles, 2008). Of great concern are weed populations with metabolic resistance, endowing simultaneous cross-resistance to many dissimilar herbicides, including never-used new herbicides if they can be metabolized by existing resistant biotypes (Yu, Powles, 2014). The widespread evolution of herbicide resistant weed populations threatens the very efficacy and sustainability of many herbicides in global agriculture.

For the remaining five Ag majors, and indeed for all aspirants in herbicide discovery, it has become increasingly difficult to discover cost-effective new herbicides satisfying the required regulatory health and environmental safety standards and with efficacy on herbicide resistant weed problems in global agriculture (Hachisu, 2021; Dayan, Duke, 2022). Stringent regulatory health and environmental safety standards have removed some herbicides and there is also opposition in some quarters of society to the use of herbicides in agricultural and other landscapes. All of these factors have contributed to the industry consolidation to the current five Ag majors. However, in response to few new herbicides and widespread herbicide resistance weed evolution, small start-up companies focused on herbicide discovery have emerged in several parts of the world (Table 3). Remarkably, from zero just a few years ago there are now thirteen geographically-dispersed start-up companies with herbicide discovery programs (Table 3). A principal focus and goal of these start-up is to meet the need for herbicide resistance-breaking herbicide products (Hachisu, 2021). With intellectual and geographic diversity, these start-ups are taking a range of approaches to herbicide discovery. Additionally, there is considerable discovery activity in China and India, which was not evident in earlier decades. From this global diversity and with the nimbleness and intense focus that can occur within small start-ups, innovation in herbicide discovery (and crop protection in general) may be fruitful.

1. Conclusions

There can be no doubt that while herbicides greatly contribute to world agricultural productivity there is a

Table 3 - Start-up companies with herbicide discovery programs (2022)

Agrematch	Israel
AgPlenus	Israel
DemAgtech	Australia
Enko	USA
FortePhest	Israel
HarpeBio	USA
KingAgroot	China
Marrone Bio Innovations	USA
Micropep	Technologies
MOA Technology	UK
Oerth Bio	USA
ProjiniAgchem	Israel
Targenomix	Germany

dearth of new herbicide discovery. There is also no doubt that widespread herbicide resistant weed evolution has reduced herbicide efficacy. New herbicides are needed, yet discovery of new herbicides with all of the required properties is very challenging (Hachisu, 2021; Dayan, Duke, 2022). It is to be hoped that the recent appearance of the start-ups listed in Table 3 and the continued efforts of the Ag majors and others will result in important new herbicide discovery. At this point it is very important to highlight that for sustainable efficacy herbicides should be only one tool used in conjunction with other weed control tools and practices. Too often there is herbicide over-reliance, raising the likelihood for resistance evolution. Critically, there are a wide range of agronomic, mechanical and crop choice/rotation tools available that help achieve high crop productivity with minimal weed interference (reviewed in Norsworthy et al., 2012). Crop cultural practices, and the use of new non-herbicide weed control tools (*e.g.*, Walsh et al., 2013) used in conjunction with herbicides can extend the life of herbicides. Also there is revolutionary recent innovation in precision herbicide application. Herbicides have traditionally been applied as broadcast spray treatments across the entirety of crop fields, regardless of the pattern of distribution of weed infestations existing within these fields. Weed infestations can be in patches and randomly present in parts of crop fields. There are now cost-effective technologies enabling precision herbicide treatment (or other control tools). Sprayers equipped with on-board optical sensors/cameras and weed identifying machine learning algorithms enable precision herbicide treatment only to detected weeds, rather than whole field spraying (e.g., John Deere See & Spray, Bilberry Spot Spraying). These technologies can operate at the speeds and in the sometimes challenging situations that often exist when herbicides are used in crop fields. Alternatively, small autonomous robots equipped with such technology are being developed that slowly move across crop fields, automatically detecting, identifying and removing weeds (e.g., Swarm Farm Robotics). Aerial drone-mounted sensors are digitally mapping weed infestations, for subsequent precision spray treatment, or for direct precision spraying from drones (e.g., Rantizo). Some of these technologies are available now, and others are becoming cost-effective for use in crop fields. It is important to emphasize and highlight that these new technologies will change many factors, from influencing herbicide discovery priorities, through to on-farm use. Equally important is to emphasize the value of non-herbicide weed control technologies. Many of these technologies will assist the sustainability of herbicides for weed control, as part of integrated, diverse strategies for sustainable weed control. Nevertheless, especially for global field crops, herbicides will remain a central plank of weed control and will be employed using these new technologies. If this view is correct, and given the widespread herbicide resistant weed issues, there is a need for new herbicides with all of the required efficacy, safety and environmental properties. Therefore, along with the research activities of existing organisations (Ag majors and others), the advent of start-ups focused on herbicide discovery (Table 3) is a welcome and promising new avenue for innovation.

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