Perspective

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Crop protection compounds – trends and perspective

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Abstract

The Industry responsible for the discovery and development of crop protection compounds has undergone dramatic changes and increasing consolidation since the initial innovations in synthetic organic fungicides, herbicides and insecticides in the late 1940s and early 1950s. Likewise, there have been striking changes in the rate of introduction of new crop protection compounds over the past 70 years. While numerous studies over the past five decades have signaled the ongoing decline in the numbers of new active ingredients (AIs), a detailed analysis of the trends in the rate of introduction of crop protection compounds shows a more complex pattern in the overall output of new AIs. The recent (post-2000) decline in the numbers of new herbicides is the primary source of the perceived decline in overall numbers. When herbicides are excluded, the output of new fungicides and insecticides has been relatively constant, especially for the past 20 years. A notable observation is that innovation, as measured by the number of compounds representing a new chemical class (First-in-Class) has been relatively constant for the past 70 years, and most recently has been driven by the appearance of new fungicides and insecticides. Thus, the discovery and development of new AIs for crop protection and public health continues, in spite of the many challenges and changes to the Industry.

Keywords: fungicide; herbicide; insecticide; agrochemicals; crop protection compound industry; biologics; pesticide innovation

1 INTRODUCTION

The advent of synthetic, organic fungicides, herbicides, insecticides and acaricides during the 1940s and early 1950s provided a new level of efficacy in pest control for agriculture and vector borne diseases, improving food production and disease prevention around the world, a need that continues today.[1] However, many of these same new pesticidal products of the 1940s and 1950s also subsequently highlighted issues and concerns around environmental impact,[2] leading to improvements in environmental standards for pesticides.[3] The advent of these new pesticides also highlighted the impact of pesticide resistance, initially towards insects, and later towards plant pathogens and weeds, and most recently traits in transgenic plants (Fig. 1). The impact of insecticide resistance on pest insect control and associated failures catalyzed concepts underlying integrated pest management (IPM)[4,5] and insecticide resistance management (IRM).[6] These factors are among those that have contributed to the shape of the crop protection industry[7–9] with the long-term resultant consolidation within the industry[8–13] (Figs 2, 3). The many mergers and consolidations among the R&D-based companies in Europe, Japan and the US have resulted in a few large (based on sales) multinational companies (Figs 2, 3), and a host of smaller R&D-based companies, mostly in Japan (Fig. 3). In addition, there are a number of research institutes and companies in China that are now increasingly involved in the discovery of new crop protection compounds.[14,15]

Since the initial discovery and development of the synthetic, organic pesticidal compounds, and in spite of the on-going consolidation, there has been a continuing expansion in the numbers of compounds being discovered and developed.[16,17] There has also been a significant broadening of the numbers of classes of chemistries over the ensuing decades that have also contributed to the current composition of available crop protection compounds.[13,16–21] However, while there has been a continuing introduction of new crop protection chemistries over the past 40+ years, there has also been a consistent view that there has been a decline in the rate of introduction of new active ingredients (AIs).[22–30] These trends are, of course, dependent on when the analysis was undertaken, how the data were compiled, or in some cases the specific timeframe examined.[31–33] Interestingly, some analyses suggest that the rate of introduction of new AIs has been relatively constant[34,35] or even expanded,[36] again dependent on the timeframe examined and the data sources. Other studies suggest that the rate of introduction of new crop protection AIs has been variable as a function of time,[28,37–39] reflecting some of the above-mentioned global trends in the industry. Herein we provide an analysis of some of these trends and the impact on the output of new crop protection AIs, along with an evaluation of innovation among these AIs as a function of time.

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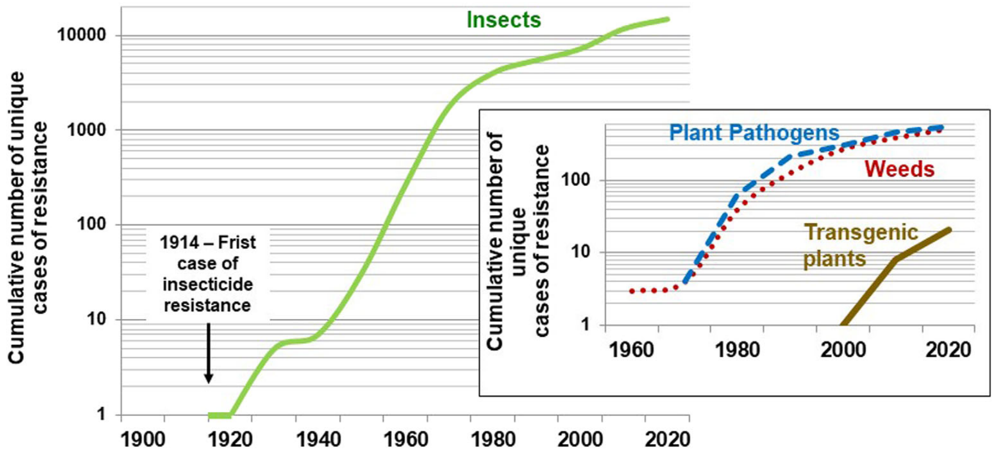

Figure 1. Cumulative number of unique cases of resistance in insects, plant pathogens, weeds and transgenic plants. First case of resistance Melander 1914.[76] Data derived, in part from.[8,18,71,77–79]

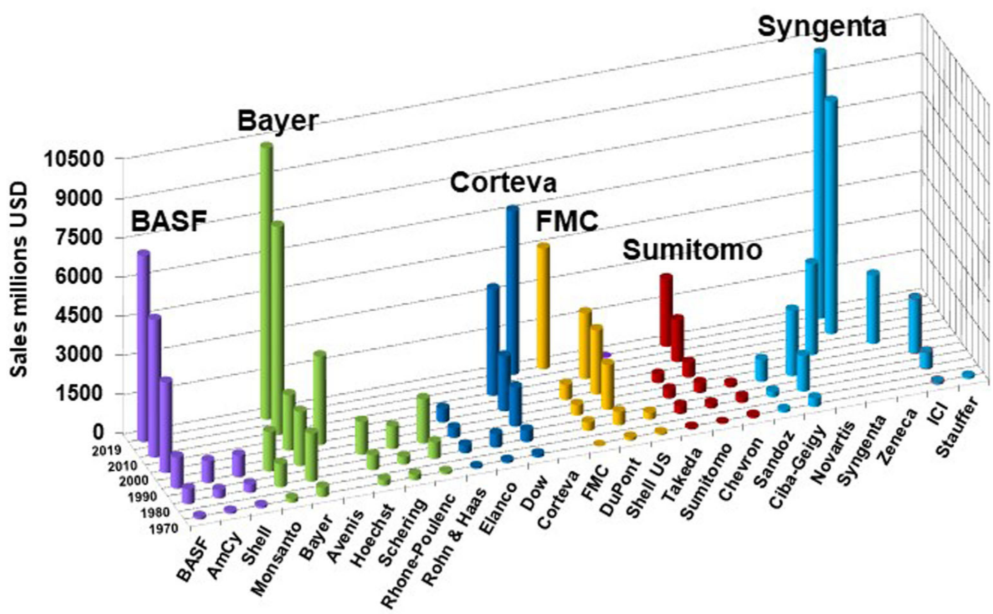

Figure 2. Examples of the consolidation (1970–2020) within the top six R&D-based crop protection companies (based on 2019 sales). Data derived, in part, from.[8,15,40,49]

2 DATA SOURCES

The dataset used in this paper (814 compounds) was derived primarily from the 2020 Agranova Crop Protection Actives database of commercialized compounds. The information in this database was supplemented by data from the Agranova Ag Chem Base database,[40] the Index of New ISO Common Names,[17] and the listings from the Fungicide, Herbicide and Insecticide Resistance Action Committees (FRAC, HRAC, IRAC, respectively).[18–20] Additional information for year of introduction (commercialization) was also derived from different editions of The Pesticide Manual,[41,42] and other selected sources,[12,43–47] as well as company websites. Some classes of compounds such as fumigants were omitted, while biologicals such as sprayable bacteria (e.g., *Bacillus thuringiensis*), viruses, proteins, plant extracts, etc., and pheromones were broadly grouped into biologics and treated separately. Chemistries that do not yet have an approved or accepted common name[17] were omitted.

Data for each AI included common name, year launched (commercialized), or if still in development, year of entry into the Index of New ISO Common Names,[17] compound type (i.e., fungicide, herbicide, insecticide) and 2018 end-user global sales value.[40] In addition, a determination was made for the date of commercialization of the first compound in each class/mode of action (MoA) grouping. i.e., first-in-class (FIC).[47,48] FIC as defined herein is the first compound in a chemical class that was commercialized, thus representing one potential measure of innovation. FIC compounds can (but not always) also be associated with a new mode of actions. Chemical classes were primarily based on the current editions of the FRAC, HRAC and IRAC classification schemes.[18–21] Non-FIC compounds are those molecules in the same class that follow a FIC compound. These non-FIC compounds are broadly classified as competitor inspired,[7,12,13] sometimes referred to as 'me-too' compounds, in that they are typically inspired by a FIC molecule and/or the patent(s) that gave rise to it.

Information on the numbers and evolution of research and development-based agrochemical manufacturers (Figs 2, 3) was derived from an array of sources[8–13,49–52] including company websites. Companies that are solely generic manufacturers, focused only on biopesticides (biologics) or do not yet have compounds with approved common names, were excluded.

3 NEW CROP PROTECTION COMPOUNDS – ANALYSIS

3.1 Global value of crop protection compound sales

The 2018 end-user value of fungicidal, herbicidal and insecticidal crop protection compounds totals $68.2 billion USD. As observed in the past,[24,27,49,53–57] herbicides make up the largest segment (approximately 45%) of the total global crop protection compound market (Fig. 4). Among the herbicides the amino acid synthesis-targeting herbicides (e.g., glyphosate) continue to represent the largest portion of the market (Fig. 4),[46,47] although sales may have seen some recent reduction,[57] while sales of other herbicide classes (e.g., very long chain fatty acid (VLCFA) inhibitors, auxin mimics) are increasing.[57] Among the fungicides, the strobilurins continue to retain the largest share of the market (Fig. 4), a trend[46,47] that appears to be continuing, along with growth some other classes of fungicides such as the succinate dehydrogenase inhibitors.[57] In the case of the insecticides, the neonicotinoids continue to retain the largest share (approximately 25%),[13,21,46,47] but this has been slowly declining from an apex of nearly 30% several years ago.[13] Among the newer chemistries, the diamides continue on their rapid rise,[13,57] now representing 13% of the global insecticide sales (Fig. 4), which is contrasted by the reduction in sales for the organophosphates, carbamates and neonicotinoids over the past several years.[13,57] These trends highlight the continued advancement of newer classes of chemistry exhibiting more favorable toxicological and environmental profiles. Thus, the makeup of the global crop protection compound market continues to evolve in response to changing grower needs, consumer desires, pest resistance and regulatory requirements.

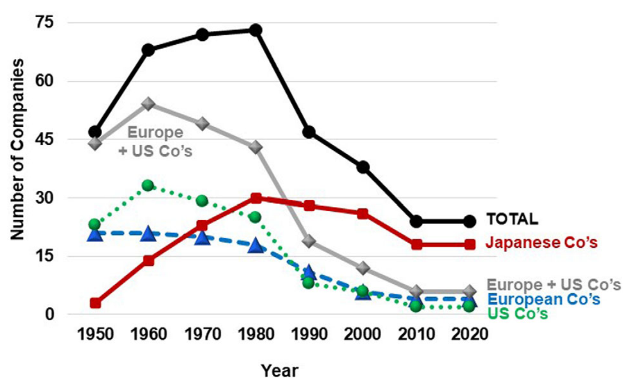

Figure 3. Time-line for the number of R&D-based companies involved in agrochemical discovery in Europe, Japan and the US. Data derived in part from.[10–13,49–51]

3.2 Analysis of the historic trends in the introduction of new crop protection compounds

As with any analysis, the patterns observed reflect the data source(s), the parameters used, and the timeframe examined. With that in mind, an examination of the present dataset shows that the rate of introduction of new crop protection compounds has shown some substantial fluctuations as a function of time (Fig. 5). From 1940 through 1970 there was a steady increase in the numbers of new crop protection compounds introduced (Fig. 5(A)). After approximately 1975 there was a sizable decline and then a second, larger peak in the 1990–2000 time period. This second peak was then followed by another substantial reduction in the numbers of new AIs being developed and introduced, and then a more gradual

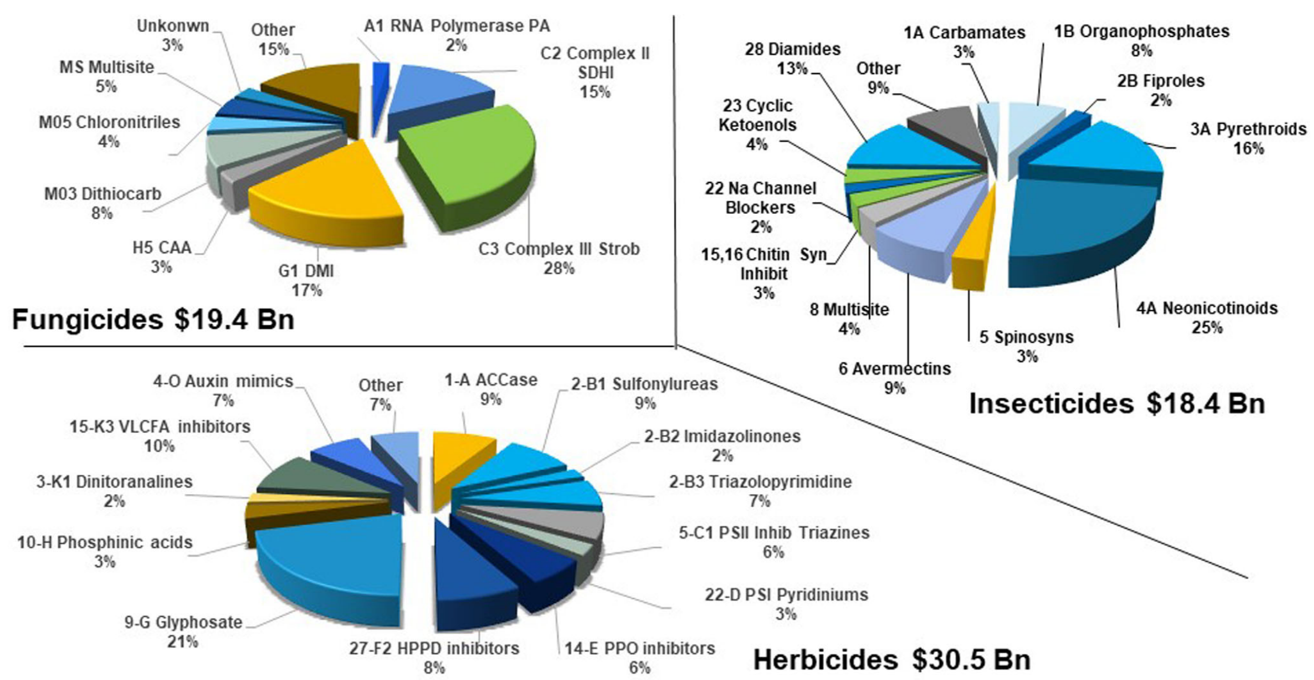

Figure 4. Primary classes of chemistry as defined by FRAC, HRAC and IRAC, and their relative 2018 end-user sales value as a percent of the total. 2018 end-user sales data from.[40]

decrease (Fig. 5(A)). Other studies with a somewhat shorter timeframe (1940–1995, 5-year intervals) and different dataset showed a different pattern involving a rise to a peak in 1965–1970 and then only a gradual reduction thereafter, there being no indication of a second peak.[29] Earlier studies examining the timeframe of 1940s–1980s show a peak in the late 1960s to early 1970s and then decline thereafter,[22–28] a pattern generally consistent with the first peak observed in the present study (Fig. 5(A)).

An examination of the product types (fungicides, herbicides, insecticides) of approximately 800 compounds in the dataset developed since 1940 shows a slightly larger proportion of herbicides (41%) compared to fungicides (27%) and insecticides (32%) (Fig. 5(B) insert). Fewer fungicides were developed during the 1950s to early 1970s compared to herbicides and insecticides (Fig. 5(B)), with all three product areas exhibiting a brief reduction in numbers in the late 1970s (Fig. 5(B)). Interestingly, the second peak in the numbers of herbicides is far larger than that observed for either fungicides or insecticides (Fig. 5(B)). The fungicides and insecticides exhibit similar patterns in the number of introductions during the 1980–2020 timeframe (Fig. 5(B)). Post-2000 there is a substantial reduction in the number of herbicides commercialized; a trend that continues. In addition, and also of interest, is the large rise in the numbers of biologics commercialized during the late 1990s, arguably exceeding the numbers of the fungicides and insecticides post-2000 (Fig. 5(B)).

The first of the two peaks observed in the commercialization of crop protection compounds (Fig. 5(A)), coincides with the rise in the discovery and expansion in the use of synthetic organic crop protection compounds starting in the late 1940s through about 1970, along with the rise in the total number of companies (Europe + Japan + US) involved in the R&D-based discovery of new crop protection compounds (Fig. 3). During the 1950s and 1960s, resistance to insecticides was on the rise (Fig. 1), in some cases leading to large control failures,[5] and also the first cases of resistance in weeds also appeared (Fig. 1). Resistance to fungicides also began to appear in the late 1960s and early 1970s[18] (Fig. 1). Importantly, the growing concerns during the late 1950s into the 1960s regarding the environmental impact of crop protection compounds[5,10] resulted in the expansion of regulatory guidelines and environmental impact testing.[3,5] Concurrently, the costs, time, and effort involved in the development of new crop protection compounds was also increasing,[8,12,38,39,58] requiring a substantial financial investment over increasingly longer periods on the part of a company, thereby increasing the risk associated with developing a new crop protection compound. These factors coincided with some of the initial reduction and consolidation in the number of crop protection companies in Europe and the US[8,10,12,13,51] (Figs 2, 3). Many of the oil companies (e.g., Esso, Gulf, Mobile, Shell US, Chevron) that were involved in the development of crop protection compounds during the

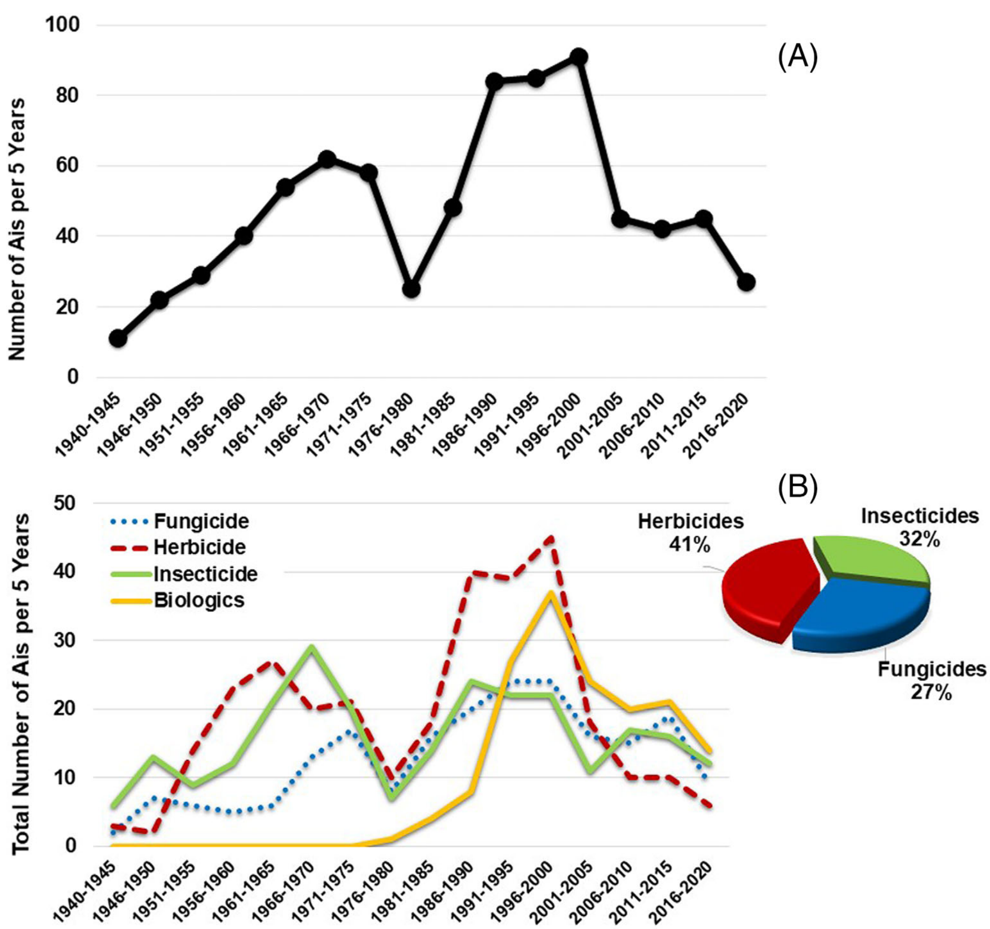

Figure 5. (A). Pattern for new crop protection compounds commercialized as a function of time. **B.- Inset** - Distribution of compounds by product area. (B). Comparison of numbers of new AIs introduced in the different product areas (n = 798), and biologics (n = 156), as a function of time.

1950s and early 1960s, dropped out or sold their interests as the costs and associated time investment escalated, especially when compared to the shorter timelines associated in drilling for oil.[59] During this timeframe, there was an increasing emphasis on the discovery and development of more selective compounds with improved toxicological and environmental profiles, especially relative to insecticides.[60–64] Additionally, the on-going lengthening of the time required for commercialization of new crop protection compounds[8,39] also has had the side-effect of essentially reducing the patent life for an AI. As such, the length of time an AI is proprietary is shorter, which in turn makes it more challenging to recoup the costs of development. All of these factors seemingly contributed to the notable drop in the rate of introduction in of new crop protection compounds during the 1970s (Fig. 5(A)) as some companies either got out of the crop protection discovery business or sought to re-direct discovery efforts and adjust to the need for products with improved environmental profiles to meet increasingly stringent regulatory requirements.

During the late 1980s and through the 1990s there was a second, larger peak in the output of crop protection compounds (Fig. 5(A)), primarily associated with the output of new herbicides (Fig. 5(B)). From 2000 to the present the numbers of crop protection compounds being introduced has declined, although this reduction is, again, primarily associated with the large reduction in the number of new herbicides (Fig. 5(B)) and has much less to do with the output of fungicides and insecticides (Fig. 5(B)). Indeed, there remains a significant interest in new insecticides as indicated by the continuing introduction of new classes of insecticides[13,65] and the increasing numbers of insecticide related patents during the past decade.[14]

The reduction in the output of new herbicides, and hence the post-2000 decline in the overall numbers of new crop protection compounds, coincides with the introduction of glyphosate (1974)[42,66] and especially with the introduction of glyphosate-resistant crops[66] in the late 1990s. This impact on herbicides had been noted previously[66–68] wherein there were fewer herbicide patents following the introduction of glyphosate-resistance crops. Also, as noted above, the increasing interest in biologics (Fig. 5(B)) and traits in transgenic crops have also contributed to the diversification of interests by crop protection companies in Europe, and especially in the US, beyond the discovery and development of new crop protection compounds.[11,14,39,57]

3.3 Recent trends in the output of new crop protection compounds

The post-2000 trends noted in Fig. 5(B) invite a closer examination regarding the recent output of the crop protection compounds. An analysis of Index of New ISO Common Names for Pesticides[17] provides another avenue to explore the output of the crop protection compound industry. Prior to commercialization, companies typically submit a proposed common name to the International Organization for Standards (ISO). Typically, the submission of a proposed common name is made (on average) 2–3 years in advance of commercialization. This index of new common names [17] lists all of the common names proposed and approved by the ISO since 1991, which at the time of this writing includes 383 compounds. Within this index, 80% of the compounds for which a common name has been proposed have been commercialized, approximately 4% of the compounds have failed to be commercialized (in a reasonable timeframe), and the remaining 16% are new or still in development. Thus, this Index provides a unique forward-looking window into what is coming in terms of new crop

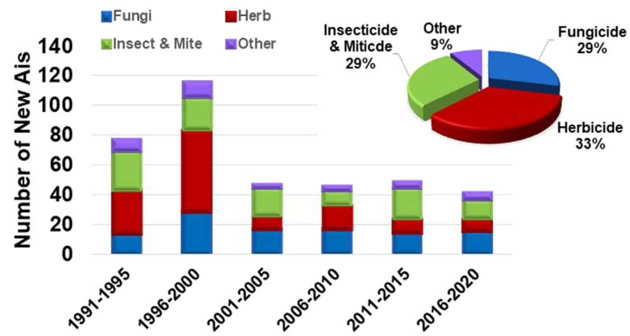

Figure 6. Numbers of compounds – 1991-2020. Index of New ISO Common Names, five-year intervals. *Data for 2020 is incomplete. n = 383. Since 2000, the overall output has been relatively constant.

protection compounds. Since 1991 there have been about equal numbers of fungicide, herbicides and insecticides (Fig. 6 insert). An examination of the pattern of appearance of new common names in the Index as a function of time reveals a peak in the numbers of new names in 1996–2000. Interestingly, there has been a near steady state in the number of new compounds listed in the index for the past 20 years (Fig. 6). However, the comparative contributions from herbicides appears smaller than that of fungicides and insecticides (Fig. 6). Thus, in spite of the aforementioned changes in the industry, these data suggest that the industry has continued to provide new options for the control of range of insect pests, plant pathogens, and to a lesser extent, weeds.

3.4 Frequency of innovation in crop protection compounds

Beyond the numbers of new crop protection compounds being introduced as a function of time, the more important question arises regarding the numbers of new modes of action or new classes of chemistry being developed. As a measure of innovation, the number of FIC compounds (defined in Section 2), representing the first member of a new chemical class of fungicidal, herbicidal or insecticidal chemistry, was determined. Overall, 24% of the compounds in the dataset were classified as FIC (Fig. 7). When examined by decade, FIC compounds are observed in every decade in a fairly constant ratio (Fig. 7). As might be expected, the proportion of FIC compounds was highest during the 1940s and 1950s (Fig. 7) when the first synthetic fungicides, herbicides and insecticides were introduced. However, innovation (as defined herein) has been a constant and continues to be observed throughout the decades of crop protection compound discovery (Fig. 7). Interestingly, there appears to be a recent upturn in the proportion of crop protection compounds that are FIC (Fig. 7). A further breakdown of the FIC compounds by product area (fungicide, herbicide, insecticide) shows that herbicides follow the general pattern of two peaks, with a dramatic decline post-2000 (Fig. 8). In contrast, the number of FIC fungicides shows an increase up to the 1960s and then a plateau to 1990, followed by a peak in 1990–2000, and then a return to pre-1990s levels (Fig. 8). Interestingly, and arguably, the overall pattern for FIC insecticides has been generally upward since the 1960s. Both fungicides and insecticides appear to be experiencing a notable recent (2011–2020) increase (Fig. 8). Thus, overall innovation in the form of FIC compounds has been relatively constant over the past seven decades, but with herbicides in particular exhibiting a distinct downturn during the past two decades.

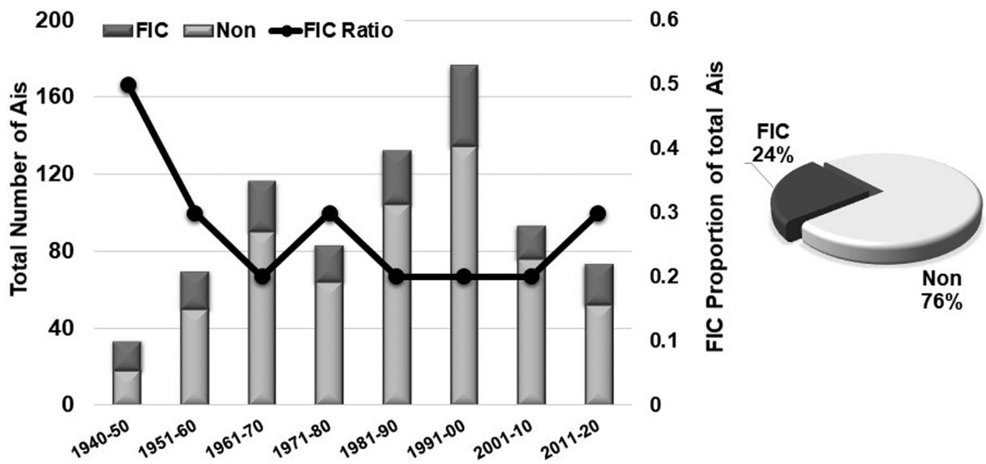

Figure 7. **Pie Chart** – Percent of First-in-Class (FIC) to non-FIC compound of the total number of compounds (n = 798). **Bars –** Total numbers of FIC compounds compared to non-FIC by decade. **Line** - Relative proportion of FIC compounds per decade.

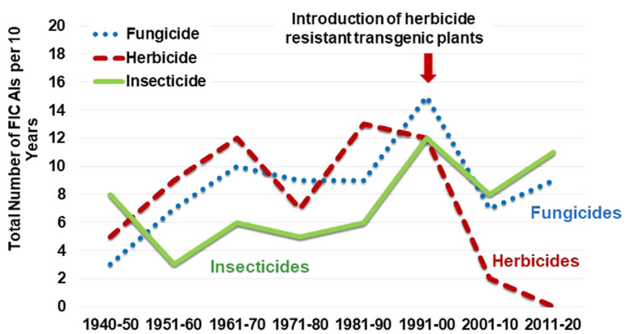

Figure 8. First-in Class (FIC) compound distribution by product area. n = 188.

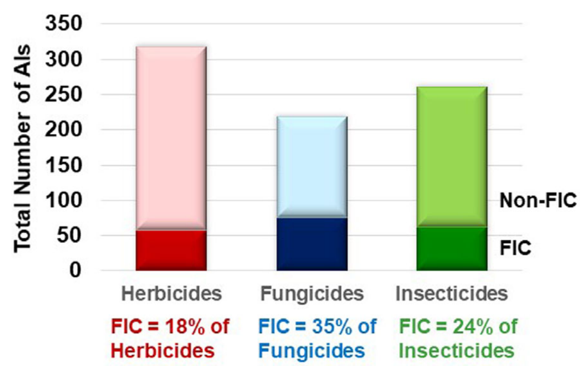

Figure 9. Distribution of commercialized compounds by product area – First-in-Class (FIC – dark color) *versus* non-FIC (light color). n = 798 compounds.

When the overall numbers of FIC compounds by product area are compared to the non-FIC compounds (Fig. 9), herbicides have proportionally the fewest FIC compounds (18% overall). Interestingly, insecticides show a higher proportion (24%) of FIC compounds, while fungicides exhibit the highest proportion (35%) of FIC compounds (Fig. 9) for this particular dataset. Thus, there appears to be some notable differences in the rate of innovation for the different product areas.

4 PERSPECTIVE

There has been a longstanding, general view that the number of new crop protection compounds being discovered and developed has been and remains on the decline. As noted above (section 3.2), in part, this view is dependent on the dataset and timeframe examined. The present analysis based on date of commercialization for approximately 800 historic and current crop protection compounds show two peaks in the numbers and corresponding declines (Fig. 5(A)). Following the second peak in the 1990s, there is a reduction in the overall numbers of commercialized compounds and those in early-stage development. However, most of the apparent post-2000 reduction appears to be associated with a dramatic decline in the numbers of new herbicides (Fig. 5(B)). In contrast, the appearance of new fungicides and insecticides has, arguably, been far more constant. Indeed, when the numbers of new entries into the Index of New ISO Common Names is examined, the overall output of new crop protection compounds has been relatively stable for the past 20 years (Fig. 6), as was previously noted for insecticides.[13]

As mentioned above (section 3.2), the decline in the numbers of herbicides has been associated with a decline in the numbers of herbicide patents following the introduction of herbicide resistant transgenic plants in the late 1990s.[67,68] An examination of herbicide patents (Fig. 10) focused on the primary historic and current R&D-based crop protection companies in Europe, Japan and the US (Figs 2, 3) shows a reduction in the average number of patents just prior to the introduction of herbicide-resistance traits into crop plants (Fig. 10). This decrease in herbicide patents is approximately 10 years prior to the decline observed in new herbicides post-2000, consistent with the 8–9-year average time required for commercialization of a new product in this same timeframe.[8,39] It is thus interesting to note the large recent increase in the number of herbicide patents (Fig. 10), suggesting a significant renewed interest in new herbicides, perhaps due in part to the rapidly increasing resistance to glyphosate and other herbicides, and/or expanding interest in herbicide resistance traits.

Interestingly, and in contrast to the 1990–2000s, while there was a reduction in the numbers of herbicides being introduced during the 1970s, this decline was not fore-shadowed by a reduction in herbicide patents (1950s–1970) (Fig. 10). On the contrary, there

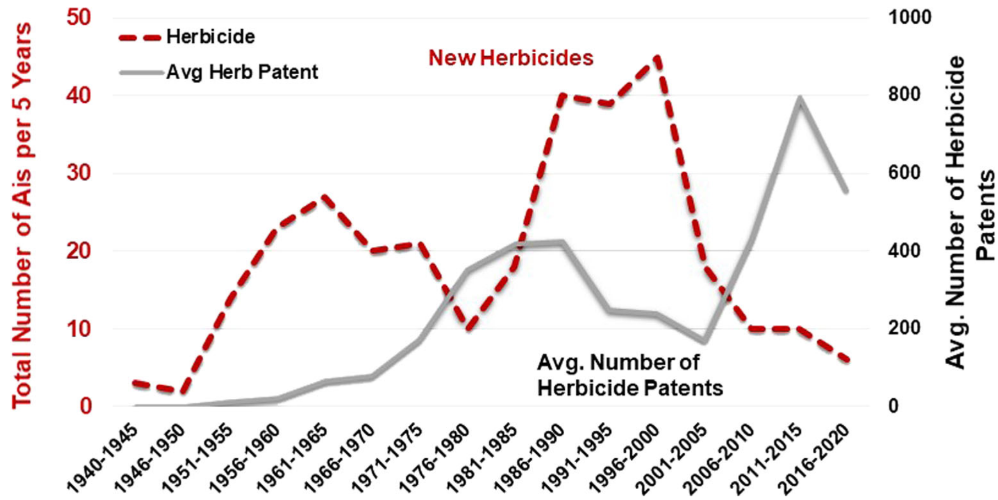

Figure 10. Plot of the total number of new herbicide AIs (red line) *versus* the average number of new herbicide patents per 5-year block of time (gray line). Total number of herbicides = 327. Herbicide patents (total = 19 996 unique patents) were largely composition of matter patents and included only those from the primary R&D-based crop protection companies in Europe, Japan and the US as represented in Figs 2 & 3. While the patent data is highly representative, it is not exhaustive. Totals for 2020 are incomplete and thus likely represent an underestimate.

was a continuous rise in the number of herbicide patents during the 1950s–1980s (Fig. 10). It is possible that during this period the ratio of new products to patents was shifting with a greater emphasis on patents for existing areas of chemistry, and/or a refocusing of emphasis towards new herbicides with improved environmental profiles. As such, it is conceivable during this timeframe that it required more patents per commercialized product by a declining number of companies (Figs 2, 3) to discover and enable each new herbicidal chemistry. A more in-depth analysis than is presently possible would be required to better understand the relationship between the herbicide discovery programs, the associated resulting patents, and the appearance of new herbicidal products during this period of time.

The large degree of consolidation that has occurred among the R&D-based crop protection companies in Europe and the US (Figs. 2, 3) has been widely noted[8–12,39,69] and certainly has the appearance of being consistent with the perception of declining numbers of new crop protection compounds. However, this perception does not consider the comparatively large number (albeit smaller in size based on sales)[15] of R&D-based companies in Japan that continue to be engaged in the discovery of new crop protection compounds (Fig. 3). Nor does this perception consider the increasing impact that research institutes and companies in China have had, and will have, on the discovery of new crop protection compounds. Certainly, in terms of recent (2007–2017) insecticide patents, China far exceeds the US, Japan and Europe,[14] although most of the Chinese patents were filed only in China with a large focus on mixtures.[14] However, as can be observed in the Index of New ISO Common Names,[17] new crop protection compounds from China are on the increase. Likewise, approximately one-third of the synthetic organic, non-biologic, crop protection compounds listed in the most recent edition of the Ag Chem New Compound Review[36] are from Chinese companies.

An important observation from the present analysis is the continuing discovery and development of new FIC crop protection compounds, especially fungicides and insecticides, that represent new classes of chemistry and often, new MoAs. Indeed, the number of new insecticide classes exhibiting new MoAs has been greater in the past 25 years, than the first 50 years.[13] Interestingly, and in some contrast to the fungicides and insecticides, there has been a notable decline in the numbers of new herbicides in general (Fig. 5(B)), and FIC herbicides in particular (Fig. 8). For quite some time, the discovery of new herbicides, especially herbicides with new MoAs has bordered on being a 'Holy Grail' for the crop protection industry.[37,67,68,70] This search for herbicides with new MoAs is all the more important given the continuing rise of resistance to herbicides[19,70,71] (Fig. 1), and especially as it relates to the rising tide of weed species displaying resistance to glyphosate.[72,73] Thus, it is interesting and important to note that there are now some new herbicidal chemistries, apparently with new MoAs, on the horizon.[36,69,74,75]

5 SUMMARY

An analysis of a large dataset of current and historic crop protection compounds spanning 70 years highlights some interesting observations. First, the global output of new crop protection compounds has not been on a long steady decline, as many might perceive or envision, but rather exhibits a more complex pattern as a function of time. Not surprisingly, some of the changes in the output appear to reflect changes in the crop protection industry as it relates to consolidation within the industry, changing consumer and grower expectations, and the increasingly stringent regulatory requirements. Second, when examined by product area, the output for fungicides and insecticides is comparatively stable, especially for the past 20 years. Third, in contrast to the fungicides and insecticides, there has been a notable decline in the output of new herbicides, which consequently impacts the whole overall pattern of the recent total output of crop protection compounds. Thus, setting aside herbicides, the discovery and development of new AIs for crop protection and public health continues, in spite of past and present challenges. Importantly, new classes of crop protection compounds continue to emerge providing new tools and options for the management of insect, plant pathogen and weed pests around the world, thereby contributing to the global efforts to provide adequate food supplies and the prevention of diseases by insect vectors. Finally, an interesting, and perhaps unexpected observation from the present analysis is that innovation, at least in the form of FIC compounds, has been a relative constant throughout the decades, in spite of the enormous changes and challenges that have confronted the industry.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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