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Review

The new age of insecticide discovery-the crop protection industry and the impact of natural products

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ABSTRACT

Improvements in food production and disease vector control, to feed and protect an expanding global population, require new options and approaches for insect control. A changing and an increasingly stringent regulatory landscape, shifts in pest spectrum due to changes in agronomic practices, and insect resistance to existing insecticides, all contribute to the challenges of, and need for, developing new insect control agents. The nature of insecticides emanating from discovery R&D-based companies in the European Union, Japan, and the United States have evolved from a concentration on a few classes of insecticides and modes of action (MoA), to a far more diversified collection of insecticidal molecules that embody many new, or under-utilized MoAs. Since 1990 there has arguably been a new age of insecticide discovery, with more new classes of insecticides introduced, with greater economic impact, than the prior 50 years combined. Although there has been an on-going evolution and consolidation in the size and shape of the crop protection industry, for the past two decades the output of new insecticides has remained relatively constant. The diversity of approaches employed in the insecticide discovery process (competitor inspired, bioactive hypothesis and natural products) has contributed to the discovery of these new classes of insecticides. Insecticide discovery is today a global enterprise, that armed with new tools and capabilities, will continue to build and provide the future insect control products to meet global grower and consumer demands.

1. Introduction

The discovery of new tools to control pest insects has been a critical need for centuries and continues today with the requisite of feeding an expanding global population (Godfray et al., 2010) and addressing the longstanding threats from insect borne diseases. Although there are many techniques and technologies for pest insect control including biological control, transgenic plants, host plant resistance, cultural controls, and increasingly biopesticides (Gunther and Jeppson, 1960; National Academy of Sciences, Insect-Pest Management and Control, 1969; National Academy of Sciences, 1972; Gross et al., 2014; Sparks and Lorsbach, 2017a), for many crop-pest-geography scenarios insecticides remain a critical component. Early solutions included natural products (NPs) such as nicotine and pyrethrum (Table 1), along with inorganic options such as sulfur and the arsenicals (Shepard, 1951; Casida and Quistad, 1998). A major transformation in pest insect control began during the 1940s and 1950s, with the introduction of synthetic organic insecticides such as DDT, organophosphates (OPs), cyclodienes, and *N*-methylcarbamates (Table 1). The late 1940s through the 1960s has been referred to as the "golden age of insecticide discovery" (Gubler, 1983; Achilladelis et al., 1987; Casida and Quistad, 1998), as highly effective, reliable and affordable pest insect control became commonplace. However, during this same time period, there was an expanded rise in insecticide resistance (Fig. 1). The rise in resistance, coupled with increasing concerns about mammalian and environmental toxicology of the available insecticides fueled the introduction of integrated pest management (IPM), and the quest for more selective insecticides that during subsequent decades resulted in numerous new additions to the existing insecticide classes (Table 1).

During the last 50 years, the crop protection industry has been successful in improving many attributes of new insecticides including improving the insecticide selectivity and lowering use rates (Sparks, 2013). Although the environmental profiles for new insecticides have improved over the past several decades, further improvement around attributes related to environmental impact continue to be an essential goal, driven in large part by increasingly stringent regulatory

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Table 1
Timing of introduction of different classes of insecticidal chemistries and their associated MoAs[a].

Year[b]	Target[c]	IRAC Grp	Chemical class/subgroup/ exemplifying active	Primary site of action/MoA[d]	Representative molecule[e]	# Compounds[f]	Market[g] Value
Pre-synthetic organic era[h]							
1746[i]	**NM**	**4B**	**Nicotine**	**nAChR Agonist**	**Nicotine**	**1**	–
1828	**NM**	**3A**	**Pyrethrum**	**VGSC Modulator**	**Pyrethrin I**	**1**	–
1848	**RSP**	**21B**	**Rotenone**	**MET I Inhibitor**	**Rotenone**	**1**	**$ < 2–3[j]**
1848	UN	UN	Sulfur	Unknown	Sulfur	1	–
1850s	UN	UN	Lime sulfur	Unknown	Lime sulfur	1	–
1867	RSP	–[k]	Arsenates	Ox-phos uncouplers	Paris green	many	–
1877	RSP	24B	Cyanide	MET IV Inhibitors	Calcium cyanide	3	–
1890	MS	8E	Tartar emetic	Multi-site	Tartar emetic	1	–
1890s	MS	8D	Borates	Multi-site	Boric acid	4	–
1892	RSP	13	Dinitophenols,	Ox-phos uncouplers	Dinitorphenol	3	$ –
1908	MS	8B	Chloropicrin	Multi-site	Chloropicrin	1	$ 276
1920s	**MG**	**11A**	***Bacillus thuringiensis***	**Midgut membrane**	***B. thuringienis***	**14**	**$ 308**
1920s	**NM**	**–**	**Ryanodine**	**Ry-R**	**Ryanodine**	**1**	**–**
1930s	RSP	24A	Phosphine	MET IV inhibitors	Al phosphide	4	$ 122
1932	MS	8A	Alkyl-halides	Multi-site	1,3-Dichloropropene	many	$ 343
1930s							
1939	NM	3B	DDT & analogs	VGSC modulator	DDT	7	$ < 1
1940s							
1943	**NM**	**1B**	**Organophosphates**	**AChE inhibitors**	**TEPP**	**165**	**$ 1462**
1945	**NM**	**2A**	**Cyclodienes**	**GGCC Antagonist**	**Chlordane**	**7**	**$ 1**
1950s							
1950	**NM**	**1A**	***N*-methyl carbamates**	**AChE inhibitors**	**Carbaryl**	**43**	**$ 551**
1950	UN	UN	Dicofol	Unknown	Dicofol	1	$ < 1
1952	MS	8F	Methyl isothiocyanate gen.	Multi-site	Dazomet	2	$ 313
1954	RSP	12D	Tetradifon	Inhibit ATP synthase	Tetradifon	1	$ 1
1960s							
1960	UN	UN	Chinomethionat	Unknown	Chinomethionat	1	$ 3
1964	RSP	12C	Propargite	Inhibit ATP synthase	Propargite	1	$ 38
1965	**NM**	**14**	**Nereistoxin analogs**	**nAChR Blocker**	**Cartap**	**5**	**$ 138**
1965	**MG**	**11B**	***Bacillus sphaericus***	**Midgut membrane**	***B. sphaericus***	**1**	**–**
1966	**NM**	**19**	**Formamidines**	**OA-R agonist**	**Chlordimeform**	**6**	**$ 7**
1967	UN	UN	Bromopropylate	Unknown	Bromopropylate	1	$ < 1
1968	RSP	12B	Organotin miticides	Inhibit ATP synthase	Fenbutatin oxide	3	$ 23
1970s							
1971	UN	UN	Benzoximate	Unknown	Benzoximate	1	$ < 1
1973	**GD**	**7A**	**Juvenoids**	**JH-R agonist**	**Methroprene**	**5**	**$ 6**
1975	GD	15	Benzoylureas	CSI	Diflubenzuron	14	$ 415
1977	**NM**	**3A**	**Synthetic pyrethroids**	**VGSC modulator**	**Fenvalerate**	**81**	**$ 2666**
1978	**NM**	**6**	**Avermectins-milbemycins**	**GluCl AM**	**Abamectin**	**4**	**$ 1534**
1980s							
1980	RSP	20A	Hydramethylnon	MET III inhibitors	Hydramethylnon	1	$ < 2–3[j]
1983	GD	10A	Hexythiazox	MGI	Hexathiazox	3	$ 46
1984	GD	16	Buprofezin	CSI	Buprofezin	1	$ 121
1985	GD	17	Cyromazine	CSI	Cyromazine	1	$ 11
1985	**GD**	**7B**	**Fenoxycarb**	**JH-R agonist**	**Fenoxycarb**	**1**	**$ 6**
1989	RSP	13	Sulfuramid	Ox-phos uncouplers	Sulfuramid	1	$ –
1990s							
1990	**NM**	**4A**	**Neonicotinoids**	**nAChR Agonist**	**Imidacloprid**	**8**	**$ 4248**
1990	**NM**	**2B**	**Fiproles**	**GGCC Antagonist**	**Fipronil**	**3**	**$ 551**
1990	**RSP**	**21A**	**MET I inhibitors**	**MET I inhibitors**	**Fenpyroximate**	**6**	**$ 250**
1991	RSP	12A	Diafenthiuron	Inhibit ATP synthase	Diafenthiuron	1	$ 42
1993	**GD**	**18**	**Diacylhydrazines**	**ECG-R agonist**	**Tebufenozide**	**6**	**$ 193**
1994	NM	9B	Pyridine azomethine deriv.	Chordotonal org. TRPV	Pymetrozine	2	$ 110
1995	**GD**	**7C**	**Pyriproxyfen**	**JH-R agonist**	**Pyriproxyfen**	**1**	**$ 71**
1995	**UN**	**UN**	**Azadirachtin**	**Unknown**	**Azadirachtin**	**1**	**$ ~5–7[j]**
1996	**RSP**	**13**	**Pyrroles**	**Ox-phos uncouplers**	**Chlorfenapyr**	**1**	**$ 89**
1997	**NM**	**5**	**Spinosyns**	**nAChR AM Site I**	**spinosad**	**2**	**$ 566**
1997	NM	22A	Oxadiazines	VGSC blocker	Indoxacarb	1	$ 266
1998	GD	10B	Oxazoles	MGI	Etoxazole	1	$ 31
1999	RSP	20B	Acequinocyl	MET III inhibitors	Acequinocyl	1	$ 27
2000s							
2000	RSP	20D	Bifenazate	MET III inhibitors	Bifenazate	1	$ 35
2002	GD	23	Tetronic/tetramic acids	Inhibitors of ACCase	Spirotetramat	4	$ 456
2002	**RSP**	**20C**	**Fluacrypyrim**	**MET III inhibitors**	**Fluacrpyrim**	**3**	**$ 23**
2004	MS	8C	Fluorides	Multi-site	Sulfuryl fluoride	2	$ 41
2004	UN	UN	Pyridalyl	Unknown	Pyridalyl	1	$ 104
2005	NM	29	Flonicamid	Chordotonal org.mod. undefined target site	flonicamid	1	$ 69

(*continued on next page*)

Table 1 (*continued*)

Year[b]	Target[c]	IRAC Grp	Chemical class/subgroup/ exemplifying active	Primary site of action/MoA[d]	Representative molecule[e]	# Compounds[f]	Market[g] Value
2007	NM	22B	Semicarbazones	VGSC blocker	Metaflumizone	1	$ 97
2007	RSP	25A	β-Ketonitrile derivatives	MET II inhibitors	Cyflumetofen	2	$ 79
2008	NM	28	Diamides	Ry-R Modulators	Flubendiamide/chlorantraniliprole	7	$ 2200
2010s							
2013	NM	4C	Sulfoximines	nAChR Agonist	Sulfoxaflor	1	$ 37
2013	NM	30	Isoxazolines	GGCC AM	Afoxolaner	6	New to ag[l]
2014	**NM**	**4D**	**Butenolides**	**nAChR Agonist**	**Flupyriaifurone**	**1**	**$ 1**
2017	NM	4E	Mesoionics	nAChR Agonist	Triflumezopyrim	1	New
2017	RSP	25B	Carboxanilides	MET II inhibitors	Pyflubumide	1	New
2018	**NM**	**9D**	**Pyropenes**	**Chordotonal org. TRPV**	**Afidopyropen**	**1**	**New**
2019	NM	30	Meta-diamides	GGCC AM	Broflanilide	1	New
2019	**NM**	**32**	**HXTX-HV1A peptide**	**nAChR AM Site II**	**GS-Omega/kappa HXTX-HV1A peptide**	**1**	**New**
2020 & beyond							
2020 +	–	–	Ethylsulfones	Unknown	Oxazosulfyl	?	New
2020 +	**NM**	–	**Flupyrimin**	**nAChR Agonist**	**Flupyrimin**	**1**	**New**
2020 +	–	–	Dimpropyridaz	Unknown	Dimpropyridaz	1	New
2020 +	–	–	Acynonapyr	Unknown	Acynonapyr	1	New
2020 +	GD	–	Benzpyrimoxan	Unknown	Benzpyrimoxan	1	New

[a] Information regarding the difference classes of insecticides (Table 1) is primarily derived from the Insecticide Resistance Action Committee (IRAC) classification scheme (Nauen et al., 2019; Insecticide Resistance Action Committee (IRAC), 2019) as is information regarding mode of action (MoA). The number of historic plus current products from each class was derived from references (Eto, 1974; Li and Vederas, 2006; Turner, 2018; Zhang et al., 2018; Agranova Alliance, 2019; Compendium of Pesticide Common Names – Insecticides, 2019).

[b] Year first example introduced (O'Brien, 1967; Martin, 1972; Eto, 1974; Martin and Worthington, 1977; United States Department of Agriculture, National Agricultural Statistics Service, 1983; Cropnosis, 2015; Sparks and Nauen, 2015; Turner, 2018; Agranova Alliance, 2019).

[c] General insecticide target based on IRAC classification; NM – nerve muscle; GD – growth & development; RSP – respiration; MG – midgut; UN – unknown or non-specific.

[d] Abbreviations used: ACCase – acetyl-CoA synthase, AChE - acetylcholinesterase, AM – allosteric modulator, CSI – chitin synthesis inhibitor, ECG-R – ecdysone receptor, GGCC - GABA gated chloride channel, GD – growth & development targets, GluCl – glutamate-gated chloride channel, JH-R – juvenile hormone receptor, MET – mitochondrial electron transport, MGI - mite growth inhibitors, MS – multisite, OA-R – octopamine receptor, Ox-Ph – oxidative phosphorylation, nAChR – nicotinic acetylcholine receptor, NM – neural & muscle targets, RSP – respiratory Ry-R – ryanodine receptor, UN – unknown or uncertain mode of action, VGSC – voltage-gated sodium channel.

[e] First example compound in the market compound within an IRAC group/subgroup.

[f] Approximate number of products/molecules (past, present and/or in development) in each class (United States Department of Agriculture, National Agricultural Statistics Service, 1983; Turner, 2018; Agranova Alliance, 2019; Compendium of Pesticide Common Names – Insecticides, 2019).

[g] 2017 sales (end user, millions USD) for the different IRAC classes of insecticides – data from Agranova (Agranova Alliance, 2019).

[h] Pre-synthetic era – typically natural products and inorganic compounds predating DDT (The synthetic organic era begins with discovery and development of DDT).

[i] Line colors: Light green- NP-based; Dark green – conceptually NP-models exist that potentially could have led to the discovery of the indicated classes of compounds but were found by others means; Lines in bold are NP-based compounds or those that conceptually could have been.

[j] Sales estimate – information from Agranova (Agranova Alliance, 2019).

[k] Not included in the IRAC classification.

[l] Too new to the crop protection market to have sales estimate.

requirements, and public expectations for more environmentally friendly options (Lamberth et al., 2013; Sparks, 2013; Corsi and Lamberth, 2015; Maienfisch and Stevenson, 2015; Sparks and Lorsbach, 2017b; Kalaitzandonakes and Zahringer, 2018; Nishimoto, 2019). Likewise, insect resistance to the available insecticides (National Academy of Sciences, 1969; Menn and Henrick, 1985; Hodgson and Kuhr, 1990; Lamberth et al., 2013; Sparks and Nauen, 2015; Sparks and Lorsbach, 2017b; Kalaitzandonakes and Zahringer, 2018) also continues to be another key driver, with the numbers of cases of resistance continuing to rise (Fig. 1) (Whalon et al., 2008; Tabashnik et al., 2014; Sparks and Nauen, 2015; Tabashnik and Carrière, 2017). Thus, new insecticides, ideally possessing new MoAs and further improvements to environmental profiles are needed to provide new options for insecticide resistance management (IRM) programs (Sparks and Nauen, 2015; Roush, 1989; Thompson and Leonard, 1996; Elbert et al., 2007; Nauen et al., 2019; Insecticide Resistance Action Committee (IRAC), 2019) and provide growers with new options that to meet or exceed current and future environmental standards.

2. The crop protection industry enters a new age of insecticide discovery

The discovery and commercialization of new insecticides has become progressively expensive, approaching, on average, $300 million USD, due to lengthened timelines and increased costs for the development and registration of new products (Lamberth et al., 2013; Corsi and Lamberth, 2015; Sparks and Lorsbach, 2017b). These factors have driven changes in the crop protection industry, in particular, consolidation among the companies (Fig. 2). During the first few decades of synthetic pesticide discovery, > 65 companies globally were involved in the discovery research and development (R&D) of new crop protection compounds. The number of R&D-based companies in the European Union (EU) peaked first in the 1950s (Fig. 2), while in the US the peak number of R&D-based companies occurred about 1960 (Fig. 2), and in Japan the peak occurred about 20 years later (Fig. 2). Since these industrial peaks, there has been a natural evolution and consolidation within the crop protection chemistry industry to achieve economies of scale and provide the necessary critical mass for success in the discovery process (Figs. 2). The net result of this evolution of the crop protection industry has been an overall reduction in the number of

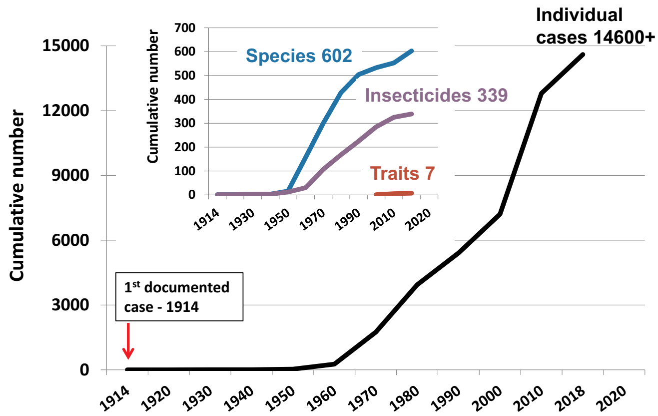

Fig. 1. Cumulative number of cases of resistance to insecticides since 1914. Insert–cumulative number of individual species, insecticides and insecticidal traits in genetically modified plants that have documented one or more cases of resistance (Tabashnik et al., 2014; Sparks and Nauen, 2015; Sparks and Lorsbach, 2017b; Tabashnik and Carrière, 2017; Nauen et al., 2019) and personal communication from Dr. David Mota-Sanchez, Michigan State University, 2018.

companies involved in discovery R&D (Achilladelis et al., 1987; Sparks, 2013; Sparks and Lorsbach, 2017b; Nishimoto, 2019) to the 22 companies within the EU, Japan and the US currently engaged in the R&D-based quest for new crop protection compounds (Fig. 2). However, the remaining companies are in many cases far larger, with greater resources (Sparks, 2013; Sparks and Lorsbach, 2017b) than their predecessors, and better positioned to innovate and participate in numerous markets and geographies. Moreover, there has been an equally important evolution in the types of insecticides available and used today (Table 1), reflecting a significant change in focus for the crop protection industry. During the past 27 years new insecticides with greatly improved environmental profiles, better able to meet the increasingly stringent regulatory requirements, have been discovered and launched. Thus, in many respects, the last 27 years (since ~1991) represents a new age or era in insecticide discovery, with twice as many new classes of insecticides developed with meaningful sales (herein defined as > $50 million USD; 2017 sales data) compared to the prior 50 years (Table 1). While these sales data clearly represent a specific window of time, these data also point to the prolific innovation that has emerged from the crop protection industry. This is not to imply that insecticides developed prior to 1990 are not of continued value or are not compatible with agriculture today. Many pre-1990 insecticides clearly remain important as exemplified by the synthetic pyrethroid insecticides, which have maintained a 15–20% share of the global insecticide market for nearly four decades (Fig. 3). Rather it is to point out that there has been a continuing growth in the number and diversity of new classes of insecticides, many with new MoAs, that continue to be discovered, and shape the global crop protection market (Table 1, Figs. 3, 4).

3. Numbers of insecticide modes of action

The insecticide market of the 1950s and 1960s was dominated by only a few classes of insecticides that included the DDT and its analogs, cyclodienes (and associated organochlorines), OPs, and the *N*-methyl carbamates (Table 1, Figs. 3, 4). These chemistries relied on just three MoAs: modulation of the voltage-gated sodium channel (VGSC), inhibition of acetylcholinesterase (AChE), and block of the *gamma*-aminobutyric acid (GABA)-gated chloride channel (Table 1). Together these groups of insecticides accounted for 94% of the total insecticide market in the US during the 1960s (Fig. 3). However, insecticide resistance, and the need for improved regulatory profiles dictated that new insecticide alternatives be brought be forward. Since this first generation of synthetic organic insecticides was commercialized, many other classes of insecticides have been discovered and come into major prominence, including the synthetic pyrethroids, the neonicotinoids, the diamides, and a range of "other" classes of insecticides. Included among these other classes are the benzoyl ureas, avermectins, spinosyns, tetronic/tetramic acids, and the diacyl hydrazines. (Table 1, Fig. 4). As such, the utilization of some earlier classes of insecticidal chemistry has declined dramatically in the past four decades (Sparks and Lorsbach, 2017a) (Table 1). As noted, previously, (Sparks and Lorsbach, 2017b) approximately 50% of global sales are now comprised of a combination of the others and the rapidly growing diamide class of insecticides (Fig. 3), highlighting the collective importance and impact of these new classes of insecticidal chemistry that have been discovered and commercialized since 1991. These new insecticides encompass a range of new or under-exploited (at the time of introduction) insecticidal MoAs (Table 1), that included the agonist site of the insect nicotinic acetylcholine receptor (nAChR) that is the target site of the neonicotinoids, an insecticidal target site that had previously only been utilized by the NP, nicotine. Other post-1991 new insecticidal target sites, including allosteric sites on the nAChR (spinosyns) and the GABA-gated chloride channel (isoxazolines, meta-diamides), acetyl CoA carboxylase (ACCase; tetronic/tetramic acids), ecdysone agonists (diacylhydrazines), Complex II of the mitochondrial electron transport chain (β-ketonitrile derivatives), VGSC-blockers (oxadiazines, semicarbazones), the allosteric site on the ryanodine receptor (diamides), and the chordotonal organ TRPV channel (pymetrozine, afidopyropen)

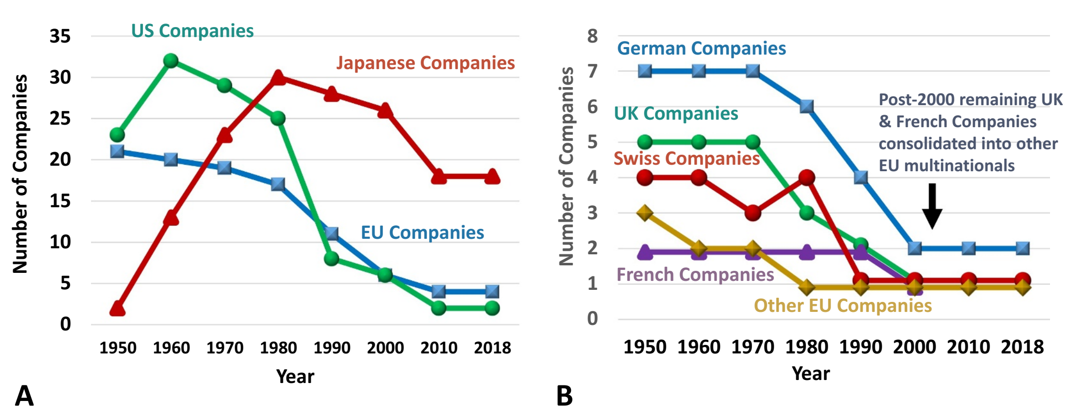

Fig. 2. A.-Number of crop protection companies in the EU, Japan and US involved in the basic discovery R&D (Copping, 2003; Bryant and Bite, 2013; Ota, 2013; Sparks, 2013; Copping, 2018). Companies principally focused on biologics or pheromones were excluded. B - Breakdown of the numbers of discovery R&D-based crop protection companies from the different EU countires.

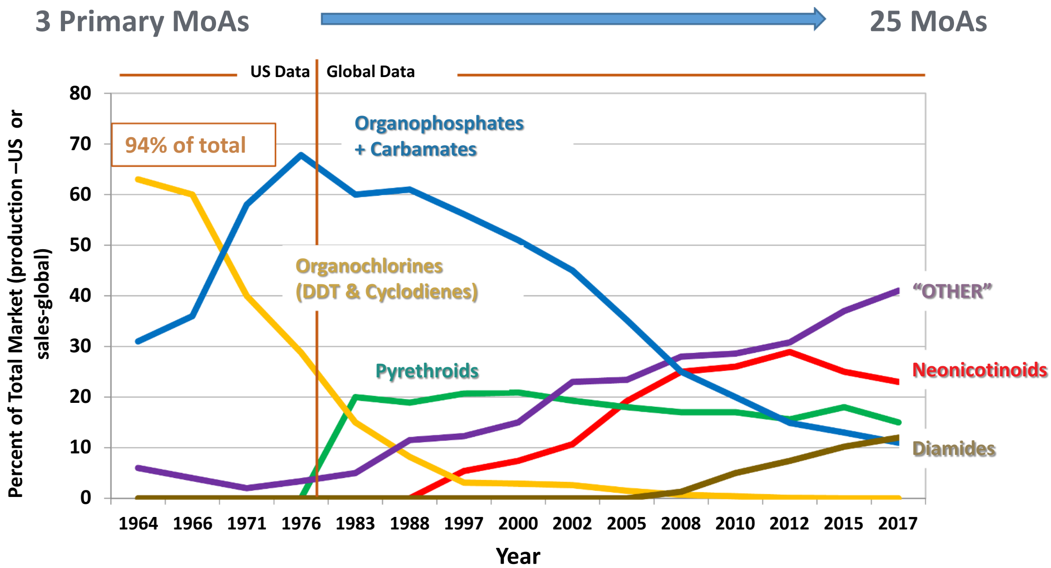

Fig. 3. Changes in the utilization of the major classes of insecticides as a function of time (United States Department of Agriculture, 1976; Sparks and Lorsbach, 2017a; A.P. Appleby, Herbicide Company "Genealogy", 2018; Agranova Alliance, 2019).

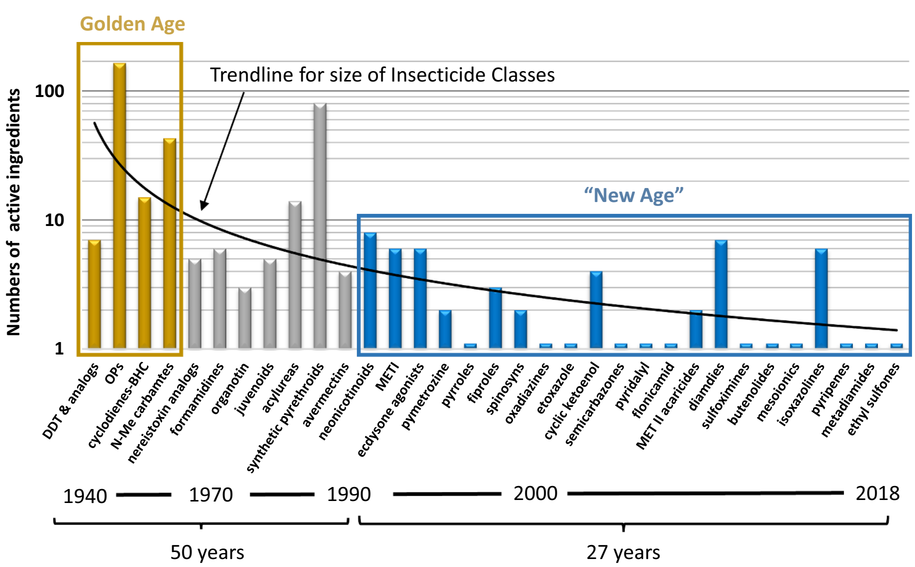

Fig. 4. Approxiamte date of commercial introduction for different classes of insecticides and the numbers of active ingredients (current & historical) associated with each class. Data on timing and numbers derived from (Eto, 1974; Schleifer, 2007; Sparks, 2012; Agranova Alliance, 2019).

(Table 1).

Interestingly, it has been argued that there are perhaps only a finite number of actionable insecticidal target sites that can lead to effective insect pest control (Casida, 1990). Since that article was published nearly three decades ago, new mechanisms of action have been discovered (Table 1). However, the new receptors or biochemical processes being targeted have been few (e.g. the ecdysone receptor, ACCase, and chordotonal organ TRPV channel). The VGSC has long been known to be a target for insecticides (pyrethrum, DDT, synthetic pyrethroids). The discovery of the insecticidal VGSC blockers represented a new insecticide binding site in the VGSC that was not previously targeted for an insecticide product, but not a new insecticide-sensitive target site. Likewise, the target sites of the isoxazolines and metadiamides (allosteric site on the GABA-gated chloride channel), spinosyns (allosteric site on the nAChR) and diamides (allosteric site on the ryanodine receptor) (Table 1) represented new insecticidal binding sites at receptors that were previously exploited for insecticidal properties. Thus, as specific targets (e.g., VGSC, nAChR), the number of exploited binding sites within these systems has increased, but the number of specific targets themselves remain relatively few, as suggested by Casida (1990). This situation is interesting to contrast with pharmaceuticals where there are many more targets, albeit, with very different requirements relative to delivery, efficacy, and the type of therapeutic effects (Swale, 2019). Within some of these known insect systems other distinct binding sites remain unutilized, including sites in VGSC (Soderlund, 2010) characterized by the *N*-butyl amides, (Elliott, 1985; Miyakado et al., 1989; Blade, 1990; Soderlund, 2017) and scorpion toxins such as *Aa*IT (Zlotkin et al., 2000). Importantly, other potential target sties in insects have been explored including the calcium, (Wang et al., 2001; Sparks et al., 2008b; Lümmen, 2013) and potassium (Swale et al., 2016) channels, muscarinic receptors, (Dick et al., 1997; Honda et al., 2007). GPCRs (Bai and Palli, 2012) such as the biogenic amine receptors (Huang, 2017; Sharan and Hill, 2017) and the systems regulating of the biogenic amines such as dopamine (Sparks et al., 1997).

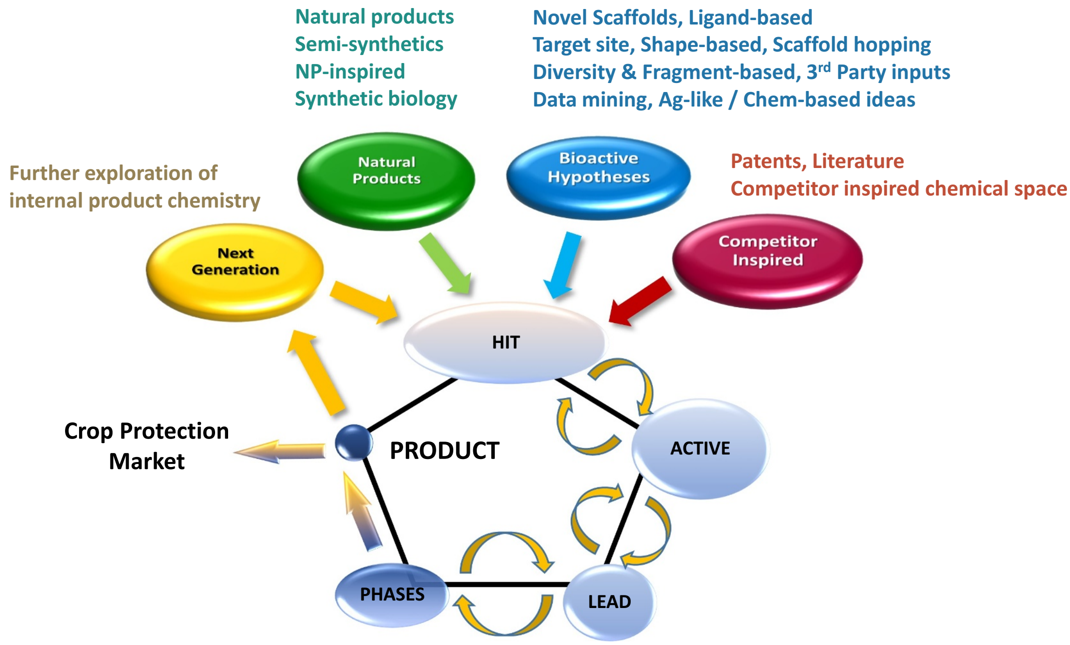

Fig. 5. Broad groupings of Lead generation approaches (Loso et al., 2017; Lorsbach et al., 2019). Builing a new insecticide is an iterative process. Once a product is developed, the interative process may be continued to build a next generation product within the class that has complementary or superior commercial attributes.

However, thus far other than the octopamine receptor these other systems remain unutilized. Perhaps, studies of these unutilized systems are similar to the situation leading to the discovery of the neonicotinoids, i.e. just waiting for the right convergence of a new chemistry, a different question (bioassay or different target insect) and a new hypothesis. Nicotine had long been known as an insecticide (Shepard, 1951; O'Brien, 1967) and nicotinoid analogs of nicotine had been explored for quite some time (Yamamoto, 1965) prior to the advent of the neonicotinoid imidacloprid. The convergence of a new chemistry scaffold (nitromethylenes (Soloway et al., 1979)), with testing against a different insect target species (brown planthopper) allowed scientists to weave together the hypotheses that ultimately contributed to the discovery of the neonicotinoids (Kagabu, 1999). This example and others serve as an illustration of the need for continued innovation to exploit a broad range of insect MoAs, and more importantly, to discover new MoAs. Thus, commercial exploitation of some of these other potential insecticide targets sites may be awaiting scientists synthesizing the right new chemistry that is then coupled with the right bioassay and a different set of hypotheses.

4. Discovering new insecticides: lead generation

Historically, there has been a wide range of approaches to insecticide discovery that has included empirical/random screening of chemical libraries, NPs as potential products and inspiration, various forms of biochemical (target-site) or bio-rational design, the open literature, competitor patents, biologically active scaffolds, internal datamining/broad screening of other areas of chemistry (herbicides and fungicides), and novel chemical scaffolds (Braunholtz, 1977; Menn, 1980; Eder and von Keyserlingk, 1985; Sparks, 2013; Shelton and Lahm, 2015; Loso et al., 2017). These different approaches can be broadly grouped into three categories: NP-based or -inspired, competitor inspired, or bioactive hypothesis-based (Fig. 6) (Loso et al., 2017; Lorsbach et al., 2019). This latter approach, bioactive hypothesis-based, as defined by Loso et al. (2017) is a divergence from *de novo* or chemistry-based design and random screening, in that it begins with a biological hypothesis, followed by the design the molecule(s) to address the hypothesis (Fig. 5) (Loso et al., 2017). Strategies included in the bioactive hypothesis-based approaches include data mining, target site-inspired, novel scaffolds, scaffold hopping, fragment-, ligand- & shape-based design, diversity screening, and literature-based ideas (Fig. 5). Not surprisingly, many lead generation activities would fall under the

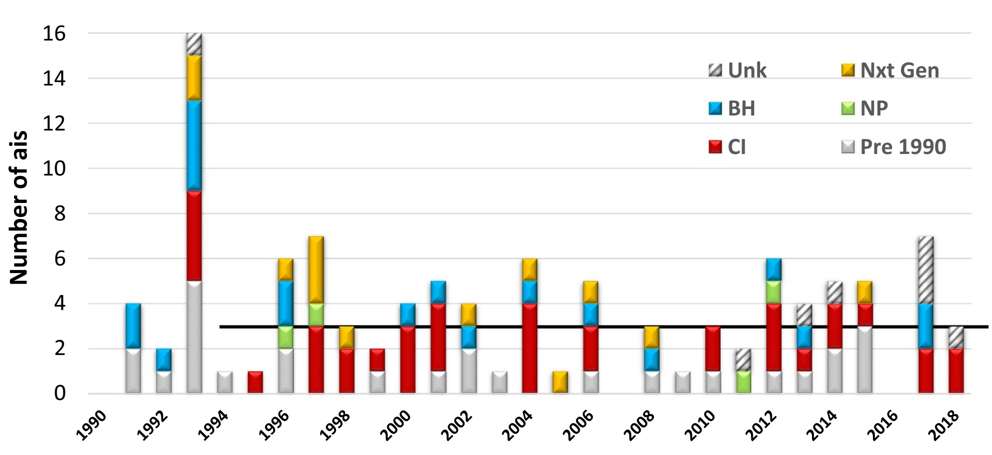

Fig. 6. Numbers of new ISO insecticide names per year since 1990 showing distribution of general lead generation approach (where known).(Compendium of Pesticide Common Names – Insecticides, 2019) Pre-1990 – compounds based on pre-1990 chemistry; OPs, carbamates & pyrethroids, CI – Competitor inspired, NP – Natural product based, BH – Bioactive hypothesis-based approaches, Nxt gen – Next generation, Unk – Lead generation approach used in presently unknown. $N = 114$, Black line – trendline for average numbers of new insecticides per year: 1994–2018.

bioactive hypothesis-based umbrella. The competitor-inspired (CI) approach to lead generation is somewhat self-explanatory. Here a competitor's chemistry is used as a starting point from which attribute hypotheses (biological or delivery based) guide the researcher towards new bioactive compounds possessing novel pharmacophore elements. As noted below, CI-based lead generation has historically been one of the most common approaches to lead generation, giving rise to a wide range of OPs, carbamates, pyrethroids, etc., that followed up on the original commercial molecules. The third category, NP-based lead generation has long been an important approach to lead generation and will be examined in more detail below.

A fourth category also exits in the form of next generation product discovery that is a company's internal follow-up to their own product (Fig. 5). With the successful launch of a new product it is naturally advantageous to determine if further extensions to the product-line are possible. This approach commonly focuses on improvements in efficacy, pest spectrum, or other useful attributes. Such investigations often occur even while the new product is still in development. Notable insecticide examples that emanated from this approach include methamidophos leading to acephate (improved mammalian selectivity profile), (Eto, 1974; Fukuto, 1984) carbofuran leading to carbosulfan (improved mammalian selectivity profile), (Fukuto, 1984) permethrin leading to cypermethrin leading to deltamethrin (improved efficacy), (Elliott, 1980) abamectin leading to emamectin benzoate (improved spectrum), (Rugg et al., 2010) imidacloprid leading to thiacloprid (improved foliar efficacy), (Jeschke and Moriya, 2019) tebufenozide leading to methoxyfenozide (improved efficacy), (Dhadialla et al., 2019) tebufenpyrad leading to tolfenpyrad (improved spectrum), (Sparks et al., 2019) spinosad leading to spinetoram (improved efficacy, spectrum, and residuality), (Sparks et al., 2008a) spirodiclofen leading to spiromesifen leading to spirotetramat (improved spectrum), (Jeschke et al., 2019) and chlorantranilprole leading to cyantraniliprole (improved spectrum and mobility) (Lahm et al., 2019).

4.1. Impact of the different lead generation approaches

A measure of the impact of the different lead generation approaches can be ascertained by examining the new insecticidal compounds with common names proposed to the International Standards Organization (ISO) during the last 27 years (Compendium of Pesticide Common Names – Insecticides, 2019). Where possible, the broad lead generation approach (NP, CI, bioactive hypothesis) was determined for each of the 114 new insecticides submitted for common names to the ISO since 1991 (Fig. 6). Presently, 73% of these insecticide have been commercialized, 7% have been discontinued and 20% are new/still in development. A large proportion of the new insecticides are CI-based, followed by bioactive hypothesis-based (Fig. 6). A more detailed breakdown of these newer insecticides (Fig. 7A) shows that 42% were CI-based, 29% were based on number of bioactive hypothesis approaches, and 13% were next generation-based. NPs accounted for the smallest portion, only 7% (Fig. 7A). However, the impact of NPs is far larger when the origins of some of the competitor inspired and next generation compounds are examined since many of those can be traced back to NPs. Considering these additions, the impact of NPs is higher with 17% of ISO insecticide entries being directly, or indirectly, NP-based (Fig. 7A).

4.2. Natural products as models for new insecticides

NPs have been an important, but less utilized source of recent new insecticides compared to the other lead generation approaches (Fig. 7A). However, when the origins of the current insecticide classes as defined by the IRAC MoA Classification Scheme (Insecticide Resistance Action Committee (IRAC), 2019) are analyzed in terms of current (2017) global insecticide sales (Fig. 7B), the overall value generated by NPs has been quite large accounting for about 37% of the total. In contrast, and perhaps not surprisingly, the competitor-inspired approach has not resulted in many products that represent new insecticide classes (Fig. 7B). There are a few exceptions as demonstrated by the VGSC blocker classes (IRAC group 22) of oxadiazines (McCann et al., 2012) and semicarbazones (Kuhn et al., 2012). (Table 1; Fig. 7B), and the more recent meta-diamide and isoxazoline classes of insecticides (Casida, 2015). However, historical data suggests that these are the exceptions, and not the rule.

In spite of the somewhat modest impact of NPs on new ISO insecticides, the potential impact of NPs has been far larger. For many of the classes of insecticidal chemistry that were discovered by other means, there are NPs that had the potential to serve as the models for many known classes of insecticides (Gerwick et al., 2014; Sparks et al., 2017). A noteworthy example are the neonicotinoids which had their origins in a third-party submission that led to the discovery of nithiazine, (Soloway et al., 1979) which in turn provided the foundation for the discovery of imidacloprid (Kagabu, 1999; Kollmeyer et al., 1999; Yamamoto, 1999). In retrospect, the relationship of the neonicotinoids

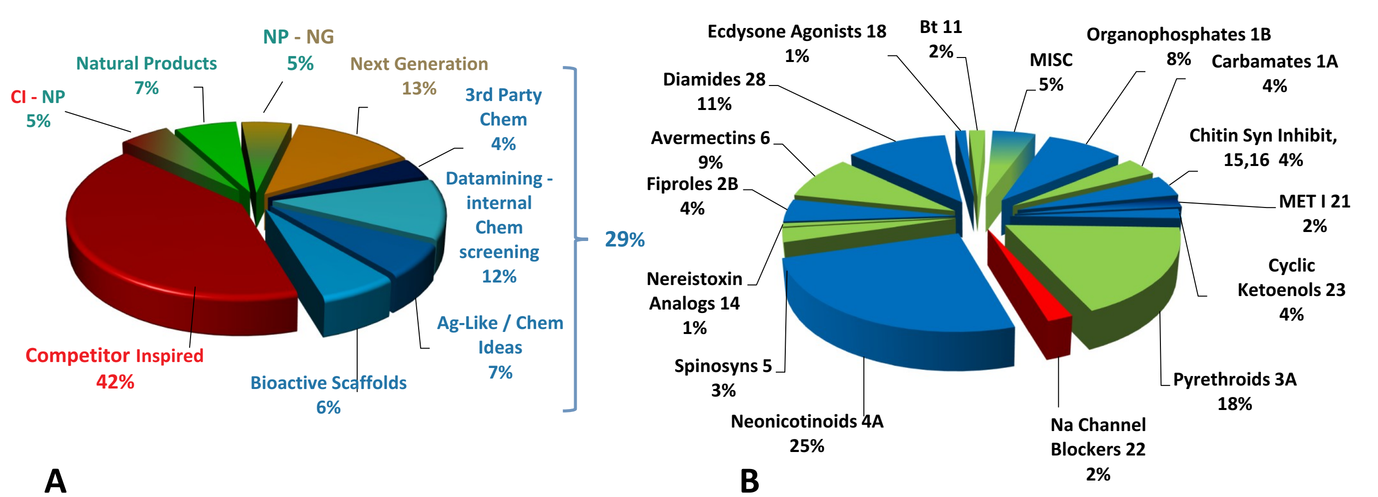

Fig. 7. A-Lead generation sources (where possible to determine) of new ISO named of insecticides (Compendium of Pesticide Common Names – Insecticides, 2019) since 1990, includes 77 compounds and excludes OPs, carbamates and pyrethroids. B-Origins (lead generation approach, see Fig. 5 and text) of the current major classes of insecticides (based on 2017 sales) (Agranova Alliance, 2019). Classes are based on the Insecticide Resistance Action Committee (IRAC) MoA classification scheme (Insecticide Resistance Action Committee (IRAC), 2019). Numbers next to the class name refer to the IRAC MoA Group Numbers.

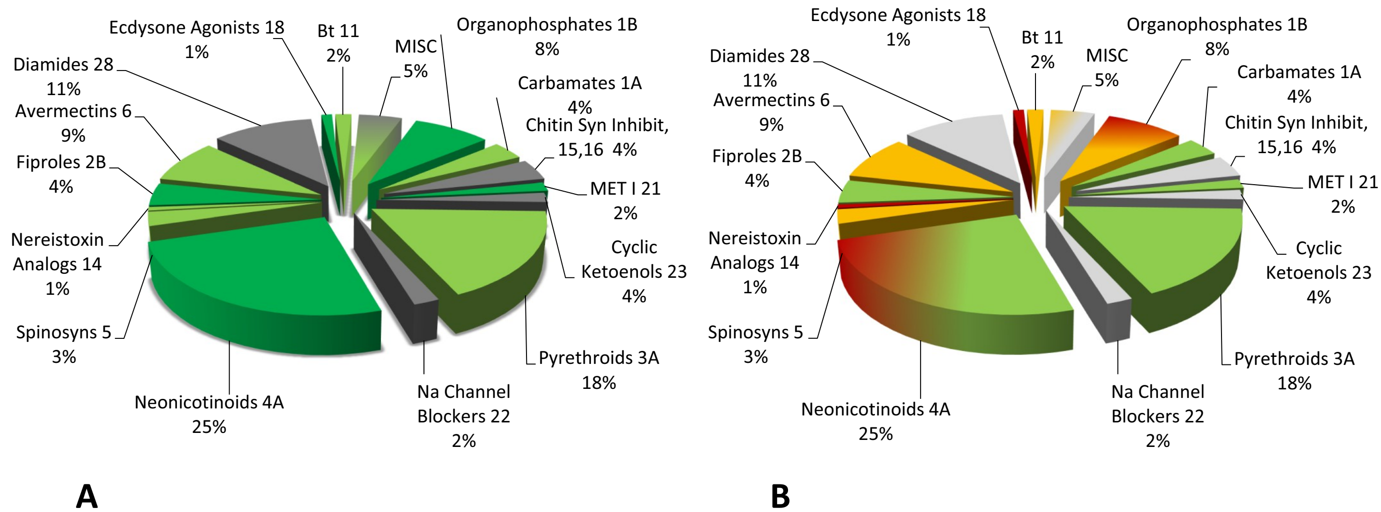

Fig. 8. A-Impact (real and potential) of natural products on current major classes of insecticides (based on 2017 sales) (Agranova Alliance, 2019). Classes are based on the IRAC MoA classification scheme (see Fig. 7 for details). Light green – class is the direct result of a NP or inspired by a NP. Dark green – area of chemistry discovered by other means not involving a NP, but for which a NP model exists. Gray – area of chemistry not derived (real or potential) from a NP. B – NP sourcing (actual and potential) of the major insecticide classes. Green -plants, Yellow – microbes, Red – animal, including insects and sponges. Gray – Non-NP. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to the NP nicotine is obvious, (Yamamoto, 1999) and under different circumstances, nicotine, or perhaps epibatidine, could potentially have served as the inspiration for the design of the neonicotinoids. Similar examples where NPs could have served as inspiration for synthetic insecticides exist for the OPs, ecdysone agonists, the mitochondrial electron transport site-1 (MET I) inhibitors, and arguably the fiproles (Sparks et al., 2017). Thus, when viewed in this light, the impact, real and potential, of NPs on insecticide discovery and sales is substantial, conceivably accounting for > 75% of the 2017 total global insecticide sales (Fig. 8A). As such, NPs as models and inspiration have been and remain an important starting point for new insecticidal chemistries (Sparks et al., 2017; Lorsbach et al., 2019). Interestingly, plant-based NPs have been the largest source of insecticidal compounds (Sparks et al., 2017). (Fig. 8B), serving as inspiration for insecticidal chemistries such as the *N*-methyl carbamates and synthetic pyrethroids as well as producing metabolites from which, theoretically the neonicotinoids, OPs, fiproles or MET I inhibitors could have been derived (Fig. 8B). In contrast, some of the more recent NP-based insecticidal products including the avermectins and spinosyns have been microbial-based.

As with any lead generation approach, NPs present some issues and some advantages. The discovery of new NPs can be a long and challenging process (Isman and Akhtar, 2007; Lorsbach et al., 2019) potentially lessening its appeal for lead generation. Additionally, once isolated and identified, NPs can be complex molecules with many stereocenters, rendering the process of designing insecticides based on them a lengthy and involved process. As such, NP-based insecticides can potentially require more time than other Lead generation approaches (Sparks, 2013; Pye et al., 2017). On the advantage side, NPs frequently uncover new insecticidal MoAs, as demonstrated by the avermectins, spinosyns, nereistoxin analogs, ryanodine, afidopyropen, and others (Table 1), providing added incentive for maintaining an interest NPs as a lead generation tool. Also, advances in synthetic biology and genetic engineering of NP sources may also provide access to new analogs of known NPs or potentially entirely new NPs (Lorsbach et al., 2019). For example, new analogs of the avermectins and the spinosyns were obtained through genetic modification of the associated biosynthetic pathways (Li and Vederas, 2006; Sheehan et al., 2006).

4.3. Tools to facilitate insecticide discovery

During the past 27 years, a variety of new tools have come to the forefront to facilitate the discovery of new crop protection compounds. Technologies that allow for the rapid preparation of chemical libraries and high throughput screening (HTS) have been commonly used in the crop protection industry for > 20 years (Allemza and Eldridge, 2007; Drews et al., 2012; Nakagawa and Harada, 2012; Shelton and Lahm, 2015). Unlike the pharmaceutical industry, the crop protection industry has the advantage of being able to exploit *in vivo* HTS using miniaturized assays in 96-well plates or related systems, targeting key pest species of interest, albeit at a throughput that is likely less than would be possible with many *in vitro* assays. The species that would ideally be employed in a HTS would include major insect pests such as aphids (e.g., *Myzus persicae*), lepidopterans (e.g., *Heliothis spp*., *Spodoptera spp*.), and as well as model insects such as *Drosophila melanogaster* or mosquitoes (e.g., *Aedes aegypti*), (Jansson et al., 1997; Ridley et al., 1998; Drews et al., 2012) all of which are also representative of larger pest insect groups, and thus provide the capability to establish *in vivo* efficacy very early in the testing process.

As an adjunct to the screening and lead generation process, *in silico,* or virtual screening of potential chemical inputs is also widely used by the crop protection industry (Böhm and Schneider, 2000; Drews et al., 2012; Nakagawa and Harada, 2012). *In silico* screening can focus on chemistries that *a priori* possess ag-like and lead-like properties (Schleifer, 2007; Drews et al., 2012; Zhang et al., 2018) as well as emphasizing computationally-based chemical fingerprints associated with certain insect pests based on prior screening results. Additionally, three-dimensional versions of potential inputs can the virtually screened against models of receptors or target enzymes. The net outcome of these types of approaches is to increase the probability of finding new active lead chemistries, while minimizing the number of compounds that need to be purchased or synthesized, prior to any bioassays. Thus, the use of *in silico* screening serves to keep the size of the HTS screening programs manageable, while improving the likelihood of finding new active chemistries.

Although widely explored, *in vitro* target site based HTS has thus far not been a major factor in the discovery of new insecticidal chemistries that have become products (Allemza and Eldridge, 2007; Nakagawa and Harada, 2012; Shelton and Lahm, 2015). In theory, identification of chemistries that are highly potent at a chosen target site could be highly advantageous. However, potency at the target site is only one factor in the success of designing a new insecticide. Optimization of a chemistry at a target site often leads to attributes or physical properties that run counter to processes involved in delivering the molecule to the pest insect or to the target site *in vivo*. Frequently, the insecticidal product ultimately developed is not the most active at the target site, but rather has the best combination of properties and cost that allow it to be used in an agricultural setting. However, as our collective understanding of insecticide – pest – plant – environment interactions improve, computational approaches to optimize both target site and all the other parameters governing insecticide efficacy may provide a path to better utilize *in vitro* data *a priori* in the discovery process.

Computational approaches including quantitative structure activity relationships (QSAR) and computer-aided molecular design (CAMD) have become mainstream approaches to aid in the discovery and development of new insecticides and understanding MoA. As one of the earliest computational aids, QSAR analysis of insecticide efficacy has been explored for many decades (Nishimura et al., 1990; Hansch et al., 1995). However, QSAR has most commonly been focused on understanding an area of chemistry after the fact, and only rarely (Plummer, 1984; Plummer, 1995; Sparks et al., 2008a) has it been successfully applied to the design or optimization of an insecticidal chemistry that has resulted in a commercial product. Typically, computational approaches are employed during the lead-generation process to aid in optimizing or understanding the parameters that guide or limit the activity of the chemistry of interest. As such they provide a lead generation scientist focused on a particular area of chemistry with a lens with which to view the chemistry and form hypotheses to test as part of the chemistry improvement program. Likewise, QSAR, CAMD and related computational approaches can also aid in understanding insecticide action at the targets site, in addition to providing directions for optimization. Interestingly, computational tools can also aid in decision making by providing a rational measure for when to end a line of inquiry for a chemistry (Plummer, 1995; Sparks, 2012).

5. Summary–new age of insecticide discovery

As highlighted above, in many respects the past 27 years denotes a new age of insecticide discovery, with the creation of many new classes of insecticidal chemistry (e.g., neonicotinoids, diamides, diacylhydrazines, spinosyns, sulfoximines, meta-diamides, isoxazolines, pyropenes, etc.) and the discovery of several new MoAs (Table 1). Such a viewpoint is supported by the fact that there have been twice as many new classes of insecticidal chemistries commercialized with significant sales (≥50 MM USD) during this past 27 years than the prior 50 years combined (Table 1, Fig. 4), with more in development. This observation clearly has a degree of subjectivity, as well as also being, in part, a function of a specific moment in time (i.e., 2017 sales). However, this observation highlights the expanding suite of new classes of insecticides that have been or are being developed in recent years. Importantly, for many of these new chemistries, the MoA is novel or presently unknown (Table 1), and as such holds the potential to provide new options for pest insect control and IRM.

Although more new classes of insecticides have been discovered in recent years, the size (number of compounds) of each of these classes, especially since 1991, is likely to be smaller than the pre-1990 classes (OPs, carbamates, acylureas, pyrethroids, etc.; Fig. 4) (Sparks and Lorsbach, 2017b). One consideration for lead generation is that the time required to find new chemical space around an existing area of chemistry (CI-based) may not be that different from the time needed for a *de novo* new area of insecticidal chemistry (Sparks, 2013). As such, a perceived advantage of being able to quickly enter an area of chemistry that is associated with CI-based lead generation may be less than otherwise expected. Also, the number of companies in the EU, Japan or US in a position to do CI-based research are fewer post-1991 (Fig. 2). Thus, once a new area of chemistry is discovered there will likely be fewer CI-based analogs than in the past. Additionally, the profitability of CI-inspired insecticidal analogs in the past 27 years may be less than that of the first compound in the class, (Sparks et al., 2018) further highlighting the benefits of entirely new classes of chemistry.

An analysis of the timing of the ISO insecticide name requests since 1991 provides a measure of the recent output by the crop protection industry. While there was a peak in 1993 in the number of new insecticides disclosed, this was followed by a relatively steady output for the next two decades (Fig. 6) averaging 3.6 new insecticides per year over a ~25-year period (1994–2018), or 2.9 per year when older classes of insecticides (OPs, carbamates & pyrethroids) are omitted. Thus, in spite of increases in costs and in the time requirements for development and registration of new crop protection compounds, along with a diversion of resources by many companies to investigating and developing biologics and genetically engineered plant-based options, the combined output of new insecticides from the crop protection industry has been relatively constant for the past 20 years (Fig. 6). Importantly, there remains a great deal of interest and need in discovering and developing new insecticides, especially given the premium placed in the marketplace on insecticides with new MoAs as tools for IPM and IRM programs.

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