Development of novel pesticides in the 21st century

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General trends and strategies for novel pesticides are summarized. Global pesticide sales and pesticide discovery research are also briefly reviewed. At least 105 chemical pesticides have been launched during the past decade or are under development: 43 fungicides, 34 insecticides/acaricides, 6 nematicides, 21 herbicides, and 1 herbicide safener. Most of them are safe to humans and environmentally friendly. The most developed fungicides are SDHI (succinate dehydrogenase inhibitors), DMI (demethylating inhibitors), QoI (quinone outside inhibitors), and QiI (quinone inside inhibitors). Due to the development of resistance to fungicides with existing modes of action, many fungicides possessing various novel modes of action have been launched or are under development. The trend of insecticide development is changing from organophosphorus, carbamate, and synthetic pyrethroids to nicotinic and diamide insecticides. During the past decade, compounds possessing a variety of novel modes of action have also been launched or are under development. Flupyradifurone and flupyradim, exhibiting extremely low honeybee toxicity, have been developed and subjected to practical use. Herbicides possessing varied modes of action, such as acetolactate synthase, p-hydroxyphenylpyruvate dioxygenase, protoporphyrinogen oxidase, and very-long-chain fatty acid elongase inhibition, have been developed, but no herbicides possessing a novel mode of action have commercialized in nearly 30 years. It is of interest that cyclopyrimorate, which was recently launched, and tetrahydropyrimidinol, which is under development, have novel modes of action: homogentisate solanesyltransferase (HST) and dihydroorotate dehydrogenase (DHODH) inhibition, respectively. The development of useful acaricides and nematicides is also progressing. Some natural product origin pesticides are getting attention.

Keywords: novel pesticides, herbicide, fungicide, insecticide, acaricide, nematicide.

Introduction

Since the practice of agriculture began about 10,000 years ago in the Fertile Crescent of Mesopotamia, mankind has battled pests and diseases that threaten the sustainable food supply. The first recorded use of pesticides is about 4500 years ago by Sumerians who used sulfur compounds to control insects and mites. The evolution of pesticides is classified into five single phases, namely, before 1000: early pest management; 1000–1850: use of plant, animal, or mineral derivatives; 1850–1940: use of inorganic products and industrial by-products; 1940–1970: use of synthetic organic compounds; 1970–present: use of lower-risk synthetic organic compounds. When organic chemistry was introduced to the pest control science field after World War II, the door of industrial pesticide science was opened. In the past century, many pesticide companies have been founded in Europe and the USA, most of which were merged in the 21st century, and various kinds of pesticides have been launched throughout the world. The wave of pesticide science came to Japan, and Japanese-origin pesticides have been developed one after another from the late 20th to the early 21st century. Currently, the pesticide production ability in Japan ranks topmost in the world.

The development and manufacture of effective, safe to humans, and environmentally friendly pesticides have been a challenge to feed the growing population of our planet. The development of pesticides that pose a lower risk to natural enemies and useful organisms and are compatible with IPM (Integrated Pest Management) was also an important target. In March 2018, a book titled Trend in Pesticide Discovery Research-Development of Safer and Environmentally Friendly Pesticides, overviewing pesticide discovery research with insecticides, acaricides, nematicides, fungicides, herbicides, natural-origin pesticides, biopesticides, and others in the world during the past decade, was published by the CMC Publishing Co. In the book, which was edited by one of the authors of the current manuscript, 43 Japanese and Chinese pesticide scientists gave an overview of the trends in pesticide discovery research in their area of expertise from around 2009 to the end of 2017. Since significant progress has been made in pesticide discovery research after publication of the book, the contents of the pesticide discovery research, including the progress until early 2019, have been summarized as
This manuscript is an attempt to summarize the overall trends in research, development, and commercialization of safer and environmentally friendly pesticides from around 2009 until early 2020 on the bases of the information on pesticide discovery research contained in the above book, the commentary articles, and the latest information thereafter.

1. General trends and strategies for novel pesticides

Since the appearance of synthetic organic pesticides, the development strategy for creating new pesticides has been as follows: (1) development of pesticides that are effective at an extremely low dosage, (2) development of pesticides that are readily degradable and less residual in the environment, and (3) development of selective toxic agrochemicals. The first strategy resulted in a remarkable decrease in the active ingredient required for the control of pest insects, fungi, mites, nematodes, and weeds and eventually brought about a reduction in the load of pesticides to the environment. The second strategy realized the remarkable lowering of pesticide residue levels in crops and the environment. The third strategy to seek a compound that is effective in targeting only organisms such as insects, fungi, mites, nematodes, and weeds, but not toxic against non-target organisms such as humans and beneficial organisms, was a tool for finding safer and environmentally friendly pesticides. These development strategies have become increasingly prominent.

The amount of active ingredient applied per unit area in the 1930s–1950s was high, about 1 to 10 kg/ha for ingredients such as DNOC, thiuram, and DDT. Therefore, the environmental impact was relatively large. However, since then, many pesticides that exhibit efficacy in a smaller amount have been developed, and the application rate per unit area has significantly decreased.

Currently, there are not a few pesticides showing efficacy at 10 g or less/ha. As a result, the environmental impact of pesticides has been significantly reduced.

2. Global pesticide sales and pesticide discovery research

2.1. Sales of pesticide companies involved in pesticide discovery research worldwide

Figure 1 shows the 2016 and 2017 sales turnover of major pesticide companies worldwide \(^{10,11}\) with acquisition and merger information. The company with the highest sales is Chem China, which acquired Syngenta, the sales turnover being $10,041 M in 2016. In second place was Bayer, but now ranks first in sales since it acquired Monsanto, followed by Corteva Agriscience (Dow AgroSciences and DuPont merged) and BASF. In fifth place is UPL, which recently acquired Arysta LifeScience. In ninth place is Sumitomo Chemical, a Japan-based pesticide company ($1,913 M). Sumitomo Chemical has recently acquired four South American subsidiaries, including a Brazilian subsidiary of Nufarm, \(^{12}\) so the sales ranking of Sumitomo Chemical is likely to become higher. Many Japanese pesticide companies, such as Kumiai Chemical, Nihon Nohyaku, Nissan Chemical, and Ishihara Sangyo Kaisha, are very active in pesticide discovery research even though the size of the company is relatively small. Their sales turnover is shown separately in the lower left part of the figure. \(^{11}\)

2.2. Trends in global agrochemical patent activity

It is important to analyze the number of patent applications by global pesticide companies and research institutes as an indicator of pesticide discovery activities. According to Phillips McDougall, \(^{13}\) the number of patent applications for active pesti-
cide ingredients with a priority date between 2008 and 2016 was 5,857. Of those, China accounted for 40% at 2,358, followed by Germany at 1,117, Japan at 706, the USA at 516, Switzerland at 487, and the Republic of Korea at 230. This suggests that pesticide discovery studies are actively carried out in these countries.

Table 1 shows the number of patent applications by company for 2008–2016. Of the total 3,298, Bayer had 638 applications and Syngenta 465, followed by BASF, Sumitomo Chemical, Corteva Agriscience (Dow+DuPont), and several other Japanese companies. In a case of patent applications by public institutions such as universities and research institutions (total 2,529), the top 10 are from China, such as the Chinese Academy of Agricultural Sciences (122), Nankai University (113), Zhejiang University (95), the Chinese Agricultural University (82), and Nanjing Agricultural University (57). This suggests that pesticide discovery studies are actively conducted by public institutions in China.

2.3. General trends in novel pesticide discovery research
During the past decade, different kinds of chemical pesticides—fungicides, insecticides, nematicides, acaricides, and herbicides, as well as biocides—have been subjected to development. Chemical pesticides launched or under development during the past decade is total at least 105, and most of them are safe to humans and environmentally friendly: 43 fungicides, 34 insecticides/acaricides, 6 nematicides, 21 herbicides, and 1 herbicide safener. Though pesticide discovery studies based on genomic information or the structure–activity relationship and by chemical biology have been actively conducted during the past decade, almost no products have been developed for practical use.

3. Fungicides
3.1. General trends in development
The fungicides for which ISO common name attached after 2010 are classified according to their mode of action and shown in Table 2.

Table 1. Number of patent applications by company from 2008–2016

| Applicant                  | Number of published patents |
|---------------------------|-----------------------------|
| Bayer CropScience         | 638                         |
| Syngenta                  | 465                         |
| BASF                      | 459                         |
| Sumitomo Chemical         | 219                         |
| Dow AgroSciences          | 196                         |
| DuPont                    | 107                         |
| Nippon Soda               | 85                          |
| Sinochem                  | 85                          |
| Ishihara Sango Kaisha     | 46                          |
| Nissan Chemical           | 45                          |
| Others                    | 953                         |
| Total                     | 3,298                       |

Table 2. ISO common names of fungicides attached after 2010 and their mode of action

| Year | Month | ISO common name     | Mode of action |
|------|-------|---------------------|----------------|
| 2010 | 1     | Fluxapyroxad        | SDHI           |
| 2010 | 7     | Pyriofenone         | Unknown        |
| 2011 | 7     | Benzenidiflupyr     | SDHI           |
| 2012 | 3     | Isofetamid          | SDHI           |
|      | 5     | Coumoxystrobin      | QoI            |
|      | 7     | Oxathiapiprolin     | OSBPI          |
|      |       |                     |                |
| 2013 | 4     | Mandestrobin        | QoI            |
|      | 2014  | 10 Dipymetritone    | Unknown        |
|      | 2015  | 4 Pydiflumetofen    | SDHI           |
|      | 2016  | 4 Ipfentrifluconazole | DMI        |
|      | 2017  | 3 Fluindapyr        | SDHI           |
|      |       | Isoflucypram        | SDHI           |
|      | 2018  | 10 Fluoxapiprolin   | OSBPI          |

Table 2. General trends in fungicide development are as follows. The first general trends in fungicide development are progress in the development of three major fungicides. The most common is SDHI (succinate dehydrogenase inhibitors) or those considered to be SDHI due to their chemical structure characteristics. SDHIIs have become one of the largest groups of agricultural fungicides, as well as DMI (demethylation inhibitors) and inhibitors of the mitochondrial electron transport chain.
complex III, i.e., QoI (quinone outside inhibitors) and QiI (quinone inside inhibitors) (see Fig. 2). The SDHI acts on complex II of the mitochondrial electron transport chains, as shown in Fig. 2. Although the number of developed SDHIs has become comparable to those of DMI and QoI, post-SDHI fungicides are now desired due to successive reports on fungal pathogen resistance to existing SDHIs. DMIs, sterol biosynthesis inhibitors of the cell membrane typified by a triazole fungicide, continue to play an important role in controlling plant diseases due to their broad spectrum, high therapeutic effect, and relatively slow development of resistance. Therefore, the development of a few, if not all, new DMI fungicides is in progress in response to the appearance of resistance to existing DMIs and the fact that many important DMIs are listed in the compounds suspected to have endocrine disrupting effects in Europe. As a QoI fungicide that acts at the quinone outside (Qo) site of the inner membrane of complex III, 10 compounds have been developed since 2010. As a QiI fungicide that acts at the quinone inside (Qi) site of the inner membrane of complex III, two compounds have been developed since 2010.

The second general trend is the development of fungicides with a novel mode of action and a unique chemical structure. Those with a completely new mode of action as agricultural fungicides and those with unique chemical structures are being developed.

Other trends are the development of novel plant defense activators and novel natural product origin fungicides.

### 3.2. Recently launched or under development

#### 3.2.1. SDHI fungicides

Table 3 shows information on 17 SDHI fungicides that were developed after 2010\(^{14,15}\) except for boscalid which was launched in 2003. Penthiopyrad (Affet™ SC, Gaia™ WDG) by Mitsui Chemicals Agro, isofetamid (Kenja™) by Ishihara Sangyo Kaisha, pyraziflumid (Parade™) by Nihon Nohyaku, and inpyrfluxam (Indiflin™) by Sumitomo Chemical have already been marketed. Pyrapropoyne is under development by Nissan Chemical.

Isofetamid was registered in December 2014 in Canada, in July 2015 in the USA, and in November 2017 in Japan. It has broad-spectrum antifungal activity against Ascomycota (such as Botrytis spp., Sclerotinia spp., Monilinia spp., and Venturia spp.) and Deuteromycota (such as Alternaria spp. and Myceovellosiel-la spp.) and is effective against existing SDHI-resistant pathogens.\(^{16,17}\)

Pyraziflumid acquired registration in Japan in 2018. It is a versatile fungicide applicable to a wide range of crops such as rice, horticulture products, and turf. It has a pyrazine carboxamide skeleton.\(^{18,19}\)

Inpyrfluxam exhibits high efficacy against major plant diseases in the European region, such as brown rust on wheat, net blotch on barley, and black scurf on potatoes.\(^{20}\)

Flubeneteram, which just obtained an ISO common name in early 2020,\(^{21}\) is an anilide fungicide and is considered to be an SDHI based on its chemical structure.

Among multinational agrochemical manufacturers, one company has multiple SDHI fungicides\(^{15}\) and is trying to separate the compounds by usage method and target crops in response to the characteristics of the compounds. As an example, Syngenta developed four SDHI fungicides. Isopyrazam (Reflect™) is for foliar application to control rust and net blotch of wheat. Sedaxane (Vibrance™) is a seed-treatment fungicide for wheat, beans, and potatoes. Benzovindiflupyr (Solatenol™) is a rust-control fungicide for soybeans. Pydiflumetofen (Adepidyn™) is for the control of powdery mildew and Alternaria disease of vegetables, fruit trees, etc., as well as wheat leaf blight and wheat scab.\(^{22}\)

Bayer launched bixafen (Aviator® Xpro™, Siltra® Xpro™, etc.), penflufen (EverGoft® Prime), and fluopyram (Luna®). Isofluopyram, under development by Bayer, exhibits efficacy for the control of leaf spot diseases on a large range of crops.\(^{23}\)

#### 3.2.2. Inhibitors of the mitochondrial electron transport chain complex III

A total of 12 compounds have been launched or are under de-
Pyribencarb  Picoxystrobin  Mandestrobin
Methyltetraprole

Coumoxystrobin (SRICI)
Enoxastrobin (SRICI)
Flufenoxystrobin (SRICI)
Pyriminostrobin (Shenyang Sciencreat Chemicals)
Triclopyricarb (SRICI)
Fenaminstrobin (SRICI)

Fig. 3. (a) Chemical structures of four QoI fungicides. (b) Chemical structures of six QoI fungicides under development by Chinese companies.

Table 3. Recently launched or under development SDHI fungicides

| Chemical structures | Company name | Registration year |
|---------------------|--------------|-------------------|
| Boscalid            | BASF         | 2003              |
| Penthiopyrad        | Mitsui Chemicals Agro | 2009 |
| Isofetamid          | Ishihara Sangyo Kaisha | 2015 |
| Pyraziflumid        | Nihon Nohyaku | 2018              |
| Fluindapyr<sup>b</sup> | Isagro/FMC  | Under development |
| Inpyrloxam          | Sumitomo Chemical | 2019 (Sept.)    |

| Chemical structures | Company name | Registration year |
|---------------------|--------------|-------------------|
| Pyrapropoyne        | Nissan Chemical | Under development |
| Flubeneteram<sup>b</sup> | Dongguan Hec Tech | Under development |
| Fluxapyroxad (Xemium®) | BASF         | 2011              |
| Bixafen             | Bayer        | 2011              |
| Penflufen            | Bayer        | 2011              |
| Flupyrpyram         | Bayer        | 2012              |

<sup>a</sup> Partially modified and added new molecule to the Fig. 3 of Ref. 15.

<sup>b</sup> Compounds considered to be SDHI based on chemical structure.
development as inhibitors of the mitochondrial electron transport chain complex III since 2010, their chemical structures being shown in Figs. 3(a), 3(b), and 4. Of them, 10 compounds are QoI fungicides.

Pyribencarb (K-I Chemical Research Institute and Kumiai Chemical) was registered in 2012 in Japan (Trade name: Fantastia® GWP, Fanbell® GWP). It is a novel benzyl carbamate-type fungicide against a wide range of plant pathogenic fungi, especially gray mold and stem rot. Though pyribencarb belongs to QoI group, it is active against strobilurin-resistant fungi.

Picoxystrobin (Acanto®, Syngenta) was discovered by Syngenta and transferred to DuPont in 2006. DuPont registered it in the USA in 2012. In Japan, Nihon Nohyaku marketed it in 2016 as a Major® Flowable. Picoxystrobin is a strobilurin fungicide (QoI inhibitor) effective against a wide range of diseases.

Mandestrobin (Sclea® flowable, Sumitomo Chemical), a strobilurin fungicide, was discovered by Shionogi & Co., Ltd., and commercially developed by Sumitomo Chemical. It is effective against sclerotinia rot, fruit tree scab, etc., with a low risk of phytotoxicity. It was launched in 2016 in Japan and is under commercial development in many countries.

Metyltetraprole (Pavecto®, Sumitomo Chemical) is a new fungicide with a unique tetrazolinone moiety that is effective against pathogens resistant to existing fungicides. It is highly effective against a wide range of fungal diseases, including important cereal diseases, such as wheat leaf blight. Sumitomo Chemical is promoting development jointly with BASF in the EU, aiming to launch after 2022. Metyltetraprole is highly effective against QoI-resistant strains of various pathogen species.

Six QoI fungicides with ISO common names are currently under development by Chinese companies: coumoxystrobin, flufenoxystrobin, triclopyricarb, and fenamin-strobin by SRICI and pyriminostrobin by Shenyang Sciencreat Chemicals (see structures in Fig. 3(b)). It is unclear whether they aim to obtain registrations around the world, as well as what characteristics each QoI has and how to segregate each product in the market.

As QI fungicides, two compounds are currently under development. Fenpicoxamid (Inatreq™, Meiji Seika Pharma, Dow; currently Corteva Agriscience), whose structure is shown in Fig. 4, is a conversion product of UK-2A isolated from the culture broth of Streptomyces spp. by Ueki et al. at Osaka City University, and its action is inhibition of the mitochondrial electron transport system complex III. Meiji Seika Pharma introduced UK-2A from the university and subjected it to joint development with Dow after converting its structure into fenpicoxamid. It is currently under development as an innovative fungicide for controlling key diseases in cereals, such as Septoria tritici and rust. It shows no cross-resistance to existing cereal fungicides. Fenpicoxamid is a propesticide, since it is converted to UK-2A in crops.

Florylpicoxamid (Adavelt™, Corteva Agriscience) is a neonicolinamide fungicide under development and presumed to be a QI, having the same mode of action as fenpicoxamid. Florylpicoxamid controls a wide range of pathogens including Septoria spp., powdery mildew, Botrytis spp., Anthracnose, Alternaria, scab, Monilinia, and others.

3.2.3. DMI fungicides

Currently, three DMIs are under development, and their structures are shown in Fig. 5. Of these, mefentrifluconazole and pyrisoxazole should be noted. Mefentrifluconazole (Revysol®) is the first isopropanol azole discovered and developed by BASF. Its registration was approved in the EU in 2019. It is highly effective against key fungal diseases in both row and specialty crops, including cereals, corn, soybeans, rice, grapevines, fruits, vegetables, and turf. Pyrisoxazole, developed by SRICI, is a pyridine-type DMI that is effective against Botrytis cinerea and tomato leaf mold. The development status for this fungicide out-
side China is unknown.

3.2.4. Mode of action is novel or unknown

Eight fungicides with a novel or unknown mode of action and marketed or under development since 2010, is given based on the review by Fushikida and on other additional information. The chemical structures of these compounds are shown in Fig. 6.

Flutianil (Gatten EC, OAT Agrio Co.) was registered in 2013 in Japan. Flutianil is chemically characterized as a cyanomethylene thiazolidine. It exhibits therapeutic and preventive effects against powdery mildew at a low dosage. The mode of action of this compound has not yet been reported.

Fenpyrazamine (Prolectus®), Pixio® DF, Sumitomo Chemical) is a novel fungicide with an aminopyrazolone structure that has shown high efficacy against gray mold, stem rot, and brown rot in field trials. The target enzyme of fenpyrazamine is the 3-keto reductase in the ergosterol biosynthetic pathway. Prolectus® was first launched in Italy in 2012, and Pixio® DF was launched in Japan in 2014.

Picarbutrazox (Pythilock®), Nae Fine®, Pisi Rock®, Nippon Soda) was registered in June 2017 in Japan. It belongs to the tetrazolyl oxime class, controlling oomycete diseases such as downy mildew and late blight. The mode of action of this compound is unknown, but it seems to have a new one, since the treatment of picarbutrazox causes swelling and hyperbranching of mycelia and inhibits zoospore formation, zoospore encystment, and cystospore germination.

Tebulquin (Try® flowable, Meiji Seika Pharma) was registered in 2013 in Japan. It is used to control rice blast disease. The mode of action of this compound has not been clarified, but it is considered a respiratory inhibitor that acts on the mitochondrial electron transport system.

Pyriofenone (Property® flowable, Ishihara Sangyo Kaisha) is a novel fungicide with a benzoyl pyridine structure and was registered in 2013 in Japan. It is very effective against powdery mildew on wheat, cucumbers, strawberries, and eggplants. It is of interest that pyriofenone is effective against QoI- and DMI-resistant fungal plant pathogens. The mode of action of this compound was reported to be inhibition of the formation of appressoria and conidia and induction of morphological abnormality of the secondary appressorium and hyphae.

Tolprocarb (Sanblas® M, Mitsui Chemicals Agro) is a rice blast fungicide registered in 2015 in Japan. It shows a stable effect against rice blast disease under various environmental conditions and treatment methods. It is also highly safe for rice seedlings with nursery box treatment. It is scheduled to launch in 2020.

Aminopyrifen (Agro-Kanesho) is a novel fungicide, and its synthesis and structure activity relationships were recently reported. It is reported that aminopyrifen inhibits the GWT-1 protein in glycosylphosphatidylinositol-anchor biosynthesis.

Dipymetitrone (Bayer) is a novel fungicide under development that is effective against Phytophthora rot, downy mildew, scab, early blight, and Botrytis cinerea. The mode of action is unknown.

The ISO common name of fluoxapiprolin (Bayer) was granted in October 2018. It is effective against Phytophthora rot and downy mildew. It seems to be in the same group of fungicides as oxathiapiprolin, under development by Corteva Agriscience.

4. Insecticides

4.1. General trends

In the history of insecticide development, trends have changed from organophosphates, carbamates, and synthetic pyrethroids to nicotinic and diamide insecticides. In recent years, compounds that are not classified into nicotinic and diamide insecticides and have or seem to have a variety of novel modes of action have been under development. This is useful in terms of resistance management.

Table 4 shows the major insecticides categorized into nicotinic, diamide, and other novel insecticides that were launched...
or under development after 2010. Four nicotinic insecticides, such as flupyrimin and triflumezopyrim, are on the market. As diamide insecticides, four compounds, such as cyantraniliprole and tetraniliprole, are on the market or under development. As other novel insecticides, nine insecticides, such as pyrifluquinazon, flometoquin, fluxametamide, broflanilide, and afidopyropen, will be mentioned below. The outline of each group of insecticides is also described below.

4.2. Trends in nicotinic insecticides

Nicotinic insecticides, which originate from nicotine, act on nicotinic acetylcholine receptors (nAChRs) and are effective against a wide range of pests at low doses; these made up about 23% of the global insecticide market in 2016. Nicotinic insecticides are classified into “first generation” (nicotine, anabasine), “second generation” (imidacloprid, thiacloprid, nitenpyram, clothianidin, acetamiprid, thiamethoxam, dinotefuran), and “third generation” (sulfoxaflor, flupyradifurone, flupyrimin, triflumezopyrim, dicloromezotiaz), which were launched or under development after 2010.50,51 Some nicotinic insecticides of the second generation have been regarded as toxic to some non-target organisms, especially honeybees, and the use of three agents is prohibited in the field in the EU.

Figure 8 shows the structure of nicotinic insecticides and their honeybee toxicity information.6) Due to the potential honeybee toxicity problem, the use of imidacloprid, clothianidin, and thiamethoxam was prohibited in the EU as a preventive measure in April 2013 and officially banned for use outdoors in 2018.

Regarding sulfoxaflor (Isoclast™), which is classified as sulfoximines, the US EPA banned its use in March 2016 due to the lack of honeybee toxicity data based on the outcome of a trial involving a beekeeper’s organization (the EPA lost). However, it was re-registered in February 2017. Sulfoxaflor shows a stable effect against sucking pests, especially stink bugs and scales, and was registered in Japan in November 2017.

| Nicotinic insecticides | before 2009 | after 2010 |
|------------------------|------------|-----------|
| Nicotinoids            | imidacloprid, acetamiprid, clothianidin, dinotefuran, nitenpyram, thiacloprid, thiamethoxam, cycloxadip, paichsongding (Both marketed in China) | flupyrimin (Registered in USA in 2018, in 2019 in Japan) |
| Sulfoximine            | sulfoxaflor, Registered in 2017 | triflumezopyrim, dicloromezotiaz, Both registered in 2018 |
| Butenolides            | flupyradifurone, Registered in 2015 | |
| Mesoionics             | trichloromezopyrim, dicloromezotiaz, Both registered in 2018 | |

### Table 4. Insecticides marketed or under development since 2010\(^a\)

#### Nicotinic insecticides

| Neonicotinoids | before 2009 | after 2010 |
|----------------|------------|-----------|
| Neonicotinoids | imidacloprid, acetamiprid, clothianidin, dinotefuran, nitenpyram, thiacloprid, thiamethoxam, cycloxadip, paichsongding (Both marketed in China) | flupyrimin (Registered in USA in 2018, in 2019 in Japan) |
| Diamide insecticides | flubendiazide (Registered in 2007), chlorantraniliprole (2009) | cyantraniliprole (Registered in 2014), cyclaniliprole (2017), tetraniliprole (under development) |

#### Insecticides other than nicotinic and diamide insecticides possessing novel or unknown mode of action

| Registered | pyrifluquinazon (Registered in 2010), flometoquin (2018), fluxametamide (2019) |
| Under development | triflumezopyrim, flupyrimin, triflumezopyrim, dicloromezotiaz, Both registered in 2018 |

\(^a\) Registered year: Unless otherwise noted, the year of registration in Japan.

![Fig. 8. Structure of nicotinic insecticides and honeybee toxicity.](image-url)
Flupyradifurone (Sivanto™), which is classified as butanoids, was registered in the USA and Japan in 2015. It is assumed to be harmless to honeybees, although like neonicotinoids, it binds to nAChRs. It was shown that flupyradifurone can reduce taste and appetitive learning performance in honeybees foraging for pollen and nectar, although only the highest concentration had significant effects.52)

Flupyrimin, which is classified as neonicotinoids, was registered in Japan in 2019 (trade name: Lydia Granules, Emilia Flowable) and exhibits remarkable biological properties featuring outstanding potency to neonicotinoid-insensitive rice insect pests and superior safety toward pollinators. Intriguingly, flupyrimin acts on the insect nAChRs as an antagonist via a recognition manner different from those of the other nicotinic insecticides.53)

Triflumezopyrim (Pyraxalt™) and dicloromezotiaz belong to the novel class of mesoionic insecticides and have already been commercialized.54) Triflumezopyrim provides outstanding control of hoppers, including the brown planthopper, which is already displaying resistance to neonicotinoids such as imidacloprid.55) Dicloromezotiaz shows excellent efficacy against a broad range of lepidopteran pests. It binds to the orthosteric site of the nicotinic acetylcholine receptor but acts primarily via inhibition of the binding site and leads to lethargic poisoning among different insect species.56)

Though the IRAC classification is not described, research and development of nicotinic insecticides by Chinese institutions are ongoing. The recently marketed flupyradifurone (Fig. 8) and flupyrimin (see structures in Fig. 9) have been developed as insecticides in China.51) The status of the development of these nicotinic insecticides outside China is unknown. Flupyrimin, developed by East China University of Science and Technology, shows outstanding activity against a variety of homopteran and lepidopteran pests and lacks cross-resistance in comparison with traditional neonicotinoids.57) It acts on insect nAChRs but has different binding sites than that of imidacloprid.

Table 5 summarizes the honeybee toxicity data for these nicotinic insecticides.4) Oral and contact toxicities to honeybees are generally low or relatively low for the nicotinic insecticides except for the three compounds banned in the EU. Among them, the contact toxicity of thiacloprid is about 1/800 that of imidacloprid. The recently marketed flupyradifurone and flupyrimin (Fig. 8) have even lower honeybee toxicities. Selective toxic insecticides were developed using honeybee toxicity as an index.

4.3. Trends in diamide insecticides

Table 6 shows the development history of diamide insecticides.4) Nihon Nohyaku developed flubendiamide and obtained registration in 2007, and this was followed by DuPont’s chlorantraniliprole. After 2010, cyantraniliprole, cyclaniliprole, tetraniliprole, cyhalodiamide, and tetrachlorantraniliprole followed. Chlorantraniliprole and cyantraniliprole, which were originally developed by DuPont, were recently transferred to FMC. These compounds have a novel mode of action, acting on ryanodine receptors, and because of their excellent control performance,
particularly with lepidopteran pests, they can be used in a wide range of crop-protection situations. In 2016, three diamide insecticides, flubendiamide, chlorantraniliprole, and cyantraniliprole, together accounted for 11.5% of the $16.46 billion global insecticide market.

Cyclaniliprole (Teppan®), which was registered by Ishihara Sangyo Kaisha in Japan in 2017, is highly effective against lepidopteran pests as well as hemipteran pests such as thrips, whitefly, and tea green leafhopper.58,59) Tetraniliprole (Vayego™), cyhalodiamide, and tetrachlorantraniliprole 4) are currently under development. In addition, many companies and universities have applied for patents for diamide insecticides. However, the number of patent applications has recently been declining, and discovery research for diamide insecticides seems to have settled down.50)

4.4. Trends in novel insecticides other than nicotinic and diamide insecticides

An overview of the 11 insecticides other than nicotinic and diamide insecticides that were launched or are under development after 2010 is described based on Suwa and Nakano’s review 50) and on other recent information. Figure 10 shows the chemical structures of these 11 insecticides and their related compounds.

Pyrifluquinazon (Colt®, Nihon Nohyaku) is an insect behavior control agent (to halt insect feeding so that they starve) for tea, vegetables, and fruit trees that was registered in Japan in March 2018.62) It is effective to control Lepidoptera, Diptera, Hemiptera, and mites. Applicable crops are fruit trees, vegetables, etc. It inhibits the electron transport system.

Fluxametamide (Gracia®, Nissan Chemical), an isoxazoline compound, was discovered and has been developed, being registered in January 2019 in Japan. The site of action is GABA: γ-aminobutyric acid (GABA Cl−, Glu Cl− channel inhibitor). The characteristics of fluxametamide include effectiveness against a very broad spectrum of important pests (Lepidoptera, Thysanoptera, Diptera, Acari, Coleoptera, and some Hemiptera). There is little influence on the bee-visiting insects.63,64)

Broflanilide (Vedira™, Tenebenal™, Mitsui Chemicals Agro), currently being jointly developed with BASF, has a unique chemical structure characterized as a meta-diamide and exhibits high activity against various pests, including lepidopteran, coleopteran, and thysanopteran pests.65,66) Broflanilide received the first registration worldwide in Australia in January 2020. Broflanilide is metabolized to desmethyl-broflanilide, and it acts as a noncompetitive resistant-to-dieldrin (RDL) γ-aminobutyric acid (GABA) receptor antagonist. The binding site of desmethyl-broflanilide was demonstrated to be distinct from that of conventional noncompetitive antagonists such as fipronil.

Benzpyrimoxan (Orchestra® flowable, Nihon Nohyaku) is currently under development. It seems to be a next-generation planthopper and green rice leafflower control insecticide.50) Benzpyrimoxan is highly active, specifically against the nymphal stages, and could act on nymphal molting as a kind of insect growth regulator (IGR). Its insecticidal activity against nymphs is much superior to that against other stages, with a unique symptom that is different from ones caused by other existing
In 2017, the common name of oxazosulfyl included in the Sumitomo Chemical patent claims was released. While many patents were released from Sumitomo Chemical after that, Nihon Nohyaku, Syngenta, Bayer, Nippon Soda, Nissan Chemical, Agro-Kanesho, Hokko Chemical, and BASF have also issued patents one after another and have become one of the major groups in recent insecticide-related patents. Oxazosulfyl is characterized by its aryl ethylsulfonyl moiety and exhibits broad-spectrum control of insect pests, including Hemiptera, Coleoptera, and Lepidoptera. Since this compound group has a broad insecticidal spectrum, it can grow into a large group of insecticides as a highly versatile pest control agent.

A patent describing a compound having a pyridin-3-yl group was published by Bayer in 2009. After that, Dow, Sumitomo Chemical, Nissan Chemical, Syngenta, BASF, Mitsu Chemicals Agro, and DuPont continued to publish related patents. These companies have been competing in exploratory research on this group of compounds. Among them, the common name tyclopyrazoflor was released by Dow (Corteva Agriscience) in 2017. The basic activity of this compound group against aphids has already reached the same level as that of neonicotinoids, and useful insecticides may be created from this group in the near future.

Spiropidion (Syngenta) is a new tetramic acid family member (IRAC MoA group 23) insecticide and acaricide and is currently under development by Syngenta. It is regarded as an inhibitor of acetyl CoA carboxylase, disrupting fatty acid biosynthesis, and is presumed to show excellent activity against aphids, whiteflies, thrips, diamondback moths, and mites in vegetables and specialty crops. It has a favorable toxicological and environmental profile and, owing to its safety to pollinators and other non-target organisms, it is perfectly suitable for IPM practices.

Afidopyropen (Inscalis®, Meiji Seika Pharma) is a structur-
ally modified compound of pyripyropene A,22) an antibiotic obtained from the culture of Aspergillus fumigatus through collaboration between the Kitasato Institute, Meiji Seika Pharma, and BASF.22,23) The circled parts in the chemical structure of afidopyropen in Fig. 10 are the structure conversion sites. The joint development company BASF applied for registration in the USA and Canada. Afidopyropen controls aphids, whiteflies, scales, and leafhoppers, being effective against pests that have acquired resistance to existing insecticides. It is presumed that afidopyropen acts on the chordotonal organ, an insect-specific hearing organ. Details of the development of this insecticide are described in Oyama’s review.74)

Isocycloseram (Syngenta) is a member of the isoxazoline class of insecticides.75) The ISO common name was given in June 2018. It is in the same family as fluxametamide from Nissan Chemical. Isocycloseram acts as a noncompetitive antagonist of the invertebrate GABA receptor.

Dimpropyridaz (BASF) is a new insecticide, the ISO common name being given in December 2018.21) It is a pyrazole carboxamide insecticide that has a pyridin-3-yl group, as in tyclopyrazoflor.50) Dimpropyridaz is effective against aphids.

5. Acaricides

5.1. General trends in acaricide development

Although the types of acaricides seem to be numerous at first glance, the key acaricides have changed over time due to the development of resistance. Though there were only a limited number of modes of action for acaricides until the 1990s, acaricides with various modes of action have been developed since the 2000s.76) The acaricides developed after 2000 are classified as “Inhibitors of the mitochondrial electron transport chain complex II,” “Acetyl CoA carboxylase inhibitors,” and “Acaricides possessing a novel mode of action or unknown mode of action.”

5.2. Trends in the development of inhibitors of the mitochondrial electron transport chain complex II

This class of acaricides started with a novel benzoyl acetonitrile acaricide, cyflumetofen (Danisaraba®), which was discovered by Otsuka Chemical (currently OAT Agrio) and registered in 2007 in Japan.76) Then cyenopyrafen (Starmite®, registered in 2008 by Nissan Chemical) and pyflubumide, a carboxyanilide acaricide (Dani-Kong®, registered in 2017 by Nihon Nohyaku), were developed and marketed.76) The chemical structure of the three acaricides is shown in Fig. 11. All three acaricides are effective at all stages of spider mite development as inhibitors of the mitochondrial electron transport chain complex II. It is of interest that pyflubumide has the same mode of action as the other two acaricides, but the site of action is different, and cross-resistance is avoided.77) Cyetpyrafen (Sinochem), the ISO common name being given in 2020,21) is presumed to be an inhibitor of the mitochondrial electron transport chain complex II based on the similarity in chemical structure to cyenopyrafen.

5.3. Trends in the development of acetyl CoA carboxylase inhibitors

Three acetyl CoA carboxylase inhibitors have been developed and marketed since 2003.76) These acaricides act by inhibiting lipid biosynthesis. There are two tetronic acid classes, spirodiclofen (Daniemon®, registered in 2003 in Japan) and spiromesifen (Danigetter®, registered in 2007 in Japan), and a tetramic acid class, spirotetramat (Movento®, Ultor®, registered in 2012 in Japan). The above three acaricides were developed by Bayer (see the chemical structure in Fig. 11). The general characteristics of biological activity are the same for the three acaricides, and they are effective not only for spider mites but also for rust mites. Characteristics of above three acaricides are as follows.76) Spirodiclofen is effective only against mites and has no systemic activity. Spiromesifen shows activity against both mites and whiteflies. It also has leaf penetration activity. Spirotetramat is effective not only for mites but also for sucking pests. It has phloem migration activity, and irrigation treatment into the soil is possible.76)

In addition to the above three acaricides, spiropidion, which was mentioned in the section on novel insecticides, exhibits acaricidal activity.70)

5.4. Trends in the development of acaricides possessing a novel or unknown mode of action

Three acaricides with a novel or unknown mode of action have been developed since 2010. Fluxametamide (Gracia®, Nissan Chemical) and pyflubumide, a carboxyanilide acaricide (Dani-Kong®, registered in 2017 by Nihon Nohyaku), were developed and marketed.76) The chemical structure of the three acaricides is shown in Fig. 11. All three acaricides are effective at all stages of spider mite development as inhibitors of the mitochondrial electron transport chain complex II. It is of interest that pyflubumide has the same mode of action as the other two acaricides, but the site of action is different, and cross-resistance is avoided.77) Cyetpyrafen (Sinochem), the ISO common name being given in 2020,21) is presumed to be an inhibitor of the mitochondrial electron transport chain complex II based on the similarity in chemical structure to cyenopyrafen.
Chemical) is an insecticide and acaricide. See item 4.4, “Trends in novel insecticides other than nicotinic and diamide insecticides”.

Acyonapyr (NA-89, Danyote®, Nippon Soda) has a characteristic azabicyclo ring in its structure⁶,⁷⁸ and was registered in March 2019 in Japan. It is reported that acyonapyr acts on inhibitory glutamate receptors and disrupts neurotransmission.⁷⁸ It has a selective effect on spider mites of Tetranychus and Panonychus. The practical concentration of acyonapyr is 100–67 ppm, and its application is currently expanding into fruit, tea, vegetables, and flowering fields.

Flupentiofenox (Kumiai Chemical) is a new acaricide, the ISO common name being given in 2020.⁷¹ Other information, including the mode of action, is not available.

5.5. Trends in the development of non-chemically synthesized acaricides

Two non-chemically synthesized acaricides have been developed since 2010. Formulated oil (safflower oil and cottonseed oil 97%, RM1963K, Suffixol® emulsion) was registered in 2015 in Japan, jointly developed by OAT Agrio and RIKEN. It can be used at a relatively high dilution ratio of 300 to 500 times (compared to machine oil, etc.). The mode of action against spider mites is suffocation by spiracle blockage of adults and larva, but at the same time, it inhibits larval escape behavior in eggs during hatching, thus exhibiting an egg-killing effect.⁵,⁷⁹ Polyglycerin fatty acid ester 82% (Fumon, Nippon Kayaku) is a food additive and was registered in 2016 in Japan, having insecticidal, fungicidal, and acaricidal activities. Its only mode of action is spiracle blockage, and it can be sprayed at a high dilution (×1,000), so the risk of phytotoxicity is relatively low.⁷⁸

6. Nematicide development

6.1. General trends

The methods of controlling plant-parasitic nematodes are largely divided into fumigant (gas) treatments and non-fumigant (contact agent) treatments. Most nematicides exhibit control effect by entering the nematode body through the surface phospholipid membrane. Methyl bromide, a typical fumigant, has a wide range of effects and was widely used around the world because of its low cost. However, the use of methyl bromide has been abolished in developed countries by 2005 due to fears of ozone depletion and groundwater pollution at the Montreal Protocol meeting in 1995.⁸⁰ In recent years, pesticide manufacturers have been actively developing safer non-fumigants.

6.2. Trends in development

The nematicides launched or under development after 2010 are shown in Fig. 12 with their chemical structures.⁸⁰ Fluopyram (Bayer and Nihon Nohyaku) was developed and marketed as an SDHI fungicide by Bayer, but it has been reported by Nihon Nohyaku that it also acts as a nematicide. Bayer marketed it as Velum™ granules and Verango®,⁸¹ Nihon Nohyaku as Nemeclean® granules (August 2017 in Japan).⁸² These are the first nematicides acting via complex II inhibition, thus selectively inhibiting the nematode’s generation of cellular energy. The nematicide exhibits a high control effect on the root-knot nematode, root-lesion nematode, cyst nematode, and potato rot nematode. Residual activity is also very high.

Tioxazafen (NemStrike™, Monsanto (currently Bayer)) is a seed-treatment nematicide developed by Monsanto to provide consistent broad-spectrum control of nematodes in corn, soy, and cotton.⁸³ Its structure has a disubstituted oxadiazole skeleton, representing a new class of nematicides. Tioxazafen obtained EPA registration in May 2017. Its use started in 2018 in 45 states in the USA. It has a broad spectrum against parasitic nematodes of corn, soybeans, and cotton. It stays in the roots of the crop for up to 75 days during crop growth.⁸⁰

Fluazaindolizine (Reklemel™ active, Salibro®, Corteva AgriScience) is a new, highly effective, and selective product for the control of plant parasitic nematodes, and it is expected to be registered in 2020.⁸⁰,⁸⁴ It has an excellent effect on the root-knot nematode and root-lesion nematode. Specificity for nematodes coupled with the absence of activity against the target sites of commercial nematicides suggests that fluazaindolizine has a novel mode of action.

Fluensulfone (Bayer and ADAMA Agricultural Solutions) is a new nematicide of the fluoroalkenyl thioether group that has an excellent effect on the root-knot nematode and significantly reduces environmental impact with low toxicity to non-target insects and mammals.⁸⁵ It was registered in the USA under the trade name Nemitz® and in Israel in 2014 for fruits and vegetables. In Japan, it was registered in April 2017 as Nemashot® granules by ADAMA Japan and SDS Biotech.⁸⁰ Fluensulfone inhibits development, egg-laying, egg-hatching, feeding, and locomotion. Fluensulfone’s mode of action is distinct from those of other currently available nematicides.⁸⁵

Cyclobutriefuran (Syngenta), the ISO common name being given in 2020,⁸³ is presumed to be an inhibitor of the mitochondrial electron transport chain complex II based on its similarity in chemical structure to fluopyram.

Nemguard (NEMguard®, Ecospray) is a non-chemically synthesized nematicide. Nemguard is a registered soil-applied nematicide based on garlic extract. It contains biologically active ingredients such as allicin and polysulfides derived from garlic concentrate. In addition to nematicidal and insecticidal prop-
Fig. 13. History of herbicide development and mode of action studies.

7. Herbicides

7.1. General trends

Since the 1940s, a large number of herbicides with different modes of action have been developed and provided for commerce use. Figure 13 shows the history of the discovery of herbicides with different modes of action, which can be roughly divided into pre-1980, the 1980s, the 1990s, and after 2018. The history of herbicide development by age group is described below based on the review by Tamai et al.87 and the latest information thereafter.

7.2. Research on the mode of action of old-fashioned herbicides

7.2.1. Before 198087

The discovery of the auxin action of 2,4-D (2,4-dichlorophenoxyacetic acid), whose basic chemical structure is phenoxyacetic acid, in 1942 led to the discovery of a selective herbicidal effect on broadleaf weeds in 1944. From 1956 to 1975, the mode of action of urea, triazine, and triazinone photosynthesis inhibitors was elucidated. In the 1970s, the mode of action of auxin transport inhibitors (naptalam), cell wall synthesis inhibitors (dichlobenil), microtubule polymerization inhibitors (trifluralin), and dihydropyrophosphate (an intermediate in folate biosynthesis) synthesis inhibitors (asulam) was revealed.

7.2.2. From the 1980s to the 2000s87

In 1980, it was revealed that the action point of pyridazine herbicides on the carotenoid biosynthesis pathway was protoporphyrinogen IX oxidase (PPO). In 1984, it was found that the action point of sulfonylurea herbicides and imidazolinone herbicides on the branched-chain amino acid synthesis pathway is acetolactate synthase (ALS), and the action point of glyphosate on the aromatic amino acid biosynthesis pathway is 5-enolpyruvylshikimate phosphate synthase (EPSPS). From 1992 to 1993, it was clarified that the action point of triketone herbicide, represented by sulcotrione, was 4-hydroxyphenylpyruvate dioxygenase (HPPD). A long-term study from 1993 to 2000 clarified that the action point of chloroacetamide herbicide, which had not been elucidated for many years, is the very-long-chain fatty acid elongase (VLCAE). Since 2000, VLCAE-inhibiting herbicides have been developed in addition to ACCase-, ALS-, HPPD-, and PPO-inhibiting herbicides.

7.2.3. After 2018

There were no reports on herbicides with a novel mode of action for approximately 30 years after the launch of clomazone (DXP inhibitor in the MEP pathway) in the late 1980s until 2017.87 However, three herbicides possessing new modes of action have recently appeared. First, it was clarified that the site of action of the herbicide cinmethryn, whose registration has expired (in Japan), is fatty acid thioesterase (FAT).88 The second herbicide is cyclopyrimorate. It has been reported that the site of action of this new herbicide, discovered by Mitsui Chemicals Agro and registered in Japan in September 2019, is the homogentisate solanesyltransferase (HST).89 The third one is a new herbicide, tetflupyrolim, discovered by FMC. It was recently reported that tetflupyrolim interferes with de novo pyrimidine biosynthesis via the inhibition of dihydroorotate dehydrogenase (DHODH).90

7.3. Herbicides developed after 2008

The herbicides launched or under development after 2008 will be described based on the review by Tamai et al.87 summarizing the herbicide discovery studies up to 2017 and on the latest information as of January 2020. Since ACCCase-, PDS-, and photosynthesis inhibitors have not been developed during this period, the description of these herbicides has been omitted.

7.3.1. ALS inhibitors

ALS-inhibiting herbicides include sulfonylureas, triazolopyrimidines, pyrimidinylsalicylic acids, imidazolones, and sulfonanilides. The number of ALS inhibitors being developed has been decreasing due to the problem of weed resistance to ALS inhibitors, and little discovery research has been conducted recently.87

Table 7 shows the chemical structures, common names, company name, group names, registered year, target crops, and dosages of ALS inhibitors. Recently developed sulfonylurea ALS inhibitors include propyrisulfuron (Zeta-One®) from Sumitomo Chemical91 and metazosulfuron (Altair®) from Nissan Chemical.92 Both herbicides have been developed for paddy rice and are characterized by their effectiveness against broadleaf weeds and Cyperaceous weeds, as well as against barnyard grass, which is difficult to control with conventional sulfonylurea herbicides.

The other two are pyrimisulfan (Best Partner®) and triafamone, which are sulfonanilides. Pyrimisulfan, developed by Kumiai Chemical, has provided outstanding efficacy against...
major weeds of Japanese paddy fields, such as Echinochloa spp., Schoenoplectus juncoides, Monochoria vaginalis, and Lindernia spp. Pyrimisulfan is the first one-shot herbicide for rice containing only one active ingredient, with an original formulation technology. In addition, it can control other troublesome weeds, including Sagittaria trifolia, Scirpus nipponicus, Bolboschoenus maritimus, Eleocharis kuroguwai, and sulfonylurea-resistant weeds, which have presented serious problems in recent years.

Triafamone (Council™ Complete (triafamone+tefuryltrione), etc.), developed by Bayer, is an herbicide for paddy rice and is highly effective against grass weeds, such as barnyard grass, as well as Cyperaceous weeds.

### 7.3.2. HPPD inhibitors

HPPD-inhibiting herbicides represent the most actively researched field, and many are being developed. They include triketones, pyrazoles, isoxazoles, and other bicyclo ring-type compounds. In addition, Bayer published a patent in 2011 for an HPPD inhibitor characterized by an amide structure. Syngenta published a patent in 2013 for an HPPD inhibitor characterized by a pyridazinone ring.

Table 8 shows information on various HPPD inhibitors. The triketone herbicides include tefuryltrione (Mighty-One®), fenquinotrine (Effedra®), and lancotrine-sodium (Promise®1 kg GR), launched in 2010, 2018, and 2019, respectively. Tefuryltrione, developed by Bayer, is effective against sulfonylurea-tolerant weeds as well as annual and perennial weeds belonging to the Cyperus microtricha Steud family. Fenquinotrine, developed by Kumiai Chemical, shows excellent control against pre/post-emergence ALS-resistant broadleaf weeds under flooded conditions. It shows high safety to high-yield rice varieties for feed equal to or better than rice varieties for food. Lancotrine-sodium, registered in Japan in 2019 by Ishihara Sangyo Kaisha, is for paddy rice.

Bicyclopyrone, a bicyclo ring-type HPPD inhibitor, is an upland herbicide developed by Syngenta. It shows a broad herbicidal spectrum against grass weeds and broadleaf weeds before and after emergence.

Tolpyralate (Brucia® flowable), a pyrazole-type HPPD inhibitor, is a foliar spray herbicide for corn developed by Ishihara Sangyo Kaisha. It shows a high level of activity against a wide range of unwanted weeds, not only broadleaf weeds but also grasses.

### 7.3.3. PPO inhibitors

The PPO-inhibiting herbicides inhibit protoporphyrinogen-IX oxidase (PPO), which catalyzes the oxidation of protoporphyrinogen to protoporphyrin in the process of synthesizing the porphyrin ring. Inhibition of this enzyme ultimately results in pigment degradation and leaf necrosis, causing the plant to die. In recent years, the number of patent applications related to PPO-inhibiting herbicides has been declining.

Table 9 shows information on three PPO-inhibiting herbicides, tiafenacil (Dongbu Hannong Chemical), trifludimoxazin (BASF), and cyclopyranil (Kyoyu Agri), that have been in development since 2008. Trifludimoxazin (Tirexor™), currently under development by BASF, is a low-use-rate herbicide, from 12 to 50 g.a.i./ha, that provides control of difficult-to-control weeds such as palmer amaranth and Kochia. It was designed to be active against existing PPO-resistant weeds, resulting in the broad-spectrum pre- and post-emergence herbicide.

### 7.3.4. VLCFAE inhibitors

The VLCFAE-inhibiting herbicides had been primarily chloroacetamides and oxyacetamides, but various skeletons have been identified since then. Very few patents for VLCFAE inhibitors
have been published since 2008, and their skeletons are based on pyroxasulfone.

Table 10 shows information on four VLCFAE-inhibiting herbicides. Pyroxasulfone (Kumiai Chemical), ipfencarbazone (Hokko Chemical), and fenoxasulfone (Kumiai Chemical) have been in development since 2008. The fourth compound, dimetsulfzet, just obtained an ISO common name in early 2020.21) Pyroxasulfone (Axeev®, Zidua®) is an herbicide for upland crops such as wheat, soybeans, and corn. It shows high efficacy against hardly controllable gramineous weeds such as Johnson grass and Urochloa platyphylla and is also highly effective against weeds that have acquired resistance to glyphosate, ALS inhibitors, ACCase inhibitors, and dinitroaniline herbicides.87,101) Ipencarbazone (Winner®, Fighter®) is a triazolinone-based herbicide developed for paddy rice and exhibits high herbicidal activity against Echinochloa spp. from pre-emergence to the three-leaf stage while being safe for transplanted rice at a dosage of 250 g a.i./ha.102,103) It has excellent effect persistence and has a

| Chemical structures | Common name | Target crop | Remarks |
|---------------------|-------------|-------------|---------|
| Tefurytrione, Bayer 2010 | Paddy rice | Triketone compound |
| Fenquinotrine, Kumiai Chemical 2018 | Paddy rice | Triketone compound |
| Lancotrione-sodium, Ishihara Sangyo Kaisha 2019 | Paddy rice | Triketone compound |
| Bicyclopyrone, Syngenta 2016 | Corn | Bicyclo ring type compound |
| Tolpyralate, Ishihara Sangyo Kaisha 2017 | Corn | Pyrazole compound |

Table 9. PPO-inhibiting herbicides

| Chemical structures | Common name | Target crop | Remarks |
|---------------------|-------------|-------------|---------|
| Tiafenacil, Dongbu Hannon Chemical Under development | Non-selectivity (dicotyledon, monocotyledon) | Uracil compound |
| Trifludimoxazin, BASF Under development | | Triazinone compound Dose: 12-50 g a.i./ha |
| Cyclopyranil® Kyoyu Agri Under development | | Pyrazole compound |

a) Although there is no report that it is a PPO inhibitor, it is presumed to be a PPO inhibitor from the chemical structure.
residual effect for about 70 days against barnyard grass. Fenoxasulfone displays excellent herbicidal activity against *Echinochloa* spp. and other annual weeds at 150–200 g a.i./ha with long residual activity. Fenoxasulfone was registered in Japan in 2014, and various products containing fenoxasulfone have been launched.

Dimesulfazet (Nissan Chemical), which belongs to trifluoromethansulfonanilides, is presumed to be a VLCFAE inhibitor, since trifluoromethansulfonanilides such as mefluidide and perfluidone have been reported to inhibit a very-long-chain fatty acid synthesis. Dimesulfazet (Sulfonanilides) is presumed to be a VLCFAE inhibitor from its chemical structure.

### 7.3.5. Auxin-like herbicides and herbicide safener

Auxin-like herbicides include phenoxy carboxylic acids, benzoic acids, pyridine/pyrimidine carboxylic acids, and quinoline carboxylic acids. In recent years, mainly pyridine/pyrimidine compounds have been subjected to development.

Table 11 shows information on two auxin-like herbicides, halaxifen-methyl and florpypaixin-benzyl. Halaxifen-methyl (Arylex™), developed by Dow (Corteva Agriscience), is a pyridine-type auxin-like herbicide and is highly effective on...
major broadleaf weeds such as pigweed, henbit, corn poppy, flxweed, and chickweed at an extremely low dosage of 5–10 g/ha, with utility in multiple crops, the primary one being winter wheat.106) It is effective in managing weed biotypes resistant to other modes of actin such as ALS-inhibitor herbicides, glyphosate, and triazine herbicides. It has been shown that the activity (sensitivity to horseweed) of halauxifen-methyl is different from that of 2,4-D and dicamba, 107) which are typical auxin-like herbicides.

Florpyrauxifen-benzyl (Rinskor ™), developed by Corteva Agriscience, is also a pyridine-type auxin-like herbicide. It was unconditionally registered in the USA in 2017 and obtained approval in the EU in 2019. It is highly effective at postemergence control of grasses, sedges, and broadleaf weeds in rice crops. It is also being evaluated for use in other crops, including corn. In a greenhouse experiment, florpyrauxifen-benzyl at 30 g a.i./ha provided ≧75% control of many weed species, such as broadleaf signalgrass, barnyardgrass, Amazon sprangletop, and large crabgrass.108)

As an herbicide safener, only one compound, metcamifen, can be mentioned. Metcamifen prevented an herbicide, clodinafop-propargyl, from damaging rice seedlings, and this was associated with the enhanced detoxication of the herbicide.109)

### 7.3.6. Herbicide with a novel mode of action

As already mentioned, since 2018, and for the first time in 30 years, three herbicides possessing new modes of action have appeared. Table 12 shows information on three herbicides possessing a novel mode of action. Cyclopyrimorate (Cyra®), developed by Mitsui Chemicals Agro and launched in 2019 in Japan, is a rice herbicide.89,110) It shows a broad herbicidal spectrum against Cyperaceae weeds and broadleaf weeds. It is also highly effective against weeds that have acquired resistance to ALS inhibitors. Further, it can be applied simultaneously to rice planting and direct sowing cultivation in paddy fields. The site of action of cyclopyrimorate is HTS (homogentisate solanesyltransferase), a downstream enzyme of HPPD. In *in vitro* assays, HTS was inhibited strongly by DMC (a metabolite of cyclopyrimorate, des-morpholinocarbonyl cyclopyrimorate) and weakly by cyclopyrimorate. Although it has already been reported that HST inhibitors have herbicidal activity, cyclopyrimorate is the first commercial herbicide having this mode of action.

Tetflupyrolimet is a novel herbicide class of aryl pyrrolidinone anilides under development by FMC, the ISO common name being given in January 2019. It interferes with *de novo* pyrimidine biosynthesis via the inhibition of dihydroorotate dehydrogenase (DHODH).90) It has demonstrated a high level of activity against grasses.

Cinmethylin is an herbicide whose registration has expired, at least in Japan. It has recently been revealed by BASF scientists that cinmethylin binds to fatty acid thioesterase (FTA), a new herbicidal site of action, and inhibits plant fatty acid biosynthesis.88) BASF has recently developed cinmethylin (Luximax, trade name: Luximo™) as an herbicide to control key grasses in cereals. It demonstrates excellent efficacy against blackgrass and ryegrass, including resistant biotypes, while maintaining crop selectivity.111) Australia granted the world’s first approval to Luximo™ in 2019.112)

### Table 12. Herbicide with a novel mode of action

| Chemical Structures | Common name | Target crop | Remarks: | Dose | Target weed |
|---------------------|-------------|-------------|----------|------|-------------|
| Cyclopyrimorate     | Mitsui Chemicals Agro | 2019 | Paddy rice | Dose: 5–7.5 g/ha | Broad-leaved weeds and broad-leaved weeds. Highly effective against weeds that have acquired resistance to ALS inhibitors |
| Tetflupyrolimet     | FMC | Under development | Paddy rice | Grass control |
| Cinmethylin         | BASF | 2019 | Existing herbicide found to have a novel mode of action |

8. Concluding remarks

During the past decade, a wide variety of useful chemical pesticides that are safe to humans and environmentally friendly have been subjected to development. In the field of insecticides, acaricides, nematicides, and fungicides, new chemicals that have or are likely to have a novel mode of action and unique chemical structure have been continuously developed. This is extremely important in avoiding the development of pesticide resistance and enabling sustainable agricultural production. It is of interest that in the herbicide field, for the first time in 30 years, herbi-
chemical pesticides possessing a novel mode of action have appeared. This is significant for dealing with herbicide-tolerant weeds that have recently become a problem.

Though several new chemical pesticides originating from China (universities and companies) during the past decade are described in the present manuscript, this may not cover all new compounds from China. China’s dissemination of information (outside the country) on new pesticides seems insufficient, and some new compounds have been developed mainly for domestic use.

Chemical pesticides developed over the past decade have played an important role in crop protection and are expected to play an important role in the future. However, it is true that in recent years, the trend of global pesticide development has been gradually shifting from chemical pesticides to biological pesticides, GM crops, seeds, RNAi pesticides, and abiotic stress control agents. Of those, biopesticides are gaining popularity as lower-environmental-impact alternatives to conventional synthetic pesticides. The research and advisory firm Lux Research in Boston, MA, USA, has made an interesting and bold prediction concerning the relationship between chemical pesticides and biopesticides. As shown in Fig. 14, they predict that biopesticides will equal synthetic (chemical) pesticides in terms of market size by the late 2040s or early 2050s.¹¹³ It will be necessary to closely monitor the future trends of chemical pesticides.

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