agronomy

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Review

From Old-Generation to Next-Generation Nematicides

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Received: 29 July 2020; Accepted: 11 September 2020; Published: 14 September 2020

Abstract: The phaseout of methyl bromide and the ban on, or withdrawal of, other toxic soil fumigants and non-fumigant nematicides belonging to the organophosphate and carbamate groups are leading to changes in nematode-control strategies. Sustainable nematode-control methods are available and preferred, but not always effective enough, especially for cash crops in intensive agriculture. A few non-fumigant nematicides, which have a relatively high control efficacy with a low toxicity to non-target organisms, have been released to the market or are in the process of being registered for use. Fluensulfone, fluopyram, and fluazaindolizine are the three main and most promising next-generation nematicides. In this paper, several aspects of these non-fumigant nematicides are reviewed, along with a brief history and problems of old-generation nematicides.

Keywords: fluazaindolizine; fluensulfone; fluopyram; nematicide; nematode control

1. Introduction

Farmers were struggling with plant-parasitic nematodes even before they had any knowledge of the pest, using methods such as sanitation, crop rotation, fallowing, the selection of superior plants, etc. The first discovered plant-parasitic nematode was *Anguina tritici*—the seed gall nematode—in 1743 [1]; the important nematodes *Heterodera schachtii* and *Meloidogyne* spp. were in discovered in 1859 [2] and 1889 [3], respectively. The first commercialized nematicide was carbon disulfide, which was initially used to control *H. schachtii* and later *Meloidogyne* spp., from the late 19th to early 20th century [4]. However, the potential of nematode damage to crops was only widely recognized after the nematicidal activity of soil fumigants was revealed in the early 20th century. Applications of fumigants such as chloropicrin, methyl bromide, a mixture of 1,3-dichloropropene and 1,2-dichloropropane (D-D), and ethylene dibromide (EDB), drastically increased the yields of several crops in most field trials conducted in the USA and other countries [5]. The results identified nematodes as a high-risk pest group among crops, and more fumigants were developed. Significant among these were 1,3-dichloropropene (1,3-D)-, 1,2-dibromo-3-chloropropane (DBCP)-, and methyl isothiocyanate (MITC)-generating compounds; however, most of these fumigants were later banned or are currently being withdrawn in many countries due to their adverse effects on humans and the environment. The most notable of these fumigants is methyl bromide, which had a broad spectrum of target pests, including nematodes, fungal pathogens, weeds, and soil arthropods, and was used for several decades before its phaseout in 2005 in developed counties and in 2015 in the rest of the world. The announcement of methyl bromide's phaseout led to the search for alternative fumigants by agrochemical companies and public institutes. Methyl iodide (iodomethane) attracted attention as a potential alternative and was registered for 1 year under restrictive provision regulation in the USA [6], but its release to the market was finally abandoned by the manufacturer, despite its relatively high pest-control efficacy. Dimethyl disulfide (DMDS) is probably the only commercial soil fumigant with a broad spectrum (effective against nematodes, weeds, and fungal pathogens) released after the ban of methyl bromide [7]. Others that are still used in many countries include 1,3-D- and MITC-generating

fumigants, such as metam sodium/potassium and dazomet. Generally, soil fumigants are applied through overhead or drip irrigation systems, or by soil injection, and they kill nematodes by multiple modes of action, such as by affecting enzymatic, nervous, and respiratory systems [8].

The major advantage of soil fumigants was, and still is, their relatively high control efficacy for a variety of nematode species and some other soilborne pests; their disadvantages include high application doses (a few hundred liters per hectare), difficult application, and the fact that they can only be used pre-planting. Non-fumigant nematicides, specifically effective against nematodes and some insect pests, were mainly developed from the 1960s [8]. These nematicides belong to the organophosphate and carbamate groups, and can be called old-generation nematicides, because most of them have been banned or withdrawn. Only a small number of new nematicides, known as next-generation nematicides, from different chemical groups have been released or are in the process of being registered for use (Figure 1, Table 1). In a recent review of new nematicides, nematicide discovery and development, modes of action, and the control efficacy, among other topics, were discussed [9].

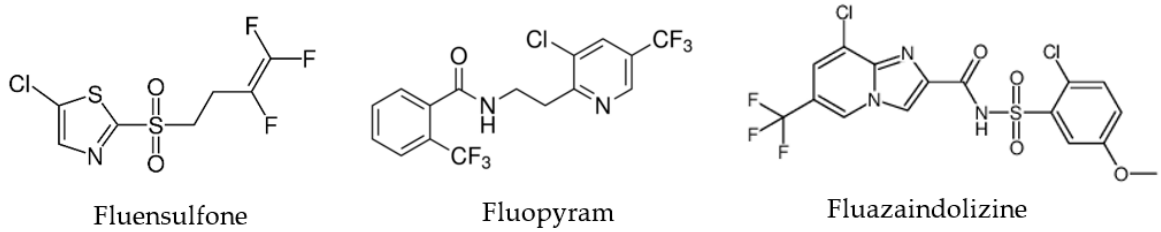

Figure 1. Chemical structures of next-generation nematicides.

In this paper, several aspects of next-generation nematicides, such as the toxicity and impact on the environment, modes of action, chemical characteristics, and control efficacy, are reviewed, along with the old-generation nematicides. Soil fumigants, which were mentioned briefly in this section and reviewed by several authors [8,10,11], are not discussed in this review.

Table 1. Characteristics of next-generation nematicides.

	Fluensulfone	**Fluopyram**	**Fluazaindolizine**
Chemical group	Fluoroalkenyl sulfone	Pyridinyl-ethyl-benzamide	Imidazopyridine
Commercial name	Nimitz	Velum, Verango, ILeVo, Indemnify, etc.	Salibro
Manufacturer	Adama	Bayer CropScience	Corteva Agriscience
Discovery (year)	2004	2009 (as nematicide)	2017 (reported)
Release (year)	2014	2014 (as nematicide)	2020 (expected)
LD_{50} (mg/kg) [a)]	671 [12] *	>2000 [13]	>1187 [14]
DT_{50} (day) [b)]	7–17 [12]	4–25 [13,15]	About 35 [16,17]
log P [c)]	1.96 [12]	3.3 [13]	Not available
Mode of action	Unknown	Succinate dehydrogenase inhibitor [18,19]	Unknown

[a)] Median lethal dose in rats by oral administration; [b)] half-life in soil; [c)] n-octanol–water partition coefficient; * reference number.

2. Old-Generation Nematicides

The development of synthetic nematicides started after the discovery of insecticides belonging to the organochlorine, organophosphate, and carbamate groups, such as dichlorodiphenyltrichloroethane (DDT), parathion, and carbaryl, during and after World War II. The first non-fumigant nematicide was dichlofenthion (V-C 13)—an organophosphate released to the market in 1957 [20]. Major

organophosphate nematicides developed thereafter and until the early 21st century were fensulfothion, fenamiphos, ethoprophos, terbufos, cadusafos, fosthiazate, and imicyafos, with the latter being released in Japan in 2010, while major carbamates were aldicarb, oxamyl, and carbofuran [8]. These nematicides were formulated as liquid or granules, and had several advantages over soil fumigants: (i) Lower application doses (a few kilograms of active ingredients per hectare); (ii) easy application methods, without the need for specialized application equipment, such as spraying or dispersion on the ground surface and incorporation, or drenching; and (iii) a low phytotoxicity, which enabled pre- and post-planting application. Some of the nematicides were reported to have systemic activity that might control nematodes inside plant tissues, even by foliar application [21].

Nematicides from both the organophosphate and carbamate groups affect the central nervous system of nematodes by inhibiting acetylcholinesterase activity [22]. This results in the buildup of acetylcholine, which is a neurotransmitter in synapses and neuromuscular junctions, and causes nematode paralysis and death. In general, however, the recommended field-application doses of these nematicides do not lead to acute nematode death. Nevertheless, at sublethal concentrations in the soil, they affect many nematode functions, including hatching, attraction to host plants, locomotion, and reproduction [23]. However, once the nematicides disappear from their surroundings, the nematodes may recover and infect plants. Therefore, this type of nematicide is called "nematostatic" [24].

Although the target enzyme exists in all parasitic and non-parasitic nematodes, the nematicidal activity of a nematicide varies among nematode genera and even species [25]. For example, sedentary endoparasitic nematodes, such as *Meloidogyne* spp., are generally more susceptible to nematicides than migratory nematodes, especially those that attack aboveground plant parts and/or those that survive via anhydrobiosis, such as *Aphelenchoides* spp., *Ditylenchus* spp., and *Pratylenchus* spp. [26]. The differences in activity might be caused by differences in the nematicide molecules' affinity to the target enzyme [27], and the nematode's cuticle structure or body size, among other aspects. Organophosphate insecticides, such as fenitrothion, malathion, and diazinon, have been reported to be more effective at killing *Aphelenchoides fragariae*, *Aphelenchoides besseyi*, *Ditylenchus dipsaci*, and *Bursaphelenchus xylophilus* than commercial nematicides [28–30]. When considering nematicide development, the possibility of finding one compound that can effectively control all plant-parasitic nematode groups seems very low. Unlike insecticides and fungicides, which have higher numbers of products, each used for relatively specific insects or fungal genera/species, only a few nematicides are registered, mainly for a few nematode groups that are of high economic importance. Free-living nematodes in the soil, including bacterial-feeding, fungal-feeding, omnivorous, and predatory nematodes, are generally more tolerant to nematicides [31,32]. This means that free-living nematodes, which play an important part in the mineral turnover and biological equilibrium of the soil ecosystem, may be less affected. Soil fumigants, on the other hand, are less specific to nematode groups and can suppress both plant-parasitic and free-living nematode populations [32,33].

The main reason for the withdrawal of most of the old-generation nematicides was their high toxicity to humans and other non-target organisms. For example, the acute median lethal dose (LD_{50}) of aldicarb (phased out in 2015)—one of the most toxic pesticides ever commercialized—was found to be about 0.65–1.0 mg kg^{-1} body weight for rats via oral administration [34]. It is well-known that aldicarb metabolite residue (aldicarb sulfoxide) in melon, even at concentrations near the lowest detection level (0.2 ppm), poisoned more than a thousand people in the USA [35]. Other nematicides have higher acute LD_{50} values (lower toxicity), such as fenamiphos (8.0 mg kg^{-1}) and cadusafos (37.1 mg kg^{-1}) for rats by oral administration [36], but are still categorized as highly toxic to humans. Oxamyl, on the other hand, is still registered in many countries as a nematicide and insecticide, despite its relatively low LD_{50} (5.4 mg kg^{-1}) [36]. One of the reasons for its continued use is its rapid degradation: The half-life (DT_{50}) of oxamyl in the soil ranges from a few hours to a few days, mainly depending on the soil pH [37]. Rapid degradation in the soil contributes to this product's safety profile, but, on the other hand, it may reduce the nematode-control efficacy. Organophosphate nematicides that are still used in some developed countries are fosthiazate and imicyafos; both nematicides are relatively new products

developed in Japan and released in 1992 and 2010, respectively, having relatively high LD_{50} values of 57 and 81.3 mg kg^{-1} for rats by oral administration, respectively [36,38].

Aside from the high toxicity, another problem of nematicide use is the decreased nematicidal activity after repeated applications of the same or a related nematicide to the same field [39–41]. This phenomenon was initially thought to be caused by the development of nematode populations that were resistant to the nematicides. However, in actuality, the decrease in nematicidal activity was found to be caused by the development of soil microorganisms that can use the nematicides as a substrate for their energy generation, termed enhanced or accelerated biodegradation [42–44]. Nematicides applied to such a soil can be degraded more rapidly than in soil with no history of the same nematicide application [45]. In general, soils with a higher pH and soil temperatures are more likely to display this phenomenon due to enhanced bacterial activity [46–48]. Such rapid degradation can also be caused by frequent applications of different nematicides that belong to the same chemical group [49,50]. Interestingly, no solid evidence for the development of nematicide-resistant populations of plant-parasitic nematodes has been reported, in contrast to animal-parasitic nematodes [51,52]. The reasons for this are not clear.

Another phenomenon responsible for the rapid disappearance of nematicides in the soil is leaching. The physicochemical properties of a pesticide, such as the mobility in the soil's water phase, can be predicted by log P (the logarithm of the partition coefficient between *n*-octanol and water), which correlates with water solubility and adsorption to soil particles [53,54]. Nematicides with low log P values, such as oxamyl (−0.47), generally leach more readily than those with high log P values, such as terbufos (4.48) and fenamiphos (3.23) [36,55], although soil types also affect nematicides' mobility in the soil. Higher clay and organic matter contents in a soil may cause less leaching of a nematicide due to its adsorption to soil particles and organic matter [56].

3. Next-Generation Nematicides

3.1. Background

Before the ban of methyl bromide and during the withdrawal of most of the old-generation nematicides, agrochemical companies initiated the search for less toxic nematicides. However, their continued interest has been hindered by the fact that the development of nematicides is fraught with both economic and technical difficulties. The global market for nematicides ($1.3 billion in 2019) is much smaller than that for insecticides ($16.4 billion in 2019), fungicides ($13.4 billion in 2019), and herbicides ($32.6 billion in 2019), while the cost of their development is as high as that of these other compounds (about $200 million) [57]. From a technical point of view, the development of a nematicide that is applied to the soil is challenging because the chemical molecule must reach the nematodes in the soil; thus, even molecules that have strong nematicidal activity in vitro are not always effective in the field. Upon application, nematicide movement may be restricted by the physiochemical effects of the soil and by the negative effects of microbial activity, such as degradation. From the point of view of environmental safety, nematicides applied to soils have more chance of leaching into the groundwater than pesticides applied to plant foliage [58]. Despite these difficulties, however, a few new compounds with a very promising efficacy have been developed and released in recent years, or are in the process of being registered for use, namely fluensulfone, fluopyram, and fluazaindolizine (Figure 1, Table 1). It is interesting that all three of these compounds contain trifluoromethyl (-CF_3). Therefore, they are called 3F or fluorinated nematicides. As regards other nematicides, spirotetramat is a relatively new systemic nematicide/insecticide that can be applied by foliar spraying. Some results indicate that the nematicide may inhibit nematode development slightly [59,60]; however, since the foliar application does not reduce the nematode infection of roots, its use as a nematicide may not be effective enough for nematode management [61,62]. Tioxazafen is about to be released for the seed treatment of soybean, cotton, and corn against several nematodes, but almost no information is available [63]. For these reasons, these latter compounds are not reviewed here. Products based on biological origins, such as

plant extracts, microbial macrocyclic lactones, and biological agents, have also been released in recent years; however, these types of nematicides are not new and they are therefore also not included in this review.

3.2. Fluensulfone

Fluensulfone (CAS No. 318290-98-1; 5-chloro-2-(3,4,4-trifluorobut-3-enylsulfonyl)-1,3-thiazole) is the active ingredient of Nimitz®, which was developed by ADAMA and first registered in the USA in 2014 for some vegetables. Fluensulfone is not an organophosphate or carbamate, but rather belongs to a new chemical group—the heterocyclic fluoroalkenyl sulfones. Three formulations, including 1.5% granular for turfgrass (Nimitz® Pro G), 2.0% granular for vegetables (Nimitz® 2% GR), and 40% and 48% emulsifiable concentrates for vegetables (Nimitz® and Nimitz® 480 EC), are currently available.

3.2.1. Toxicity and Impact on the Environment

In contrast to old-generation nematicides, fluensulfone is much less toxic to humans and non-target organisms. For example, acute LD_{50} for rats via oral administration is 671 mg kg^{-1} body weight [12], indicating that the compound is about a thousand to a hundred times safer than most of the old-generation nematicides. However, fluensulfone is relatively toxic to aquatic organisms. For example, its median effective concentration (EC_{50}) at 48-h exposure for *Daphnia magna* is 0.35 mg L^{-1}, and about 0.04 mg L^{-1} at 72-h exposure for green algal species (*Pseudokirchneriella subcapitata* and *Scenedesmus subspicatus*) [12]. Therefore, its use near aquatic environments should be restricted. The disadvantage of this compound is its phytotoxicity, restricting its use to pre-planting only, except for turfgrass. The recommended application doses often cause phytotoxicity to plants if applied after seeding or transplanting [64]. Tomato, pepper, and eggplant are more sensitive to the compound than melon and squash. The phytotoxicity varies among crops; however, application timing of at least 7 days before planting is recommended. In contrast to soil fumigants, a restrictive buffer zone is not required, and the re-entry interval is basically only 12 h after application.

The fate of fluensulfone in soil has not been studied much. Log P of the compound is 1.96 [12], which suggests that it is much less leachable than oxamyl, but leaching is still possible [65]. Its DT_{50} is 7–17 days, depending on the soil type and environmental conditions, such as the soil temperature and water contents [12]. Fluensulfone is degraded in the soil to three main metabolites: Methyl sulfone, thiazole sulfonic acid, and butene sulfonic acid [12]. The latter two are the major metabolites of fluensulfone taken up by plants [12]. The maximum residue levels of fluensulfone and its metabolites in food are generally set at 0.3–0.5 mg kg^{-1} for vegetables, depending on the crop and country [12].

Not much work has been conducted on the impact of fluensulfone on free-living nematodes. The number of free-living nematodes was reduced by one-third to one-quarter after application at 5 mg L^{-1} to sandy soil, and 4 weeks after application, their numbers had still not recovered under laboratory conditions (Oka, unpublished). Fluensulfone did not change the diversity level of free-living nematode fauna and had a very low suppressive effect on free-living nematodes while controlling *Meloidogyne* spp. effectively [32]. In the same study, fosthiazate was found not to affect the free-living nematodes' density, but it did affect their diversity. Similarly, free-living nematodes in the turfgrass soil were much less affected by fluensulfone compared to abamectin or fluopyram, although the latter two improved the turfgrass green cover [66].

3.2.2. Mode of Action

The exact target site of fluensulfone remains unclear. However, the compound has been suggested to affect several functions of nematodes, and to have a different mode of action compared to organophosphate and carbamate, as well as macrocyclic lactone nematicides [67]. Fluensulfone affected the functions of *Caenorhabditis elegans*, which are much more tolerant to the compound than *M. javanica* J2, with respect to locomotion, pharyngeal pumping, egg-laying, and development [67]. The compound was also found to inhibit hatching and to interact with serotonin signaling to stimulate

stylet and pharyngeal activity of *Globodera pallida* [68]. Fluensulfone may kill *G. pallida* via metabolic impairment. *M. javanica* J2 that were temporarily inactivated by fluopyram were less sensitive to fluensulfone than untreated active J2 [69]. The results suggest that the target site for fluensulfone in the nematode may be related to that of fluopyram, which is a succinate dehydrogenase inhibitor (SDHI) [18,19].

3.2.3. Characteristics

The feature that most distinguishes fluensulfone from old-generation nematicides is the irreversibility of its nematicidal activity; in other words, the compound kills nematodes by irreversible paralysis [70,71]. However, it affects and paralyzes nematodes much more slowly than organophosphates [69] or fluopyram [71]. Interestingly, even when second-stage juveniles (J2) of *Meloidogyne* spp. were motile after exposure to fluensulfone, followed by rinsing in water, the J2 gradually lost their motility and infectivity [69–71]. In the case of *Meloidogyne hapla*, for example, after exposing the J2 to fluensulfone at 1.0 mg L^{-1} for 24 h, followed by rinsing in water, more than 90% of them were motile at rinsing, but more than 80% of them became immobilized 48 h later in water [69]. In in-vitro experiments using lettuce seedlings in Pluronic Gel, *Meloidogyne incognita* J2 exposed to fluensulfone at 4.0 mg L^{-1} for 17 h, followed by rinsing in water, were mobile at inoculation, but they were not attracted to lettuce seedling roots, and did not infect the seedlings [71]. Similar results were obtained in experiments in which the number of root galls was highly reduced by the exposure of *Meloidogyne* J2 to fluensulfone, followed by rinsing in water, although the J2 were motile at inoculation [69].

This distinct nematicidal activity of fluensulfone makes it very effective for nematode control, especially for *Meloidogyne* spp. Like other nematicides, the nematicidal activity varies among nematode genera, and even among species in a genus. For example, migratory nematodes, such as *Ditylenchus dipsaci*, *Bursaphelenchus xylophilus,* and *Aphelenchoides* spp., were much more tolerant to the compound than *Meloidogyne javanica* J2 [72]. *D. dipsaci* and *B. xylophilus* were not immobilized, even after exposure to fluensulfone at 16 mg L^{-1} for 48 h [72], whereas *M. hapla* J2 were immobilized by exposure to 0.25 mg L^{-1} for 48 h [69]. In contrast, *Tylenchulus semipenetrans* J2 were highly sensitive to fluensulfone; EC_{50} for J2 immobilization by 48-h exposure was about 0.5 mg L^{-1} (Oka, unpublished), which is similar to *M. javanica* J2 [71]. Mixed stages of *Mesocriconema xenoplax* were immobilized at a rate similar to *M. incognita* J2 by 72-h exposure at 8 mg L^{-1}; however, the *Mesocriconema xenoplax* population in peach tree pot soils decreased after fluensulfone application at 4 mg L^{-1} soil, whereas *M. incognita* J2 did not [73].

Differences in sensitivity to fluensulfone were found to exist among *Meloidogyne* spp. [69,71], and even populations of the same species [71]. *M. javanica* J2 were more tolerant than *M. incognita* and *M. hapla* J2 [69,71]; EC_{50} values for J2 immobilization in two different *M. incognita* populations and one *M. hapla* population by 48-h exposure were 0.12, 0.41, and less than 0.25 mg L^{-1}, respectively, while that of *M. javanica* was 0.83 mg L^{-1}. In contrast to the very high nematicidal activity against *Meloidogyne* J2, hatching inhibition by fluensulfone is very limited. The exposure of *M. javanica* eggs to the compound at 8 mg L^{-1} for 3 days, followed by rinsing, caused only a slight reduction in J2 hatching [70]. EC_{50} for hatching reduction in *M. incognita* was between 25 and 50 mg L^{-1} for 3-day exposure (Oka, unpublished). Interestingly, the hatching inhibition was irreversible, probably due to ovicidal activity. Furthermore, most of the J2 from the eggs, which had been exposed to fluensulfone, followed by rinsing, became immobile in water. For example, more than 80% of the J2 were immobilized after hatching from eggs which had been exposed to 25 mg L^{-1} fluensulfone for 3 days, followed by rinsing. This irreversible hatching inhibition and J2 immobilization after hatching from fluensulfone-treated eggs were also observed in *Globodera pallida* at high concentrations (≥500 μM) [74].

Another interesting feature of the compound is its systemic activity in plants. Although fluensulfone is phytotoxic, foliar spraying at 3 g L^{-1} 2 days before the inoculation of pepper seedlings, which are

relatively tolerant to the compounds, reduced the number of root galls of *M. incognita*, but not by post-inoculation spraying [75]. Systemic activity via foliar application was also reported for tomato inoculated with *M. incognita* after spraying [76]. However, this application method may not be practical because of the phytotoxicity risk, the high concentrations of the compound required for spraying, and residue problems in terms of the yield.

3.2.4. Field Application, Efficacy, and Environmental Conditions

Fluensulfone is currently registered for several crops (including tomato, cucumber, bell pepper, squash, potato, cabbage, broccoli, melon, lettuce, strawberry, and turf) associated with several important nematode genera and species, including *Belonolaimus*, *Globodera*, *Hoplolaimus*, *Meloidogyne*, and *Pratylenchus*, depending on the country and crop. The application doses are generally 1.9–3.3 kg ha^{-1}. Most of the published work on fluensulfone under field conditions addresses the control of *Meloidogyne* spp. For example, the application of 2.95 kg ha^{-1} fluensulfone reduced the root galling of carrots caused by *M. incognita* in sandy soil [77]. The root galling of lima bean and the final *M. incognita* J2 population in infested field microplots were reduced by fluensulfone at 1.64 and 2.34 kg ha^{-1} [78]. The application of 3.0 kg ha^{-1} fluensulfone via drip irrigation reduced root galling and increased the yield of cucumber and tomato grown in fields infested with a *Meloidogyne* sp. [76,79]. Similar results of reduced root-galling of tomato in *M. javanica*-infested fields were obtained by the application of 4.14 kg ha^{-1} fluensulfone via drip tapes [80]. The amount of marketable sweet potato in *M. incognita*-infested fields was increased 1.9–3.4 times by fluensulfone (1.96–3.36 kg ha^{-1}) [81]. However, the control efficacy of the compound seems to be lower against nematodes from other genera. Fluensulfone (4.05 kg ha^{-1}) resulted in less effective control of *Globodera pallida* on potato than fosthiazate or oxamyl [82]. Fluensulfone at 1.4–3.9 kg ha^{-1} reduced the population of *Belonolaimus longicaudatus*, but not of a *Paratrichodorus* sp. in potato fields [83]. The reduction of a *Pratylenchus* sp. population by the same fluensulfone treatments was not consistent in the potato fields. Fluensulfone (3.9 kg ha^{-1}) applied via drip tapes was inconsistently effective at reducing populations of *Belonolaimus longicaudatus* and *Pratylenchus penetrans* on strawberry, and at increasing yields [80]. Fluensulfone is also registered for turf against *Belonolaimus, Hoplolaimus*, and *Meloidogyne* spp.; however, details of its control efficacy are not available.

As noted earlier, the same nematicide should not be applied frequently to the same field due to the possibility of enhanced biodegradation and the development of resistance to the nematicide in nematode populations. Although the recommended application frequency of fluensulfone to the same field is one application per year and not more than 3.8 kg ha^{-1} per year, intensive repeated application—as many as five applications at 2-week intervals—to the same pot soil at 1.0 mg L^{-1} did not cause enhanced biodegradation of the compound under laboratory conditions, in contrast to fenamiphos or cadusafos [84]. Furthermore, the soils that showed enhanced degradation of fenamiphos or cadusafos did not have any such effect on fluensulfone, probably because the latter is not an organophosphate nematicide. In addition to the enhanced biodegradation test, experiments for the selection of *M. javanica* that are tolerant to fluensulfone were conducted: J2 that survived exposure to fluensulfone at 1–4 mg L^{-1} for 48 h were used as inoculum for tomato seedlings. J2 from their offspring (generation 1) on the tomato roots were again exposed to the fluensulfone solution and used as inoculum. This procedure was repeated for 2 years. No difference in sensitivity to fluensulfone was found between J2 from fluensulfone-treated generations and control generations, even after 18 generations (Oka, unpublished). Like other nematicides, the occurrence of nematode population resistance to the compound may be low under field conditions.

Environmental conditions, such as the soil temperature, affect the nematode-control efficacy of nematicides. The metabolic activity of nematodes is low at low temperatures, and they may thus be less sensitive to nematicides [69]. *M. javanica* and *M. hapla* J2, which had been inactivated in water at 4 and 15 °C, were more tolerant to fluensulfone than active J2 at 25 °C, resulting in a higher EC_{50} for J2 immobilization and root-gall reduction on lettuce seedlings by 24- or 48-h exposure. Interestingly,

M. javanica J2 that were temporarily inactivated by fenamiphos were as sensitive to fluensulfone as untreated active J2 [69]. Similar to other nematicides, the soil type affects the mobility of fluensulfone in the soil. Fluensulfone in water-diluted EC solutions moved a greater vertical distance in a column filled with sandy soil than in one filled with loess soil [84]. Organic matter is another factor affecting the mobility of the compound in the soil; peat moss mixed into the sandy soil also reduces the vertical movement of compounds [84]. The reduction in distance moved in the soil is mainly due to adsorption to organic matter and clay [65,85].

3.3. Fluopyram

Fluopyram (CAS No. 658066-35-4; N-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl)benzamide) is the active ingredient of Velum® and its related products, developed by Bayer CropScience [86,87]. The compound, which belongs to the pyridinyl-ethyl-benzamide group, was first developed as a fungicide against several fungal pathogens, such as *Botrytis*, *Sclerotinia*, *Erysiphe*, and *Pyrenophora* spp., under the commercial name of Luna®. Its nematicidal activity was discovered later and it was registered as a nematicide in several countries. Currently, several products against nematodes, fungal pathogens, and insects are available, including Verango®, Velum® Prime, Velum® One, COPeO® Prime, Indemnify®, and ILeVo® (all without additional active ingredients), and Velum® Total (with an insecticide).

3.3.1. Toxicity and Impact on the Environment

In general, fluopyram has a low toxicity to vertebrates and invertebrates. The acute LD_{50} of fluopyram is more than 2000 mg kg^{-1} for rats via oral administration, indicating its safety compared to the old-generation nematicides [13]. The compound has a low toxicity to bees (LD_{50} > 100 µg per bee), but more moderate toxicity to fish (LC_{50} > 0.98 mg L^{-1}) [88]. The maximum residue limits in food, for example, tomato and cucumber, are 1.0 and 0.6 ppm in the USA [89]. The impact of fluopyram applied to the soil as a nematicide or fungicide on non-target organisms has been little studied. Fluopyram was found to reduce the number of free-living nematodes for a long period (up to 238 days after application), especially bacterivores, fungivores, and omnivores, and to have the potential to affect all nematode feeding groups [66]. In peanut fields, 0.24 kg ha^{-1} fluopyram did not affect any free-living nematode trophic groups or individual genera, although the same treatment also did not reduce the population of *Meloidogyne arenaria* [90]. In a study on the soil microbial activity, fluopyram (0.5–5 mg kg^{-1} soil) decreased total phospholipid fatty acids, the biomass of both gram-negative and gram-positive bacteria, the fungal biomass, and the microbial community structure in the soil [91]. In contrast, fluopyram applied at the same concentrations increased the number of phosphate-solubilizing bacteria, the abundance of nitrogen-fixing genes in the pepper rhizosphere, and pepper seedling growth [92]. The application dosage recommended by the manufacturer is very low, i.e., 197–207 g ha^{-1} and not more than 494 g ha^{-1} per year, which is about one-tenth of that of fluensulfone. These very low application doses may prevent the destruction of soil microbial ecosystems, such as free-living nematodes and beneficial fungi like mycorrhiza, and minimize the residue in the produce; on the other hand, higher application doses could be more effective in controlling plant-parasitic nematodes.

3.3.2. Mode of Action

Fluopyram controls fungi by inhibiting succinate dehydrogenase as an SDHI, which affects the respiratory chain in mitochondria [87]. In nematodes, the compound has been reported to inhibit complex II (succinate–ubiquinone reductase), which is also involved in mitochondrial respiration [18]. *Caenorhabditis elegans* with a mutation in complex II were resistant to fluopyram and structurally related compounds. However, fluopyram is the only commercial SDHI fungicide that is highly nematicidal against *C. elegans*, as well as *M. incognita* and *Rotylenchulus reniformis* at low concentrations, compared to other SDHIs, such as boscalid, flutolanil, benzodanil, and solatenol [18,19]. These results may

indicate that fluopyram has a higher affinity or specificity to nematodes' complex II than other SDHIs. Another fungicide that is known to have nematicidal activity is benomyl, which is used for rice seed treatment against *Aphelenchoides besseyi*, although this fungicide is not an SDHI [93].

3.3.3. Characteristics

Fluopyram affects nematodes much more rapidly than fluensulfone; almost 100% of *M. javanica* J2 were immobilized after 24-h exposure to 2.0 mg L^{-1} fluopyram. The same concentration of fluensulfone required 48-h exposure, followed by another 24-h period of incubation in water, in order to reach the same level of J2 immobilization [71]. The EC_{50} of fluopyram required for the immobilization of *M. incognita* J2 in 24 h was 0.5 mg L^{-1}, in contrast to 52.7 mg L^{-1} for fluensulfone [94]. Fluopyram can be called a "real nematicide" which causes irreversible immobilization and leads to nematode death after short exposure periods at relatively low concentrations. For example, *M. javanica* or *M. incognita* J2 species exposed to 4 mg L^{-1} fluopyram for 48 h caused 100% J2 immobilization, and they did not recover after rinsing in water [71]. However, irreversible J2 immobilization was not obtained at lower concentrations. For example, exposure of the same J2 to 2 mg L^{-1} fluopyram for the same period only caused reversible immobilization. Such exposure period- and concentration-dependent irreversible immobilization was also observed for *Caenorhabditis elegans* [89]. The *M. javanica* and *M. incognita* J2 that recovered from fluopyram-induced paralysis retained their infectivity to lettuce seedlings [69,71]. The infectivity of recovered *M. incognita* J2 was also reported after exposure to 0.5 mg L^{-1} fluopyram for 24 h [94]. Reversible immobilization was also observed with *Rotylenchulus reniformis* and *M. incognita* J2 by 2-h exposure to 5.15 mg L^{-1} fluopyram [19]. The interesting thing is that the difference in the concentrations causing reversible or irreversible immobilization during the same exposure period is very small. Nematostatic compounds, such as oxamyl, have much greater differences in concentrations that cause reversible vs. irreversible immobilization [24].

Fluopyram has much higher hatching-inhibition activity against *Meloidogyne* J2 than fluensulfone. Incubation for 3 days in 5 mg L^{-1} fluopyram solution inhibited *M. incognita* J2 hatching from eggs separated from egg masses by 96%, whereas the same concentration of fluensulfone resulted in only 48.5% inhibition (Oka, unpublished). However, the hatching began after rinsing the eggs in water, even from eggs that had been exposed to 100 mg L^{-1} fluopyram for 3 days, and the final hatching rate was very close to that of the control. This reversible hatching inhibition of fluopyram was also observed on eggs within egg masses, although higher concentrations of the nematicide were required (Oka, unpublished). Fluopyram also inhibited the hatching of *Globodera pallida* J2 by the exposure of cysts [74] and of *Heterodera glycines* J2 from eggs [95]. In contrast, the hatching inhibition was irreversible when *G. pallida* cysts were exposed to concentrations of ≥50 μM for 32 days, probably due to the very long exposure period [74]. Exudates from soybean seeds treated with fluopyram also inhibited *H. glycines* J2 hatching [96,97].

Fluopyram is reported to have acropetally systemic activity (from the roots to the leaves) against fungal pathogens in plants [98]. When soil was drenched with fluopyram, the compound moved upward in the xylem and controlled *Alternaria solani* on potato plants. To the best of the author's knowledge, the systemic control of nematodes inside plant roots or foliage by fluopyram has not been reported. However, due to its nematicidal and fungicidal activity, this nematicide may have an advantage for fungal diseases associated with nematodes, such as soybean sudden death syndrome [99,100].

3.3.4. Field Application, Efficacy, and Environmental Conditions

As already noted, a salient characteristic of fluopyram is its very low recommended application dose (about 0.2 kg ha^{-1}). Fluopyram-based products are currently registered for many crops and associated nematodes, depending on the country and crop, including *Belonolaimus longicaudatus*, *Globodera rostochiensis*, *Globodera pallida*, *Helicotylenchus* spp., *Heterodera* spp., *Longidorus* spp., *Meloidogyne* spp., *Pratylenchus* spp., *Radopholus similis*, *Tylenchulus semipenetrans*, and *Xiphinema* spp. In field trials, 0.24 kg ha^{-1} fluopyram did not reduce *M. arenaria* populations, although it increased the peanut yield

in one of two field trials [90]. In fields infested with *M. incognita*, 0.256 kg ha^{-1} fluopyram reduced the galling index for carrots, but not the total yield [77]. Fluopyram at 0.22 kg ha^{-1} reduced an *M. incognita* J2 population in field microplots of lima bean and increased the pod weight [78]. In an experiment with 15-L containers, fluopyram at 7.5 mg per container reduced the number of *M. incognita* and root galling at an early stage of tomato growth, but not the final population or root galling [101]. Fluopyram (at 0.25 kg ha^{-1}) increased the fruit yield and suppressed the populations of *Belonolaimus longicaudatus* at the end of the season in a strawberry field [102]. Higher application doses of fluopyram could improve the control efficacy, but the reported low application doses were probably chosen to preserve the microbial ecosystem and beneficial microorganisms. Fluopyram was also used as a seed treatment for soybean to protect plants at the early developing stage from several nematodes (*Heterodera glycines*, *M. incognita*, *Rotylenchulus reniformis*, *Pratylenchus* spp., and *Hoplolaimus* spp.) and fungal pathogens (*Fusarium virguliforme* and *Septoria glycines*) [96,97,99,100,103], and for cotton against several nematodes (*M. incognita*, *R. reniformis*, and *Hoplolaimus* spp.) [104]. In laboratory experiments, applying fluopyram to seeds of cotton and soybean was less effective than soil application against *M. incognita* J2 [104]. Under field conditions, soybean seed treatment reduced *Heterodera glycines* eggs and J2 and increased yields compared to controls, but did not suppress nematode reproduction [100].

Persistence and movement of the nematicide in the soil may affect its control efficacy. Not much work has been done on the effect of environmental conditions on fluopyram's nematode-control efficacy. However, fluopyram, like most other nematicides, moves a longer distance in sandy soil than in sandy loam soil [104], with a log P of 3.3 [13]. The half-life of the compound ranges widely under field conditions (3.8–24.8 days), probably depending on the soil type, concentration, and environmental conditions [15,92,105,106], in contrast to 64.2–93.9 days under laboratory conditions [86]. No relationship between its nematode-control efficacy and half-life has been reported.

3.4. Fluazaindolizine

Fluazaindolizine (CAS No. 1254304-22-7; 8-chloro-N-[(2-chloro-5-methoxyphenyl)sulfonyl]-6-(trifluoromethyl)imidazo [1,2-a]pyridine-2-carboxamide) is the active ingredient of the nematicide Salibro™, developed by Corteva Agriscience while screening N-phenylsulfonylimidazopyridine-2-carboxamides [16]. The compound is a sulfonamide nematicide from the imidazopyridine group. Although no commercial product has been released, a suspension concentrate (500 SC) and granular formulations are about to be launched onto the market [16].

3.4.1. Toxicity and Impact on the Environment

There is very little available information on fluazaindolizine's toxicity. The acute LD_{50} for rats via oral administration is more than 1187 mg kg^{-1} [14]. Its effect on non-target organisms has been briefly mentioned [16]. The exposure of adult *Caenorhabditis elegans* to 300 mg L^{-1} for a period over 120 h was not lethal. The continuous exposure of *Acrobeles buetschlii*, which is a bacteriophagous nematode, to fluazaindolizine at up to 250 mg L^{-1} did not affect the nematode's motility [107]. The life cycle of *Drosophila melanogaster* was not affected after feeding with a diet containing 200 ppm fluazaindolizine. The DT_{50} of the compound in the soil is strongly affected by the soil type and environmental conditions, but it reaches approximately 35 days in the root zone [16,17]. The fate of fluazaindolizine applied to a tomato field was studied, and metabolites in the soil and plants were analyzed, and it was found that fluazaindolizine was an easy degradable-nematicide [17].

3.4.2. Characteristics and Mode of Action

The most notable feature of fluazaindolizine is its slow effect on nematodes, unlike the knockdown effect of organophosphates and carbamates. Exposure to >1000 mg L^{-1} fluazaindolizine for 24 h would likely result in the acute death of *Meloidogyne* spp. J2; however, *Meloidogyne* J2 exposed to 5 mg L^{-1} fluazaindolizine, even for only 24 h, followed by rinsing, lost their motility and infectivity during further incubation in water [107]. The LC_{50} for *M. incognita* J2 exposed for 24 h was 180.6 mg L^{-1}; however,

nematodes that were motile after the treatment became immobile with time when incubated in water and lost their infectivity [94]. Once nematodes are affected by the compound, they do not recover, even after rinsing in water [107]. This kind of residual and irreversible nematicidal effect, even after rinsing, is very similar to fluensulfone [69–71]. Differences in sensitivity among *Meloidogyne* spp., and even populations of a *Meloidogyne* sp. to fluazaindolizine have been mentioned [108]. Fluazaindolizine has no obvious hatching inhibition or ovicidal activity. The hatching of *M. incognita* and *M. hapla* was not inhibited during exposure of up to 21 days to 50 and 250 mg L^{-1} of the compound, respectively [107]. The latter concentration also did not inhibit the hatching of *Acrobeles buetschlii*.

The mode of action of fluazaindolizine is unknown, but it is probably novel. Known target sites of nematicides, including acetylcholinesterase of *Diabrotica undecimpunctata*, mitochondrial electron transport, nicotinic acetylcholine receptors of *Caenorhabditis elegans*, and glutamate-gated chloride channels of *Periplaneta americana*, were not affected by the compound at concentrations of up to 30 μM [16].

3.4.3. Field Application, Efficacy, and Environmental Conditions

Although no commercial product is yet available, results from a few field trials with fluazaindolizine, with or without other nematicides for comparison, have been reported, mainly against *Meloidogyne* spp. Application doses suggested by the manufacturer are in the range of 0.25–2.0 kg ha^{-1}, depending on the crop and application method [16]. The final population densities of *M. incognita* were reduced, and cucumber yields were increased, by the application of 2.24 kg ha^{-1} fluazaindolizine to field microplots inoculated with different levels of the nematode [109]. Fluazaindolizine at application doses of 1.12–4.48 kg ha^{-1} reduced the at-harvest galling of carrots in an *M. incognita*-infested field [77]. The highest marketable yield of carrots was obtained with 2.24 kg ha^{-1} fluazaindolizine, compared to yields obtained with other nematicides, including oxamyl, fluensulfone, and fluopyram. The application of 1.12 kg ha^{-1} fluazaindolizine to *M. javanica*-infested tomato fields reduced the galling index for up to 2 months after transplanting in one of two trials, but no difference was found in final nematode populations or total yields compared to the control in either trial [80]. Similar results of a slight reduction in tomato root galling were observed by application at 0.9 kg ha^{-1} fluazaindolizine to *M. javanica*-infested fields [110]. In strawberry fields, the application of fluazaindolizine at 1.12 kg ha^{-1} at transplanting, with or without additional application at 0.56 kg ha^{-1} 30 days after transplanting, did not reduce the populations of *Belonolaimus longicaudatus*, *M. hapla*, or *Pratylenchus penetrans* during the experimental periods, nor did they increase the yield [102]. Information about nematicidal activity against other important nematode species and the effect of environmental conditions on this activity is still unavailable. However, low temperatures delayed the nematicidal effect of fluazaindolizine on *M. incognita* and *M. hapla* J2 in vitro [107].

4. Future Perspectives

In the absence of broad-spectrum soil fumigants such as methyl bromide, the use of non-fumigant nematicides will continue to be the main nematode-control method applied in the intensive agriculture of high-value crops. An ideal nematicide should be highly effective for all plant-parasitic nematodes at a low cost and dose, but not toxic to non-targets, including crops, with easy application, and safe for users, consumers, and the environment. The three next-generation nematicides covered in this review fulfill some of these requirements and will play an important role in nematode-control strategies. In addition to the low toxicity of these nematicides, new application methods, such as seed treatment, can lower the application dose and cost, and protect plants at an important stage of plant development, while protecting the environment from nematicide pollution. The three nematicides probably have different modes of action, and this can be an advantage in nematode management. Although resistance to these nematicides in plant-parasitic nematodes and their enhanced biodegradation have not yet been reported, their use in rotation, dependent on nematode species, crop, and the application timing and method, will surely lower these risks.

All of these nematicides have very good nematicidal activity toward *Meloidogyne* spp., probably because the molecules were selected after screening against J2 from this genus, which contains the most economically important nematode species. Published and personal observations indicate that these nematicides are generally more effective against sedentary vs. migratory nematodes; however, sedentary nematodes attacking foliage and bulbs are especially tolerant. Although some of these latter nematodes cause serious economic damage, such as *Bursaphelenchus xylophilus* on pine trees, the three nematicides are probably not effective against them in the field. Furthermore, the development of a nematicide, especially against *B. xylophilus* and other sedentary nematodes that attack upper plant parts, is not likely to be initiated by agrochemical companies because of its relatively small market and difficulties in development. However, due to recent advances in genomic and proteomic studies, the nematicide development process may change from screening chemical libraries in vitro to computerized molecule screening and design for some target nematode species. Such a change might reduce the time and cost of development and increase the nematode-control efficacy, and may even lead to the ideal nematicide.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

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