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MINI-REVIEW

Biodegradation of fipronil: current state of mechanisms of biodegradation and future perspectives

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Abstract

Fipronil is a broad-spectrum phenyl-pyrazole insecticide that is widely used in agriculture. However, in the environment, its residues are toxic to aquatic animals, crustaceans, bees, termites, rabbits, lizards, and humans, and it has been classified as a C carcinogen. Due to its residual environmental hazards, various effective approaches, such as adsorption, ozone oxidation, catalyst coupling, inorganic plasma degradation, and microbial degradation, have been developed. Biodegradation is deemed to be the most effective and environmentally friendly method, and several pure cultures of bacteria and fungi capable of degrading fipronil have been isolated and identified, including *Streptomyces rochei*, *Paracoccus* sp., *Bacillus firmus*, *Bacillus thuringiensis*, *Bacillus* spp., *Stenotrophomonas acidaminiphila*, and *Aspergillus glaucus*. The metabolic reactions of fipronil degradation appear to be the same in different bacteria and are mainly oxidation, reduction, photolysis, and hydrolysis. However, the enzymes and genes responsible for the degradation are somewhat different. The ligninolytic enzyme MnP, the cytochrome P450 enzyme, and esterase play key roles in different strains of bacteria and fungal. Many unanswered questions exist regarding the environmental fate and degradation mechanisms of this pesticide. The genes and enzymes responsible for biodegradation remain largely unexplained, and biomolecular techniques need to be applied in order to gain a comprehensive understanding of these issues. In this review, we summarize the literature on the degradation of fipronil, focusing on biodegradation pathways and identifying the main knowledge gaps that currently exist in order to inform future research.

Key points

- *Biodegradation is a powerful tool for the removal of fipronil.*
- *Oxidation, reduction, photolysis, and hydrolysis play key roles in the degradation of fipronil.*
- *Possible biochemical pathways of fipronil in the environment are described.*

Keywords Fipronil · Abiotic degradation · Biodegradation · Metabolic pathways · Molecular mechanisms

Introduction

Fipronil[5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]4-[(trifluoromethyl)sulfinylidene]-1H-pyrazole-3-carbonitrile] is a phenyl pyrazole insecticide that was first successfully synthesized by Bayer Crop Science in 1987 (Tingle et al. 2003; Bhatt et al. 2021a). It is one of the most persistent lipophilic and toxic insecticides after dieldrin, lindane, and DDT, with a broad spectrum and low application rate (Mohapatra et al. 2010).

Fipronil is slightly soluble in water and more soluble in lipids, oils, proteins, and lipophilic organic solvents. It can remain stable for about 1 year at room temperature but is readily decomposed in the presence of metal ions or under alkaline conditions (Stevens et al. 1998; Bonmatin et al. 2014). Fipronil is denser than water and more difficult to volatilize, and it can be degraded by photolysis (Bonmatin et al. 2014; Simon-Delso et al. 2015). The physicochemical properties of fipronil are summarized in Table 1.

Unlike the classic insecticides, such as organophosphates, carbamates (both cholinesterase inhibitors), and pyrethroids

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Table 1 Physicochemical properties of fipronil (all parameters are at 25 °C unless specified)

Physicochemical property	Medium	Value
Chemical Abstract Service registry number (CAS#)		120,068–37-3
Molecular weight (g/mol)		473.2
Color/state of matter		White solid
Melting point (°C)		200–201
Density (g/mL 20 °C)		1.48–1.63
Vapor pressure (mPa; calculated)		3.7×10^{-4}
Henry's constant (m^3· atm/mol; experimental)		6.60×10^{-6}
Henry's constant (m^3 · atm/mol; calculated)		8.50×10^{-10}
Octanol–water partition coefficient (log *Kow*)		3.50
Organic carbon normalized partition coefficient (averaged *Koc*)		825
Aqueous photolysis (d; pH = 5)		0.33
Solubility	Water (mg/L; pH = 5)	1.90
	Water (mg/L; pH = 9)	2.40
	Hexane (mg/L)	28.0
	Toluene (mg/L)	3000

(sodium channel activators) (Aajoud et al. 2003), fipronil acts on the neurotransmitter γ-amino butyric acid (GABA) receptor (Tian et al. 2019). It disrupts the normal neuronal inward flow by interfering with the passage of chloride ions through the γ-aminobutyric acid channel (Jiang et al. 2020). Fipronil is widely used in agriculture to control rice borer and longitudinal leaf roller, and it is excellent at low field application rates for insects resistant to other insecticides, such as pyrethroids, organophosphates, and carbamates. In addition, it is also frequently used as a sanitary insecticide in cities because of its pesticidal spectrum (Simon-Delso et al. 2015; Qian et al. 2020). The combination of neonicotinoids and fipronil reportedly comprised 30% of the worldwide market for insecticides in recent years, while the use of fipronil is increasing (Casida and Durkin 2013; Pang et al. 2020).

However, a large amount of residual fipronil in the environment has raised public concern. Fipronil-contaminated eggs were found in Europe with residual concentrations up to 1.1 mg/kg and an average concentration of 0.065 mg/kg (Anagnostopoulos et al. 2020). Residual fipronil has been reported to have a significant negative impact on the environment and humans (Fig. 1). For example, mammals eat food that absorbs fipronil (Gunasekara et al. 2007; Gibbons et al. 2016; Cheng et al. 2020). Fipronil and its metabolites can cause significant contamination of the field around application sites (Al-Badran et al. 2019). It typically has adverse physiological effects that threaten the survival of a wide range of non-target invertebrates in terrestrial, aquatic, marine, and benthic environments (Pisa et al. 2015; Mulvey and Cresswell 2020). Moreover, fipronil has been classified as a possible human carcinogen, because it can be harmful to the liver, thyroid, and kidneys of mammals (Shi et al. 2020b; Bhatt et al. 2021a). Furthermore, some of its metabolites, such as fipronil sulfone and fipronil sulfide, can also cause a significant contamination of the fields and streams around application sites (Ghaffar et al. 2018; Carrao et al. 2019). Acceptable operator exposure levels for workers have been determined to be approximately 26 $\mu g \cdot kg^{-1} \cdot day^{-1}$. The inhalation of volatile or atmospheric particle-bound fipronil is the most likely route of human exposure (Lewis et al. 2016).

In the natural environment, fipronil is degraded by various pathways: principally oxidation, photolysis, hydrolysis, reduction, and microbial degradation. Four types of degradation products are formed: fipronil-sulfide, fipronil-desulfuryl, fipronil-sulfone, and fipronil-amide (Gunasekara et al. 2007; Weston and Lydy 2014; Han et al. 2020). Fipronil sulfone and fipronil sulfide were previously declared to be more poisonous than their parent compounds (Weston and Lydy 2014). Due to the low efficiency of natural degradation and the toxicity and persistence of fipronil, human intervention is essential (Ying and Kookana 2001; Bhatt et al. 2021a). To mitigate the health and environmental risks associated with fipronil, the development of effective and eco-friendly remediation strategies is necessary. Numerous abiotic and biotic methods have been proposed to address fipronil residues in the natural environment, such as chemical oxidation and activated carbon adsorption, plant adsorption, catalyst induction, and plasma technology (Tan et al. 2008; Qian et al. 2020; Prada-Vasquez et al. 2021). However, these approaches are often inefficient and expensive. In addition, traditional treatment processes (e.g., ozonation) cannot easily and effectively degrade fipronil due to the presence of halogen, aromatic, and heterocyclic structures in fipronil (Anandan and Wu 2015; Ahmad et al. 2019).

At the point of fipronil degradation, the advantages of biodegradation are clear, such as its low cost, minimal environmental damage, and in situ remediation and the fact that it does no harm to the ecosystem. To date, a variety of

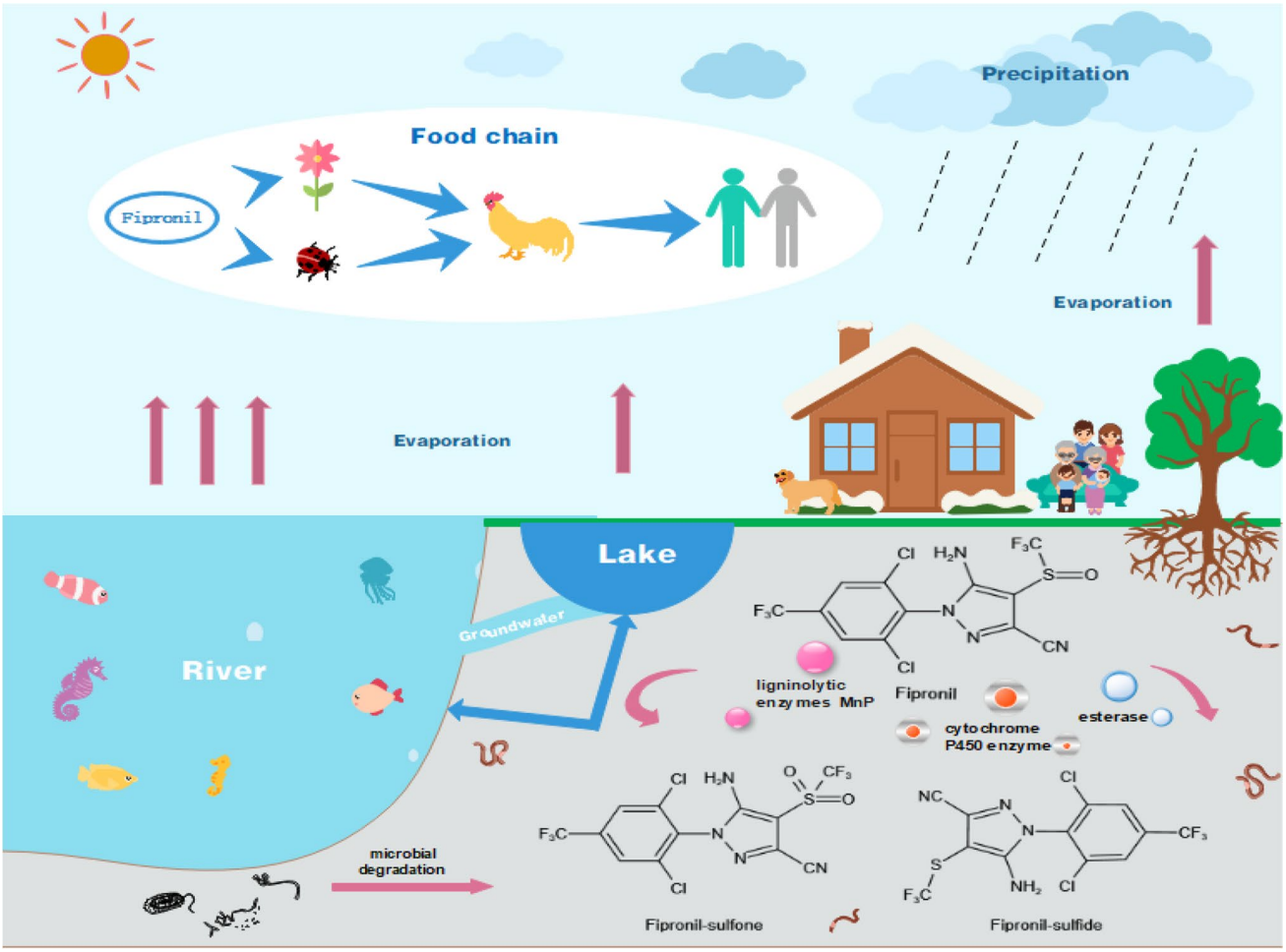

Fig. 1 The fate and occurrence of fipronil in the environment

potential microorganisms for fipronil biodegradation have been reported (Uniyal et al. 2016; Gajendiran and Abraham 2017). However, a review of the degradation mechanisms and pathways of fipronil is lacking. In this paper, we summarize the abiotic and biotic degradation pathways of fipronil, biodegradation mechanisms, and the microbial bioremediation potential in fipronil-contaminated environments.

Abiotic degradation of fipronil

The main abiotic transformations of fipronil occur due to photolytic hydrolysis and chemical redox reactions, which form four main products: sulfonyl-fipronil, amide-fipronil, sulfide-fipronil, and desulfinyl-fipronil (Fig. 2) (Bobe et al. 1998; Mukherjee 2006; Masutti and Mermut 2007b; McMahen et al. 2016).

Mulrooney (2002) reported that fipronil has a half-life ($t_{1/2}$) of 34 days on soil exposed to light, with a slow degradation rate. A study by Zhou et al. (2004) showed that fipronil residues in soil were below the detection limit after 47 days of pesticide spraying at levels of 24 and 48 g a.i./ha. The $t_{1/2}$ of fipronil in the soil was calculated to be 7.3 days. The $t_{1/2}$ of fipronil residues found in rice soil were 9.50 days and 10.31 days for dose applications of 7.5 and 15.0 kg/acre, respectively, and it was degraded in the soil according to biphasic first-order kinetics. Ying and Kookana (2002) showed that the total time fraction half-lives of field soil treated with fipronil at high (0.15 g/m^2) and low (0.075 g/m^2) concentrations were 178 days and 198 days, respectively. They studied the degradation of fipronil and its three metabolites in the field soil and found that the desulfinyl derivatives were absent, as the desulfinyl derivatives were degraded more rapidly in soil, with a $t_{1/2}$ of 41–55 days. Fenet et al. (2001) reported that under tropical field conditions, a slightly faster dissipation of sulfides than other metabolites, such as fipronil sulfone and desulfuryl alcohol, was observed. Saini et al. (2014) studied the degradation of fipronil in field soil and found the metabolites, sulfone, desulfinyl, and sulfide in the soil. The mean residues of

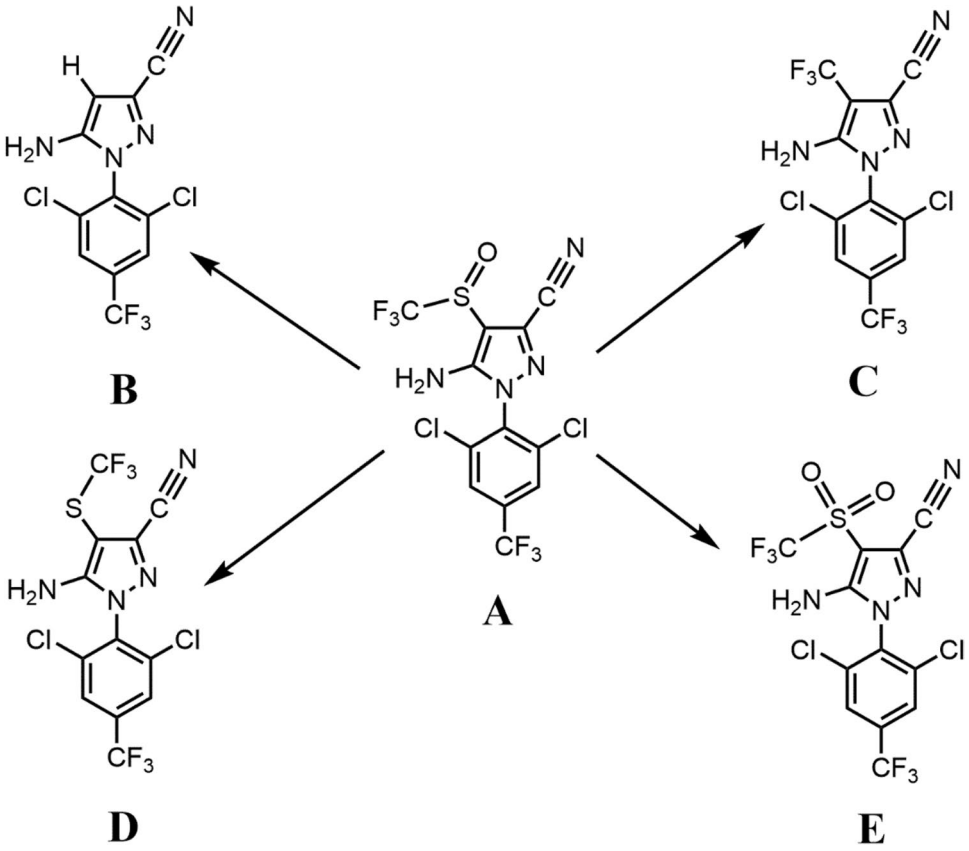

Fig. 2 The degradation products of fipronil (**A**) under environmental conditions, (**B**) amide-fipronil, (**C**) desulfinyl-fipronil, (**D**) sulfide-fipronil, and (**E**) sulfonyl-fipronil (Gunasekara et al. 2007)

fipronil, sulfone, sulfide, and desulfuryl reached 0.001 mg/kg on days 90, 15, and 60 after treatment. A $t_{1/2}$ of 8.14 days and 13.05 days was observed for fipronil at application rates of 50 mg/kg and 100 mg/kg, respectively.

In tropical soil with a sand content of 80% in Niger, an aqueous solution of fipronil was exposed to natural daylight conditions at pH 5.5, and its half-life was calculated to be 4.1 h and 20 min, which is consistent with a rapid first-order degradation kinetic pattern. Similar results (7.92 h) were obtained for experiments in similar conditions but in different types of soil (Gunasekara et al. 2007). In addition, it was reported that 1% H_2O_2 can accelerate the degradation of fipronil by a factor of three. Similar studies also confirmed that the presence of H_2O_2 accelerated the formation of fipronil-desulfinyl: the $t_{1/2}$ of fipronil in H_2O_2 was reduced to 0.87–4.51 h (Hainzl et al. 1998; Caboni et al. 2003; Cryder et al. 2021). We hypothesize that the acceleration of fipronil degradation is due to the generation of hydroxyl radicals in H_2O_2 by light exposure. The fipronil–desulfinyl complex is reported as the major photo-degradation product of fipronil, with a $t_{1/2}$ of 41–55 days, which is the longest of the four degradation products. Therefore, it is considered as the major persistent residue on applied crops (Ying and Kookana 2002; Goff et al. 2017).

The photo-degradation of fipronil was found to be negatively correlated with adsorption. Repeated photo-degradation experiments with fipronil in soil showed that the photo-degradation rate was slower in soil than in aqueous solution due to the lack of a light source in the environment (Shuai et al. 2012; Wang et al. 2016; Shi et al. 2020b). It was also found that the degradation rate of fipronil was closely related to the nature of the soil and urban pesticide application methods and correlated with the Freundlich adsorption coefficient (Raveton et al. 2006; Ramasubramanian and Paramasivam 2017). These factors can significantly affect the degradation rate of fipronil in soil. Qu et al. (2016) studied the degradation of fipronil in aquatic systems and found that the light-dependent hydrolysis of the parent compound from the sulfur and nitrile side chains bound to the heterocyclic ring over a 3-month period yielded two different degradation products: fipronil sulfide and fipronil amide. In the absence of oxygen in water, fipronil degraded slowly, with an average $t_{1/2}$ of 123 days, which is much longer compared to the half-life of fipronil in an aerobic soil system (Aajoud et al. 2003).

The effect of different pH on the non-photo-degradation of fipronil in water at 22 °C was also investigated, and it was found that fipronil was stable in acidic (pH 5.5) and neutral (pH 7.0) solutions. Under all the pH conditions, about 80% of fipronil was still detectable after about 100 days. However, the degradation of fipronil under alkaline conditions (pH 9–12) increased as the pH was

increased, with subsequent pseudo-first-order degradation kinetics (Lao 2021; Wan et al. 2021). At pH 12, fipronil degraded about 300 times faster in water than at pH 9. Changes in temperature also affect the degradation of fipronil in water, and the increase of temperature increases its hydrolysis rate. It has been found that the $t_{1/2}$ of fipronil decreases from 114 to 18 h when the temperature is raised from 22 to 45 °C, respectively (Ngim and Crosby 2001). Generally speaking, hydrolysis should not be the main degradation pathway for fipronil, as it is steady under a typical environmental pH (Shi et al. 2020a).

In recent years, several physical and chemical methods have been developed to address the problem of fipronil residues in the environment, such as activated carbon adsorption and chemical oxidation techniques (Ikehata and El-Din 2005; Luo et al. 2014). Ngim et al. (2000) found that fipronil in aqueous solution was mainly degraded by a photo-degradation pathway to generate desulfurized compounds, which were further degraded to other compounds by processes such as photosensitive dichlorination, trifluoromethyl substituted chlorine, and pyrazole ring cleavage. In addition, the methanol did not affect the photolytic product formation. However, due to the complex structure of fipronil, with halogen, aromatic, and heterocyclic rings, treatment using conventional processes is usually costly and ineffective (Zhang et al. 2019). With a multiphase catalyst coupled with ozone, 89% of fipronil could be degraded in 40 min (Anandan and Wu 2015). Gomes et al. (2017) used titanium dioxide (TiO_2) to induce a multiphase photocatalytic degradation of alachlor, with a degradation efficiency of 90.9%. However, the use of a catalyst has the potential for secondary contamination. After the treatment has been completed, it is essential that the catalyst is filtered, which complicates the steps and also increases the cost.

The applications of different catalyst-free plasma-based technologies (including high-voltage arc discharge plasma, pulsed corona discharge plasma, and dielectric barrier discharge (DBD) plasma) for pesticide degradation have appeared in numerous reports (Yin et al. 2006; Wang et al. 2010a, b). Among them, medium-blocking discharge plasma degradation is considered the most promising chemical degradation method for research and application. It can generate strong oxidants that are very beneficial for compound degradation, such as hydroxyl radicals and ozone (Hu et al. 2013; Li et al. 2013). Plasma degradation can take a long time to achieve the desired degradation rate. Additionally, the use of a plasma treatment requires a very extraordinary degree of precision in the equipment unit. The microwave-induced plasma degradation of fipronil systems in aqueous solutions consists mainly of oxidation, reduction, nitro reduction, dehydration, and thiourea generation to urea (Qian et al. 2020). However, this process is very complex and can only occur in liquid media, making it difficult to achieve the desired degradation effect.

Microbial degradation of fipronil

Determining the mechanisms and pathways of fipronil degradation is a difficult task, because biodegradation and abiotic degradation reactions can occur simultaneously. The combination of basic biotic and abiotic reaction mechanisms (oxidation, reduction, photolysis, and hydrolysis) may yield a very complex network of transformation products (Fig. 3).

The biodegradation pathway of fipronil is mainly achieved through the action of microorganisms. For pesticide residues in soil and water, microbial degradation is the most effective degradation method, and the factors affecting the degradation are the physicochemical properties of the pesticides, soil conditions, environmental conditions, and diversity of soil microorganisms (Cycoń et al. 2017; Arora et al. 2018; Zhan et al. 2018; Birolli et al. 2019; Huang et al. 2020; Bhatt et al. 2021b). Microbial degradation can be used to remediate organic compound contamination in soil and water, which is a clean, efficient, and eco-friendly method and does not cause secondary pollution, unlike physicochemical methods (Chen et al. 2014; Mishra et al. 2020; Bhatt et al. 2020).

The microbial degradation of fipronil in soil was first investigated by Zhu et al. in 2004. It was found that fipronil could be degraded by microorganisms in non-sterile clay loam soil to form the metabolite, fipronil-sulfide. In non-sterile clay loam soil, the half-lives were 9.72 and 8.78 days at 25℃ and 35℃, respectively. In sterile soil, the half-lives at the same temperatures were 33.51 and 32.07 days, respectively, indicating that the degradation of fipronil is affected by soil microorganisms. A microbial viability test also demonstrated the presence of living microorganisms in the non-sterile clay loam soil during the test (Zhu et al. 2004). This study concluded that fipronil does not threaten the survival of microorganisms after they have adapted to the soil environment in the presence of fipronil.

Tan et al. (2008) studied the microbial degradation of fipronil in three different rice soils under aerobic and flooded (anaerobic) conditions. The dissipation of fipronil in active soil under these two types of conditions was determined using high performance liquid chromatography (HPLC) in accordance with primary degradation kinetics. Their $t_{1/2}$ values were calculated to be 21–34 days in aerobic degradation experiments and 8–19 days in flooded incubation conditions. The main products of fipronil degradation were identified as sulfone and sulfide derivatives formed by oxidation and reduction, respectively. Under anoxic conditions, fipronil was degraded more rapidly than under aerobic conditions, and the main metabolite was determined to be fipronil

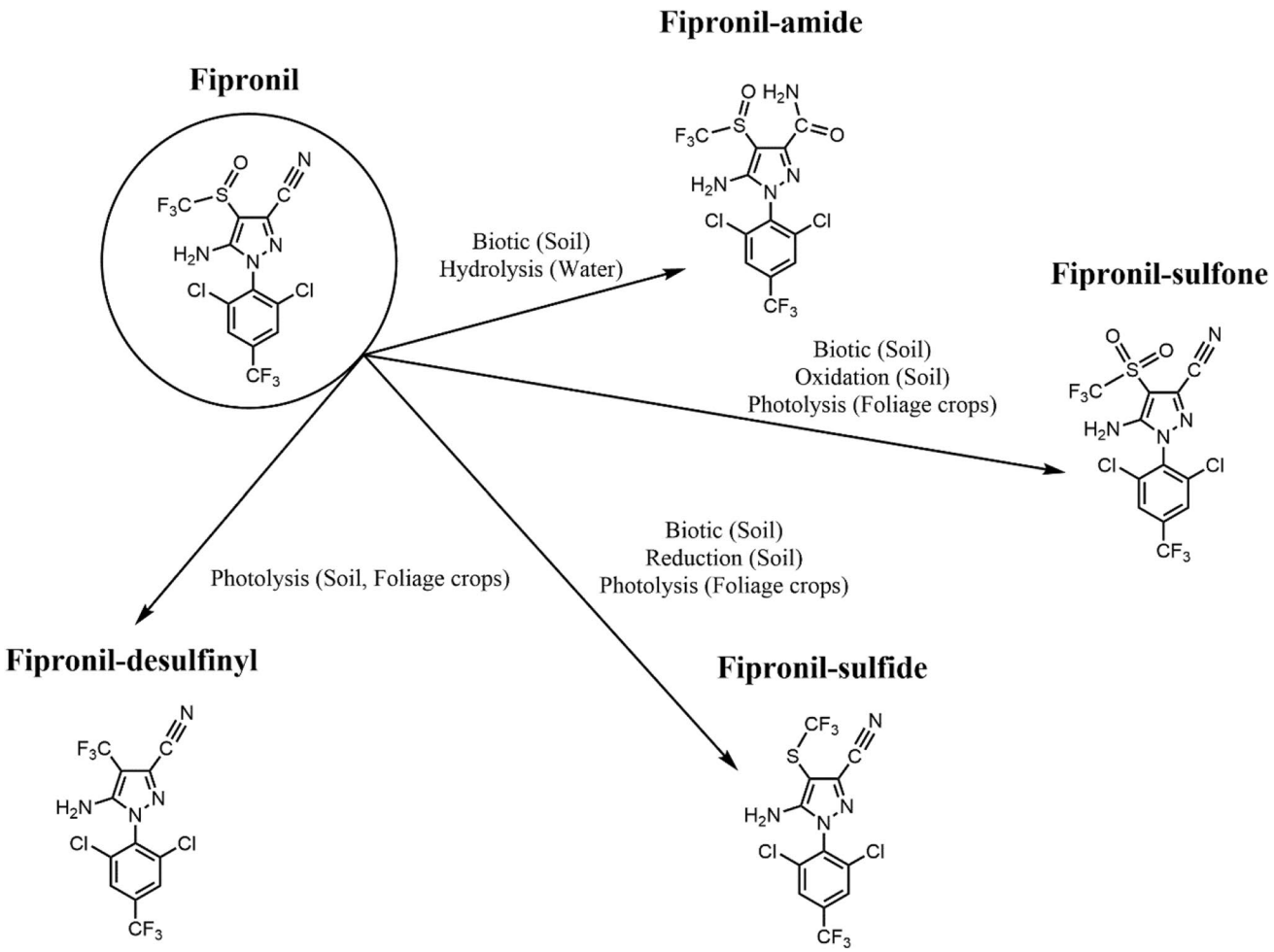

Fig. 3 Degradation network of fipronil in the environment

sulfide. In sterile soil experiments, little transformation of fipronil was observed, suggesting that fipronil was degraded due to microbial-mediated action in the rice soil (Zhou et al. 2004). These results can be used to better assess the environmental and ecological risks of chiral pesticides. However, the abovementioned study only demonstrated the presence of microorganisms that can degrade fipronil in soil, and no corresponding degrading strains were isolated.

In a subsequent study, several fipronil degrading strains were isolated and characterized (Table 2). Kumar et al. (2012) isolated two bacterial cultures identified as *Paracoccus* sp. and *Gamma proteobacteria* from cotton field soil that could degrade fipronil. The fipronil degradation potential of these two bacterial strains was evaluated in three different soils (loamy sand, sandy loam, and clay loam). It was found that fipronil was detectable in the three soils treated with 20 µg/kg fipronil after 30 days. When the same treated soils were amended with *Paracoccus* sp., fipronil was found to be undetectable after only 10 days. The same fortified soils were amended with Gamma Proteobacteria, and the fipronil was completely degraded in 20 days. The same results were obtained after increasing the concentration of fipronil to 80 µg/kg. *Paracoccus* sp. were found to be superior to Gamma Proteobacteria in terms of fipronil degradation in soil. However, the mean recovery and degradation rate of fipronil in this study were less than satisfactory, and further exploration is needed to achieve precise bioremediation, especially given that a limited or no range of uncertainty and variability of the microbial functions has been reported.

In another study, *Bacillus thuringiensis* was isolated and enriched in a culture from soil samples collected from different sugarcane farms of the Gurdaspur district, and the persistence of the fipronil in soil fortified with *B. thuringiensis* was found to be very low, compared to untreated soil (Mandal et al. 2013). The half-lives of fipronil in clay loam soils with 0.50 mg/kg of fipronil were 4.07, 4.70, 4.85, 5.10, and 5.90 days, respectively, while in the soil of the control experiment, the value was 100.33 days, and the most detected metabolites were sulfide, followed by sulfone and amide. No desulfurized phenol metabolites were detected in any of

Table 2 Microbial degradation of fipronil

No	Microorganisms	Type	Detected metabolites	Comments	Isolation source	References
1	*Paracoccus* sp.	Bacterium	No data	The mean recoveries of fipronil in different types of soil were found to be more than 85%	Clay loam, sandy loam and loamy sand	Kumar et al. (2012)
2	Gamma Proteobacteria	Bacterium	No data	The mean per cent recovery of fipronil and its metabolites, viz. sulfone, sulfide, amide, and desulfinyl from the fortified samples, were found to be more than 85%	Clay loam, sandy loam and loamy sand	Mandal et al. (2013)
3	*Bacillus thuringiensis*	Bacterium	Sulfide, sulfone, and amide	The mean per cent recovery of fipronil and its metabolites, viz. sulfone, sulfide, amide, and desulfinyl from the fortified samples, were found to be more than 85%	Soil samples collected from different sugarcane growing fields	Mandal et al. (2013)
4	*Bacillus firmus*	Bacterium	Fipronil sulfide, fipronil sulfone, and fipronil amide	Residues were not detected after 35, 35, 35, 42, and 49 d in soil samples after fortification with fipronil 0.50, 0.75, 1.00, 1.25, and 1.50 mg/kg	Soil samples collected from sugar fields	Mandal et al. (2014)
5	*Stenotrophomonas acidaminiphila*	Bacterium	Fipronil sulfone, sulfide, and amide	The bacterial strain was able to metabolize 25 mg/L fipronil with 86.14% degradation in Dorn's broth medium under optimum conditions	Soil of Zea mays	Uniyal et al. (2016)
6	*Trametes versicolor*	Fungus	Hydroxylated fipronil sulfone, glycosylated fipronil sulfone, and two compounds with unresolved structures	Fipronil is rapidly metabolized by *Trametes versicolor* to fipronil sulfone and multiple previously unknown fipronil transformation products, lowering fipronil concentration by 96.5%	American Type Culture Collection	Wolfand et al. (2016)
7	*Aspergillus glaucus* strain AJAG1	Fungus	Bis[2-Chloro-4-ethoxyphenyl] sulfone,sulfuricacid-5,8,11-heptadecatrienyl methyl ester, D-asycarpidan-1-methanol, and isomenthone	Strain AJAG1 could degrade 900 mg/L of fipronil efficiently in both aqueous medium and soil	Soil sample was obtained from *Abelmoschus esculentus* field	Gajendiran and Abraham (2017)
8	*Burkholderia thailandensis*	Bacterium	Fipronil sulfide and fipronil sulfone	The method presented linearity of 0.99, precision between 1.5 and 10.9%, while the recovery ranged from 78 to 98%	Fertilized soil	Cappelini et al. (2018)

Table 2 (continued)

No	Microorganisms	Type	Detected metabolites	Comments	Isolation source	References
9	*Streptomyces rochei* strain AJAG7	Bacterium	Benzaldehyde, (phenylmethylene) hydrazone and 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester	Strain AJAG7 was able to degrade 500 mg/L concentration of fipronil in the liquid medium and in soil after 6d and 7d of incubation, respectively	Fipronil contaminated turmeric field	Abraham and Gajendiran (2019)
10	*Staphylococcus arlettae*	Bacterium	No data	Paired sample T-test and degradation kinetic study recorded that the bacterial strain *S. arlettae* was more efficient (81.94%) in fipronil degradation than *B. thuringiensis* (65.98%)	Fipronil contaminated soils in the cardamom plantations	At et al. (2019)
11	*Bacillus* sp. FA3	Bacterium	Benzaldehyde (phenyl methylene) hydrazine and 1,2 benzene dicarboxylic acid	Strain FA3 efficiently metabolized fipronil in mineral salt medium (MSM) and degradation was 76.0% in 15 days	Contaminated agricultural field	Bhatt et al. (2021b)
12	*Bacillus* sp. FA4	Bacterium	N-Phenylmethacrylamide, N-Methyl bis (trifluoromethyl sulfin) amide, Hexadecane-1-sulfonic acid, 4-hydroxy-, delta-sultone	The degradation of fipronil in soil was 35%, 52%, and 77% after 5, 10, and 15 days of incubation	Contaminated agricultural field	Bhatt et al. (2021a)

the samples (Mandal et al. 2013). Subsequently, this team also isolated another strain of *Bacillus firmus* that was also capable of degrading fipronil in soil. However, its required degradation time was dose-dependent (Mandal et al. 2014).

The degradation efficiency of fipronil can be affected by many factors, such as the temperature, pH, humidity, application method, soil composition, and biodiversity. In order to achieve effective bioremediation with an enhanced degradation efficiency, the optimization of the process appears to be crucial (Zhu et al. 2004; Prakasham et al. 2005; Masutti and Mermut 2007a; Paliwal et al. 2016). However, none of the previous studies have optimized the environmental factors affecting the rate of microbial degradation of fipronil. Uniyal et al. (2016) isolated the fipronil-degrading strain, S1 (*Stenotrophomonas acidaminiphila*), from inter-rhizosphere soil of maize and used the response surface methodology (RSM), based on the Box-Behnken design, to determine the optimal environmental conditions for the growth and degradation of this bacterium. The growth curve of strain S1 showed that it grew rapidly within 8 days of incubation. At the same time, the fipronil concentration also decreased rapidly. The strain degraded 86.14% of a fipronil concentration of 25 mg/L in a Dorn broth medium over about 14 days at pH 7.5, 35 °C, and 0.175 g/L inoculum. The metabolites were detected using gas chromatography analysis, and the results showed that the fipronil was degraded by oxidation, reduction, and hydrolysis reactions, producing sulfone, sulfide, and amide in the presence of S1, which is also a different metabolic pathway from the previous one (Fig. 4).

Gajendiran and Abraham (2017) isolated fipronil-degrading strains, AJAG1 and AJAG7, from contaminated soil. Among them, AJAG1 was identified as *Aspergillus griseus*, which is reported as the first fipronil-degrading fungus. It was able to efficiently degrade fipronil at 900 mg/L, both in aqueous medium and in soil, and it can also degrade the metabolite fipronil sulfone. High-performance liquid chromatography (HPLC) analysis showed that strain AJAG7 was able to degrade fipronil at a concentration of 500 mg/L in both liquid medium and soil. After 96 h of incubation, a complete degradation of the metabolite fipronil sulfone was detected (Abraham and Gajendiran 2019).

In addition, *Staphylococcus arlettae* (At et al. 2019), *Burkholderia thailandensis* (Cappelini et al. 2018), *Bacillus* sp. FA3 (Bhatt et al. 2021b), and *Bacillus* sp. FA4 (Bhatt et al. 2021a) were found to be effective fipronil-degrading microorganisms. In addition to microorganisms, some studies have found that earthworms also contribute to the degradation and remediation of fipronil in soil (Qin et al. 2015; Wang

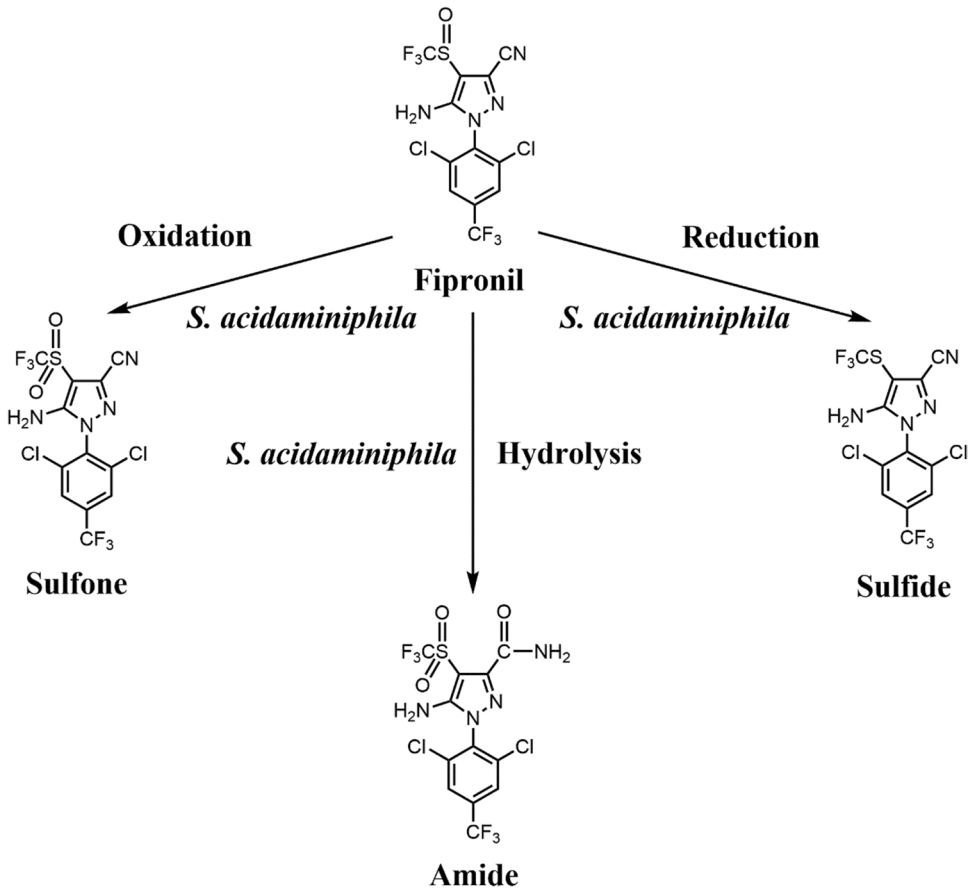

Fig. 4 Degradation pathways of fipronil in microorganisms (Uniyal et al. 2016; Bhatt et al. 2021a)

et al. 2019). However, there are few studies on the molecular mechanisms of fipronil degradation. Therefore, in the following, the degradation mechanisms of fipronil are summarized in order to better analyze their bioremediation potential in fipronil-contaminated environments.

Molecular mechanisms of fipronil biodegradation

The biodegradation of fipronil is associated with functional gene-encoding degradation enzymes in the corresponding microorganisms (Liu et al. 2017; Yang et al. 2018). During fipronil accumulation, microorganisms can use fipronil as a carbon and/or nitrogen source for growth, while enzymes in their bodies can convert fipronil into their metabolites. Previous studies have found that enzyme preparations are more effective than direct microbial use (Chen et al. 2011; Bhatt et al. 2020; Lin et al. 2020). However, few studies have mentioned the fipronil degradation genes and enzymes related to microorganisms.

Both bacteria and fungi play an irreplaceable role in the remediation of environmental contamination (Chen et al. 2014; Bhatt et al. 2021c; Zhang et al. 2021). However, for some specific compounds, fungi are more suitable (Feng et al. 2020; Zhang et al. 2020; Lin et al. 2021). Especially in filamentous fungi, pollutants in the environment can be assigned and transferred into the mycelium (Chen et al. 2008). Among them, *Aspergillus* spp. are frequently reported to be tolerant to a wide range of contaminants, and ligninolytic enzymes (Lac, MnP, and LiP) are considered a potential bio-remediator for various pesticides in soil (Pizzul et al. 2009). Strain AJAG1 showed activity on both MnP and LiP. In the initial stage of fipronil degradation, the enzyme activities of MnP and LiP were detected to reach a maximum in the supernatant, and this value gradually decreased as the incubation time increased. The enzyme activity of MnP was higher than LiP, indicating that MnP may play a dominant role in the degradation of fipronil by strain AJAG1. The enzyme activity was higher in the culture supernatant than in the cell lysates, which indicates that these enzymes are extracellular (Gajendiran and Abraham 2017).

A study conducted by Wolfand et al. (2016) on fipronil degradation by White Rot Fungus (WRF) demonstrated that fipronil was degraded by the cytochrome P450 enzyme. The levels of metabolites produced by *Trametes versicolor* were detected to be significantly lower in the presence of the inhibitor of the cytochrome P450 enzyme, 1-aminobenzotriazole (Wolfand et al. 2016). WRF can metabolize compounds intracellularly through the cytochrome P450 complex in a manner similar to that of the mammalian liver. No pretreatment is required to treat contaminants with WRF, as their enzymes are produced under constitutive or nutrient-limited conditions (Cerniglia 1997; Pointing and Vrijmoed 2000; Pinedo-Rivilla et al. 2009).

The biodegradation of pesticides in soil can be tracked by gene expression patterns (Mishra et al. 2020). An increase in gene levels during bacterial growth is usually associated with a higher metabolic rate of degrading a compound (Monard et al. 2013). With the biodegradation of fipronil, an increase in the level of mRNA encoding the esterase gene was detected in fipronil-degrading strains, FA3 and FA4 (Bhatt et al. 2021d; Bhatt et al. 2021a, b). More in-depth studies on the macrogenomic and transcriptomic aspects of pesticide-degrading bacteria could provide more comprehensive assistance in monitoring pollutants and understanding the molecular mechanisms of the remediation of environmental pollution.

Moreover, some studies have identified some fipronil resistance genes and detoxification enzymes in some insects, and the elucidation of the resistance mechanism can also be applied to the fipronil degradation mechanism. The quantitative enzyme profiling of esterase, cytochrome P450, and glutathione sulfotransferase (GST) was performed in *Rhipicephalus microplus* (a tick parasite in zoos and wildlife) to determine the possible correlation between fipronil resistance and functional enzymes (Ghosh et al. 2007; Chigure et al. 2018). The results of the enzyme profile analysis showed elevated levels of β-esterase, CYP450, and GST. The same results appeared in a resistance study against German cockroaches (*Blattella germanica* L.). One strain, GNV-R, showed a 36-fold resistance to topically applied fipronil at the LD50 level, and the bioassays performed indicated that it was in the presence of cytochrome P450 that the detoxification and resistance developed (Gondhalekar and Scharf 2012).

When studying the relationship between detoxification enzymes and resistance to butenaflutole in locusts, the synergistic effects of three synergists, piperonyl butoxide, triphenyl phosphate, and diethyl maleate, were found to be 4.20-fold, 3.31-fold, and 2.56-fold, respectively, for the resistant strain. The synergistic effect of PBO was the greatest. The activities of multifunctional oxidase, carboxylesterase, and glutathione sulfotransferase were significantly increased compared to the sensitive strain, and these phenomena suggest that P450, CarE, and GST may jointly contribute to the metabolism and detoxification of exogenous chemicals such as butenyl fipronil in locusts. Transcriptome sequencing revealed 226 detoxification enzyme genes and 23 up-regulated deacetylase genes. The evolutionary tree of related gene families included 59 P450 genes, 52 carboxylesterase (CarE) genes, and 25 glutathione transferase (GST) genes. The results of reverse transcription-polymerase chain reaction (RT-PCR) analysis of overexpressed genes in the resistance population combined with the evolutionary tree showed that P450 genes belong to 14 families including

CYP6, CYP4, CYP18, and CYP302, and all members of the P450 family have functional annotations of "secondary metabolite biosynthesis, transport, and metabolism" in the COG database. Of the 86 CarE genes, 35 sequences belong to Clade A, 7 to Clade H, 4 to Clade D, 3 to Clade E, and 3 to Clade F. These genes play an important role in insecticide metabolism, and all CarE genes are annotated in the GO database as All CarE genes are annotated in the GO database as "hydrolase activity" and "carboxylate hydrolase activity" and in the COG database as "lipid transport and metabolism." Twenty-five GSTs were successfully constructed as phylogenetic trees, belonging to six families and microsomal, and the above family members were annotated in the transcriptome database as genes that metabolize insecticides and are candidates for further studies on fipronil resistance and metabolism mechanisms (Jin et al. 2020).

However, the opposite occurred in another study. The WX-F strain of *Laodelphax striatellus* (Hemiptera: Delphacidae) was selected from a field collection of 77 generations of successive fipronil selections. It showed an 86.6-fold (LD_{50} compared to the first generation) resistance to fipronil, but the bioassays and analysis of its detoxification enzyme activity showed no significant correlation between the detoxification enzymes and resistance of the WX-F strain to fipronil. An additional molecular analysis suggested that the fipronil resistance was probably attributable to the target site insensitivity. Sequencing of a single cDNA fragment cloned from the Rdl GABA receptor gene revealed an 80% frequency of A2'N mutations in the WX-F. It carried a mutated LsRdl allele that replaced Ala (GCC) with Asn (AAC). The high-level frequency of the LsRdl-Asn allele in strain WX-F suggests that the A2'N mutation in the GABA receptor gene might be related to resistance to fipronil in *Laodelphax striatellus* (Gao et al. 2014).

Future perspectives and conclusions

The increased use of fipronil in agriculture and urban areas has led to the release of residual pollutants into the environment, particularly as a pesticide in agricultural soil. Fipronil moves through the food chain, causing environmental damage and health risks to non-target organisms. These contaminated resources require urgent attention, and remedial measures need to be developed. Microbial degradation is one of the most effective and environmentally friendly methods for fipronil degradation. In recent years, a large number of studies have focused on the degradation of pesticides by microorganisms and the isolation, characterization, and application of bioremediation strains in soil and water environments. However, only a small number of bacteria or fungi have been found to metabolize fipronil. The degradation pathways and metabolites of some strains have been basically elucidated, but some intermediates, related degrading enzymes, and functional genes have not yet been studied and tested. At present, the CYP6, CYP4, CYP18, and CYP302 gene families, identified as cytochrome P450 enzymes, have been annotated in transcriptome databases as detoxification enzyme genes of metabolic insecticide. An improved exploration of the microorganisms, enzymes, and genes in charge of fipronil biodegradation will bring multiple benefits in terms of environmental remediation. Firstly, it will enable more accurate predictions of the fate of fipronil and other phenyl pyrazole insecticides in the environment, including degradation kinetics, possible degradation products, and the factors that determine them. Secondly, these developments will allow us to work on effective microbial or enzymatic agents to eliminate fipronil contamination in the environment. Finally, if we can take advantage of advanced molecular biotechnologies, such as metagenomics, proteomics, and genetic diagnostics, to identify the genes encoding the degradation of fipronil, this will make it possible to develop fipronil-specific biosensors, which are of particular interest with respect to the rapid detection of fipronil residues. In addition, fipronil-degrading microflora can be studied, rather than a single strain, which is conducive to the practical application of biodegradation in the environment. This provides a general direction for future research on fipronil degradation.

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Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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