Review

Environmental fate and toxicology of fipronil

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Fipronil is a relatively new insecticide that controls a broad spectrum of insects at low field application rates. It is a "new generation" insecticide because its mode of action, interference with the normal function of γ-aminobutyric acid (GABA)-gated channels, differs from the classical insecticides, such as organophosphates and carbamates, to which some insects have developed resistance. Fipronil is extensively used throughout the world and numerous studies have evaluated its toxicity and environmental fate. However, a concise review summarizing and combining the recent scientific findings available in the scientific literature is lacking even though the pesticide has been found to be highly toxic to some aquatic organisms. Thus, this document evaluates, summarizes, and combines important toxicological and environmental fate information from recent scientific articles and other literature to produce a detailed review of fipronil. © Pesticide Science Society of Japan

Keywords: fipronil, environment, fate, toxicity, degradation, detections.

Introduction

Fipronil {5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile; Fig. 1} is a phenylpyrazole insecticide first synthesized by Rhône-Poulenc Ag Company (now Bayer CropScience) in 1987,[1] introduced for use in 1993,[2] and registered in the U.S. in 1996.[3] It controls a broad spectrum of insects such as cockroaches, mosquitoes, locusts, ticks and fleas at both their larval and adult stages.[4,5] Fipronil is effective at low field application rates against insects that are resistant to other agents such as pyrethroids, organophosphates, and carbamates.[6] For instance, Stevens *et al.*[7] found that fipronil applied to rice seed at 12.5 g active ingredient (a.i.)/ha is more efficacious than malathion at 300 g a.i./ha and provides protection against chironomid insects for 9–14 days after sowing.

Fipronil can be formulated as a solid (*e.g.*, insect bait), a liquid spray, or as a granular product (*e.g.*, turf application)—all of which can influence its environmental fate.[8,9] Ngim and Crosby[10] found that granular fipronil was the most persistent,

with an aqueous half life ($t_{1/2}$) of 125 hr and a soil $t_{1/2}$ of 438 hr. Fipronil is the active ingredient in Icon®, Frontline®, Termidor®, and Top Spot®. It is classified as a chiral pesticide and released to the environment as a racemic mixture; approximately 66,824 lbs were used in California in 2005, primarily for structural pest control.[11] The insecticide is not registered for agriculture use in the state of California.
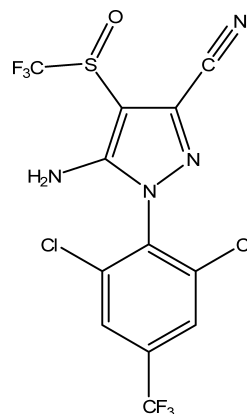

Fig. 1. Structure of fipronil.

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Table 1.   Physicochemical properties of fipronil; all parameters are at 25°C unless specified

Chemical Abstract Service registry number (CAS #)[a]		120068-37-3
Molecular weight (g/mol)[a]		473.2
Solubility[a]	Water (mg/L; pH=5)	1.90
	Water (mg/L; pH=9)	2.40
	Hexane (mg/L)	28.0
	Toluene (mg/L)	3000
Melting point (°C)[a]		200–201
Density (g/mL 20°C)[a]		1.48–1.63
Vapor pressure (mPa; calculated)[b]		3.7×10^{-4}
Henry's constant (m$^3\cdot$atm/mol; experimental)[c]		6.60×10^{-6}
Henry's constant (m$^3\cdot$atm/mol; calculated)[b]		8.50×10^{-10}
Octanol–water partition coefficient (log K_{ow})[b]		3.50
Organic carbon normalized partition coefficient (averaged K_{oc})[d]		825
Aqueous photolysis (d; pH=5)[c]		0.33
Hydrolysis half-life (d)[e]	pH=5.5	>100
	pH=7.0	>100
	pH=9.0	32.08
	pH=10	4.75
	pH=11	0.45 (11-hr)
	pH=12	0.1 (2.4-hr)
Aerobic soil half-life (d)[f]		188
Anaerobic soil half-life (d)[c]	Dry flowable formulation	19.3–22.2
	Granular formation	18.3
Anaerobic water half-life (d)[a]	Dry flowable formulation	0.92–2.83
	Granular formation	5.20

[a] Data from Ref. 2. [b] Data from Ref. 18. [c] Data from Ref. 10. [d] Data from Ref. 17. [e] Data from Ref. 20. [f] Data from Ref. 21.

Chemistry

1.   Physicochemical properties

Fipronil is low-to-moderately soluble in water, prefers lipophilic (organic) matrices such as lipids, oils, lignin, proteins, and organic solvents, and is stable at room temperatures (Table 1).[5] It has a low-to-moderate affinity for organic carbon (*e.g.*, humus in soils) as well as biota (log octanol−water partition coefficient [K_{ow}]=3.9–4.1), and falls between highly insoluble pesticides such as DDT (log K_{ow}=6.2) and soluble ones such as atrazine (K_{ow}=2.6).[12] Fipronil is more dense than water, not particularly volatile, is degraded *via* photolysis, susceptible to hydrolysis under alkaline conditions, and possesses varying microbial degradation rates depending on soil conditions (anaerobic *versus* aerobic; Table 1).

2.   Mode of action

Fipronil is a "new generation" insecticide in that its mode of action differs from the organophosphates and carbamates (both cholinesterase inhibitors) and some pyrethroids (sodium channel activators)—classical insecticides to which numerous insects have developed resistance.[5] It interferes with the function of γ-aminobutyric acid (GABA)-gated channels; fipronil disrupts normal neuronal influx (*e.g.*, passage of chloride ions) by targeting the GABA-gated chloride channel and, at sufficient doses, causes excessive neural excitation, severe paralysis, and death.[5,13–15] Fipronil possesses a greater binding affinity for the GABA-regulated chloride channels of insects than mammalian GABA receptors.[16]

Environmental Chemodynamics

1.   Soil

Several studies have examined the distribution of fipronil in

soil. For instance, fipronil adsorption was found to increase as soil organic matter content increased from 0.1 to 6.5%.[5] A similar observation was noted using eight Australian soil types, with K_{oc} values ranging from 542–1176 (average, 825±214), depending on soil type, and indicating low-to-moderate sorptive capability (Table 1).[17] Similar K_{oc} values were obtained from studies of fipronil with British and French loams (427–1248).[18] These results indicate that fipronil is relatively mobile in soils, which was confirmed by subsequent leaching studies where 31–37% of surface-applied fipronil rapidly moved into the 6–12 cm layer.[18] The $t_{1/2}$ for fipronil in the 0–10 cm soil layer has been calculated to be approximately 36 hr.[14] However, it could be much longer depending on soil type. For instance, the $t_{1/2}$ in a loam was found to be 34 days while in a sandy loam it ranged from 30 to 194 days.[1,18]

The leaching of fipronil's degradation products under sub-Saharan soil conditions has also been studied.[14] Except for the very water-soluble fipronil-amide, the degradation products (Fig. 2) were found to not move below 10 cm. The study also noted that leaching of fipronil-amide coincided with rainfall.

The K_{oc} values of fipronil-sulfide and fipronil-desulfinyl in several Australian soils were higher than the parent compound, ranging from 1479–7159 and 669–3976, respectively.[17] Similar results were reported elsewhere[18]; in sediments and loams the K_{oc} for fipronil-sulfide ranged from

1695–5621, while for fipronil-sulfone and fipronil-amide it ranged from 1447–6745 and 96–203, respectively. Additionally the major photodegradation product, fipronil-desulfinyl, possessed a slightly larger soil sorption affinity than the parent compound with K_{oc}s ranging from 1150–1498.[18]

Degradation of fipronil in the soil results from exposure to sunlight at the surface to produce fipronil-desulfinyl, oxidation near the surface to yield fipronil-sulfone, hydrolysis throughout the upper layer to produce fipronil-amide and reductive processes below the surface which lead to production of fipronil-sulfide (Fig. 2). The $t_{1/2}$s of fipronil and its products in soil indicate that they are persistent; degradation typically ranges from 111–350 days, depending upon soil conditions.

Degradation products have been detected in sediment samples from the Mermentau River, which drains a major rice growing region in Louisiana.[12] Fipronil-sulfide, the main product detected, was measured at concentrations ranging from 0.636–24.8 μg/kg, while the photolytic product fipronil-desulfinyl ranged from 0.55–7.01 μg/kg; fipronil-sulfone was also detected at concentrations up to 10.5 μg/kg. Degradation product concentrations were noted to increase with increasing downstream distance from the rice field sources. In general, fipronil's behavior in soil reveals that it is low-to-moderately sorptive and is thus relatively mobile in soils. Fipronil and its products have been detected in several water bodies in the U.S., but at relatively low concentrations.[19]
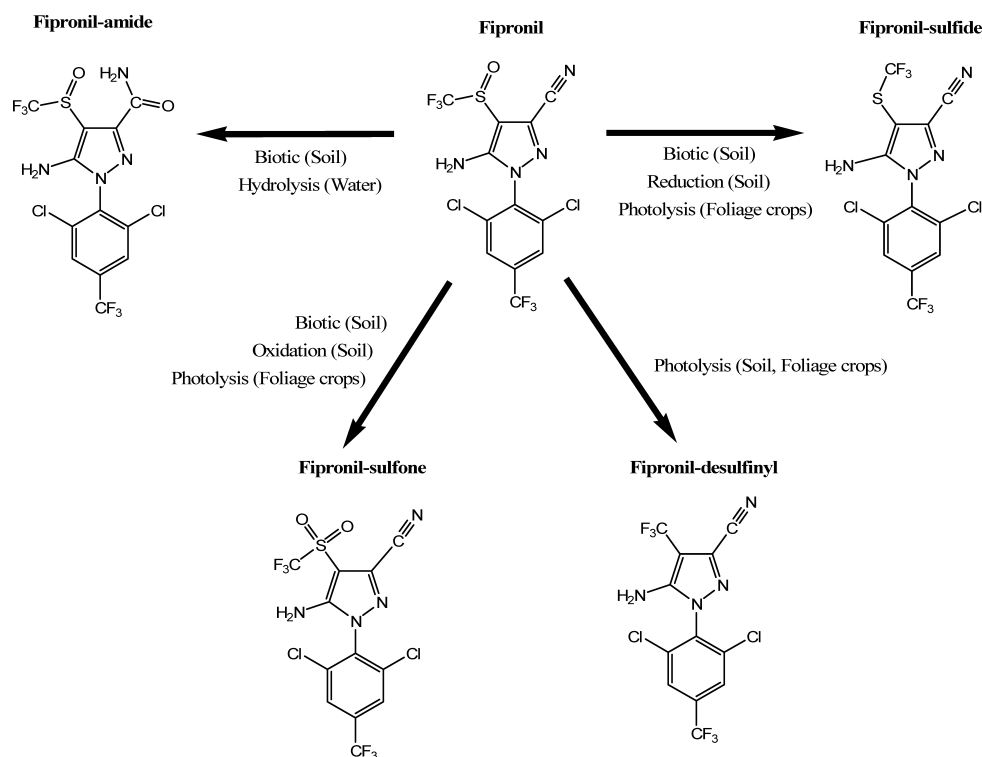

Fig. 2. The degradation of fipronil to fipronil-sulfide, fipronil-desulfinyl, fipronil-sulfone, and fipronil-amide *via* reductive, oxidative, photolytic, hydrolytic, and biotic reaction mechanisms, respectively. Bracketed text indicates the medium in which the reaction is expected to occur.

Table 2.   Residues of fipronil and its degradation products in several U.S. states

State	Fipronil			Fipronil-sulfone			Fipronil-sulfide		
	Type of land use	Number of detections[a]	Concentration range (µg/L)	Type of land use	Number of detections[a]	Concentration range (µg/L)	Type of land use	Number of detections[a]	Concentration range (µg/L)
Alabama	Urban	9	0.007–0.017	Urban	4	0.004–0.008	Urban	5	0.005–0.013
California	Urban	37		Urban	30		Urban	31	
	Agriculture	1	0.004–0.080	Mixed	2	0.005–0.022	Mixed	3	0.005–0.014
	Mixed	7							
Colorado	Agriculture	1	0.003–0.050	Agriculture	1	0.038	Agriculture	1	0.008
	Mixed	2							
Connecticut	Urban	4	0.006–0.008	Urban	1	0.005	Urban	3	0.005–0.008
Georgia	Urban	26	0.001–0.026	Urban	10	0.005–0.008	Urban	11	0.003–0.009
	Mixed	39		Mixed	3		Mixed	8	
Iowa	Mixed	1	0.007	Agriculture	1	0.003	Mixed	1	0.007
	Urban	14		Urban	1		Urban	3	
Illinois	Agriculture	4	0.005–0.0191	Agriculture	3	0.005–0.010	Agriculture	3	0.003–0.008
	Mixed	12		Mixed	1		Mixed	2	
	Urban	6					Agriculture	1	
Indiana	Agriculture	23	0.002–0.020	Agriculture	4	0.002–0.007	Mixed	2	0.003–0.005
	Mixed	14							
	Urban	8		Urban	8		Urban	8	
Louisiana	Agriculture	7	0.002–0.117	Agriculture	12	0.002–0.016	Agriculture	16	0.004–0.015
	Mixed	11		Mixed	13		Mixed	13	
Massachusetts	Urban	1	0.002–0.011	Mixed	2	0.005–0.008	Mixed	2	0.007–0.008
	Mixed	7							

State	Fipronil-desulfinyl			Fipronil-amide		
	Type of land use	Number of detections[a]	Concentration range (µg/L)	Type of land use	Number of detections[a]	Concentration range (µg/L)
Alabama	Urban	6	0.002–0.008	Urban	3	0.002–0.006
	Mixed	2		Agriculture	1	
California	Urban	36	0.005–0.158	Urban	12	0.002–0.009
	Mixed	8		Mixed	4	
	Urban	1				
Colorado	Agriculture	1	0.003–0.006	—	—	—
	Mixed	2				
Connecticut	Urban	3	0.002–0.005	—	—	—
	Urban	11		Urban	7	
Georgia	Agriculture	2	0.002–0.008	Mixed	3	0.004–0.008
	Mixed	13				
Iowa	Mixed	1	0.005	—	—	—
	Urban	5				
Illinois	Agriculture	3	0.002–0.007	Agriculture	1	0.009
	Mixed	3				
	Urban	1				
Indiana	Agriculture	4	0.002–0.008	—	—	—
	Mixed	9				
	Urban	8		Urban	5	0.002–0.011
Louisiana	Agriculture	12	0.004–0.037	Agriculture	11	
	Mixed	10		Mixed	10	
Massachusetts	Mixed	2	0.006–0.007	Mixed	2	0.006–0.008

Source: U.S. Geological Survey, 2006; [a] Data since 2003.

2. Water

Although to date no direct run-off studies have been reported in the literature, fipronil run-off from agriculture, urban, and mixed land use to adjacent waterways can occur. U.S. Geological Survey monitoring work confirms the presence of fipronil, its sulfone, and sulfide degradates in low ppb (µg/L) concentrations in urban creeks feeding into the Sacramento and San Joaquin Rivers of California. Table 2 provides a listing of detections for fipronil and its products reported in sev-

eral U.S. states from agriculture, urban, and mixed land use. U.S. Geological Survey ambient monitoring reported the highest concentration for fipronil (0.117 µg/L) in Louisiana, while for fipronil-sulfone, fipronil-sulfide, fipronil-desulfinyl, and fipronil-amide it was 0.038 µg/L (Colorado), 0.015 µg/L (Louisiana), 0.158 µg/L (California), and 0.011 µg/L (Louisiana), respectively[19]; the values from Louisiana were from surface waters in agricultural areas. Fipronil levels as high as 5.29 µg/L from a Louisiana rice field have been re-

ported[12] and that fipronil and its aerobic degradation products (fipronil-desulfinyl and fipronil-sulfone) were detected at maximum concentrations during March and April—months that coincide with the release of rice field water. It is important to note that although fipronil is primarily produced for agriculture, domestic urban use is substantial (Table 2) and accounts for about half of all detection types.

3. Air

Volatilization of fipronil was confirmed to be slow (Table 1)[10]; the Henry's law constant was experimentally determined to be $6.60 \times 10^{-6} \, m^3$ atm/mol. Also, the degradation product fipronil-desulfinyl was found to be virtually nonvolatile from water.[10] These findings suggest that fipronil does not readily dissipate *via* volatilization and thus will not be regularly found in air. However, aerosol drift during its spray application may still occur.

Environmental Degradation

Fipronil degrades by means of oxidation, reduction, hydrolysis and photolysis to form four major products (Fig. 2)[20]:

fipronil-sulfone, from oxidation near the surface of soils; fipronil-sulfide, a product of reduction in soils; fipronil-amide, a product of hydrolysis in both water and soils; and fipronil-desulfinyl, a result of photolysis.[6] The parent insecticide and its degradation products each possesses unique dissipation kinetics which are presented below.

1. Photolysis

Exposure of aqueous fipronil to natural sunlight conditions at pH 5.5 with Sahelian soil (tropical soil of Niger with 80% sand) led to rapid first-order degradation kinetics with a calculated $t_{1/2}$ of 4.1 hr.[20] Similar results (7.92 hr) were obtained in a separate study using similar conditions but different soils.[18]

The photodegradation of fipronil has been further studied by several groups, who have discovered four photoproducts (Fig. 3).[16,20] In addition, it has been reported that the formation of fipronil-desulfinyl can be accelerated three-fold by adding H_2O_2 (1%).[16] A similar study confirmed that the presence of H_2O_2 leads to a smaller fipronil $t_{1/2}$; it was 0.87–4.51 hr compared to 7.97–9.42 hr for fipronil in the ab-
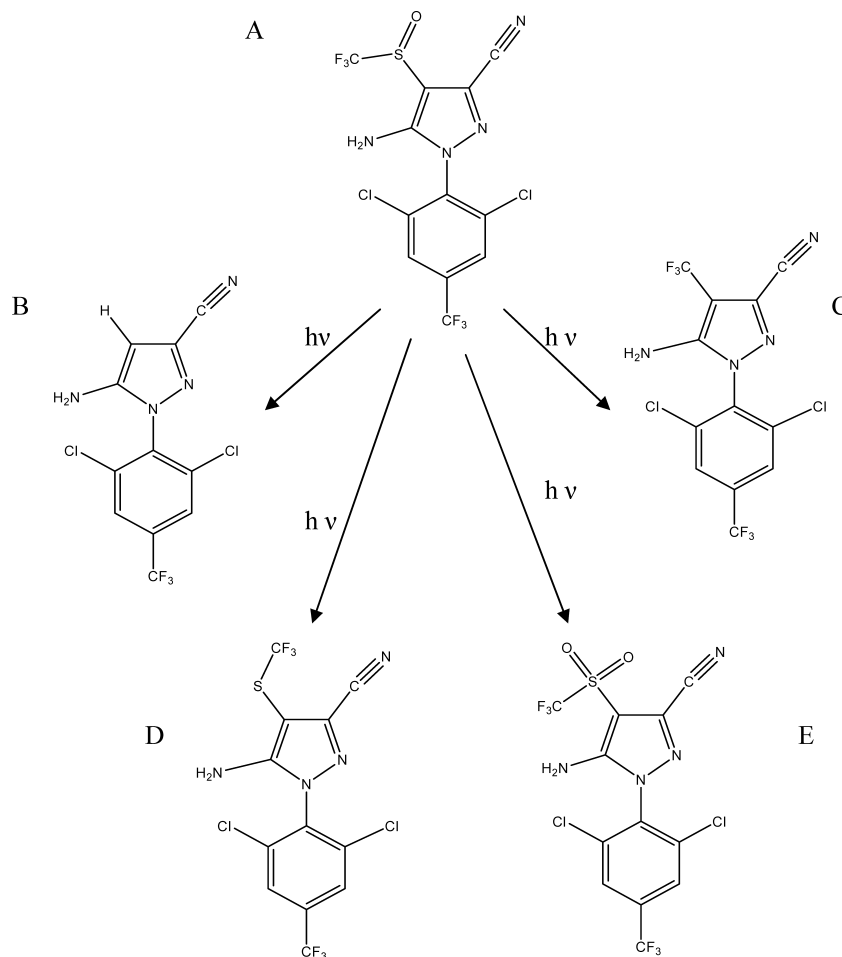

Fig. 3. The photoproducts of fipronil (A) under environmental conditions: (B) fipronil-detrifluoromethylsulfinyl; (C) fipronil-desulfinyl; (D) fipronil-sulfide; and (E) fipronil-sulfone.

sence of H_2O_2.[10] The dramatic acceleration is due to the photochemical generation of hydroxyl radicals.

Fipronil-desulfinyl has been reported to be the major photodegradation product from fipronil application to corn, peas, or pears; thus it is proposed to be the primary persistent residue on foliage-treated crops.[16] This byproduct had a $t_{1/2}$ of 41–55 days and was also the most abundant among all the degradation products.[21] No polar products were found.[16]

Photodegradation has been found to be inversely proportional to sorption.[6] Aqueous fipronil photodegradation experiments have been extended to solid phases[20] (soils) and the results show that photolytic degradation was slower in soils as compared to water as a result of the "light-shielding" effect.[22] Additionally, the degradation rate was found to depend on the nature of the soil and correlate with the Freundlich adsorption coefficient (K_F or sorption capacity). These factors can significantly reduce the dissipation of fipronil in soils.

2. Hydrolysis

The dissipation of fipronil in an aquatic system over three months revealed two transformation products from the parent compound both resulting from photo dependent hydrolysis of the sulfur and nitrile side chains bound to the heterocyclic ring.[5] Under anaerobic conditions, fipronil degrades slowly in water. The $t_{1/2}$ on average is 123 days, much longer than any aerobic soil system where both the fipronil and fipronil-desulfinyl $t_{1/2}$ is only 5 days.[1,18] Two major products were formed under these water conditions: fipronil-sulfide and fipronil-amide.

The degradation of aqueous fipronil in the absence of light at 22°C and at different pHs has been studied.[20] The insecticide was stable in acidic (pH 5.5) and neutral (pH 7.0) solutions; some 80% remained after 100 days in both conditions.

However, under alkaline conditions (pH 9–12) degradation increased with pH and followed pseudo-first order transformation kinetics.[20] At pH 12, aqueous fipronil was hydrolytically degraded some 300 times faster than at pH 9. Temperature can also influence the hydrolysis of fipronil. For example, $t_{1/2}$ was reported to decrease from 114 to 18 hr as temperature was increased from 22°C to 45°C.[20] The suggested reaction mechanism involves nucleophilic addition of hydroxide to the polar nitrile bond of fipronil. The $t_{1/2}$ of fipronil-amide by hydrolysis required 542 hr at pH 9.[10] In general, hydrolysis probably does not represent a major degradative pathway for fipronil since it is stable at typical environmental pHs.

3. Biotic processes

The microbial degradation of fipronil in soils was studied by Zhu *et al.*[23] who found that the $t_{1/2}$ of fipronil in non-sterile clay loam was 9.72 and 8.78 days at 25°C and 35°C, respectively (Table 3); it took three times longer (approx. 33 days) in sterile soils. However, longer half lives have been reported— as long as 342 days in a loam,[1] and 126 days in sandy loams.[18] Similarly, the reported $t_{1/2}$ of fipronil in a sandy loam was 122 days, with fipronil-amide and fipronil-sulfone accounting for 27–38% and 14–24% of the total byproducts, respectively.[9]

Anaerobic soil degradation was reported to be comparable or faster in California rice fields than reported aerobic systems; in water the $t_{1/2}$ ranged from half a day to 5 days while in soil it was longer (2–22 days; Table 1).[10] A longer soil $t_{1/2}$ (113 days) was reported elsewhere and the product of reduction, fipronil-sulfide, was found after 365 days of incubation.[18]

The major degradation product in soil was fipronil-sulfide (reduction) and in water fipronil-desulfinyl (photolysis; Figs.

Table 3. Fipronil half-lives ($t_{1/2}$) from laboratory and field studies

Soil and conditions	$t_{1/2}$ (d)
Field	
High treatment plot (application rate of 0.15 g/m²)[a]	139
Low treatment plot (application rate of 0.075 g/m²)[a]	124
Laboratory	
Sandy loam sterile with 15% maximum water holding capacity[a]	217
Sandy loam sterile with 60% maximum water holding capacity[a]	210
Sandy loam non-sterile with 15% maximum water holding capacity[a]	198
Sandy loam non-sterile with 30% maximum water holding capacity[a]	161
Sandy loam non-sterile with 60% maximum water holding capacity[a]	68
Clay loam sterile at 25°C[b]	33.5
Clay loam sterile at 35°C[b]	32.1
Clay loam non-sterile at 25°C[b]	9.72
Clay loam non-sterile at 35°C[b]	8.78

[a] Data from Ref. 21. [b] Data from Ref. 23.

2 and 3). Fipronil-amide (hydrolysis) and fipronil-sulfone (oxidation) degradation products were also found but at low concentrations.[10] The microbial degradation of fipronil-desulfinyl (major soil photoproduct) has also been studied.[18] Calculated $t_{1/2}$s were 630–693 days depending on the soil. The results show that the major photolytic product of fipronil is persistent in soil.

Soil moisture is an important factor because it increases the degradation of fipronil. The $t_{1/2}$ of fipronil decreased from 198 to 68 days as the soil moisture content increased (Table 3). However, shorter $t_{1/2}$ values about 10 days have been reported.[23] Similarly, about 14.5 days was found to be the $t_{1/2}$ for fipronil in pond water and sediment (aerobic), and the major degradation product was fipronil-sulfide.[18] Ying and Kookana[21] found that moisture in the soil determined the type of degradation product formed. For instance, soil with more than 50% moisture content tended to have more fipronil-sulfide; result of the reduction pathway since high moisture promotes a reduced environment due to the lack of aeration. In contrast, soils with good aeration and less than 50% moisture had more fipronil-sulfone. Zhu et al.[23] showed that temperature increased the dissipation time by about one day. In both studies, the sterile soils had much longer dissipation times as compared to the non-sterile soils (Table 3).[21,23]

Bacteria, fungi, and actinomycetes populations, as measured by plate counts, revealed no consistent pattern with fipronil concentration; the populations varied throughout the incubation period.[23]

Toxicology

1. Direct actions

1.1. Insects

Fipronil is highly effective against larvae of the mosquito *Culex quinquefasciatus*, as its reported LC_{90} was $0.90\,\mu g/L$ while the LC_{50} was $0.35\,\mu g/L$.[24] Its toxicity to larvae of the mosquito *Aedes aegypti* produced 24-hr and 48-hr LC_{50}s of 24.8 nM ($\sim 11.7\,\mu g/L$) and 15.1 nM ($\sim 7.14\,\mu g/L$), respectively.[5] The degradation products are also highly toxic to *A. aegypti* larvae; the LC_{50} for fipronil-sulfide and fipronil-sulfone was the same ~ 8.8 nM ($\sim 3.79\,\mu g/L$).[5] Fipronil is also highly toxic to midges (*Chironomus tepperi*), common pests in rice fields, at very low concentrations; the LC_{50} and LC_{90} are $0.43\,\mu g/L$ and $1.05\,\mu g/L$, respectively.[7] Nearly the same LC_{50} for midges was observed in another study.[25] Table 4 summarizes data from several studies addressing the toxicity of fipronil to various insects.

Low concentrations have also been shown to control the onion maggot, *Delia antique*. Fipronil at a seed-treatment concentration of $25\,\mu g/mg$ controlled the onion maggot population with only about 4% seed loss.[26] Fipronil is also highly toxic to the boll weevil (*Anthonomus grandis*; Table 4), and leaf residues as low as 3 ng/cm² have been shown to kill about 48% of the weevils exposed to the insecticide.[27] The red imported fire ant (*Solenopsis invicta*) is another insect highly sensitive to fipronil, with granular baits containing $3–30\,\mu g/mg$ eliminating colonies within 8–11 weeks after treatment.[28] A corresponding field trial by the same authors showed that $15\,\mu g/mg$ granular bait provided over 80% colony mortality at six and 12 weeks after application. Further, Costa and Rust[29] reported the mortality rates of $\geq 93\%$ on Argentine ant (*Linepithema humile*) colonies in as little as one week; queen ants were killed within four weeks after exposure to fipronil.

Like ants that live in soil, termites are also affected by fipronil. For example, Hu[30] studied the efficacy of fipronil on populations of the termites *Reticulitermes flavipes* and *Coptotermes formosanus*; exposed soils were monitored for tunneling depth and insect mortality. In clear dose-response fash-

Table 4.   The toxicity of fipronil to various insects

Insect	Species	Test	Amount ($\mu g/L$ unless specified)
Mosquito[a]	*Aedes aegypti*	LC_{50}	1.54
Mosquito[a]	*Aedes albopictus*	LC_{50}	23.0
Mosquito[a]	*Aedes taeniorhynchus*	LC_{50}	0.43
Mosquito[a]	*Culex nigripalpus*	LC_{50}	0.87
Mosquito[a]	*Culex quinqefasciatus*	LC_{50}	0.35
Midges[a]	*Chironomus crassicaudatus*	LC_{50}	0.42
Midges[a]	*Glyptotendipes paripes*	LC_{50}	0.42
Honeybee[b]	*Apis mellifera*	LD_{50}	4–6.2 ng/bee
Honeybee[c]	*Apis mellifera*	LD_{50}	<5 ng/bee
Boll weevil[d]	*Anthonomus grandis*	48-hr LD_{50}	$0.040\,\mu g$/weevil
Boll weevil[d]	*Anthonomus grandis*	72-hr LD_{50}	$0.029\,\mu g$/weevil
German cockroach[e]	*Blattella germanica*	LD_{50}	4.6–5.4 ng/cockroach

[a] Data from Ref. 25. [b] Data from Ref. 1 and 33. [c] Data from Ref. 31. [d] Data from Ref. 27. [e] Data from Ref. 47.

Table 5.   Toxicity of fipronil to aquatic animals

Aquatic organism	Test	Amount (μg/L unless specified)
Oysters[a]	EC_{50}	770
Mysid shrimp[a]	EC_{50}	0.14
Sheephead minnow[a]	EC_{50}	130
Daphnia[a]	EC_{50}	200
Bluegill sunfish[a]	96-hr LC_{50}	83.0
Rainbow trout[a]	96-hr LC_{50}	250
Crayfish (Red swamp)[b]	96-hr LC_{50}	14.3
Crayfish (White river)[b]	96-hr LC_{50}	19.5
Ceriodaphnia dubia[c]	48-hr LC_{50}	17.7
Ceriodaphnia dubia[c]	48-hr LC_{50} [(+) enantiomer]	10.3
	48-hr LC_{50} [($-$) enantiomer]	31.9
Daphnia pulex[d]	10-d LC_{50}	16

[a] Data from Ref. 9. [b] Data from Ref. 37. [c] Data from Ref. 39. [d] Data from Ref. 36.

ion, the termites tunneled to $87\pm0.21\%$ and $47\pm0.18\%$ of the 50-mm depth with 50 and 100 mg/L fipronil, respectively, before dying. Fipronil was observed to be a non-repellent insecticide that retards the activity of termites before death.[30]

At concentrations of approximately an order of magnitude below the LC_{50}, fipronil did not interfere with the locomotive activity of honeybees (*Apis mellifera*) regardless of the route of administration (topical and oral: 0.1, 0.5, and 1 ng/bee).[31] The effects of fipronil on honeybee sucrose activity was also examined since the disaccharide is essential to making foraging decisions and organizing the division of hive labor.[31,32] Orally-absorbed fipronil had no significant effect on sucrose activity at the 0.5 ng/bee concentration. Further, the insecticide induced no significant impairment of performance for either learning or memory retention; however, the same concentration did impair their olfactory learning.[31] The LD_{50} of fipronil to the honeybee *Apis mellifera* has been reported to be either 4 or 6.2 ng/bee.[1,33]

At very low doses (*e.g.*, 0.6 g a.i./ha) fipronil can effectively control adult grasshopper (*Pyrgomorpha cognate*) outbreaks; application rates of 1–2 g a.i./ha resulted in high mortality rates, with more than 90% of the insects disappearing within 3–10 days.[34] An increase in mortality in a shorter time period was also found with higher doses in the same study.

In contrast to the above findings, fipronil had minimal effect on three nematode species at a concentration of 250 mg/L and applied field rate of 12–60 mg/L.[35] For example, 2000 mg/L fipronil exposure for 72 hr resulted in only 17% mortality for *Heterorhabditis bacteriophora* and similarly for *Steinernema carpocapsae*. However, a 100% mortality was observed for *S. arenarium*[35] at an application rate that was about 33 times greater than the highest field application rate of 60 mg/L.

The degradation products of fipronil were also found to

have strong insecticidal properties in mosquitoes; fipronil-desulfinyl and fipronil-amide had LC_{50}s of 62.7 nM (29.7 μg/L) and 121.6 nM (57.5 μg/L), while they were 8.8 nM (3.79 μg/L) for fipronil-sulfide and fipronil-sulfone, respectively, to the larvae of *Aedes aegypti*.[5] In a similar study with the boll weevil, the 48-hr LD_{50}s of fipronil, fipronil-desulfinyl, fipronil-sulfone, and fipronil-sulfide were 0.040, 0.174, 0.068, and 0.035 μg/weevil, respectively. At 72 hr the LD_{50}s were lower for the same degradation products, respectively: 0.029, 0.126, 0.031, and 0.020 μg/weevil.[27] Also, the photoproduct desulfinyl-fipronil was found to be toxic to both houseflies and mice; the LD_{50}s for the housefly were 130 and 58 μg/kg for fipronil and fipronil-desulfinyl, while it was 41 and 23 mg/kg for the common mouse, respectively.[16]

1.2.   Aquatic organisms

Fipronil is highly toxic to many aquatic species,[9] and it can bioaccumulate in some. For example, at pptr (ng/L) levels, fipronil affects mysid shrimp (*Americamysis bahia*) and ppb (μg/L) levels affected freshwater Daphnia (*Daphnia pulex*) and Bluegill sunfish (*Lepomis macrochirus*; Tables 5 and 6). It has also been determined that only certain concentrations— those approaching the LC_{50}—can negatively affect population parameters such as reproductive rate, birth rate, death rate, and doubling time of the water flea, *Daphnia pulex* (Table 5).[36] The LC_{50} for *D. pulex* was about 16 μg/L (relatively toxic), according to the same study; it also reported that increased fipronil concentrations led to a decline in the population growth rate of the water flea, and a negative rate (leading to population extinction) was observed at an 80 μg/L concentration.

Ngim and Crosby[10] found fipronil to be very toxic to resident crayfish of rice fields at ppb levels (14.3–19.5 μg/L; Table 5). Further, its degradation products have been found to

Table 6. Toxicity of fipronil degradation products to aquatic animals

Aquatic organism	Test	Metabolite concentration (μg/L unless specified)		
		Fipronil-desulfinyl	Fipronil-sulfone	Fipronil-sulfide
Bluegill sunfish[a]	96-hr LC_{50}	20	25	—
Rainbow trout[a]	96-hr LC_{50}	31	39	—
Daphnia magna[a]	21-day EC_{50}	230	4.5	27
Daphnia magna[a]	48-day EC_{50}	—	29	100
Mallard duck[a]	LC_{50}	437 mg/kg	—	—

[a] Data from Ref. 18

have similar or greater toxicity—the 96-hr LC_{50}s for fipronil-sulfone, fipronil-sulfide, and fipronil-desulfinyl were 11.2, 15.5, and 68.6 μg/L, respectively.[37] Interestingly, the fipronil-sulfone and sulfide LC_{50}s were similar to, or lower than, that of the parent fipronil (11.1–14.3 μg/L). When compared to the parent, fipronil-sulfone was found to be 3.3 times more toxic to *L. macrochirus* (bluegill sunfish), while both it and fipronil-sulfide are 6.6 and 1.9 times more toxic, respectively, to freshwater invertebrates.[9] Differences in the abundance of invertebrate families present in rice fields under conventional (pesticide use) and organic management practices (no pesticide use) have also been reported.[38] Fipronil was found to be a main factor that could explain these differences, as it may have a negative impact on predatory invertebrates.

Exposure of *Daphnia* to fipronil was found to affect health and reproduction (Table 5).[9] In a more detailed study,[39] the acute enantioselective toxicity of fipronil, the racemate, and desulfinyl derivative on *Ceriodaphnia dubia* was studied. Enantiomers have the same physical-chemical and abiotic degradation properties but different biological activities, microbial degradation rates, and toxicities. The 48-hr LC_{50} for the (+) enantiomer was $10.3\pm1.1\,\mu$g/L, while it was $31.9\pm2.2\,\mu$g/L for the (−) enantiomer; the LC_{50} of the racemate (mixture) was $17.7\pm1.3\,\mu$g/L.[39]

The toxicity of fipronil's degradation products on several aquatic organisms are presented in Table 6. It shows that the degradation products are just as toxic as the parent compound. For example, EC_{50} of fipronil-sulfone is 4.5 μg/L for *Daphnia magna*, a benchmark aquatic invertebrate. At low concentrations, the degradation products have been found to hinder reproduction in aquatic organisms.[18]

1.3.   Birds
Fipronil has been found to be toxic to terrestrial game birds on both an acute oral and subacute dietary basis; however, it is not very toxic to some waterfowl.[9] Low toxicity to some birds has also been reported by the manufacture and listed elsewhere[40]—mallard duck, pigeon, and field sparrow had LD_{50}s of 2150, >2000, and 1120 mg/kg, respectively, while the LD_{50} for the northern bobwhite quail is 11.3 mg/kg.

1.4.   Mammals
Although fipronil has an affinity toward insects, studies have shown that fipronil also binds to mammalian $GABA_A$ and $GABA_C$ receptors.[41,42] Studies of the effects of fipronil on the behavior, synaptic excitability, and sleep patterns of Sprague–Dawley rats revealed that the insecticide induced minor excitability.[43] Fipronil-sulfone was found to be the major metabolite in mice and appears in the brain, liver, kidney, fat and feces. In rats, however, the two main metabolites were conjugates of ring-opened pyrazole products.[2] The LD_{50}s for rats and rabbits are 97 and 354 mg/kg, respectively, and according to the U.S. EPA,[9] the no observable exposure level (NOEL) was determined to be 0.5 mg/kg. Thus, results suggest that fipronil has some toxicity to mammals.

Fipronil poisoning in seven humans has been reported,[44] and was characterized by vomiting, agitation, and seizures. Human cases included a 77-year-old woman who ingested ant bait containing 0.01% fipronil (<0.1 mg), and a 50-year-old man that complained of short-lived, non-specific, symptoms after being exposed to a dilute spray of fipronil.[45,46] There are no human fatalities reported as a result of fipronil exposure.

2.   Indirect actions
Very low doses of fipronil, applied to control *P. cognate* (grasshoppers), had a measurable impact on non-target insects from the orders Coleoptera, Hymenoptera, and Diptera.[34] Application rates of 1 and 2 g a.i./ha were found to increase grasshopper mortality rates while having low consequences to non-target insects such as beetles. Many beetles are of agricultural importance because they may prey on other pests.

Mesléard *et al.*[38] found that fipronil had an indirect effect on heron's diet, as more herons were observed foraging for insects in organic rice fields than in those treated with the insecticide. This difference was attributed to a reduction in invertebrate populations (particularly their larvae) in fipronil-treated rice fields. For instance, 30 and 22 invertebrate families were represented in untreated (organic) and treated plots, respectively.[38] In contrast, fipronil was not found to negatively affect birds that consumed fipronil-treated rice seeds.[40] In a controlled caged experiment, fipronil-treated seed was fed to

red-winged blackbirds, brown-headed cowbirds, and boat-tailed grackles and the results showed that at a seed treatment rates in the range of 325–500 mg/kg the insecticide did not affect feeding activity.[40]

3.   Antagonized toxicity

In the German cockroach (*Blattela germanica*), the effectiveness of fipronil was reported to be antagonized by *S,S,S,*-tributyl phosphorotrithioate (DEF) and the metabolic inhibitor piperonyl butoxide (PBO).[47] Fipronil was found to be roughly 2.3–3.0 times less toxic to cockroaches pretreated with either DEF or PBO. The same study discovered that fipronil is activated metabolically in cockroaches, forming fipronil-sulfone as the primary metabolite.

Summary and Conclusions

Fipronil, a phenylpyrazole insecticide, exhibits neurotoxic activity by blocking the GABA-regulated chloride channels of neurons. It is useful for the control of many domestic and agricultural insect pests, especially since its mechanism of toxicity is different than traditional insecticides to which resistance has been developed. Many insects (both beneficial and pests) are highly sensitive to fipronil at low doses in both their larval and adult stages; the major degradation products also possess toxicity. Fipronil is extremely toxic to honeybees, highly toxic to aquatic organisms and toxic to terrestrial game birds, but not to some waterfowl.

Due to its low vapor pressure and Henry's Law constant, fipronil is not likely to dissipate to the atmosphere. Fipronil has low-to-moderate environmental persistence dependent on the processes of photolysis, hydrolysis, sorption, and volatilization. Five degradation products are found in the environment: fipronil-sulfone, fipronil-sulfide, fipronil-desulfinyl, fipronil-amide, and fipronil-detrifluoromethyl-sulfinyl. In soils, fipronil possesses a low-to-moderate sorption capacity which increases in proportion to organic matter content. Dissipation from soils is *via* gradual microbial breakdown; anaerobic and aerobic $t_{1/2}$s extend from four months to one year, respectively, while on a soil surface, photolysis represents the primary degradation pathway. Soil moisture content determines the type of degradation products that form in soils. Fipronil is significantly more susceptible to degradation *via* photolysis than hydrolysis in water at typical environmental pHs. However, under alkaline conditions fipronil is unstable and readily degrades *via* base-catalyzed hydrolysis.

Fipronil has been detected in many water bodies throughout California and other U.S. states. However, in California it is not registered for crop use. Given fipronil's persistence, toxicity of parent and degradation products to aquatic invertebrates and other non-target organisms, and detections in surface waters, thorough assessments should be made before its application to water or near water bodies and prevention measures should be taken to mitigate its runoff to surface waters.

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