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Review

Environmental fate and properties of pyriproxyfen

Jonathan J. SULLIVAN* and Kean S. GOH

California Environmental Protection Agency, Department of Pesticide Regulation, 1001 I Street, P.O. Box 4015, Sacramento, CA 95814, USA

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Pyriproxyfen is a broad-spectrum insect growth regulator (IGR) with insecticidal activity against public health insect pests such as houseflies, mosquitoes and cockroaches. In agriculture and horticulture, pyriproxyfen has registered uses for the control of scale, whitefly, aphids and fire ants. It is used extensively worldwide, particularly in developing countries, although it has no significant uses in California. Pyriproxyfen acts on the endocrine system of insects by mimicking the juvenile hormone, thereby hindering molting and subsequently inhibiting reproduction. IGRs are unique in that they are specific for insects and have very low mammalian toxicity. As such, pyriproxyfen has received U.S. EPA status as a Reduced Risk insecticide and an organophosphate alternative and is the only pesticide approved by the World Health Organization (WHO) for treatment of potable water against mosquito. However, concerns about its environmental persistence and latent toxicity to nontarget organisms have been recently raised and discussed. In this context, a detailed review of the environmental fate and physicochemical properties of pyriproxyfen from the available scientific literature and from data gathered in its development and testing is needed. This paper gathers, combines, and abridges important environmental fate and property data on pyriproxyfen for academics, environmental scientists and agricultural professionals needing ready access to this information.

Keywords: Pyriproxyfen, physicochemical properties, environmental fate, abiotic degradation.

Introduction

The insecticide pyriproxyfen, 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine, is an aromatic, non-terpenoidal juvenile hormone (JH) agonist and a potent suppressor of embryogenesis and adult formation in insects, first synthesized and developed by Sumitomo Chemical Co., Ltd. in the 1990's.[1)] It is often promoted as a *biorational pesticide*, *i.e*., a pesticide of natural origin that ostensibly has limited or no adverse effects on the environment or beneficial organisms. Biorational pesticides, known more generally as biopesticides, are derived from biological sources, *e.g*., viruses, bacteria, fungi, *etc*., or from biochemicals such as insect growth regulators (IGRs) or pheromones (it should be noted, however, that there is no definitive legal or scientific meaning for the term *biorational* in the United States; the U.S. EPA describes a biorational insecticide simply as having a mode of action that is different than that of conventional, broad-spectrum insecticides, with greater selectivity, relatively brief residual activities, and tending to have reduced impact on non-target organisms). Pyriproxyfen is toxic to insects during their embryonic, last larval, or reproductive stages and is particularly effective against pests that are relatively insensitive to conventional insecticides, such as whiteflies, mealworms, scales and thrips.[2–4)] The LC_{90} values for whiteflies and scale insects exposed to plants treated with pyriproxyfen, for example, are reported to be 0.05 ppm and 0.02 ppm, respectively.[5)] It is also effective against public health insect pests such as mosquitoes, houseflies, cockroaches and cat fleas, especially when it is applied to housefly and mosquito breeding sites. Pyriproxyfen is said to have 95% inhibition of emergence for mosquito larvae, and no effect on predator populations.[6)] Nayar *et al*.[7)] observed that pyriproxyfen applied at 0.02 ppm completely inhibited adult mosquito emergence for several weeks. Kamimura and Arakawa[8)] observed that pyriproxyfen was extremely effective against larvae of *Cx. Pipiens* pallens and *Cx. tritaeniorhynchus* that showed high resistance to organophosphorus (OP) insecticides. Complete inhibition of adult emergence continued for 3 weeks or more in open containers and irrigation ditches at a concentration of 0.01 ppm, in cesspools at 0.05 ppm and in sewers with inflow of house wastewater at 0.1 ppm. Accordingly, pyriproxyfen is one of only four insec-

* To whom correspondence should be addressed.
E-mail: jsullivan@cdpr.ca.gov

ticides (temephos, methoprene, pyriproxyfen, permethrin) and a bacterial larvicide (*Bacillus thuringiensis israelensis*) recommended by the WHO for addition to drinking water for public health purposes. Its recommended dosage is 0.01 mg/l in drinking water containers.[9–10] Pyriproxyfen has exhibited little adverse effect on non-target species such as bees, vertebrates, and natural enemies, but may be moderately to highly toxic to some aquatic organisms.[11–14]

In agriculture, pyriproxyfen has been the most used insecticide for controlling the California red scale, *Aonidiella aurantii*, an important pest in citrus groves worldwide. It has also been effective against silverleaf whitefly, *Bemisia argentifolii*, in cotton, vegetable crops, and peanut. Pyriproxyfen is one of several insecticides being used in California for the control of the Red Imported Fire Ant (*Solenopsis invicta*), a major agricultural, horticultural, and urban pest throughout the Southeastern and Southwestern United States.[15] Pyriproxyfen is formulated as a general insect growth regulator (IGR) for agriculture (Knack®, Esteem®), fire ant bait (Distance®), flea and tick spray (Nylar®), and as a component in mixed-pesticide products such as shampoos, foggers, and carpet sprays. Pyriproxyfen is a practically non-toxic pesticide in EPA toxicity class III. It is a General Use Pesticide (GUP), and labels for products containing it must bear the Signal Word CAUTION. There are currently 106 registered products containing pyriproxyfen in California. In 2005, 9,946 pounds of pyriproxyfen were applied in California, 77% of which was applied on oranges (4222 pounds), almonds (2475 pounds), and cotton (922 pounds). Public health and structural pest control uses each accounted for less than 100 pounds.[16] Because of its overall low non-target toxicity, pyriproxyfen is considered suitable for integrated pest management (IPM) programs.[17] The U.S. EPA's Reduced Risk Committee has granted reduced-risk and OP alternative status for use of the insecticide pyriproxyfen to control scale insects on a variety of crops, including apple, avocado, papaya, mango, pineapple, banana, and coffee.[18]

Chemistry

1. Mode of action

Molting and metamorphosis in insects are under the control of two hormones, the steroid ecdysone and a group of acyclic sesquiterpenoids known collectively as juvenile hormones (JH). Ecdysone induces and regulates molting, but the character of the molt is mediated by JH. When JH is present, there is no differentiation in form. In its absence, ecdysone initiates the switching in gene expression necessary for metamorphosis, first to the pupa, then to the adult.[19] There are five homologous structural forms of JH (Fig. 1), all of them having one or more *asymmetric* (chiral) centers (although only the absolute configurations of JH-I and JH-III have been rigorously established). The morphogenetic activities of synthetic racemic samples of the JHs shows that JH-1 has the highest biological activity against most insect species, while JH-III is the most pervasive and has been found in all insect orders. JH-O and 4-Methyl JH-I were isolated from the developing embryos of the tobacco hornworm *Manduca sexta*, while Lepidoptera produce JH-I, JH-II, and JH-III. The bis-epoxide JHB_3 is biosynthesized *in vitro* by the ring gland of third instar fruit fly larvae (*Drosophila melanogaster*), but it is much less active than JH III in bioassays on this species.

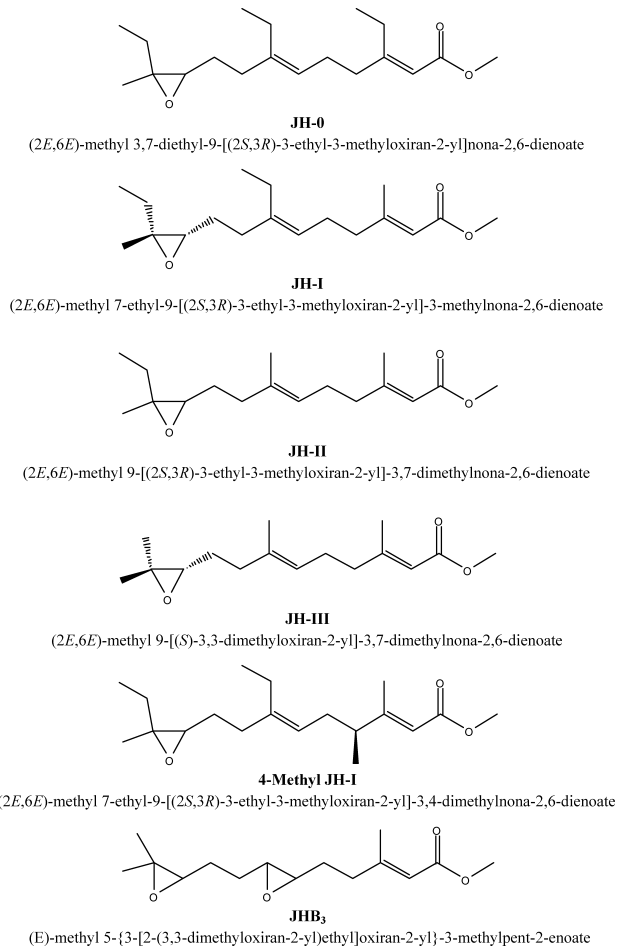

Fig. 1. Chemical structures of the six natural forms of juvenile hormone (JH 0, JH I, JH II, JH III, JHB_3, 4-Methyl-JH I).

Juvenile Hormone Agonists (JHAs) such as pyriproxyfen and fenoxycarb act in the same manner as JHs, but are much more chemically stable. Although these active JHAs bear little structural resemblance to JHs, their high stability allows them to compete for JH binding site receptors. Ordinarily, when sufficient growth has occurred, JH production ceases and triggers the molt to the adult stage. Pyriproxyfen mimics the action of JH and maintains the insect in an immature state. Insects treated with these chemicals are unable to molt successfully to the adult stage, and cannot reproduce as normal.[20]

As a potent hormone agonist, pyriproxyfen is classified as an endocrine disruptor. An endocrine disruptor is defined as an exogenous substance or mixture that alters function of the

endocrine system and consequentially causes adverse health effects in an intact organism, its progeny or a population or subpopulation.[21] In 2007 the U.S. EPA, in response to a Congressional mandate in the Federal Food, Drug, and Cosmetic Act (FFDCA), began the systematic screening of certain pesticides, chemicals and environmental contaminants for their potential to affect the estrogen, androgen or thyroid hormone systems.[22] Although at this time the evidence is largely putative, some pesticide active and inert ingredients are suspected of being endocrine disruptors, i.e., chemicals that can lead to an increase in birth defects, sexual abnormalities and reproductive failure in both wildlife and human populations.[23] According to the U.S. EPA, while pyriproxyfen is known to produce juvenoid effects on arthropod development, this mechanism-of-action in target insects and some other arthropods has no relevance to any mammalian endocrine system. Extensive evaluation of acute, sub-chronic, chronic, developmental, and reproductive toxicology show no evidence of any endocrine-mediated effects. Pyriproxyfen is therefore not considered to possess estrogenic or endocrine disrupting properties to mammals.[24]

2. *Physicochemical and general chemodynamic properties*

Pyriproxyfen is an unclassified pyridine-based phenyl ether and a derivative of the JHA fenoxycarb in which part of the aliphatic chain has been replaced by pyridyl oxyethylene (Fig. 2). Technical pyriproxyfen (4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether, CAS No. 95737-68-1) has a molecular weight of 321.5 g mol^{-1} and the molecular formula $C_{20}H_{19}NO_3$ (Table 1). It is a yellow waxy solid with a melting point of 47.4°C and a density greater than that of water (1.242 g/ml at 25°C). At ambient temperature (25°C) and pH 6, pyriproxyfen is sparingly soluble in water (0.367±0.004 mg/l) but is highly soluble in organic solvents such as hexane (400 g/kg at 20°C) and xylene (500 g/kg at 20°C). It has a pH of 6.41 at 20°C and no discernible acidic or basic characteristics.

If discharged into the air, a vapor pressure of 0.013 mPa (23°C) and estimated Henry's Law constant of 1.1×10^{-7} atm cm^3/mol indicates that pyriproxyfen is only slightly volatile and will not dissipate appreciably into the atmosphere *via* mass transfer across the air–water or air/soil pore water interface. Moreover, these properties suggest that the potential for non-occupational exposure by inhalation is not significant. Further, gas/particle partition models predict that pyriproxyfen will exist in both the vapor and particulate phase in the ambient atmosphere, and that particulate-phase pyriproxyfen will be removed from the air by wet and dry deposition.[25] It is predicted that vapor-phase pyriproxyfen will degrade rapidly with photochemically-produced hydroxyl radical in the atmosphere at an rate of 5.2×10^{-11} cm^3/sec at 25°C.[26] The average half-life for this reaction is estimated to be 7.4 hr, based on a mean atmospheric hydroxyl radical concentration of 5×10^5 mol/cm^3.[27] Because of its low volatility, low mam-

Table 1. Physicochemical properties of technical pyriproxyfen[a]

Chemical abstracts service (CAS) registry number	95737-68-1
Molecular weight (g mol^{-1})	321.5
Molecular formula	$C_{20}H_{19}NO_3$
Chemical name	
IUPAC	4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether
CAS	2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine
Color and physical state	Pale yellow waxy solid
Odor	Faint characteristic odor
Melting point	47.4°C
Density	1.242 g/ml at 25°C
Vapor pressure	<0.013 mPa at 23°C
Henry's law constant	1.1×10^{-7} atm m^3 mol^{-1} at 20°C
Ultraviolet (UV)–visible spectrum	λ_{max} (in water)=270 nm
Solubility (g/kg)	
Water	0.367±0.004 mg/l at 25°C
Hexane	400 g/kg at 20°C
Methanol	200 g/kg at 20°C
Xylene	500 g/kg at 20°C
n-Octanol–water partition coefficient (K_{ow})	log K_{ow}=5.37 at 25°C
pH	6.41 at 20°C

[a] Data from Ref 10.

Table 2. Adsorption characteristics of pyriproxyfen and its major metabolites in five representative agricultural soils and one sediment[a)]

	Pyriproxyfen		Metabolite (**2**)[b)]		Metabolite (**3**)[c)]	
	K_D	K_{OC}	K_D	K_{OC}	K_D	K_{OC}
Sediment	11.7	4980	2.76	2757	0.12	120
Sand	20.4	11600	5.5	4250	0.11	85
Sandy Loam	126	12600	21.5	3811	0.12	21
Silt Loam	174	26900	32.8	3062	0.34	32
Silty Clay Loam	282	34200	—	—	—	—
Clay Loam	324	11000	11.5	921	0.11	9

[a)] Data from Refs. 25–26.

[b)] 4-{4-[2-(Pyridin-2-yloxy)propoxy]phenoxy}phenol

[c)] 2-(2-Pyridyloxy)propionic acid

malian toxicity, and the low (10–15% weight) concentration of its liquid formulations, vapor-phase pyriproxyfen is expected to be a minor exposure hazard and minimally toxic when inhaled.

Pyriproxyfen has high soil adsorption coefficients (K_D, K_{OC}) and is strongly absorbed to most agricultural soils (Table 2). It is not expected to be mobile when applied in a manner consistent with its labeled uses. Fathulla[28)] reported organic carbon-based partition coefficient (K_{OC}) values for pyriproxyfen ranging from 4,980 (lake sediment) to 34,200 (silty clay loam). Nambu[29)] observed K_{OC} values of 13,000 in a loam soil-water suspension, 58,000 in clay loam soil-water suspension, and 27,000 in the sandy loam soil-water suspension. A strong correlation between pyriproxyfen adsorption and the clay content (r=0.945) and cation exchange capacity (r=0.948) of the tested soils was noted, which is generally indicative of the increased number of available binding sites in soils with moderate to high organic matter and clay content. The mobility of the pyriproxyfen soil degradation products (**2** and **3**) (see Fig. 2 for names and structures of degradation and metabolic products) were also investigated. The hydroxylation product (**2**) had K_{OC} values ranging from 920 (clay loam) to 4250 (sand), and K_{OC} values for the oxidation product (**3**) ranged from 9 (clay loam) to 120 (lake sediment). Based on these analyses, **2** is considered having slight to low mobility, while **3** has high to very high mobility with a high potential to leach to groundwater.

Although pyriproxyfen has a high octanol/water partitioning coefficient (log P=5.37 at 25°C) and a high propensity to bioaccumulate, cumulative toxicological effects resulting from bioaccumulation are unlikely following short-term, intermittent exposures because of its relatively short elimination half-life. Steginsky *et al*.[30)] reported that ^{14}C-pyriproxyfen residues accumulated in Bluegill sunfish continuously exposed to pyriproxyfen at 20 μg/l for 28 days under flow-through conditions, yielding mean bioconcentration factors (BCF) of 465–478× for edible tissues, 2390–2482× for non-edible tissues and 1379–1495× for whole fish. After a two-week depuration period, 93% of accumulated residues had been eliminated. The depuration half-life of pyriproxyfen was 1–2 days. In a similar study with carp, a BCF of 350–400 was reported for pyriproxyfen with a depuration half-life of 0.4–0.6 days. Consequently, pyriproxyfen is not expected to bioconcentrate in fish under environmentally relevant conditions due to the rapid depuration of the parent compound from fish.

Due to its low solubility, high partition coefficients, and hydrophobicity, and because it is applied outdoors to agricultural crops, the potential for pyriproxyfen to reach surface waters and sediments from runoff or spray drift is a major concern and has been evaluated by the U.S. EPA. For the assessment of ground and surface potable water, the U.S. EPA uses the Generic Estimated Environmental Concentration (GENEEC) or the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) to estimate pesticide concentrations in surface water and Screening Concentrations in Ground Water (SCI-GROW), which predicts pesticide concentrations in groundwater. From these simulations, estimated environmental concentrations (EECs) are generated for high exposure agricultural scenarios. The EECs for pyriproxyfen in surface water ranged from a peak of 0.677 ppb to a 60-day average of 0.142 ppb, to a 1-year average of 0.103 ppb. These estimates are based on 2 applications at a rate of 0.11 lb. active ingredient per acre. For ground water, estimated 60-day average concentrations of pyriproxyfen were 0.006 ppb. These predictions suggest that if released to natural waters or soil, pyriproxyfen is likely to absorb onto soil particles, suspended solids, and sediment and be unavailable for leaching into groundwater or transport into surface waters.[31)]

Environmental Degradation

1. Abiotic transformations

1.1 Hydrolysis

Pyriproxyfen does not react significantly with water and is

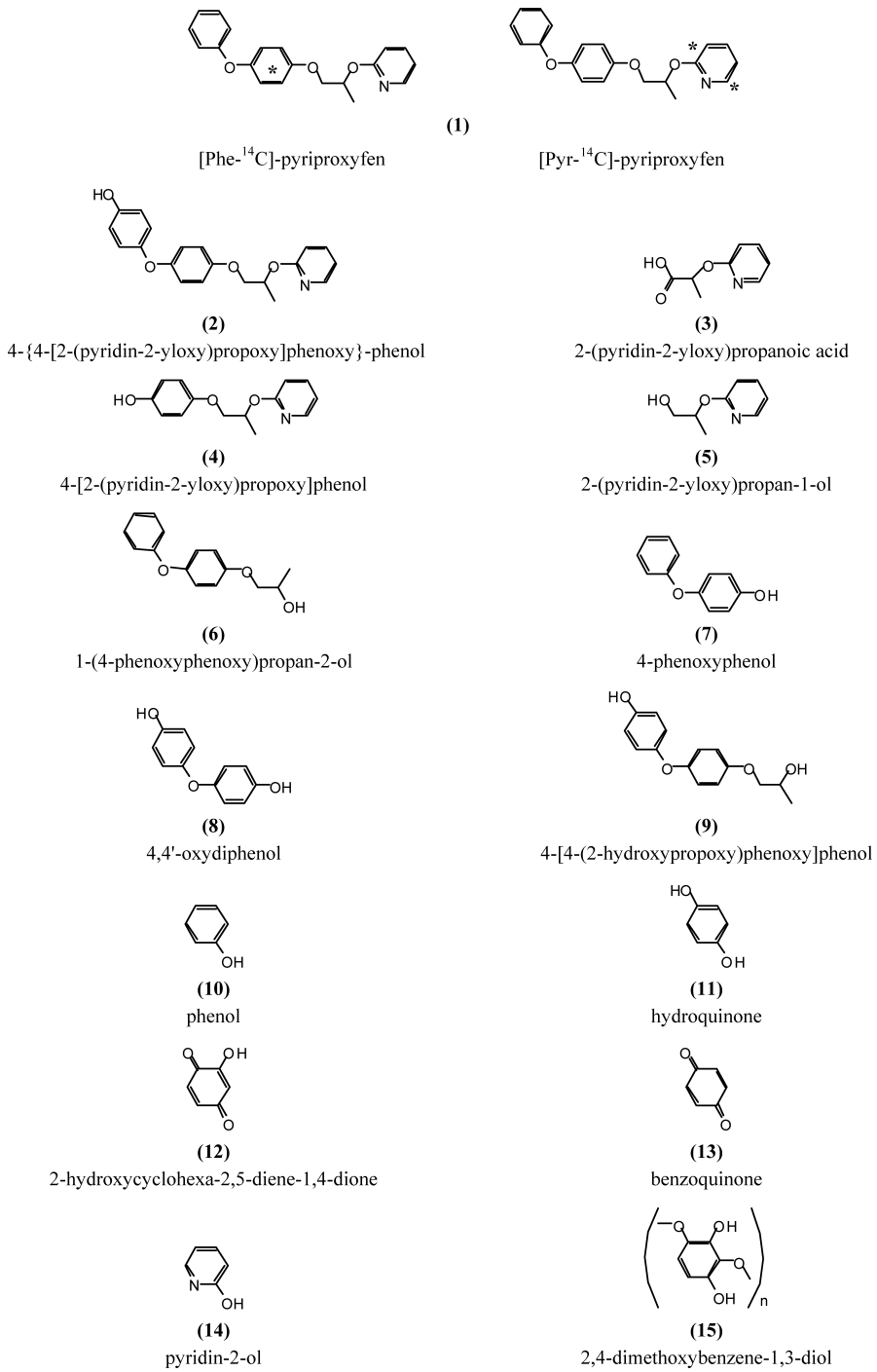

Fig. 2. Structure of pyriproxyfen (**1**) and its metabolic and degradation products.

neither acid nor alkaline labile, *i.e.*, it is not susceptible to either acid or base catalysis. Consequently, hydrolysis is not an important transformation route of pyriproxyfen in the environment. In a representative study. Katagi *et al*.[32] found that radiolabeled pyriproxyfen is stable when dissolved in sterile acetate buffer (pH 5.0) or borate buffer (pH 7.0 and 9.0) at 25°C for 30 days in darkness. This study yielded hydrolysis half-lives ranging from 147.8–604.6 days at pH 5.0, 241.2–1292.5 days at pH 7, and 161.4–511.4 days at pH 9.0. In 30 days, two unidentified minor transformation products were formed at less than 2.5% of the applied parent compound.

1.2 Aqueous photolysis

Pyriproxyfen readily undergoes photolysis in aqueous media, which yields various hydroxylated and oxidized products that

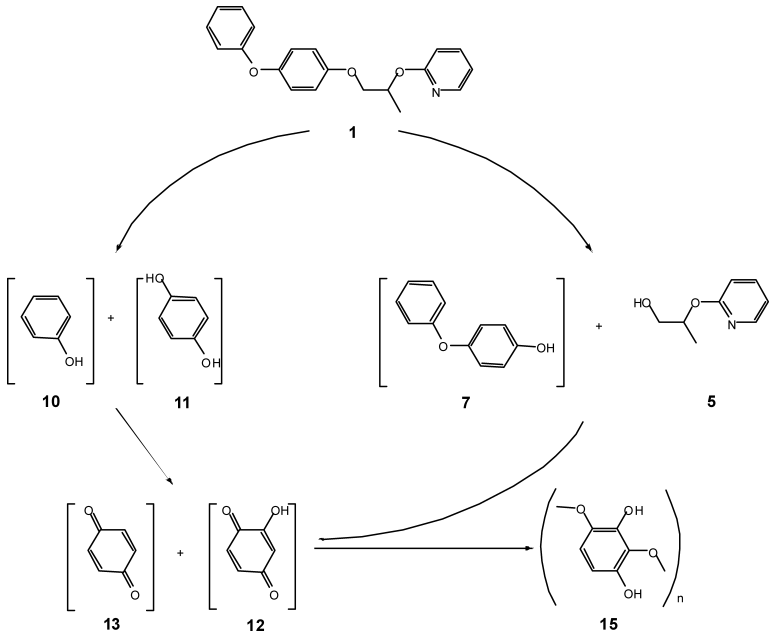

Fig. 3. Photodegradation pathway for pyriproxyfen in aqueous buffer at pH 7 and 25°C.

subsequently form less toxic phenolic polymers [compounds **10**–**14**]. When radiolabeled pyriproxyfen (see Fig. 1 for label locations) was subjected to artificial sunlight in aqueous buffer solution at pH 7 and 25°C for 30 days, photodegradation was rapid, with calculated half-lives of 6.4 days for the [Phe-^{14}C]-label and 3.7 days for the [Pyr-^{14}C]-label. Only one major degradate, (5), has been identified in artificial sunlight experiments, although several other uncharacterized polar compounds also formed that may be polyphenolic in nature. Fathulla[33] noted that after day 14, this polar material comprised 60% of the applied amount of the [Phe-^{14}C]-labeled substrate and 22% of the [Pyr-^{14}C]-labeled substrate. In the latter case, the pyridinyl alcohol (**5**) accounted for 70% of the applied amount. Based on these findings, a photodegradation pathway for pyriproxyfen in buffered aqueous solution was proposed (Fig. 3). When exposed to natural light for 8 hr/day for five weeks from November to December at 40°N latitude, solutions containing 0.2 mg/l of radiolabeled pyriproxyfen in sterilized distilled and river water degraded with half-lives of 17.5 and 21 days, respectively, and was stable in the dark controls. Photodegradation involved cleavage of the three ether linkages, and the major products were CO_2, which accounted for 11–29% of the applied radioactivity, and a pyridinyl alcohol formed by loss of the phenoxyphenyl group (**5**), (16–30%). The degradates **4**, **6** and **7** were minor identified products. In the natural sunlight experiment, the formation of polar polyphenolic compounds was neither observed nor proposed.[34]

1.3 Soil photolysis

The photodegradation of radiolabeled ^{14}C-pyriproxyfen was investigated on sandy and silty loam soils in natural sunlight for 8 weeks and on a sandy loam soil artificially irradiated for 12 hr per day at 25°C for 18 and 20 days.[35–36] In natural sunlight and sandy loam soil, [Phe-^{14}C]-labeled pyriproxyfen decayed with a half-life of 12.5 weeks and [Pyr-^{14}C] labeled pyriproxyfen degraded with a half-life of 10.3 weeks. In silty loam soil, the half-lives of [Phe-^{14}C] and [Pyr-^{14}C] labeled pyriproxyfen were 18 and 21 weeks, respectively. In the artificial sunlight system on sandy loam soil, the half-life of [Phe-^{14}C]pyriproxyfen was 8.5 days in irradiated samples and 26.6 days in dark control samples. For [Pyr-^{14}C] pyriproxyfen, half-lives were 6.8 days irradiated and 12.4 days dark. Three major degradation byproducts were identified in the soil photolysis studies, **2**, **3**, and **4**. The proposed degradation pathway in soil is initiated by the hydroxylation of pyriproxyfen to form **2**, which subsequently degrades to **4**. Oxidation of pyriproxyfen, **2** or **4** to form **5** is suggested, although **5** was not detected. Further oxidation of **5** would produce **3**, which was isolated and identified. All of these degradates are reactive, and readily undergo oxidative cleavage to form various phenolic products, all of which eventually degrade to hydroquinone (Fig. 4). Hydroquinone was not isolated in these studies, suggesting that it is transient and quickly undergoes further reaction to form various terminal residues.

2. Degradation in soil

2.1 Field dissipation.

In 1993 and 1994, numerous field dissipation studies were conducted to evaluate the mobility and persistence of pyriproxyfen when applied to bare ground. A representative study was performed in California on a loamy sand soil (74% sand, 22% silt, 4% clay, 0.3% organic matter in the top 30 cm surface layer) using a single broadcast application of

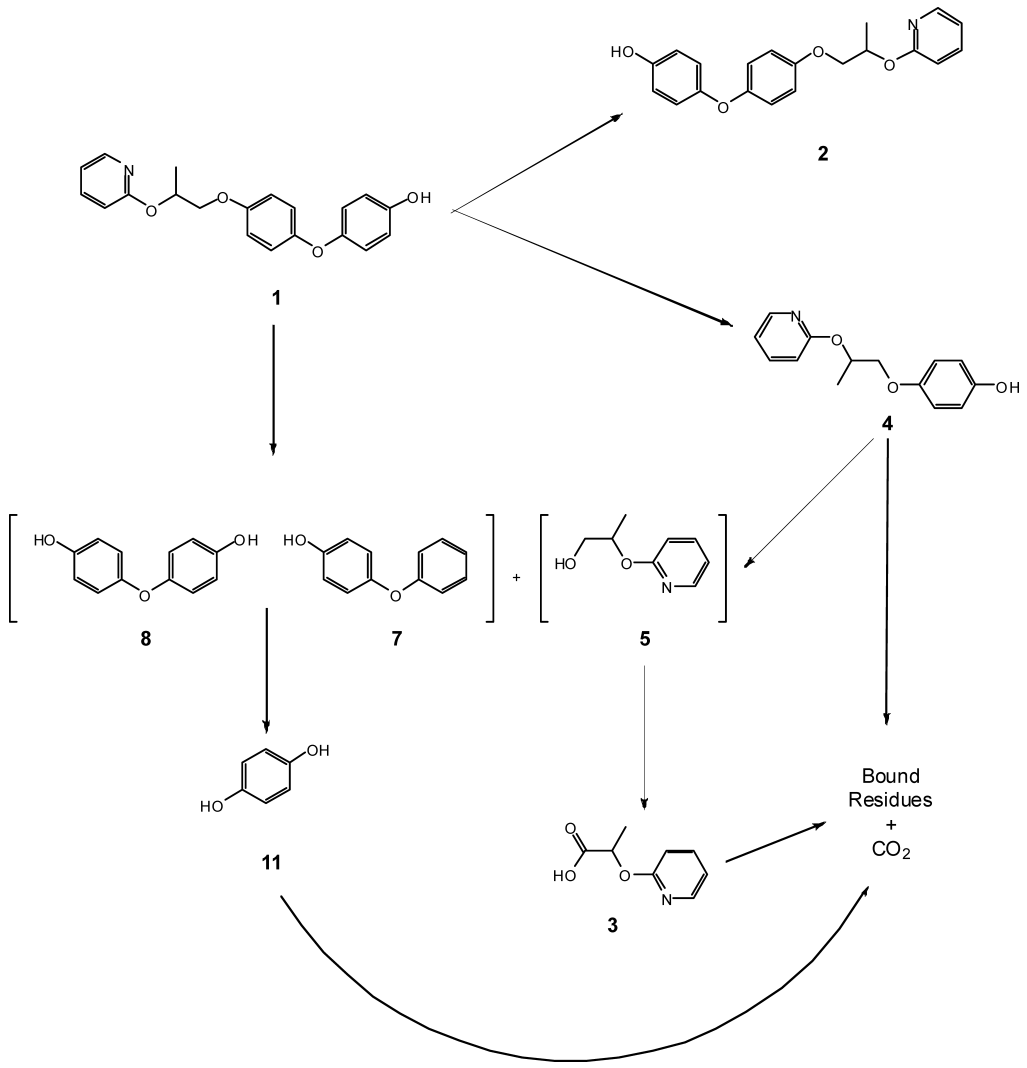

Fig. 4. Photodegradation pathway of pyriproxyfen on soil in natural light at 25°C.

pyriproxyfen formulated as a 10% emulsifiable concentrate.[37] The application rate was 0.64 lbs. pyriproxyfen per acre. Soil core samples were taken to 36 inches deep at specified intervals immediately before and after application. Core composites were analyzed for pyriproxyfen and two metabolites, **2** and **3**. Both metabolites were found to be stable in soil for up to a year under the storage conditions of the field samples. Average pyriproxyfen concentrations found in the 0–6 in inch soil layer were 0.34 ppm on day zero and 0.012 ppm on day 181. In the 6–12 inch layer, average residue concentrations were found to be up to 0.027 ppm through day 31, and below the 0.010 ppm level of quantitation thereafter. No pyriproxyfen residues were found above the level of quantitation at any level below 12 inches. The half-life of pyriproxyfen in the 0–6 inch soil layer was 36 days. Average concentrations of **2** found in the 0–2 inch soil layer reached a maximum of 0.026 ppm on day 23. No residues of **2** were found above the level of quantitation at any level below 2 inches or greater than 120 days. The half-life of **2** in the 0–2 inch soil layer was 83 days. Average concentrations of **3** found in the 0–2 inch soil layer reached a maximum of 0.023 ppm on day 7. No residues of **3** were found above the level of quantitation at any level below 2 inches or greater than 60 days. The half-life of **3** in the 0–2 inch soil layer was 33 days.

Similar studies conducted in Georgia, Mississippi, and at a second site in California produced comparable results, yielding pyriproxyfen half-lives of 86.4 days, 3.5 days, and 15.6 days, respectively.[38–40] In each study, pyriproxyfen was detected primarily in the top 0–12 inches of soil, and residues did not appreciably migrate down the soil profile. All the core samples analyzed for pyriproxyfen were also analyzed for the metabolites **2** and **3**. Metabolite **3** was not detected ($<$0.01 mg/kg) in any sample, and metabolite **2** was detected only in the top layers and very low concentrations. Results of these studies indicate that pyriproxyfen is neither persistent nor mobile in representative agricultural soils.

2.2 Soil metabolism.

Samples of California sandy loam soil (62.6% sand, 29% silt, 8.4% clay, 0.87% organic content, pH 7.6) were fortified with ^{14}C-pyriproxyfen at a concentration of 0.60 mg test material/kg soil and incubated for 189 days in glass chambers maintained in a dark, temperature-controlled room at 25±2°C.[41] Humid air was passed through the system continuously to create a humid aerobic environment. Pyriproxyfen was found to degrade *via* biological catalysis, serving as a carbon source for soil microorganisms. Three degradation products, **2**, **3**, and **4**, were identified. Hydroxylation of the parent to the metabolite **2** is followed by degradation to the phenol **4**. Oxidation to the intermediate pyridinyl alcohol **5** then forms the acid **3**, which decomposes to CO_2 or binds to soil. Mineralization was slow with 13.9% of the ^{14}C from the [Phe-^{14}C]-pyriproxyfen label and 31.1% from the [Pyr-^{14}C]-pyriproxyfen label evolved as CO_2 after 180 and 189 days, respectively. The disappearance of pyriproxyfen was rapid, with a half-life of 6.4 days for [Phe-^{14}C]-pyriproxyfen and 9.0 days for [Pyr-^{14}C]-pyriproxyfen after 14 days. A proposed degradation pathway of pyriproxyfen in California sandy loam soil is shown in Fig. 5.

Two analogous studies were conducted using a sandy clay loam soil (73% sand, 8% silt, 19% clay, 2.4% organic content, pH 5.7) and sandy loam soil (54% sand, 36% silt, 10% clay, 0.8% organic content, pH 6.5) incubated at 0.5 mg/kg under aerobic conditions at 25°C in the dark for 30 and 91 days, respectively.[42–43] In the first study, pyriproxyfen disappeared rapidly initially but later more slowly. Its estimated half-life after the first 7 days was 28 days. The main identified residue was **2**. Other minor products were **3**, **4** and **6**. A significant fraction of the ^{14}C quickly became bound in the soil organic matter. In the latter experiment, the estimated half-lives of pyriproxyfen were 8.2 days during days 1–14 and 20 days during days 14–91. The metabolite **3** was the principal degradation product, exceeding pyriproxyfen from day 28. Metabolite **2** was a minor product. Bound residues accounted for approximately 50% of the applied ^{14}C by day 28.

3. Water and sediment

Fathulla (1993)[44] conducted aerobic and anaerobic aquatic metabolism studies using [Phe-^{14}C]-pyriproxyfen and [Pyr-^{14}C]-pyriproxyfen in lake sediment and water. In the aerobic experiment, fifty-two samples were prepared by adding 20 ml of lake water to 2 g (dry-weight equivalent) of 2-mm sieved lake sediment. Twenty-six lake sediment/water samples were fortified with [Phe-^{14}C]-pyriproxyfen, and 26 were fortified with [Pyr-^{14}C]-pyriproxyfen. For [Phe-^{14}C]-pyriproxyfen, the labeled parent compound was found to be the major component in the combined sediment extracts and water layers,

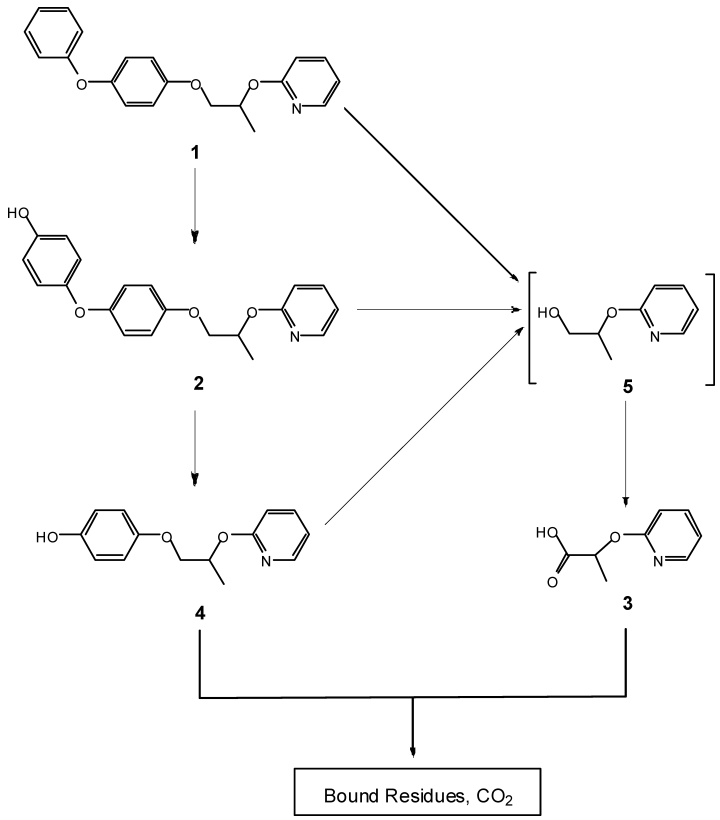

Fig. 5. Fate of pyriproxyfen in sandy loam soil at 25°C under aerobic conditions. Hydroxylation of the parent compound (**2**) is followed by degradation to 4-(2-(pyridin-2-yloxy)propoxy)phenol (**4**). Oxidation to the intermediate 2-(pyridin-2-yloxy)propan-1-ol (**5**) forms 2-(pyridin-2-yloxy)propanoic acid, which decomposes to CO_2 or binds to soil. Adapted from Fathulla (Ref. 38).

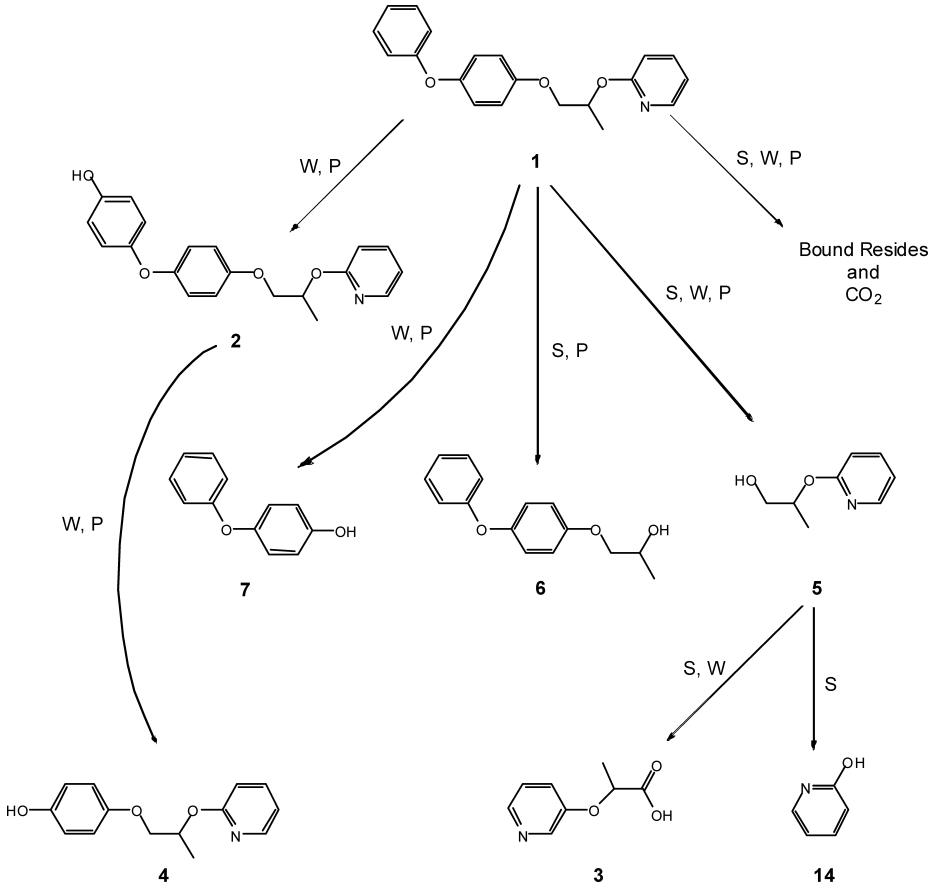

Fig. 6. Proposed metabolic and degradation pathways of pyriproxyfen in soil (S), water (W), and via photodegradative processes (P).

ranging from 91.3% (day 0) to 27.3% (day 31). The half-life for [Phe-^{14}C]-pyriproxyfen was 16.2 days. For [Pyr-^{14}C]-pyriproxyfen, the labeled parent compound was found to be the major component in the combined sediment extracts and water layers, ranging from 91.8% (day 1) to 37.4% (day 21). The half-life for [Pyr-^{14}C]-pyriproxyfen was 20.8 days. The formation of bound residues and the concomitant formation of $^{14}CO_2$ suggest that the degradation pathway is governed by biological catalysis. Metabolism in aerobic aquatic media proceeds through oxidative cleavage of the ester linkages. The phenolic scission fragments react to form polar polymers, oligomers, and additional products. Pyriproxyfen degraded quickly under aerobic aquatic conditions (lake sediment and water) to two major metabolites, **2** and **3**, as well as several minor intermediate metabolites, bound residues, and CO_2.

The anaerobic aquatic metabolism study was performed with 80 samples prepared by adding 20 ml of lake water to 2 g (dry-weight equivalent) of 2-mm sieved lake sediment.[45] As in the aerobic study, half the sediment/water samples were dosed with [Phe-^{14}C]-pyriproxyfen and half with [Pyr-^{14}C]-pyriproxyfen, with quantification performed using LSC. Pyriproxyfen was the main residue in both the [Phe-^{14}C]- and [Pyr-^{14}C]- labeled systems throughout the studies. In the [Phe-^{14}C]-pyriproxyfen labeled experiment, the degradation process appeared to be biphasic, with a lag period (180 days) followed by a more rapid substrate decay. Presumably, these results were due to enzyme induction or to the slow adaptation of the anaerobic organisms to the conditions and substrate during the initial phase. The estimated half-life for the early phase was 750 days, while the latter phase 105 days. In the water phase, pyriproxyfen decreased from 28% to undetectable over the course of the one-year study. The amount of pyriproxyfen in the sediment peaked at 92% 60 days after dosing. Identified degradation products were at very low levels, except metabolite **3**, which accounted for 16% of the total dose after one year. Volatile ^{14}C (including CO_2) was negligible. Metabolic and degradation pathways of pyriproxyfen in soil and water have been proposed and are illustrated in Fig. 6.[46]

4. Kinetic profiles of biodegradation processes

Based on data developed from aerobic soil metabolism, aerobic aquatic metabolism, and anaerobic aquatic metabolism studies, kinetic profiles and degradation pathways were proposed for the biotransformation of pyriproxyfen in soil and water (Fig. 7).[47] First-order rate laws were assumed for each reaction sequence, which yielded the sets of kinetic expressions for the aerobic soil metabolism and aerobic aquatic

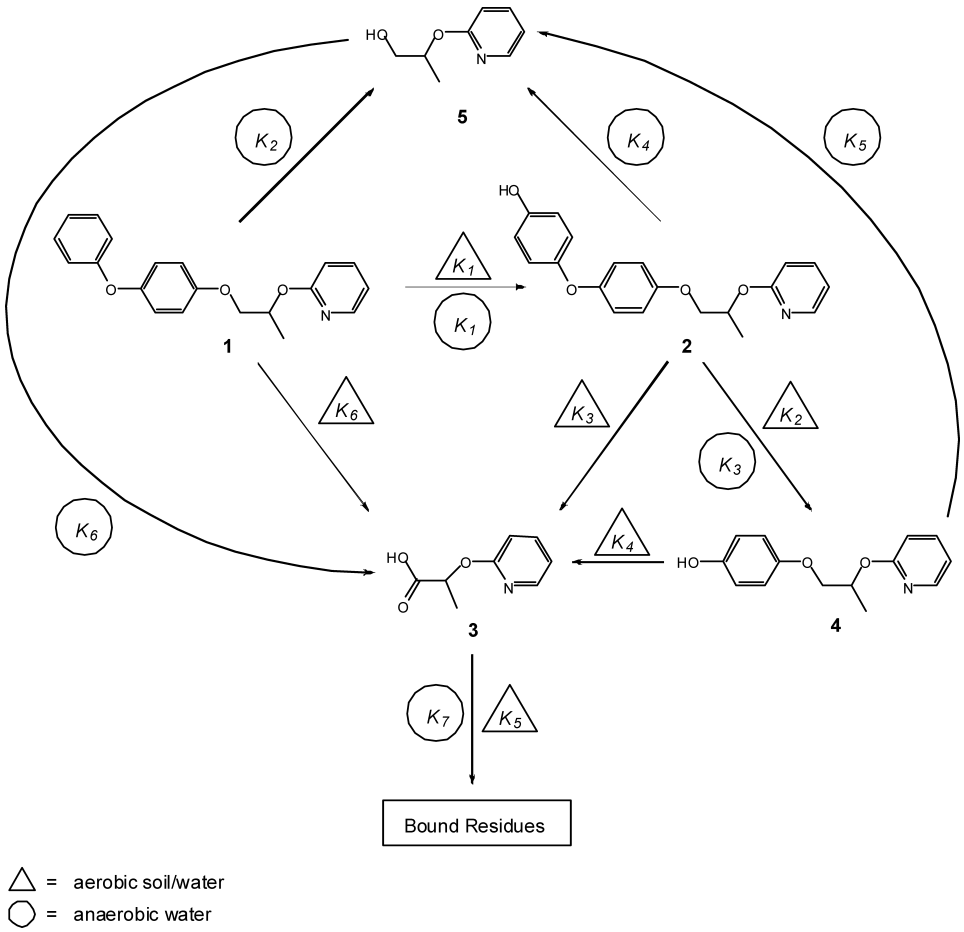

Fig. 7. Proposed pyriproxyfen biotransformation pathway and kinetics in aerobic soil and water and anaerobic water.

studies.[39,43,44)]

The degradation rate constant and half-lives of pyriproxyfen and degradation products **2** and **3** were calculated for each study in accordance with the models. Due to the low concentrations of degradation products [**4**–**6**], estimated half-lives could not be determined. For products produced in sufficient quantities, the estimated half-lives generated from the proposed kinetic models were comparable (Table 3). For example, the measured half-lives of the parent compound were 9, 20.8, and 288.9 days (the latter value based on a presumed biphasic degradation process) in aerobic soil, aerobic water, and anaerobic water, respectively. In contrast, the correspon-

Table 3. Calculated degradation rate constants and half-lives for pyriproxyfen and major degradates in aerobic soil/water and anaerobic water matrices[a)]

Product	Study system	Rate equation	Rate (day^{-1})	Half-life (day)
Pyriproxyfen	Aerobic soil	$-(k_1+k_6)[\mathbf{1}]$	0.056	12.4
Pyriproxyfen	Aerobic aquatic	$-(k_1+k_6)[\mathbf{1}]$	0.03	23.1
Pyriproxyfen	Anaerobic aquatic	$-k_1[\mathbf{1}]-k_2[\mathbf{1}]$	0.002	346.5
Metabolite **2**	Aerobic soil	$-(k_2+k_3)[\mathbf{2}]+k_1[\mathbf{1}]$	1.000	0.69
Metabolite **2**	Aerobic aquatic	$-(k_2+k_3)[\mathbf{2}]+k_1[\mathbf{1}]$	1.000	0.69
Metabolite **2**	Anaerobic aquatic	$k_1[\mathbf{1}]-k_4[\mathbf{2}]-k_3[\mathbf{2}]$	0.145	4.8
Metabolite **3**	Aerobic soil	$-k_5[\mathbf{3}]+k_6[\mathbf{1}]+k_3[\mathbf{2}]+k_4[\mathbf{4}]$	0.085	8.17
Metabolite **3**	Aerobic aquatic	$-k_5[\mathbf{3}]+k_6[\mathbf{1}]+k_3[\mathbf{2}]+k_4[\mathbf{4}]$	0.044	15.8
Metabolite **3**	Anaerobic aquatic	$k_6[\mathbf{3}]+k_7[\mathbf{5}]$	0.017	41.25

[a)] Data from Ref 43.

ding predicted half-lives were 12.4, 23.1, and 346.5 days, respectively. Thus, the proposed degradation and kinetic profiles for each study provided a reasonable overall approximation for the biodegradation of pyriproxyfen in the evaluated test systems.

Summary and Conclusions

Pyriproxyfen is a pyridine-based juvenile hormone agonist that competes for juvenile hormone binding site receptors in insects, mimicking the action of juvenile hormone and thus maintaining an immature state. Insects treated with pyriproxyfen are unable to molt successfully to the adult stage, and cannot reproduce as normal. It has insecticidal activity against public health insect pests such as houseflies, mosquitoes, and cockroaches. In agriculture and horticulture, pyriproxyfen has registered uses for the control of scale, whitefly, bollworm, aphids and cutworms. It is particularly efficacious against mosquitoes, exhibiting up to 95% inhibition of emergence for mosquito, and having no effect on predator populations. It has low mammalian toxicity and is recommended by the WHO for treatment of potable water against mosquito.

The use of pyriproxyfen as an agricultural and residential insecticide will result in its direct release to the environment. If released into the air, pyriproxyfen will not readily disperse into the atmosphere due to its low vapor pressure and Henry's Law constant. Particulate-phase pyriproxyfen is dissipated *via* dry deposition, while vapor-phase pyriproxyfen will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. Pyriproxyfen is practically insoluble in water and has high K_{OC} values, so it has a propensity to adsorb onto soil surfaces, particularly those having high clay content and organic matter. If released in water, pyriproxyfen adsorbs onto suspended solids and organic matter and retains biological activity for up to two months. Its persistence in water in the absence of organic matter declines with increasing temperature and sunlight exposure. Pyriproxyfen is hydrologically stable in acetate buffer at pH 5.0 and borate buffers at pHs 7.0 and 9.0 due to the absence of hydrolyzable functional groups. It is highly susceptible to photodegradation in water, with photolysis half-lives less than 10 days in aqueous buffer and up to 20 days in river water. In soils, photodegradation proceeds much slower, with half-lives in the range of 10–20 weeks. If released to soil, both the parent compound and its major degradates (4-{4-[2-(pyridin-2-yloxy)propoxy]phenoxy}phenol and 2-(pyridin-2-yloxy)propanoic acid) are readily decomposed, with dissipation half-lives varying from 3.5–86 days. Pyriproxyfen degrades rapidly in aerobic water and soils *via* biological catalysis, in which it serves as a carbon source for soil microorganisms. Metabolism in aerobic media proceeds relatively quickly ($<$100 days) through oxidative cleavage of the ester linkages, while anaerobic metabolism is much slower, progressing via a biphasic mechanism with half-lives up to 700 days.

The low solubility, high partition coefficients, and hydrophobicity of pyriproxyfen are consistent with chemicals that are known to be environmentally persistent. However, its susceptibility to aquatic photodegradation, metabolic breakdown in aerobic soils and waters, and its apparent short depuration half lives in aquatic fauna lead to rapid dissipation in biotic and environmental matrices. In anaerobic conditions, such as brackish waters or sediments, pyriproxyfen is much more stable, immutable, and toxic to aquatic invertebrates. Given its potential to persist, prudence should be used when applying pyriproxyfen to or near water bodies, and precautions must be taken to avoid or mitigate drift and runoff to surface waters.

Acknowledgements

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