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REVIEW ARTICLE

Fate and ecotoxicological effects of pyriproxyfen in aquatic ecosystems

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Abstract

Pyriproxyfen is an insect growth regulator acting as larvicide against a large spectrum of public health insect pests, especially dipterans. It is also widely used in agriculture and horticulture for the control of many insect species. Disrupting the endocrine system by mimicking the activity of the juvenile hormone, pyriproxyfen interferes with metamorphosis in insects and prevents them from reaching maturity and reproducing. Because the aquatic ecosystems can be directly or indirectly contaminated by pyriproxyfen, the goal of this study was to establish the aquatic ecotoxicological profile of pyriproxyfen and to identify the gaps that need to be filled. Pyriproxyfen is photodegraded quickly in water. In the absence of organic matter, its persistence in aerobic water media is also limited especially with high temperature and sunlight. Analysis of the laboratory and in situ results for more than 60 aquatic algae, plants, invertebrates, and vertebrates shows that the toxicity of pyriproxyfen is highly variable including within a same taxonomical group. Abiotic and biotic factors can highly influence the toxicity of the molecule. Pyriproxyfen disrupts the development of numerous species and adversely impacts various physiological events. It can also disturb the behavior of the organisms such as their predatory and swimming performances. Although some experimental studies focus on the environmental fate of pyriproxyfen metabolites, those dealing with their aquatic ecotoxicity assessment are scarce. In the same way, the limited number of studies dealing with the search of pyriproxyfen residues in lake, river, and other natural aquatic media does not include the identification of the metabolites.

Keywords Pyriproxyfen, insect growth regulator, environmental fate · Aquatic toxicity · Residue analysis

Introduction

Pyriproxyfen is the common name for 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether (CAS RN: 95737-68-1, Fig. 1), an aromatic, non-terpenoidal insecticide belonging to the class of juvenile hormone mimics, aiming at disrupting the hormonal system of the target insects (Devillers 2009). Larvae treated with an effective dose (or concentration) of pyriproxyfen are unable to molt successfully to reach the imago stage (Devillers et al. 2014). In agriculture and horticulture, this juvenoid has registered uses for the control of many insect species including the California red scale (*Aonidiella aurantii*) (Eliahu et al. 2007), the silverleaf whitefly (*Bemisia tabaci*), biotype B (Qureshi et al. 2009), the mulberry scale (*Pseudaulacaspis pentagona*) (Isayama and Tsuda 2008), and the red imported fire ant (*Solenopsis invicta*) (Hwang 2009). Pyriproxyfen is used for the sanitation of indoor areas to fight household insects such as the German cockroach (*Blattella germanica*) (Saltzmann et al. 2006) and the common housefly (*Musca domestica*) (Biale et al. 2017). It is also marketed as a spot-on topical treatment for prophylactic flea control on cats and dogs, generally in combination with other biocides (Ross et al. 1997; Stanneck et al. 2002). Pyriproxyfen is particularly efficacious against all the species of mosquitoes, inhibiting the emergence of their larvae at very low concentrations (Estrada and Mulla 1986; Kawada et al. 1988; Yapabandara and Curtis 2002). In some countries, the regulation allows a direct application of the insecticide in aquatic media. Thus, pyriproxyfen has been considered by WHO (2006a), under its Pesticides Evaluation Scheme, at a recommended larvicidal dose of 5–10 g a.i. (active ingredient)/ha (as granules) in non-potable water and at a concentration not exceeding 10 μg a.i./L for controlling disease-carrying mosquitoes in drinking water

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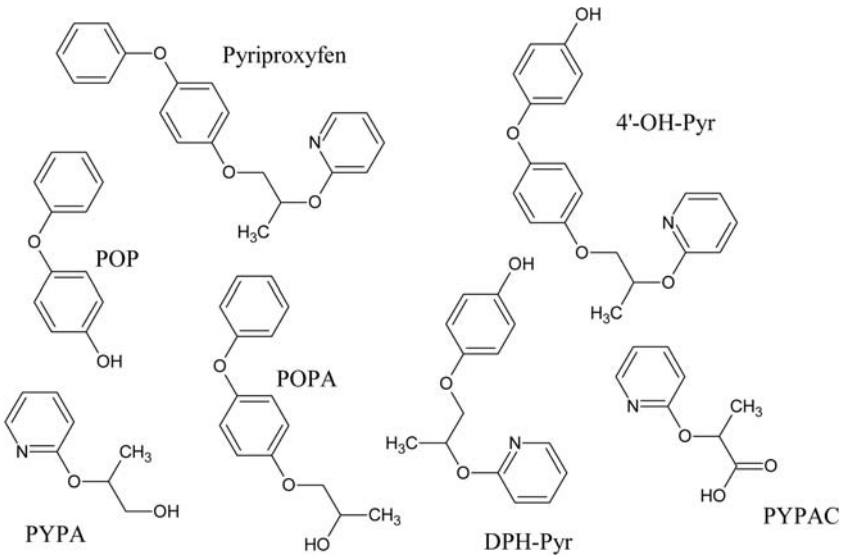

Fig. 1 Pyriproxyfen and its degradation products in aquatic ecosystems

containers. In the *Aedes* species, the skip oviposition behavior of the gravid females is also exploited to efficiently disperse pyriproxyfen to larval habitats. Because even very low concentrations of pyriproxyfen (Gómez et al. 2011) are enough to profoundly disrupt the development of mosquito larvae of *Aedes aegypti* and *Ae. albopictus*, female-dispersed contamination doses can successfully prevent adult emergence in visited larval habitats. The process, which is known under the term of autodissemination method (Devine et al. 2009), is also used with *Anopheles* mosquitoes (Kiware et al. 2015). It is worthy to note that the method is currently the subject of intensive work and debate worldwide (Faraji and Unlu 2016; Maoz et al. 2017).

The different uses of pyriproxyfen result in its direct or indirect release into the aquatic ecosystems. While this molecule has been assessed for its ecotoxicity against specific non-target organisms occupying different trophic levels in the environment, to our knowledge, no attempt has been made to critically analyze the whole available literature on the subject. Even more, very few studies have been undertaken to evaluate the fate of pyriproxyfen in relation with its usages and to compare the concentrations in pyriproxyfen leading to lethal and sublethal effects on these organisms to the actual concentrations found in the aquatic ecosystems. In this context, the goal of our study was to fill these different gaps. This was carried out by collecting and critically analyzing 30 years of literature on pyriproxyfen.

Aquatic fate of pyriproxyfen

Studies with radiolabeled material

At 25 °C and pH = 6, the solubility in water of pyriproxyfen (99.4%) is only equal to 0.367 ± 0.004 mg/L, while the value of its *1*-octanol/water partition coefficient (log Kow) is 5.37 at 25 °C and pH = 5.6. With a vapor pressure < 1.33×10^{-5} Pa at 22.8 °C, technical pyriproxyfen (100%) shows a low affinity for the air compartment (WHO 2006b). Pyriproxyfen has no discernible acidic or basic characteristics and is stable to hydrolysis in aqueous buffer at pH 5, 7, and 9 at 25 °C in darkness, but it is prone to photolysis in aqueous media (FAO 1999; Sullivan and Goh 2008).

[Pyr-^{14}C]- and [Phe-^{14}C]-radiolabeled pyriproxyfen (RP) were exposed to artificial sunlight in aqueous buffer solution at pH = 7 and 25 °C for 30 days. A rapid photodegradation was observed with calculated half-lives of 6.4 and 3.7 days for the phenyl- and pyridine-radiolabeled forms, respectively. (*RS*)-2-(2-Pyridyloxy)propanol (PYPA) (Fig. 1) was identified as the major photoproduct, although several other uncharacterized polar molecules were also detected (Sullivan and Goh 2008).

[Pyr-^{14}C]- and [Phe-^{14}C]-RP dissolved at nominal concentrations of 0.2 mg/L with Tween 85 at 7.5 mg/L in sterilized distilled water and in sterilized Muko river water (Japan) were exposed to natural light for 8 h/day for 5 weeks from November to December at 40° N latitude. Half-lives of 17.5 and 21 days were found for pyriproxyfen in distilled and river water, respectively. The solutions were stable in the dark controls. A theoretical half-life of 16 days was estimated for 40° N latitude from the quantum yield for the photolysis of pyriproxyfen. Photodegradation involved cleavage of the three ether linkages, and the major products were CO_2 (11–29% of the applied radioactivity) and PYPA (16–30%). 4-Hydroxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether (DPH-Pyr), (*RS*)-2-hydroxypropyl 4-phenoxyphenyl ether (POPA), and 4-phenoxyphenol (POP) (Fig. 1) were minor identified products (FAO 1999; Sullivan and Goh 2008).

The effect of illumination on pyriproxyfen degradation in a water-sediment system (WSS) was studied by Kodaka

et al. (2011). The WSS consisted in coarse sediment (Derbyshire, UK) with relatively low organic carbon content to represent a worst-case scenario minimizing pyriproxyfen adsorption to sediment. Water and sediment were passed through 0.2 and 2 mm sieves, respectively. The sediment included sand (66%), silt (12%), and clay (22%). The dissolved organic carbon content of the associated water was 7.8 mg C/L, the suspended solids were included in water at 10 mg/L, and the pH equaled 6.9. It was verified that microbial activity in the overlying water was not affected by illumination. A first study was conducted in darkness for 100 days using [Phe-^{14}C]-RP and [Pyr-^{14}C]-RP (7 μg ^{14}C-RP in 88 or 92 μL acetonitrile). The illuminated study with a light (> 290 nm) simulating natural sunlight was then conducted with [Pyr-^{14}C]-RP (1.3 μg/unit in 14 μL acetonitrile) during 30 days. A dark control was used. In both studies, the ^{14}C recovery was very good. In darkness, aqueous ^{14}C decreased to 33.5% ([Phe-^{14}C]-RP) and to 38.6% ([Pyr-^{14}C]-RP) after 2 days by partitioning to the bottom sediment. The amount of bound ^{14}C increased with incubation to 51.4% ([Ph-^{14}C]-RP) and 30.9% ([Pyr-^{14}C]-RP) at the end of the experiment. Based on single first-order kinetics, the DT_{50} and DT_{90} values of pyriproxyfen in the total system were estimated to be 8.0–10.5 and 27–35 days, respectively (Kodaka et al. 2011). 4-(4-Hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether (4′-OH-Pyr) (Fig. 1) was a common metabolite to both labels. It was mainly detected in the sediments with 4.8% and 2.3% of the applied radioactivity for [Phe-^{14}C]-RP after 50 and 100 days, respectively. 9.2% and 3.3%, also in the sediment phase, were found for [Pyr-^{14}C]-RP after 50 and 100 days, respectively. The other common metabolite was DPH-Pyr which reached 11.8% in the water phase of the [Phe-^{14}C]-RP WSS after 2 days but was not detected or stayed at no more than 4.4% the other days. At best, low percentages were recorded in the [Pyr-^{14}C]-RP WSS. (*RS*)-2-(2-Pyridyloxy)propionic acid (PYPAC) (Fig. 1) was detected as a major metabolite specific to the [Pyr-^{14}C]-RP WSS with 31.2% of the applied ^{14}C after 100 days, most of which being present in the water phase (23.6%). PYPAC led to the formation of PYPA and POP (Kodaka et al. 2011). In the illuminated experiment, the partition of ^{14}C to sediment was quicker under illumination than in the dark but the final distribution between both phases was similar. PYPA, PYPAC, 4′-OH-Pyr, and DPH-Pyr were also the main metabolites found. PYPAC was detected at 25.3% of the applied radioactivity in the water phase and 13.4% in the sediment phase after 14 days in the WSS under light. After 30 days, 9.5% and 5.4% were found in the water and sediment phases, respectively. PYPA was found at < 3% in the water phase before 7 days and at < 0.5% in the sediment phase of the [Pyr-^{14}C]-RP. In the dark control, PYPAC was detected at 4.4% of the applied radioactivity in the water phase and 0.6% in the sediment phase after 30 days. On contrary, 4′-OH-Pyr was detected at 0.2% and 11% after 30 days in the water and sediment phases, respectively (Kodaka et al. 2011).

Aerobic and anaerobic aquatic metabolism studies were conducted with [Phe-^{14}C]-RP and [Pyr-^{14}C]-RP in lake sediment and water. Samples were prepared by adding 20 mL of lake water to 2 g of 2-mm-sieved sediment. Twenty-six lake sediment/water samples were fortified with [Phe-^{14}C]-RP and 26 with [Pyr-^{14}C]-RP. Experiments were performed at 25 °C under aerobic conditions either for 31 days ([Phe-^{14}C]-RP) or 28 days ([Pyr-^{14}C]-RP). The half-life of [Phe-^{14}C]-RP was 16.2 days. Pyriproxyfen was the main residue in the sediment throughout the experiment with 27% of the applied radioactivity at day 31. In water, at the same date, it was not detected and only 0.3% was found at day 21. A mixture of unidentified polar compounds accounted for 35% of the original ^{14}C at day 31. 4′-OH-Pyr was the main identified product in both phases but it was not detected in the water phase after 21 days. The half-life of [Pyr-^{14}C]-RP was 20.8 days. Levels of the pyriproxyfen and 4′-OH-Pyr were in general agreement with those found from [Phe-^{14}C]-RP. However, from day 12, PYPAC was the main constituent in the water phase. At day 28, 25% and 2.8% of the applied radioactivity were found in water and sediment, respectively. As regards 4′-OH-Pyr, 2.3% and 0.5% were found, respectively (FAO 1999; Sullivan and Goh 2008).

A similar experiment was performed under anaerobic conditions for a duration of 368 days for [Phe-^{14}C]-RP and 363 days for [Pyr-^{14}C]-RP. Sediment and water included anaerobic spores and numerous microorganisms. Lake water alkalinity was equal to 205 mg/L as $CaCO_3$. Pyriproxyfen was the main residue in [Phe-^{14}C]-RP and [Pyr-^{14}C]-RP systems and was found mainly in the sediment rather than in the water. Pyriproxyfen in the [Phe-^{14}C]-RP study was degraded in two phases, slowly for 180 days (half-life = 750 days) and then more quickly for the next 6 months (half-life = 105 days). Adaptation of the anaerobic organisms to the experimental conditions and substrate during the 6 months might explain the phenomenon. Pyriproxyfen in the sediment peaked at 92% 60 days after dosing and was at 24% at day 368. In water, less than 10% was found after day 14. The estimated half-life of [Pyr-^{14}C]-RP was 280 days. PYPAC accounted for 16.4% of the dose after 363 days in water and 0.3% in sediment. The preference for the water phase is explained by its solubility. Other identified products were either missing or at very low levels (FAO 1999; Sullivan and Goh 2008).

In situ studies

Most of the studies were performed in the frame of the evaluation of the efficacy of pyriproxyfen against mosquito larvae.

Stability of pyriproxyfen in water was studied by Schaefer et al. (1988) under various experimental conditions in laboratory and then in situ. The combined effect of temperature (10, 24, and 38 °C) and pH (6.5, 7.4, 7.7, and 10) on the stability of 0.02 mg/L of pyriproxyfen (technical, 98.9%) in darkness was first investigated in laboratory during 9 days. It was shown that the stability of pyriproxyfen decreased with temperature and increased with pH increasing. However, no interaction between temperature and pH was observed.

In a complementary work, three beakers (600 mL) with solution of 0.02 mg/L of pyriproxyfen were placed in laboratory at 10, 24, and 38 °C and in the dark. Three other beakers were placed outside in direct sunlight under clear summer conditions and at the same temperatures. After exposures of 0, 24, 48, and 72 h, all the samples were extracted and analyzed. Schaefer et al. (1988) showed that the loss of pyriproxyfen increased with temperature and with exposure to sunlight. It was greatest when both temperature and sunlight exposure increased simultaneously. At 38 °C and after 72 h of exposure, the measured concentration was 0.0064 mg/L in direct exposure to sunlight and 0.017 mg/L in darkness. The possible loss of pyriproxyfen (0.02 mg/L) from water by the combination of microbial decomposition and adsorption onto organic material was evaluated by comparing stability in tap water with stability in filtered and unfiltered sewage effluent. After 48 h, 0.017 mg/L was found in the tap water, while in the filtered and unfiltered sewage, pyriproxyfen was lost within 24 h (detection limit (DL) = 0.0004 mg/L) (Schaefer et al. 1988).

Flood-irrigated pasture plots of 0.02 ha each and filled with 6 L of water were treated with 0.011 kg/ha of pyriproxyfen (EC, 10 g a.i./100 mL) by a hand sprayer. Daily samples (600 mL) were collected from different areas for residue analysis (DL = 0.0004 mg/L). A series of 37 m^2 ponds was treated by hand sprayer with 2 L of water per plot. Pyriproxyfen was applied at the rate of 0.045, 0.022, 0.011, and 0.0056 kg/ha. Water samples (1 L each) were collected 1 h post treatment and then at 24-h intervals until the chemical was not detected (DL = 0.0002 mg/L). In all cases, no residues were detected after 24 h (Schaefer et al. 1988).

Schaefer and Miura (1990) studied the effects of pyriproxyfen (EC, 10%) on mosquitoes and on non-target organisms as well as its persistence in experimental rice plots. The facility consisted of plots; each measured 37.2 m^2 and was 0.5 m deep. Rice was seeded at a rate of 179 kg/ha. Three plots were treated with pyriproxyfen at 0.05 kg a.i./ha and three others at 0.11 kg a.i./ha. Three plots were used as control. A first treatment was done in July. Air and water temperatures were equal to 27 °C and 25.6 °C, respectively. Air movement was about 134 m/min. Average water depths of control, high-, and low-rate plots were 21, 18.5, and 16 cm, respectively. Rice plants were 10 to 15 cm above the water surface. Identical treatments were repeated in August. Air and water temperatures were 27 °C and 24 °C, respectively. There was no air movement, and depths of water of control, high-, and low-rate plots were 21, 20, and 20 cm, respectively. The entire water surface was covered by the rice canopy, which was 50–60 cm in height (Schaefer and Miura 1990). Two composite samples (1 L each) were collected from each pond for extraction and then residue analysis. Mud samples were also collected from the upper 2.5 cm directly beneath the water. No detectable residues were found after 1 day in plots treated with pyriproxyfen at 0.05 kg a.i./ha and after 2 days at the higher rate of 0.11 kg a.i./ha (DL = 0.00005 mg/L). No pyriproxyfen was detected in mud (108 samples analyzed) (Schaefer and Miura 1990).

A dairy wastewater lagoon of about 0.32 ha and 2 m in depth was sprayed with 0.11 kg a.i./ha of an emulsifiable concentrate formulation of pyriproxyfen (Schaefer et al. 1991). Samples of floating organic debris were collected before treatment and at 1, 4, and 8 days and then at a weekly interval during 8 weeks. Water samples were collected before and 1 h after the treatment as well as concomitantly to the sampling times for the organic matter. The average concentration in pyriproxyfen of triplicate samples of organic matter slowly decreased during the 64-day study. The half-life was estimated to be 7.47 days. The concentration of pyriproxyfen in triplicate water samples collected 1 h after treatment was 0.0013 ± 0.00041 mg/L. The molecule was not detected (< 0.00004 mg/L) in water samples taken from 1 to 64 days after treatment. Pyriproxyfen appeared to be readily adsorbed onto organic matter and then its concentration decreased at an exponential rate (Schaefer et al. 1991). In another study on dairy wastewater lagoons, Mulligan and Schaefer (1990) showed that residual efficacy of pyriproxyfen was enhanced in the presence of organic matter. The adsorbed material was available for ingestion by the *Culex* mosquito larvae which were concentrated near the organic floatage. In the same way, Ohashi (2017) showed that pyriproxyfen was adsorbed by leaves of *Cinnamomum camphora* fallen in catch basins and led to an increase in the efficacy of the insecticide against *Aedes albopictus* larvae. Contact with or ingestion of treated organic matter enhanced the toxicity of the insecticide as well as its activity duration against the larvae. It is obvious that what has been observed with mosquito larvae is transposable to the larvae of non-target arthropods.

The persistence of pyriproxyfen 90 CS (90 g/L microencapsulated formulation) in a brackish medium was studied by Webb et al. (2011). One-liter glass jars were placed in a shaded and sheltered environment and filled with 1 cm of mangrove sediment and topped up to 1 L with sea water. Jars were shaken vigorously and let them settle for 24 h, at which, pyriproxyfen was added at a rate of 11 g a.i./ha (equivalent to ca. 7 μg/L). It was shown that pyriproxyfen declined below the limit of quantification (i.e., 1 μg/L) before 6 days post application (Webb et al. 2011).

Ritchie et al. (2013) showed that the concentrations in pyriproxyfen (Sumilarv 0.5G) declined steadily in treated 2-liter plastic buckets placed inside a semi-field cage protected from direct sunlight exposition. The decline was dose dependent. After 2 weeks, pyriproxyfen was only detected in the highest tested dose (i.e., 100 mg/L). No active ingredient was detected in the smallest dose (i.e., 0.1 mg/L) at any time, and concentrations in water for the 1 and 10 mg/L fell below the limit of detection (0.05 μg/L) after 2 weeks and 1 week after the treatment, respectively. Pyriproxyfen was detected for 60 weeks for the highest treatment dose of 100 mg/L, but levels in the bucket water rapidly declined to < 1 μg/L by 12 weeks (Ritchie et al. 2013).

With the autodissemination method applied to the control of mosquitoes, the bloodfed females transfer some amount of pyriproxyfen to water bodies leading to the disruption of the development of their own larvae. Itoh (1994) and Itoh et al. (1994) measured the amounts of pyriproxyfen (95.2%, technical grade) picked up by *Ae. aegypti* females from a pyriproxyfen-treated film. The amounts of pyriproxyfen detected per female at days 0, 1, 2, 5, and 7 were equal to 1.49, 0.86, 0.49, and 0.05 μg, and inferior to the detection limit (which was not given). On the other hand, the concentrations in pyriproxyfen detected in water samples collected from the treatment sites of an autodissemination device ranged from 0.004 to 0.0113 μg/L. It is worthy to note that the former concentration led to 70% of pupal mortality and the latter to 95% of mortality (Unlu et al. 2017).

Aquatic toxicity

Laboratory experiments

Algae and plants

Pyriproxyfen (97.2%) inhibited growth of *Selenastrum capricornutum* (*Pseudokirchneriella subcapitata* or *Raphidocelis subcapitata*) with a 72-h ErC_{50} (median effective concentration for growth rate after 72 h of exposure) and a corresponding non-observed-effect concentration (NOErC) of 0.15 and 0.05 mg/L, respectively (Afsset 2007). Depending on the bibliographical source, the selected value for the 72-h EbC_{50} (median effective concentration for biomass after 72 h of exposure) of pyriproxyfen was found to be 0.064 mg/L (WHO 2006b) or 0.094 mg/L (Afsset 2007). The 72-h EbC_{50} and 72-h ErC_{50} values of pyriproxyfen 10 EC selected by EFSA (2019) were equal to 0.074 mg/L and 0.11 mg/L, respectively. The 72-h EbC_{50} and 72-h ErC_{50} of the metabolite PYPAC (100%) on *P. subcapitata* in a static test were equal to 26 and 30 mg/L, respectively. The 72-h EbC_{50} and 72-h ErC_{50} of the metabolite 4′-OH-Pyr (98.6%) on *P. subcapitata* in a test using *N*,*N*-dimethylformamide (DMF) were both > 2.5 mg/L, respectively (Afsset 2007).

The effect of pyriproxyfen (98.4%) on growth of *Lemna gibba* G3 was tested under static conditions at 25 ± 1 °C, pH = 5, and under 4300–5800 lx. The 14-day EC_{50} was > 0.18 mg a.i./L and the NOEC was fixed to 0.18 mg/L (EPA 1996).

Protozoans

Acute toxicity of pyriproxyfen (Cyclarte-SG 0.5%) against the ciliate *Colpoda aspera* was tested in a monoxenic culture with *Alcaligenes faecalis* IFO 13111. The EC_{10} and EC_{50} (effective concentration at which the growth rate was decreased to 10% and 50%) were equal to 44.16 ± 9.49 mg/L and 164.28 ± 25.5 mg/L, respectively (Kakiichi et al. 1996). It is worthy to note that these toxicity values have to be considered with high caution because they are above the solubility value of pyriproxyfen. Wang et al. (2005b) showed that a colony of *Paramecium* sp. reared in laboratory was non-sensitive to pyriproxyfen at 0.1 mg/L.

Crustaceans

Daphnids Daphnids are small cladoceran crustaceans that inhabit freshwater ecosystems. Generally, they exhibit a sex determination that is under the dependence of the environmental conditions. Broods of female offspring are produced when the abiotic conditions are favorable and when the resources are abundant. In that case, the population expands through parthenogenic reproduction. When the conditions become unfavorable, such as the shortening of the photoperiod or a decrease in food availability, the populations begin to produce males and undergo a sexual reproduction generating resting eggs termed ephippia. They allow the daphnid populations to survive until the environmental conditions become better. This explains why these organisms are very interesting in ecotoxicology testing because they can be reared easily in laboratory under controlled conditions that allow the production of genetically identical females irrespective of the seasons (Devillers 1988; Devillers and Chambon 1988).

Daphnia carinata neonates (< 12-h old) exposed to pyriproxyfen (technical grade 96.6%) in acute toxicity trials produced a 48-h LC_{50} (lethal concentration 50%) of 0.08 mg/L (0.06–0.11 mg/L). Continuous exposure to 0.01 mg/L of pyriproxyfen during a three-brood period (14-day test) did not impact the survival (100%) but reduced the number of broods to two with a significant reduction of their size. Ephippial eggs were produced while no resting eggs were found in the water and solvent controls (Trayler and Davis 1996). In *Daphnia magna*, the 48-h EC_{50}, NOEC, and LOEC (lowest-observed-effect concentration) were estimated to 2.5 μg/L (2.39–2.71), 0.63 μg/L (0.58–0.67), and

1.25 μg/L (1.17–1.41), respectively (Vieira Santos et al. 2017). It is worthy to note that in a dynamic test with pyriproxyfen (95.3%), a 48-h EC_{50} value of 400 μg/L was found for pyriproxyfen (Afsset 2007). This value has been selected in other regulatory documents such as EC (2012) and EFSA (2019). A static limit test with PYPAC (100%) led to a 48-h EC_{50} value > 95,000 μg/L while a dynamic test with 4′-OH-Pyr in DMF led to a 48-h EC_{50} equal to 1800 μg/L (Afsset 2007).

A 21-day reproduction test on *D. magna* was conducted with nominal concentrations of pyriproxyfen (technical grade 96.6%) (Tatarazako et al. 2003). The medium was changed every 2 days and the neonates were removed. At the end of the experiment, the biological material was placed for 8 days in the standard culture medium to see whether the adverse effects were reversible. Pyriproxyfen at 10–30 ng/L reduced significantly the number of offspring. The sex ratio changed as the concentrations in pyriproxyfen increased, and at 1 μg/L, all the produced neonates were males. In the control, only female neonates were produced. In the wash out experiment, the absence of male neonates was obtained after 7–8 days. When adults of 2–3 weeks old carrying embryos in their brood chamber were exposed to 300 ng/L of pyriproxyfen, only males were obtained after 3 days (Tatarazako et al. 2003). Ginjupalli and Baldwin (2013) showed that the LOEC for fecundity in *D. magna* was 25 ng/L of pyriproxyfen (analytical 99%) while the LOEC for male production was 50 ng/L. Exposure of 3-day-old female *D. magna* to 50 ng/L of pyriproxyfen for 0, 2, 4, 8, or 12 days delayed the reproduction process, produced males but not efficaciously, and reduced initial brood size and the overall fecundity in a time-dependent manner. A recovery was only observed in the 2-day and 4-day exposed groups by day 17, thus about 10 days after the withdrawal of pyriproxyfen. The same experiment with 10-day-old *D. magna* led to different results. Male production occurred in all groups 6 days after the initial exposure. Male production, which was equal in all groups, increased in a time-dependent fashion over the course of the experiment. The daphnids exposed to 2–4 days recovered more quickly than those exposed to 8–12 days. Ginjupalli and Baldwin (2013) concluded that production of males was greater in exposed adults but overall fecundity was more perturbed in exposed juveniles certainly due to delayed maturity. This demonstrated that pyriproxyfen impacted differently the juvenile and adult daphnids.

Wang et al. (2005a) showed that gravid female daphnids (7–14 days old) exposed to pyriproxyfen at 0.1 μg/L showed 100% of males in their third released brood. Matsumoto et al. (2008) also showed that 0.1 μg/L was the critical concentration to obtain 100% of males.

It is noteworthy that slight variations can be observed in the literature for the same concentrations of pyriproxyfen tested under broadly the same conditions. These are due to the slight differences in the protocols but Oda et al. (2006) have shown that the genetic differences among the strains of *D. magna* were also important to consider.

Methyl farnesoate is the endocrine signaling hormone that regulates male sex determination in daphnids and pyriproxyfen mimics the action of this hormone (Olmstead and LeBlanc 2003; Mu and LeBlanc 2004).

Methyl farnesoate is also at the origin of sexually ambiguous (gynandromorphic) individuals. Thus, Olmstead and LeBlanc (2007) showed that the incidence of spontaneous gynandromorphism was < 0.01% in populations of *D. magna* (8918 offspring analyzed). In daphnids exposed to 48–50 μg/L of methyl farnesoate, the incidence of gynandromorphism reached 0.14% (5710 offspring), while < 48 μg/L (13,190 offspring) and > 50 μg/L (10,113 offspring), the incidence was comparable with the control daphnids. Exposure at 30 °C instead of 20 °C resulted in a 46-fold increase in the occurrence of gynandromorphism. Maternal daphnids were also exposed to various concentrations of pyriproxyfen at 20 and 30 °C and the production of gynandromorphic offspring was evaluated. At 20 °C, incidence of gynandromorphism was equal to 0.08% at 0.1 μg/L of pyriproxyfen. As observed with methyl farnesoate, a window of occurrence at intermediate concentrations of insecticide was observed. At 30 °C, the incidence of gynandromorphism was 37-fold greater than at 20 °C in *D. magna* exposed to 0.20 μg/L of pyriproxyfen (Olmstead and LeBlanc 2007). Last, it has been demonstrated that pyriproxyfen altered the metabolism of lipids in *D. magna* (Tokishita et al. 2006; Jordão et al. 2016; Fuertes et al. 2019).

In a 21-day reproduction test, Miyamoto et al. (1993) showed that at 60 μg/L of pyriproxyfen, the body length of *Daphnia pulex* was shorter than that of the control and the daphnid also included fewer embryos in their brood chamber. Concentrations of 0.01, 0.03, 0.06, 0.12, and 1.88 μg/L did not have significant impact on the survival in 21 days, while from 0.03 μg/L to 1.88 μg/L, the number of young produced per female was significantly affected, especially at the highest concentration where this number was very low. A recovery was obtained 1 week after the transfer of the water fleas in clean water, except at 1.88 μg/L as regards the number of young/female.

Other crustaceans Trapp et al. (2015) assessed potential male reproductive disorders in the amphipod *Gammarus fossarum* exposed during two consecutive spermatogenesis cycles (2 weeks) to 0.5, 5, and 50 μg/L of pyriproxyfen. During exposure, survival was > 85%. Males exposed to 50 μg/L of pyriproxyfen showed significantly fewer egg-shaped spermatids ($6.7 \times 10^2 \pm 4.5 \times 10^2$) compared with the organisms from the solvent control ($13 \times 10^2 \pm 4.5 \times 10^2$). A significant dose-dependent impact on spermatozoon production was also observed showing an inhibition ranging from 40% at 5 μg/L to 73% at 50 μg/L. This reveals that the most susceptible phase is

the differentiation phase leading to the maturation of the spermatozoa. The dynamics of testis proteomes was also analyzed leading to the identification of proteins modulated by exposure to pyriproxyfen (Trapp et al. 2015). In another proteomic study (Trapp et al. 2018), the comparison of protein abundance between controls and testis of *G. fossarum* showed that 32 and 21 proteins were modulated at 0.5 μg/L and 50 μg/L of pyriproxyfen, respectively. It was also shown that the expression of the RXR (retinoid-X-receptor) transcript was overexpressed (× 2.8) by 5 μg/L of pyriproxyfen in *G. fossarum* at C2/C1 stage (14 days) (Gouveia et al. 2018).

Effects of pyriproxyfen against wintering female crayfish *Cherax quadricarinatus* were studied by Abdu et al. (2001). Five first-time spawners of 35.2 ± 3.3 g, 35.6 ± 1.2 mm, and with a mean oocyte diameter of 1100 ± 250 μm were placed with a mature male in 120-L tanks for 17 weeks under the ambient light and a temperature of 26 ± 0.5 °C to 28 ± 0.7 °C. Because eyestalk ablation increases spawning activity of first-time spawners, the ablation was done on one group of females to constitute a positive control. Three groups were fed with wheat grains immersed in pyriproxyfen dissolved in ethanol to give doses of 0.2, 2, or 20 μg/g animal body weight/week. A negative control with ethanol was also used. The animals were fed three times a week but only twice with grains treated with pyriproxyfen or ethanol. Table 1 shows that pyriproxyfen was present in significant amounts in the treated females after 119 days of exposure. The amounts found in the hepatopancreas were higher than those in the muscle tissue, ovaries, and gills (Table 1). Survival was high in all conditions (Table 2). This table also shows that pyriproxyfen has a tendency to increase molting and to inhibit spawning at the higher doses (Abdu et al. 2001).

Acute toxicity of pyriproxyfen was estimated against the males of the estuarine copepod *Eurytemora affinis* (Legrand et al. 2017). Contaminated water (10 to 250 μg/L) was renewed every day after the counting and elimination of the dead organisms. During the experiment, the copepods were not fed. An absolute 48-h LC_{50} value of 63.17 μg/L (44.90–81.44) was obtained. The relative LC_{50}, which corresponds to a 50% increase of the basal mortality for a null concentration of the chemical, was equal to 73.24 μg/L (56.63–89.86) and 29.70 μg/L (16.09–54.85) after 48 h and 96 h of exposure, respectively. The lowest concentration tested (i.e., 10 μg/L) did not affect the short-term mortality of the organisms (Legrand et al. 2017).

Table 2 Percentage of survival, spawning, molting, and molt increment in *C. quadricarinatus* females after 17 weeks of exposure at three doses (C1 to C3 in μg/g animal body weight/week) (adapted from Abdu et al. 2001)

Dose	Survival	Spawning	Molting	Molt increment
Control	90	66.6	44	27.2 ± 5.4
Destalked	80	93.7	100	30.4 ± 6.3
C1 = 0.2	85	59	52.9	26.7 ± 8
C2 = 2	80	43.7	38	20.2 ± 6.1
C3 = 20	95	26	63.1	26.2 ± 6.1

The effects of pyriproxyfen were evaluated on the mortality, fecundity, longevity, and predation performances of *Mesocyclops pehpeiensis* and *Megacyclops viridis* under laboratory conditions (Wang et al. 2005b). At 0.1 mg/L, there were no differences in mortality during the developing stages, number of emerged adults, or sex ratio of each brood among the treated and control groups of *M. pehpeiensis*. On contrary, a high mortality was observed at 0.1 mg/L with *M. viridis* during the egg-hatching-nauplius stage. There were no significant effects on the later developing stages or in sex ratio, although the number of emerged adults at 0.1 mg/L decreased. Development time was not impacted in *M. pehpeiensis* while it was shortened in *M. viridis*. Longevity and frequency of egg-bearing events were not affected in *M. pehpeiensis* with or without the supply of mosquito larvae. In *M. viridis*, a longer life span was observed at 0.1 mg/L but no difference of frequency of egg-bearing events was recorded in comparison with the control. The predatory behavior of *M. pehpeiensis* was not affected by pyriproxyfen while *M. viridis* killed more mosquito larvae than did the control group. Pyriproxyfen at 0.1 mg/L did not affect fecundity of *M. pehpeiensis* while the same concentration led to the production of more eggs in *M. viridis* (Wang et al. 2005b).

Pyriproxyfen was tested by Vandekerkhove et al. (2007) on the freshwater ostracod *Eucypris virens*. A nominal concentration of about 10 μg/L leads to 100% mortality after 15 days of exposure. From a large range of concentrations, the authors

Table 1 Distribution of pyriproxyfen in the tissues (μg/g) of *C. quadricarinatus* females after 17 weeks of exposure at three doses (C1 to C3 in μg/g animal body weight/week) and residual concentration in water (μg/ml) (adapted from Abdu et al. 2001)

Dose	Muscle	Gills	Ovary	Hepatopancreas	Water
Control	ND	ND	ND	ND	ND
C1 = 0.2	5.3 ± 1.13	7.3 ± 0.42	19.25 ± 3.89	95.50 ± 4.95	ND
C2 = 2	0.72 ± 0.69	1.79 ± 0.6	10.33 ± 4.12	143.67 ± 34.53	0.01
C3 = 20	3.99 ± 1.07	78.5 ± 20.5	31.7 ± 6.65	561 ± 114.55	0.02

ND not detected

showed that pyriproxyfen did not reduce fecundity of the females. However, a high variability was observed in the replicates. Nevertheless, Vandekerkhove et al. (2007) concluded that pyriproxyfen did not interfere with sex determination in parthenogenetic lineages of *E. virens*.

Nauplii of branchiopod *Artemia salina* were tested in artificial seawater for their acute toxicity to pyriproxyfen. NOEC, LOEC, and 48-h EC_{50} of 0.63 μg/L (0.57–0.66), 1.25 μg/L (1.17–1.36), and 2.5 μg/L (2.37–2.69) were obtained, respectively (Vieira Santos et al. 2017). Silva Alves et al. (2019) tested the effect of 0.0001, 0.001, 0.01, 0.1, 1, 10, 100, and 1000 mg/L of Sumilarv 0.5 G on the survival of nauplii. Only the four last concentrations induced significant mortality after 48 h of exposure.

Larvae of decapod *Palaemonetes pugio* (grass shrimp) and *Rhithropanopeus harrisii* (estuarine mud crab) were reared through complete larval development during static renewal exposures to nominal concentrations of 10 μg/L pyriproxyfen (Tuberty and McKenney 2005). Significant longer developmental durations were observed in both species. In control crabs, the mean duration of development was 13.6 days versus 14.2 days with pyriproxyfen. In shrimp, the duration of development was 19.6 days (controls) versus 20.8 days with the juvenoid. In addition, significantly altered free and conjugated ecdysteroid titers were found in both crustaceans exposed to pyriproxyfen (Tuberty and McKenney 2005).

Adult shrimps of the decapod *Leander tenuicornis* were collected from salt marsh pools and tested after a 3–4-day acclimation period. Static tests were performed at 25 °C under a 12:12 light/dark regime. The 96-h LC_{50} value obtained for pyriproxyfen equaled 0.098 mg/L (0.081–0.117) (Brown et al. 1996).

The effects of pyriproxyfen on the early ovary synthesis in the gecarcinid land crab *Gecarcoidea natalis* was studied by Linton et al. (2009). Crabs were fed with different regimens including or not 0.5% (wt/wt) of the juvenoid. Intake of pyriproxyfen impacted development of the ovaries as regards their dry mass, total nitrogen, and morphology.

Insects

Although this review is focused on non-target aquatic organisms, it is worth mentioning that one of the main uses of pyriproxyfen relies on its larvicidal activity against mosquitoes. There exist numerous studies showing the high toxicity of pyriproxyfen against mosquito larvae. The severity of the adverse effects, inhibition of emergence and lethality, depends on the mosquito species and strain, the larval stage, the formulation used, the nature of the substrate, the temperature of the medium, and so on (Kawada et al. 1988, 1993; Ali et al. 1995, 1999; El-Shazly and Refaie 2002; Darriet and Corbel 2006; Suman et al. 2013). Illustrative examples of this toxicity variability are given in Table 3. This high larvicidal activity is also found against non-target insects.

Pyriproxyfen consisting of 0.5% w/w of active ingredient on granules was tested against late instar larvae of the chironomid *Polypedilum nubifer*. Five nominal concentrations ranging from 0.001 to 0.02 mg/L were tested. Test was terminated when pupal mortality in the controls reached 20%. Under controlled conditions, 90% inhibition of emergence was obtained with a concentration of 0.01 mg/L (Trayler et al. 1994).

Larvae of *Chironomus fusciceps* were collected with sand in a volcanic area of Nagasaki (Japan) and reared in glass vials (Takagi et al. 1995). Fifty mature larvae were introduced into each vial and no food was provided. Temperature was 27–28 °C and the pH equaled 2–3. Six nominal concentrations of pyriproxyfen ranging from 0.1 to 0.00001 mg/L were tested. The effects of pyriproxyfen were shown clearly by the total number of emerging adults and the peak of adult emergence. The total number of emerging adults decreased according to the increase in concentration. The peak of adult emergence was observed 4 days post treatment in the control and in the lowest 3 concentrations. At 0.01 and 0.05 mg/L, the adult emergence was delayed and the peak was observed at 5 and 8 days, respectively. The 50% and 90% emergence inhibitions were estimated to 1.77 μg/L and 53.69 μg/L, respectively (Takagi et al. 1995).

The toxicity of pyriproxyfen against *Chironomus riparius* was estimated in a two-generation test (Tassou and Schulz 2009). First, instar larvae were exposed to nominal concentrations of 1, 3, 10, 30, and 100 μg/L of pyriproxyfen diluted in *N*,*N*-dimethylformamide. Control of the actual concentrations was made on days 0 and 28 leading to an acceptable concordance at to beginning of the experiments and to concentrations < 0.04 ng/mL (LOD) at day 28. Exposure was made at 20 ± 2 °C, 16:8 light/dark regime, and a light intensity of 708 ± 50 Lx. Larvae were fed daily with fish food. The criterion of validity was at least 70% of emergence with the solvent control. In the P generation, there was 93% emergence in the solvent control and no significant decrease in the emergence was recorded at 10 μg/L (NOEC) while adverse effects were observed at 30 μg/L (LOEC). The NOEC for the F1 generation was 3 μg/L, and at 10 μg/L, only 43% of the larvae emerged. As regards the development rate, 10 μg/L was the NOEC for the P generation but the LOEC for the F1 generation. Egg rope production of P generation was dose related and a significant impact was observed at 30 μg/L. At this concentration, none of the eggs were fertile (Tassou and Schulz 2009). Influence of temperature (16 vs. 24 °C) on the different endpoints was also investigated using 1, 3, 10, 30, and 100 μg/L of pyriproxyfen (Tassou and Schulz 2012). Emergence at P and F1 generations in the controls did not differ at the two temperatures. With pyriproxyfen, effects on the emergence ratio in the F1 generation were more important at 16 °C than at 24 °C. An earlier emergence was observed at

Table 3 Toxicity of pyriproxyfen against mosquito larvae (μg/L)

Species	Test conditions	Results	
Aedes aegypti	TG98.7; L3; S-Bo	LC_{50} = 0.11	[1]
		LC_{95} = 0.32 (0.29–0.36)	[1]
Ae. albopictus	TG97; L3/L4; S-VB	LC_{50} = 0.11 (0.074–0.143)	[2]
		LC_{90} = 0.376 (0.257–0.692)	[2]
Anopheles gambiae	EC5; L4; S-LU	EC_{50} = 0.025	[3]
	EC5; L4; DLD-R	EC_{50} = 0.0098 (0.0025–0.038)	[3]
	EC5; L4; DDT-R	EC_{50} = 0.0040 (0.0028–0.0057)	[3]
An. stephensi	EC5; L4; S-SMU	EC_{50} = 0.043 (0.011–0.16)	[3]
	EC5; L4; MLT-R	EC_{50} = 0.025 (0.019–0.034)	[3]
An. albimanus	EC5; L4; S-LU	EC_{50} = 0.016	[3]
	EC5; L4; OPC-R	EC_{50} = 0.00042 (0.000035–0.005)	[3]
An. farauti	EC5; L4; S-SI	EC_{50} = 0.0017 (0.011–0.16)	[3]
Culex pipiens pallens	TG97.2; L4; S-Go	EC_{50} = 0.0046	[4]
	TG97.2; L4; R-TH	EC_{50} = 0.016	[4]
Cx. quinquefasciatus	TG97; L3/L4; FC	LC_{50} = 0.29 (0.23–0.35)	[5]
		LC_{90} = 1.1 (0.84–1.3)	[5]

TG technical grade in %, *EC* emulsifiable concentrate in %, *L3* third instar larvae, *L4* fourth-instar larvae, *S-Bo* susceptible Bora-Bora strain, *S-VB* susceptible Vero Beach strain, *S-LU* susceptible strain from London University, *DLD-R* dieldrin-resistant strain, *DDT-R* DDT-resistant strain, *S-SMU* susceptible strain from St. Marianna University, *MLT-R* malathion-resistant strain, *OPC-R* organophosphate- and carbamate-resistant strain, *S-SI* susceptible strain from Solomon Islands, *S-Go* Gose susceptible strain, *R-TH* organophosphorus-resistant strain, *FC* field collected

[1] Darriet and Corbel (2006); [2] Ali et al. (1995); [3] Kawada et al. (1993); [4] Kawada et al. (1988); [5] Ali et al. (1999)

24 °C than at 16 °C. A combined effect of temperature and pyriproxyfen was found for the P and F1 generations. Development time decreased as temperature increased. In the controls, at both temperatures, a lower development rate was observed at F1 compared with P. No significant combined effect of temperature and pyriproxyfen on the mean development rate at P generation was found, whereas a significant effect was noted at F1. However, no significant interaction effect of the three parameters on the mean development rate of midges was obtained (Tassou and Schulz 2012).

Fish

Second-generation larvae of *Melanotaenia duboulayi* (< 72 h) were exposed to a 1-h pulse of 10 μg/L of pyriproxyfen in fresh reverse osmosis water. Fish were then placed in a recovery tank with aerated clean water for 24 h to account for the number of surviving. No difference was found with the controls revealing a lack of acute toxicity (Brown et al. 2002). A lot of studies have shown the limited acute (short term) toxicity of pyriproxyfen against fish species with LC_{50} values superior to the limit of solubility of the molecule (WHO 2006b; Miyamoto et al. 2008; Park et al. 2017).

Adult males of 60 days of the larvivorous freshwater fish *Xiphophorus maculatus* (0.4 ± 0.17 g, 3 ± 0.16 cm) were acclimatized for 1 week in a 20-L aerated aquarium at 25–26 °C, with a 16/8 light/dark cycle (Caixeta et al. 2016). Reconstituted water (pH = 7.4, dissolved oxygen = 8 mg/L, total hardness = 44 mg $CaCO_3$/L) was used for testing pyriproxyfen. Fish were fed twice daily until 24 h prior to start the bioassays in a semi-static system using 10 fish in duplicate. In a first experiment, fish were exposed to 20, 10, 5, 2.5, 1.25, and 0.63 μg/L of pyriproxyfen. It was shown that pyriproxyfen was not lethal to *X. maculatus* at the concentration used to control *Aedes aegypti* in Brazil (i.e., 10 μg/L). However, pyriproxyfen impacted swimming performances of *X. maculatus*. Signs of stress were observed at 5, 10, and 20 μg/L, which included erratic swimming, loss of equilibrium, and lethargy after 24 and 72 h of exposure. Immobility was detected at 20 μg/L, after 24, 72, and 96 h of exposure. According to these behavioral responses, the NOEC and LOEC values were estimated to 2.5 and 5 μg/L, respectively. In a second experiment, prey capture performance was tested in fish exposed to the NOEC value of pyriproxyfen and the recommended concentration in vector control. The test was based on quantification of the number of *Ae. aegypti* L4 larvae captured by individual fish over a 6-h test duration. For each test, 50 larvae/fish were used. Results showed that the ability of *X. maculatus* to capture larvae was significantly decreased at 10 μg/L while it was not the case at the NOEC and in the controls (Caixeta et al. 2016).

Embryos of zebrafish (*Danio rerio*) of about 3-h post fertilization (hpf) were exposed to 0.16, 0.33, and 1.66 mg/L of pyriproxyfen (≥ 98%). Nominal concentrations were quantified in the exposure medium (Maharajan et al. 2018). During exposure period under semi-static condition, the embryos were observed under inverted microscope to study the developmental abnormalities at 24, 48, 72, and 96 hpf. At 0.33 and 1.66 mg/L, pericardial edema and scoliosis were observed. Elongation of heart, yolk sac edema, and hyperemia were also found at 1.66 mg/L. DNA damage and apoptosis were also found at the highest concentration (Maharajan et al. 2018). In the same way, developmental toxicity in zebrafish was also recorded by Truong et al. (2016) but at very high concentrations.

Increased temperatures and uncontrolled human activities lead to the eutrophication of the lentic ecosystems with very often the occurrence of cyanobacterial blooms releasing toxins that can induce severe adverse effects on the biota (Guyot et al. 2004; Devillers et al. 2007). Azevedo-Linhares et al. (2018) have tested the co-exposure effects of realistic concentrations of microcystins (M1 to M3) and pyriproxyfen (P1 and P2) against embryos/larvae of the omnivorous fish *Rhamdia quelen*. Indeed, according to the Brazilian law, 1 μg/L (M1) is the maximum allowed concentration in microcystins in drinking water; 10 μg/L (M2) and 100 μg/L (M3) are concentrations that can be found in cyanobacterial blooms. P1 (10 μg/L) is the recommended concentration in pyriproxyfen in drinking water and P2 (100 μg/L) is the concentration in pyriproxyfen that may be found in residential water tanks with low volume capacity. Actual concentrations of microcystins and pyriproxyfen were tested leading to very slight differences. Thus, Azevedo-Linhares et al. (2018) showed that hatching rate decrease after exposure from 8 to 28 hpf was significantly more important in M2, P1M2, and P2M1 rather than M1, M3, P1, P2, P1M1, P2M2, and P2M3. Survival (96 hpf) was of 79.17% in the control group and 43.98% in M2, 58.85% in P1, 36.33% in P1M2, 54.17% in P2M1, and 52.09% in P1M3. After 48 hpf, the medians of deformity indices were higher than that of the control for most of the tested groups, except P1. Possible interactions were observed in P1M2, P2M1, and P2M2. At 72 hpf, deformity indices increased in P1M2 but no effect was observed in P1 and M2 and a potential synergy was noted in P2M2. At 96 hpf, there were no significant differences between the treatment and control groups. An agent-based model was used to predict long-term effects. Thus, for example, P1M2 led to extinction in 6 years (Azevedo-Linhares et al. 2018).

Bluegill sunfish (*Lepomis macrochirus*), averaging 6.3 cm and 4 g, were dynamically exposed to 0.15 mg/L of technical pyriproxyfen (243 mL/min) during 96 h followed by a continuous flow rinse period of 96 h with tap water (Schaefer et al. 1988). Residual analysis of water samples after 24, 48, 72, and 96 h showed that the concentration in pyriproxyfen was broadly the same with time. No fish mortality or impact on the behavior was recorded throughout the test. The highest residues occurred in the viscera of *L. macrochirus* and bioconcentration reached a plateau after 72 h. The highest visceral residues were about 647 times that of water concentration, whereas that in the edible tissue was 30 times. Residue decline was observed in all the tissues during the rinse period and no irreversible persistence was observed. In the viscera, the decline was of 90% in 96 h.

Soil without debris was treated with pyriproxyfen at 0.045 kg/ha. Aliquots of treated soil were placed in 24 tanks, aged under aerobic conditions during 14 days, flooded to 13 cm depth, and then held for 30 additional days (Schaefer et al. 1988). Channel catfish (*Ictalurus punctatus*), ranging from 6 to 10 cm and from 3 to 10 g, were added to the tanks (0.8 g/L) and exposed 1, 3, 7, 14, 22, and 30 days to pyriproxyfen in a static mode. After each exposure period, fish samples were analyzed. The treated soil was analyzed just after the treatment, after 7 and 14 days of aerobic aging, and after 30 days of flooding. No detectable residues were found after 7, 14, and 30 days. In the same way, no residue of pyriproxyfen was found in whole bodies, edible tissue, and viscera of *I. punctatus* in any of the exposure periods (Schaefer et al. 1988).

Acute toxicity of pyriproxyfen on the larvivorous fish *Pseudomugil signifer* was estimated in a static assay with serial concentrations of the juvenoid (Brown et al. 1998). Adults were collected from salt marsh pools and tested after a 3–4-day acclimation period. The 96-h LC_{50} value was equal to 0.845 mg/L (0.76–0.971) in the test milieu with a salinity, pH, dissolved oxygen, turbidity, and temperature of 31 g/L, 7.5, 3.2 g/L (± 0.3), 0 nephelometric turbidity unit, and 25 °C, respectively. It is worthy to note that the toxicity value is significantly higher than the hydrosolubility of pyriproxyfen. Araújo et al. (2018) investigated the effect of pyriproxyfen on the acetylcholinesterase (AChE, EC 3.1.1.7) activity measured in brain of *Hoplosternum littorale*, a freshwater tropical fish belonging to the group of Siluriformes. The concentration able to inhibit the enzyme activity by 20% (IC_{20}) was observed when 0.33 mg/L of the juvenoid was used.

Tadpoles

Premetamorphic *Odontophrynus americanus* tadpoles (15 ± 0.25 mm; 0.35 ± 0.05 g) were exposed to nominal concentrations of 0, 0.01, 0.1, 1, and 10 mg/L of pyriproxyfen as EC Dragon® (2% active ingredient) (Lajmanovich et al. 2019). The LC_{50} values for 24- and 48-h exposure to the juvenoid were found to be superior to its solubility in water being equal to 3.73 mg/L (2.66–6.43) and 2.51 mg/L (1.62–3.89), respectively. No mortality was observed in the controls. Glutathione S-transferase (GST), acetylcholinesterase (AChE), and carboxylesterase (CbE) activities were significantly increased

following a 48-h exposure to pyriproxyfen at 0.1 mg/L. Premetamorphic tadpoles were also exposed to 0.1 mg/L and 0.01 mg/L of pyriproxyfen for 22 days in order to assess enzymatic activities, hormone levels, and behavioral activity. The GST activity increased at 0.01 and 0.1 mg/L. Pyriproxyfen exposure only increased AChE at 0.1 mg/L. CbE activity was not modified for both concentrations. T4 hormone level was increased of 70% in tadpoles at 0.1 mg/L. Swimming performances as well as distance moved, mean speed, and global activity were altered in the 22-day subchronic test (Lajmanovich et al. 2019).

African clawed frog, *Xenopus laevis*, at the Nieuwkoop and Faber (NF) stage 51 were exposed to pyriproxyfen (purity 99.1%) labeled with ^{14}C at the phenoxyphenyl ring via a flow-through system (pH = 6.9–7.6, dissolved oxygen = 5.3–8.2 mg/L, temperature = 22–23.6 °C) (Ose et al. 2017). Because the 96-h LC_{50} was > 300 μg/L, exposures were made at the nominal concentrations of 3 and 300 μg/L. Mortality and adverse symptoms were recorded daily, and dead frogs were removed to maintain good water quality. After 22 days, all surviving tadpoles were transferred to 20 L of clean water for a 3-day depuration phase. Neither an incidental mortality nor abnormal behavior was observed in controls and exposure groups throughout the study. The ^{14}C concentrations in *X. laevis* gradually increased and almost reached the plateau after 7 and 15 days at 3 and 300 μg/L, respectively. The steady-state bioconcentration factors were calculated to be 550–560 and 590–610 at 3 and 300 μg/L, respectively. During the depuration phase, > 95% of pyriproxyfen in tadpoles were eliminated within 3 days. The $T_{1/2}$ values in *X. laevis* equaled 0.37 and 0.61 days at 3 and 300 μg/L, respectively. A significant amount of ^{14}C was detected in the gut as pyriproxyfen, followed by the liver as the conjugated metabolites. The main metabolic reactions were hydroxylation in 4′ of the phenoxyphenyl group and cleavage of the ether linkage, followed by sulfate conjugation (Ose et al. 2017). In another study (Ose et al. 2019), *X. laevis* tadpoles at NF stage 51 exposed to 300 μg/L of pyriproxyfen under the same experimental conditions also showed a delayed development based on decreases in NF stages and a decrease in the body weight, snout-vent length, and normalized hindlimb length as well as a reduction in food consumption (Ose et al. 2019).

Spirhanzlova et al. (2018) investigated whether environmentally relevant concentrations of pyriproxyfen and its main metabolite (4′-OH-Pyr) modified thyroid hormone (TH) signaling and early neuronal development. [^{125}I]T3 Competitive binding assays showed that 4′-OH-Pyr bound to TRα1 with low affinity. Transgenic Tg(thibz:GFP) *X. laevis* tadpoles were exposed to 4′-OH-Pyr or pyriproxyfen with or without T3 (5 nM). In the latter case, pyriproxyfen, significantly reduced fluorescence emitted from the tadpole head region at 10^{-5}, 10^{-4}, 10^{-2}, and 3×10^{-1} mg/L. With T3, no thyroid hormone-disrupting activity was recorded. On contrary, the metabolite was not active without T3, but in its presence, the signal was reduced at all the tested concentrations. *X. laevis* tadpoles exposed to pyriproxyfen for 72 h reacted to the light stimulus depending on the concentration but moved significantly less than controls. 4′-OH-Pyr at 0.1 and 0.3 mg/L led to a reduction of mobility. The latter concentration also reduced *X. laevis* head size.

Semi-field and field studies

In experimental rice plots of 37.2 m^2 (0.5 m deep), Schaefer and Miura (1990) studied the impacts of pyriproxyfen (EC, 10%) on rice plants and on non-target invertebrates. Nine plots were treated twice (July and August). Each time, three plots were treated with pyriproxyfen at 0.05 kg a.i./ha, three other at 0.11 kg a.i./ha, and the last three plots were used as control. Analysis of pyriproxyfen in rice plant vegetation was made after 1 h and after 1, 2, 3, 7, and 14 days. Mean concentrations (in mg/kg) are shown in Table 4. No residues were found in rice plants of the control plots on any of the sampling dates. The residues found were much lower after the second application than following the first one. This might be related to the increase of the area of the vegetative canopies. In all cases, the residues in rice plant vegetation declined below detectable limits (0.005 mg/kg) 7 days after the treatments (Schaefer and Miura 1990).

Dipping, drag-netting, and trapping were used to monitor the aquatic organisms (Schaefer and Miura 1990). Dipping allowed to collect numerous invertebrate taxa but the Cladocera, Eucopepoda, and Rotifera were the most widely found. Among them, only the cladoceran populations were

Table 4 Residues in rice plant vegetation (mg/kg) after the first and second treatment with pyriproxyfen (EC 10%) at 0.05 and 0.11 kg a.i./ha (adapted from Schaefer and Miura 1990)

Treatment	Time	0.05 kg a.i./ha	0.11 kg a.i./ha
First	− 1 d	nd	nd
	1 h	1.18 (± 0.16)	3.98 (± 0.90)
	1 d	0.54 (± 0.12)	4.04 (± 0.69)
	2 d	0.84 (± 0.19)	2.29 (± 0.51)
	3 d	0.38 (± 0.14)	0.96 (± 0.17)
	7 d	0.095 (± 0.003)	0.20 (± 0.19)
	14 d	nd	nd
Second	− 1 d	nd	nd
	1 h	0.24 (± 0.08)	2.11 (± 0.43)
	1 d	0.26 (± 0.02)	1.70 (± 0.59)
	2 d	0.34 (± 0.01)	0.80 (± 0.08)
	3 d	0.012 (± 0.01)	0.16 (± 0.06)
	7 d	0.042 (± 0.08)	0.025 (± 0.01)
	14 d	nd	nd

h hour, *d* day, *nd* not detected (< 0.005 mg/kg, the lowest detectable limit)

affected. Indeed, 65% and 53% of reduction were observed with pyriproxyfen at 0.11 kg a.i./ha and 0.05 kg a.i./ha, respectively. Nine taxonomical groups were regularly collected by drag-netting, namely, Oligochaeta, Podocopa (a subclass of ostracods), Chironomidae, Zygoptera, Anisoptera, Turbellaria, Notonectidae, Gastropoda, and Hydrozoa. While the results obtained on Notonectidae and Hydrozoa were not statistically significant, pyriproxyfen impacted the other taxa at the low and/or high treatment rates. Podocopa appeared the most sensitive to pyriproxyfen with a population reduction of 50% and 63% at 0.11 kg a.i./ha and 0.05 kg a.i./ha, respectively. Chironomidae were also sensitive with a population reduction of 45% and 29% at the high and low treatment rates, respectively. Just after the treatment, the fourth-instar chironomids were collected and reared in the laboratory. Although the control larvae emerged normally into adults, those collected from the treated plots died during the pupal-adult ecdysis. The same phenomenon was also observed with the Odonata (Anisoptera and Zygoptera). Three to 4 days after each treatment, a few deformed adults (about 13%) were observed in the treated plots. Typical abnormalities included dead adults in nymphal skins and partially emerged dead adults. In this case, the compound eyes, head capsule, thorax, wings, and legs were usually separated from the exuvium. These deformed adults were observed only during 4–10 days after treatment. Twelve taxonomic groups were collected by trapping. Among them, Hydrophilidae, Dytiscidae, Notonectidae, Anisoptera, Zygoptera, and Lycosidae were always found. Notonectidae were highly sensitive with a population reduction of 86% and 79% at the high and low treatment rate, respectively. Ostracods, Ephemeroptera, Corixidae, and Belostomatidae were collected periodically but their analysis did not lead to conclusion for both application rates. Aquatic beetle adults, dragonfly nymphs, and lycosid spiders showed no adverse effects against the treatments (Schaefer and Miura 1990). However, it is interesting to note that Mikhali (2015) found that pyriproxyfen (Sumilarv 0.5G) presented a nymphocidal activity against the dragonfly nymphs in laboratory at a concentration of 0.05 and 0.1 mg/L.

In another study, two rice plots of 37 m^2 including cladocerans, copepods, ostracods, damselflies, dragonflies, beetles, chironomids, culicoids, and hydra were exposed to 0.0056 kg/ha of EC pyriproxyfen (Schaefer et al. 1988). No significant adverse effects were observed at 2, 5, 7, and 9 days after the treatment comparatively to the control without juvenoid (Schaefer et al. 1988). Experimental ponds treated with 0.5% pyriproxyfen granules at 0.0112 kg/ha or 0.028 kg/ha did not impact the number of *Callibaetis pacificus*, *Tarnetrum corruptum*, *Anax junius*, *Cypridopsis* sp., and *Cyprinotus* sp. at 7, 14, and 21 post treatments (Mulla et al. 1986).

Enclosures in the littoral region of a eutrophic wetland were treated with pyriproxyfen at the rate of 50 g a.i./ha which was equivalent to a nominal concentration of 0.01 mg/L in the enclosed water (Trayler et al. 1994). Each enclosure surrounded an area of water 25 m^2 and comprised a clear, polyethylene plastic sheet supported at the top and bottom by PVC pipes. Larvae of chironomids were monitored by taking three sediment samples from each enclosure and collected 6 days and then 1 day prior to the juvenoid application and 7 and 20 days afterwards. Emergence of *Polypedilum nubifer*, *Kiefferulus intertinctus*, *Chironomus aff. alternans*, and *Cryptochironomus griseidorsum* declined to zero within 5 days of the application and then remained below that of the control enclosures. The emergence of the two first species was suppressed for 24 days. Results on the two other species were too variable to be statistically interpretable (Trayler et al. 1994).

In their rice plots, Schaefer and Miura (1990) also studied the accumulation potential of EC 10% pyriproxyfen in *L. macrochirus* following treatments at 0.05 kg and 0.11 kg a.i./ha, repeated twice. Whole body, edible tissue, and viscera were analyzed at days 1, 2, 3, 7, and 14. The lowest detectable concentration in fish tissues was 0.005 mg/kg_{bw}. The results are listed in Table 5. The residues found were much lower

Table 5 Residues (mg/kg_{bw}) in bluegill sunfish tissues from rice plots treated at 0.05 and 0.11 kg (a.i.)/ha (adapted from Schaefer and Miura 1990)

Treatment/tissue	Day	0.05 kg a.i./ha	0.11 kg a.i./ha
First/whole body	1	0.38 (± 0.16)	2.29 (± 0.74)
	2	0.12 (± 0.064)	1.04 (± 0.31)
	3	0.067 (± 0.0052)	0.82 (± 0.13)
	7 and 14	nd	nd
Second/whole body	1	0.12 (± 0.021)	0.68 (± 0.28)
	2	0.091 (± 0.012)	0.30 (± 0.17)
	3	0.041 (± 0.004)	0.27 (± 0.10)
	7 and 14	nd	nd
First/edible tissue	1	0.11 (± 0.043)	0.38 (± 0.054)
	2	0.06 (± 0.01)	0.27 (± 0.092)
	3	0.031 (± 0.012)	0.081 (± 0.016)
	7 and 14	nd	nd
Second/edible tissue	1	0.03 (± 0.004)	0.13 (± 0.041)
	2	0.019 (± 0.0098)	0.047 (± 0.017)
	3	nd	0.030 (± 0.013)
	7 and 14	nd	nd
First/viscera	1	0.83 (± 0.39)	3.59 (± 0.36)
	2	0.48 (± 0.12)	2.65 (± 0.45)
	3	0.34 (± 0.087)	1.13 (± 0.45)
	7 and 14	nd	nd
Second/viscera	1	0.26 (± 0.081)	1.55 (± 0.49)
	2	0.065 (± 0.027)	0.48 (± 0.14)
	3	0.077 (± 0.015)	0.35 (± 0.13)
	7 & 14	nd	nd

nd not detected (< 0.005 mg/kg_{bw}, the lowest detectable limit)

after the second application than after the first one. Much more pyriproxyfen was found in the viscera than in the whole body and edible tissue. Nevertheless, no residues were found after 3 days (Schaefer and Miura 1990).

Contamination of aquatic ecosystems by pyriproxyfen

When reviewing laboratory- and field-derived data on the adverse effects of pyriproxyfen to aquatic organisms, it is important to compare the reported ecotoxicity data to the concentrations in pyriproxyfen found in the aquatic ecosystems for risk assessment. Unfortunately, the number of studies dealing with residue analysis of pyriproxyfen in these media is rather limited.

Samples of water and fish were collected by Belenguer et al. (2014) in the Júcar river that flows through the Teruel, Cuenca, and Valencia provinces in Eastern Spain under a typical Mediterranean climate. Among the 40 pesticides analyzed, 23 were detected in water and/or fish samples. Pyriproxyfen was found in all the water samples with concentrations ranging from about 83 ng/L to 100 ng/L but it was not detected in fish. A more extensive study was made by Ccanccapa et al. (2016b) on this river but also on the Turia river of more limited dimension and also typically under the dependence of Mediterranean climate. Water and sediments were collected at 44 sampling points along the two rivers. Sampling campaigns were performed in autumn after a month without rainfall events, during two consecutive years. Pyriproxyfen was found in the 15 samples collected the first year in the Júcar river at a median concentration of 83.21 ng/L and at a maximum concentration of 99.59 ng/L (LOD/LOQ = 0.5/1.5 ng/L). The molecule was not detected the second year in this river as well as the first year of sampling in the Turia river. Among the 29 samples collected in this river the second year, pyriproxyfen was detected 15 times with a median concentration of 0.35 ng/L and a maximum concentration of 3.27 ng/L. Pyriproxyfen was only detected in sediment of the Júcar river the first year of sampling in 93% of the samples with a median concentration of 1 ng/g dw (LOD/LOQ = 0.42/1.25 ng/g) and a maximum concentration of 5.54 ng/L (Ccanccapa et al. 2016b). In the Ebro River, which is located at the northeast of Spain and drains an area of approximately 85,000 km^2, Ccanccapa et al. (2016a) found pyriproxyfen in 95% of the water samples the first year of sampling with a minimum, maximum, and mean concentration of 0.89 ng/L, 37.74 ng/L, and 24.38 ng/L, respectively. The second year of sampling, pyriproxyfen was detected in only one sample at 4.76 ng/L. It is noteworthy that pyriproxyfen was not found in the sediment and fish samples analyzed (Ccanccapa et al. 2016a).

In the northeast of Catalonia (Spain), the Llobregat river and its tributaries Anoia and Cardener were sampled by Masiá et al. (2015) during 2 years. Pyriproxyfen was only found once the first year in water at the concentration of 1.72 ng/L (LOD/LOQ = 0.5/1.5 ng/L). The molecule was not detected in sediment (LOD/LOQ = 0.42/1.25 ng/g) and fish (LOD/LOQ = 0.94/2.81 ng/g) samples. Interestingly, Campo et al. (2013) analyzed samples of 16 sewage treatment plants dumping their effluents to the Ebro, Jucar Llobregat, and Guadalquivir rivers. Ninety percent of the wastewater samples collected the first year of sampling included pyriproxyfen at the minimum, maximum, and mean concentration of 0.48 ng/L, 75.46 ng/L, and 17.92 ng/L, respectively. The second year of sampling, pyriproxyfen was found once at 1.58 ng/L. In the sludge samples, the first year, pyriproxyfen was found in 41.67% of the samples at the minimum, maximum, and mean concentration of 4.09 ng/g dw, 40.92 ng/g dw, and 12.60 ng/g dw, respectively. The second year, pyriproxyfen was detected in 35.71% of the samples with a minimum, maximum, and mean concentration of 2.72 ng/g dw, 63.04 ng/g dw, and 20.96 ng/g dw, respectively (Campo et al. 2013).

Surface waters of the Volvi, Doirani, and Kerkini lakes located in Northern Greece were collected in two periods, namely, fall/winter and spring/summer the next year for pesticide residue analysis (Kalogridi et al. 2014). Pyriproxyfen was only found in the Volvi Lake during the first sampling period. The minimum and maximum concentrations found were equal to 3.5 ng/L and 19 ng/L, respectively.

Conclusions

Pyriproxyfen is used worldwide in agriculture against numerous pest species and in vector control especially as larvicide against mosquitoes. The amounts used in agriculture are considerably higher than those employed in vector control. The affinity of pyriproxyfen for the air compartment is very limited due to its low vapor pressure and Henry's law constant. After a release in the environment, pyriproxyfen will be preferentially found in the soil, sediment, and water compartments where its very low water solubility and high 1-octanol/water partition coefficient (log Kow) should be consistent with a persistent behavior in these compartments and the biota. In fact, the persistence of pyriproxyfen in water in the absence of organic matter decreases with increasing temperature and sunlight exposure and it seems to increase with increasing pH. In river water, the molecule is quickly photodegraded with a photolysis half-life of about 3 weeks. In the presence of sediment or organic matter, pyriproxyfen is adsorbed, increasing the persistence and potential adverse effects of the molecule. The aerobic aquatic metabolic half-life of pyriproxyfen is

estimated to be from about 2 to 3 weeks. Pyriproxyfen degrades quickly in water and sediment to two major metabolites namely 4′-OH-Pyr and PYPAC. Degradation under anaerobic conditions is much longer taking months.

Although the number of studies is reduced, pyriproxyfen appears toxic against algae and to a lower extent against small aquatic plants. On contrary, protozoa seem to be more tolerant to the juvenoid. However, more studies are necessary for better assessing the potential toxicity of the molecule on these taxa. It is also the case for the aquatic gastropods for which information is lacking. This is of first importance due to the ecological importance of the aquatic Mollusca and their well-known sensibility to various endocrine disruptors (Oehlmann et al. 2000; Jobling et al. 2003; Devillers 2013).

Conversely, the effects of pyriproxyfen against the larvae of crustaceans and insects either in laboratory and in situ are well documented. Pyriproxyfen is highly toxic to both Arthropoda taxa but the former group is a little bit less sensitive than the latter. Analysis of the different results shows that the severity of the adverse effects (inhibition of emergence and lethality) depends on the species and its larval stage, the formulation used, the substrate, the temperature, and so on. Temperature is an important abiotic parameter increasing the adverse effects of pyriproxyfen (El-Shazly and Refaie 2002; Olmstead and LeBlanc 2007; Tassou and Schulz 2012) but also decreasing its persistence in the aquatic ecosystems. This forestalls what could be the effects of climate change on the aquatic fate and toxicity of this kind of juvenoid.

The acute toxicity of pyriproxyfen again fish and tadpoles is rather limited, the effects being often expected at concentrations above the water solubility limit of pyriproxyfen. However, physiological and behavioral effects can be observed at lower concentrations. Pyriproxyfen is quickly taken up to fish and tadpoles, then metabolized and excreted as metabolites, which resulted in low bioconcentration of the juvenoid in these organisms.

Analysis of the whole ecotoxicity results clearly reveals that the concentrations in pyriproxyfen that are efficient against mosquitoes also impact most of the non-target organisms occupying the different trophic levels in the aquatic ecosystems. This clearly means that the direct use of pyriproxyfen in water media for controlling mosquito population has to be avoided. Use of the autodissemination method seems to be a better solution to limit the spillage of pyriproxyfen in the aquatic ecosystems. However, more work is needed to know the amounts of biocide carried by female mosquitoes and those actually deposited in the laying areas. Indeed, while the method seems working, the number of studies supported by an analysis of the residues is very scarce.

Although the number of residue analyses performed in rivers and lakes is rather low and should be imperatively increased, the available studies clearly reveal that the concentrations found in pyriproxyfen, which originated from agriculture, can adversely impact the functioning of the biota in these ecosystems.

Last and not least, while pyriproxyfen is metabolized in the natural water media, there is a need of data of quality on the acute and sublethal effects of the different metabolites in aquatic ecosystems. In the same way, to our knowledge, there is no study in which the presence of metabolites of pyriproxyfen has been searched in natural aquatic media while the experiments in controlled environment show that their presence cannot be neglected.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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