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Possible teratogenic and adults abnormalities induced by insecticide pyriproxyfen on non-target organisms.

Hani S. Hafez[a]; Rasha A. Sedeek[a,*]; Mahmoud E. Mohallal[b]; Nour E. Sherif[b]; Yomn M. Mobarak[a]

[a]Zoology Department, Faculty of Science, Suez University, Suez, Egypt

[b]Zoology Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

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ABSTRACT

Pyriproxyfen is an insecticide that is used in a wide range against various insects and causes potentially harmful effects on animals and their embryological stages such as effective microcephaly and other teratogenic abnormalities. Pyriproxyfen has the ability to cross react with retinoic acid receptors, part of the mammalian regulatory system for neurological development, inducing neurodevelopmental abnormalities like microcephaly. This causal chain offers strong support for conducting a thorough investigation of pyriproxyfen's involvement in neurodevelopmental disorders and neurodevelopmental toxicity such as low brain weight in rat pups. More incentive research carried out in widespread usage of pyriproxyfen in Brazil revealed its coincidental association with a rise in incidence of microcephaly. So, It is important to take into account other theories on the causes or contributing variables to the incidence of microcephaly among higher animals.

1. General characters and biological activity of the pyriproxyfen.

Pyriproxyfen (PPF) is an insecticide with multiple uses, such as antiparasitic for pets and pest management in homes, and farms. It functions as a juvenile hormone analogue. PPF thus interferes with both adult emergence and development. PPF application in the field can minimize agricultural losses and reduce tropical arbovirus vectors when added to drinking water with parallel negative impact on aquatic ecosystems (Cox et al., 1990; Vieira Santos et al., 2017). PPF residues have been shown to contaminate food and may be a dietary risk factor (Du et al., 2017). PPF is a pyridine-based insecticide {(C20H19NO3), 4-phenoxyphenyl (RS)-2-(2-pyridyloxy) propyl ether} that is widely used as a larvicidal, general insect growth regulator, and component of mixed pesticide products (Ramos et al., 2019). PPF is often promoted as a biopesticide, a pesticide made from plants that has little to no risk to the environment or beneficial animals. Biopesticides, often referred to as biorational pesticides, are derived from biological sources such as bacteria, fungi, viruses, and other biochemicals such pheromones and insect growth regulators.

Their mode of action is different from that of broad-spectrum insecticides; they tend to be less harmful to organisms that are not their intended targets, are more selective, and have relatively short-lived effects (Chen et al., 2014).

However, the tolerable daily intake of PPF established by the WHO is 100 mg/kg of body weight/day for a lifetime. On the other hand, at >5,000 mg/kg b.w, PPF resulted in an increase in liver weight and induced changes in plasma lipid concentrations in rats, induced hepatic enzymes in dogs, and affected cholesterol levels (WHO, 2007). Due to its low toxicity in humans, PPF has been approved by the WHO to kill mosquito larvae in drinking water supplies since 2014. It is one of four insecticides (temephos, methoprene, pyriproxyfen, and permethrin) recommended by the WHO in addition to drinking water for community health drives. Their recommended dosage is 0.01 mg/l in drinking water containers. However, PPF is believed to be responsible for the increased incidence of microcephalic babies in Brazil from 2015 to 2016 (Parens et al., 2017). In addition, PPF was believed to be the cause of delayed brain development in children; therefore, it might be one of the potential causes of microcephaly recorded in Brazil.

The wide range of PPF use may induce direct or indirect contamination of aquatic ecosystems. The toxicity of PPF on aquatic organisms is in the form of disruption of their embryonic and larval development by inhibiting their growth, and adversely influencing various physiological events in adults. The analysis of findings from several investigations revealed that there are many other aspects

* Corresponding author at Suez University

E-mail addresses: Rasha.abdallah@sci.suezuni.edu.eg. (Rasha A. Sedeek)

such as the species and its larval stage, the formulation employed, the substrate, the temperature, and other variables all affect the PPF negative severity that effect fatality mechanisms. Additionally, temperature is considered one of the significant abiotic elements not only raising the negative effects of PPF but also reducing its ability to persist in aquatic environments . This return to the potential influence of temperature on the metabolic rate, motility, and feeding behavior of organisms, thereby impacting the uptake and removal of toxicants as well as detoxification rates (El-Shazly and Refaie, 2002; Olmstead and LeBlanc, 2007; Tassou and Schulz, 2012). PPF can also distract the endocrine system and predation mechanisms. The acute toxicity of PPF also had minor effects on fish and tadpoles, with effects typically anticipated at concentrations higher than the chemical's dissolved limit in water. However, at lesser concentrations, physiological and behavioral impacts are visible. Fishes and tadpoles rapidly absorb PPF, which processed and eliminated as produced metabolites that excreted with low PPF bioconcentrations.

2. Pyriproxyfen Effects on Invertebrates

Despite the known efficiency of PPF in malaria vector control, in anaerobic conditions, such as brackish waters or sediments, PPF is much more stable, irreversible, and toxic to aquatic invertebrates (Sullivan and Goh, 2008). Its toxicity on the ciliated Colpoda aspera protozoans was in the form of a decrease in growth rate with concentration dependent mechanisms (Kakiichi et al., 1996). While, colonies of Paramecium sp. treated with 0.1 mg/L PPF did not reveal negative effects on their growth (Wang et al., 2005). Abdul-Wahid and Elbanna, (2012) revealed that higher doses of PPF increased molting and prevented spawning among the wintering female crayfish species Cherax quadricarinatus. The adverse effects of PPF on other invertebrates were studied (Cotgreave et al., 2016). Moreover, Wang et al., (2005) investigated the effects of PPF on physiological and behavioral mechanisms of Mesocyclops pehpeiensis and Megacyclops viridis. The study revealed no significant differences in death rates during the embryological phases of M. pehpeiensis using 0.1 mg PPF/L. Conversely, during the egg-hatching stages impairments revealed a significant death rate with M. viridis was seen with the same dose of PPF. Moreover, the exposure of the amphipod Gammarus fossarum to PPF through two consequent spermatogenesis cycles over a period of 2 weeks resulted in a noteworthy dose-dependent that influenced on spermatozoa's production and an inhibition of spermiogenesis during spermatid metamorphosis (Trapp et al., 2018). Tatarazako et al., (2003) stated that PPF treatment at 10–30 ng/L for Daphnia magna standard culture medium significantly induced reproduction toxicity with reduced number of offspring and changes in the sex ratio, and increased concentration at 1 µg/L induced male neonates (Ginjupalli and Baldwin, 2013) with altered lipid metabolism (Fuertes et al., 2019; Jordão et al., 2016).

3. Pyriproxyfen Effects on Vertebrates

PPF has diverse effective metabolic consequences among vertebrates due to their sharing with retinoic acid receptors among developing embryos (Cotgreave et al., 2016) which could activate or block the activity of retinoic acid at incorrect times of development, cooperating with the gene expression cascades that lead to congenital anomalies (Parens et al., 2017).

3.1. Pyriproxyfen Effects on Fishes

Aquatic vertebrates are useful toxicology models because they are the most susceptible to human activities, as well as being sensitive to low water pesticide pollution levels and other ecological toxins which can disrupt their enzymes and hormonal secretions (Khan and Law, 2005). Additionally, the early developmental stages of fish are more sensitive to pollution stress due to their higher metabolic rate, immature immune system and skin, high superficial area/volume ratio, and limited mobility on the water column. PPF is used in a variety of ways that cause direct or indirect release into aquatic environments and can persist for up to six months in various aquatic habitats. Therefore, PPF is one of the main toxicants contributing to decreasing fish and amphibian populations worldwide (Chavasse et al., 1995; Sihuincha et al., 2005; Vythilingam et al., 2005; Lajmanovich et al., 2019).

Schaefer et al., (1987) revealed that there were no mortality rate or behavior differences among bluegill sunfish (Lepomis macrochirus) treated individuals using different concentrations of PPF with variable exposure times. While, the highest PPF residues have bio-accumulated in the fish viscera through 72 h after treatment with about 647 times that that was detected in water and in muscles was 30 times. On the contrary, using the same exposure periods and concentrations, no residue of PPF was detected in I. punctatus body. Caixeta et al. (2016) used adult males of the larvivorous freshwater fish Xiphophorus maculatus for testing PPF (10 µg PPF/L, control Aedes aegypti in Brazil) impacts and acclimatized them for 1 week induced impaired swimming behavior and without lethal effects in a dose- dependent manner. Additionally, Araújo et al., (2018) found inhibition of the enzyme acetylcholinesterase (AChE, EC 3.1.1.7) activity in the brain of the freshwater tropical fish Hoplosternum littorale exposed to PPF.

During embryogenesis of zebrafish (Danio rerio), embryos were exposed once to a very high concentration of PPF (1670 µg PPF/L) and exhibited facial deformities among larvae, a high mortality rate, craniofacial defects, adverse behavioral effects, thinning of heart muscles, pericardial edema, hyperemia, and morphological defects with mandibular and eye deformities (Truong et al., 2016).

On the other hand, zebrafish embryonic development, PPF was lethal at high doses without teratogenic impacts at the highest suggested dosage in actual practice (Dzieciolowska et al., 2017). Furthermore, they discovered that PPF had no effect on the quantity of stem cells in the zebrafish embryos' developing central nervous system or on abnormalities of the brain. The study showed that

exceeding 1 µg PPF/ml at extremely high dosages had a significant teratogenic effect, and that zebrafish embryos exposed to these high levels earlier in development could not survive for more than two days. Additionally, a different study showed that PPF might only have a negative impact on zebra fish early development at greater concentrations (Maharajan et al., 2018) with developmental abnormalities with DNA damage at the highest concentrations.

Gusso et al., (2020) conducted their investigation to find out how PPF affected adult zebra fish's endocrine, behavioral, and cognitive aspects. They verified that PPF exposure damaged zebrafish's inhibitory avoidance memory and changed their cortisol levels. These consequences might have a major influence on fish persistence in their native environments, which could disrupt the ecosystem as a whole and have an impact on a wide range of aquatic creatures. de Oliveira et al., (2021) The study investigated the effects of PPF on D. rerio zebrafish in vivo and in vitro, revealing that its toxicity in the testis is due to Ca2+ overloading. PPF increases lipid peroxidation, decreases antioxidant capacity, induces GSH depletion, alters spermatogenesis progress, and causes high liver basophilia, contributing to testicular toxicity and spermatogenesis disruption.

Recently, Li et al., (2022) concluded that PPF had detrimental toxic effects on Labeo rohita fish tissues by increasing DNA damage, increasing oxidative stress biomarkers, and reducing antioxidant enzyme concentrations.

3.2. Pyriproxyfen Effects on Amphibia

It is generally known that amphibian tadpoles are the most famous developmental stage for ecotoxicological contaminants among terrestrial amphibian adults (Yan et al., 2012). However, PPF is recognized as an interfering agent with thyroid hormones essential for amphibians' development and signaling (Spirhanzlova et al., 2018; Wegner and Stolt, 2005). Additionally, Ose et al., (2017) reported that there were no observed mortality rate and other adverse symptoms through recorded daily actions through the Nieuwkoop and Faber stage 51 of African clawed frog, Xenopus laevis, exposed to pure PPF. Spirhanzlova et al., (2018) claimed that low affinity binding activities of PPF to TRα1 on transgenic Tg (thibz:GFP) X. laevis tadpoles triggering the impacts of ecologically relevant concentrations of PPF and its primary metabolite (4′-OH-Pyr) on thyroid hormone signaling and early brain development exhibited their abnormalities. Lajmanovich et al., (2019) investigated the impacts on enzymatic activities, hormone levels, and behavioral activity of PPF on pre-metamorphic tadpoles, after their exposure to 0.1 mg PPF/L and 0.01 mg/L of PPF for 22 days. Their out-puts were without significant impacts for different concentrations with significant exception for antioxidant system and neurotransmitters. Additionally, 70% of tadpoles at 0.1 mg PPF/L had elevated thyroxin T4 hormone levels, changed swimming patterns, and reduced heart function, indicating sub-lethal PPF dosages induce antioxidant response. Using animal models, pesticides like PPF can have their environmental and health risks assessed. Bourdineaud et al., (2013) and Azevedo et al., (2021) revealed that studies of PPF on zebrafish induced mitochondrial bioenergetics, AChE activity, central nervous system development, neurobehavior, toxicokinetics, and toxicodynamic impairments. Furthermore, studies on the mitochondria of zebrafish have brought the numerous biochemical processes that mitochondria govern into the spotlight. It is well-known that the amount of ATP in mitochondria can identify them. Additionally, mitochondria has a major influence on a number of cellular functions, including oxidative stress, cell death, reactive oxygen species generation, Ca+2 homeostasis, redox signaling, and epigenetic crosstalk. (Cowie et al., 2017; Weinhouse, 2017). The relationship between pesticide impacts and mitochondrial function has made it possible to precisely identify the ways in which these chemical compounds impact physiological systems and cell function. Also, PPF exhibited significant inhibitory effects on zbAChE at IC20 and IC50 of 0.33 mmol/L and 92.5 mmol/L, respectively, indicating its potential role in neurological damage (Maharajan et al., 2018). Few PPF binding sites in the AChE structure are situated at the omega loop of the enzyme, which is situated behind the choline binding site of the active center and is also referred to as the Cys-Cys loop or W-loop (Shi et al., 2001). PPF exposure similarly disrupted Ca+2 release that is crucial for neural fitness and function (Azevedo et al., 2021).

Conclusion:

PPF is a pyridine-based pesticide that acts as an analogue of juvenile hormones. PPF is a common larvicidal agent. Because of its minimal toxicity to human, WHO recommended the use of this insecticide for treatment of drinking water supplies against disease-transmitting insects like mosquitoes. Although PPF exhibits selectivity towards insects, numerous prior investigations have revealed the potential toxicity of PPF against non-target invertebrates, as well as vertebrates such as fish and amphibians. In recent times, there has been a significant focus on PPF due to assertions suggesting that its extensive utilization could potentially be linked to the increasing incidence of neonatal microcephaly observed in Brazil. Therefore, studying the mechanisms of its toxicity can provide a better understanding of how this insecticide disrupts hormonal regulation, interfere with developmental pathways, and impair neurological development. This knowledge can then be used to develop mitigation strategies and regulatory measures to minimize exposure to PPF, as well as explore alternative pest control approaches. Further research in this area can uncover new information and contribute to the overall understanding of the effects of PPF on the development of non- target organisms.

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