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Review Article

PYRETHROIDS INFLUENCE ON FISH

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Summary: Pyrethroids belong to the most commonly used pesticides worldwide. Their massive expansion is a threat to the natural environment including the aquatic ecosystems. Although pyrethroids are rapidly degraded in soil and plants, they are extremely toxic to fish because of fish high sensitivity to them.
Pyrethroids are divided by characteristic into type I and type II. Both types cause similar neurological symptoms. They affect sodium channels of nerve filaments and type II pyrethroids even affect chloride and calcium channels. Critical in fish pyrethroid intoxication is slower elimination than in birds and mammals. Pyrethroids are absorbed by fish gills readily. After distribution to bile, liver, kidney and red blood cells, they are metabolized by hydrolysis, hydroxylation and conjugation to glucuronides and sulphates. Disorders of movement and breathing during acute poisoning are followed by death. Chronic effects of pyrethroids induce behaviour changes, blood profile changes, histopathological changes, decreased growth, immune system effects and endocrine effects. Both types of toxicity reduce reproductive potential. Toxicity of pyrethroids depends on many external and internal factors.

Key words: pyrethroids; fish; neurotoxicity; sensitivity; physiological disturbances

Abbreviations & Units: ALP - alkaline phosphatase; ALT - alanine transaminase; AST - aspartate transaminase; ATP - adenosine triphosphate; CA - carbonic anhydrase; CK - creatine kinase; EPA - Environmental Protection Agency; GABA - gamma-aminobutyric acid; GDH – glutamate dehydrogenase; Hb - haemoglobin; HSP - heat shock protein; LDH - lactate dehydrogenase; MCH - mean cell haemoglobin; MCHC - mean corpuscular hemoglobin concentration; MCV - mean cell volume; mRNA - messenger ribonucleic acid; PCV – packed cell volume, haematocrit; PGF2α – F-type prostaglandin; RBC - erythrocyte counts

Introduction

Pyrethroids are synthetic analogues of the natural pyrethrins, extracts of the ornamental *Chrysantemum cinerariaefolium* and its related species. Pyrethrins had been used for decades for control of insects. They were selective, safe and had short half lives. Although they were acutely toxic to fish, very few accidental poisoning occured because they were not registered for aquatic use and they seldom had enough persistence to reach water from normal application (1).

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The 1st generation of pyrethroids was developed in the 1960s, the 2nd generation was developed in 1970s. Many of pyrethroids have been produced with improved physical properties (involatility, lipophilicity) and greater insecticidal activity (knockdown) since then (2). Pyrethroids disrupt the insect nervous system and this determines them to protect food grains and other agricultural products against pests. They began to be used as ectoparasiticides in veterinary and human medicine too (3, 4). They have replaced natural pyrethrins especially due to their better photostability gradually. Pyrethroids use has increased rapidly in the past three decades. Pyrethroids are thermostable and photostable, slightly soluble in

water and highly soluble in fats. The presence of halogens in some pyrethroids contributes to the greater persistence and provides better residual activity against insect together with higher potential negative effects on the environment (5).

Classification of pyrethroids

Pyrethroids are divided into type I and type II, based on their structure, chemical and neurophysiological properties and toxicological action. Type I pyrethroids are without a cyano moiety at the α-position (i.e. permethrin, bifenthrin, allethrin, tetramethrin, resmethrin, phenothrin, bioresmethrin, etofenprox, prallethrin, tefluthrin), while type II pyrethroids have an α-cyano moiety at the benzylic carbon of the alcohol portion of the ester (i.e. cypermethrin, cyfluthrin, deltamethrin, cyphenothrin, flumethrin, cycloprothrin, fenvalerate, fluvalinate). Type II pyrethroids are more effective (6). All pyrethroids affect the sodium channels of nerve filaments. They extend time of opening and closing of sodium channels and extend their depolarisation phase. Moreover, type II pyrethroids affect the GABA receptors in the nerve filaments and affect chloride and calcium channels (6-9). Type I pyrethroids cause a type I poisoning called *"T syndrome"*, whereas type II pyrethroids induce a type II poisoning, known as *"CS syndrome"* in mammals (2). T- syndrome mainly includes symptoms like aggressive sparing behaviour, increased sensitivity to external stimuli, fine tremors, prostration, coarse body tremor, increase of body temperature. Pyrethroids that induce a "choreoathetosis with salivation" response are called CS-syndrome pyrethroids and result in a broader range of toxic events due enhanced neurotransmitter release. Their main symptoms are: chewing, profuse salivation, pawing and burrowing, coarse body tremor, increased startle response, abnormal locomotion of posterior limbs, sinuous writhing (choreoathetosis) and clonic and tonic seizures (7). They cause cardiac contractions (3).

Summarized all pyrethroids interfere with nerve cell function by interacting with ion channels. Pyrethroids also modulate the release of acetylcholinesterase in the brain (10) and can inhibit ATP-ases (11). They can disrupt hormon-releated functions. But their effects on the endocrine system are not described uniformly (12).

Presence in the aquatic environment

Pyrethroids are absent in natural water normally. They may contaminate aquatic ecosystems as pollutants, because they are an important group of pesticides. The contamination of surface waters by pesticides used in agriculture is a problem of worldwide importance (10, 13). Ecological catastrophes following application of deltamethrin for mosquito control have already been in 1991 and 1995. Deltamethrin exposure have been one of main causes of massive eel (*Anguilla Anguilla L.*) devastation in Lake Balaton, Hungary (14). Pesticides are also very important in veterinary medicine as ectoparasiticides. They are popular due to their strong and extended insecticidal and simultaneously acaricidal effects. Pyrethroids are also used as antiparasitic drugs in human medicine and they are used extensively in urban settings to control several medically important insects that vector diseases. In aquaculture, pyrethroids are applied to control some parasitic diseases caused by, for example, *Lepeophtherius salmonis* or other sea lice in salmon farming. These products mainly based on deltamethrin are used in Scandinavian countries or Canada (15, 16). In addition to the recent increased interest in introduction of using deltamethrin in warm waters too, there are encouraging therapeutic results against isopoda with no side effects on the sea bass (*Dicentrarchus labrax L.*) (17).

Aquatic organisms can be affected by pesticides during their improper application or improper handling. Pesticides can get into the water directly due to the incorrect application. They can get into the water during the disposal of unused residues or due to accidents during transport. Pesticides also can get into the water indirectly after running off from surrounding treated products (18). The residues of cypermethrin have been widely detected in water and sediment samples from streams and rivers draining major agricultural districts (19).

Toxicity in the aquatic environment

Pyrethroids are fairly rapidly degraded in soil and plants in the environment (2). Pyrethroids induce rapid onset of poisoning symptoms but persist only for a short time in the water column due to ability of adsorption by organic matter and deg-

radation (20). The major degradation processes are ester hydrolysis and oxidation at various sites of the molecule. Pyrethroids have high hydrophobicity and they are rapidly and strongly adsorbed into particulate material (21). The pyrethroids are strongly adsorbed on soil and sediments. Pyrethroids are widely recognized as being strongly lipophilic, and thus highly hydrophobic (21-23), adsorbing almost exclusively to organic carbon molecules in water sediment slurries within 24 hours (24). Furthermore, pyrethroids have shorter chemical half-lives than their organophosphate predecessors, ranging from several days (22) to around one month in aerobic sediments (25). Sediment organic carbon plays a critical factor in determining the bioavailability of a given pyrethroid in a particular aquatic system, and accordingly, the pyrethroid's potential toxic effects (24). Microbial biodegradation of pyrethroids in aquatic system (in the sediment and water column) has been acknowledged to play an important role in the degradability and the persistence of the residues (26).

Fish sensitivity

Pyrethroids have been shown to be up to 1000 times more toxic to fish than to mammals and birds at comparable concentrations (5, 27). Fish sensitivity to pyrethroids may be explained by their relatively slow metabolism and slow elimination of these compounds (7, 28). It may be explained as a result of exposure of toxicokinetic (i.e. absorption, biotransformation, distribution and elimination) and toxicodynamic (i.e. biochemical and physiological effects) factors (7). Unlike most animals, in which pyrethroids have a short life and are readily metabolized, fish are reported to be deficient in enzymes that hydrolyze these insecticides (1, 29-31).

The hypersensitivity of fish to pyrethroid intoxication is due partly to species specific differences in pyrethroid metabolism, but second important factor is higher sensitivity of the piscine nervous system to these pesticides. Fish brain seems to be more susceptible to pyrethroids than mammal and bird brains are (1, 32). The third factor is route of exposure. Pyrethroids are absorbed directly via the gills into the blood stream (31).

Pyrethroids are inhibitors for fish carbonic anhydrase enzymes, and might cause undesirable results by disrupting acid–base regulation as well as salt transport. The most potent inhibitor is deltamethrin. The most affected CA enzymes are in muscle tissue and the lowest inhibition of CA enzymes is in liver tissue (33).

Types of poisononig

Acute toxicity

Acute toxicity is defined as a significant reduction in survival of the exposed organisms within a relatively short time and is expressed as the species specific median lethal concentration (LC50) (12). The value 96 h LC50 is under 10μg/L in fish generally. Salmonid species are more susceptible than carp species (5, 7). The 96 h LC50 of cypermethrin is 3.14 μg/L in rainbow trout (*Oncorhynchus mykiss*) (34) and 4.0 μg/L in Indian carp (*Labeo rohita*) (10). But deltamethrin is described to be more toxic in common carp (*Cyprinus carpio*) than in rainbow trout on the contrary (35). Acute toxicity also influences viability of embryos and leads to significant increase of dead larvae even if concentarion is orders of magnitude less (31, 36).

Chronic toxicity

Chronic toxicity effects can occur at exposure levels far below the concentration that causes lethality. Sublethal biological responses include behavior changes, reduced growth, immune system effects, endocrine effects including decrease of reproductive success, histopathological and biochemical changes (12). Disturbance of the non-specific immune system is connected with decreased production of leucocytes. Changes of colours and integrity of body surface develop during the weeks of exposure (37). Early life stages are more susceptible to chronic toxicity of pyrethroids than adult fish (5, 12, 38). Fingerlings of Indian carp change shape of their bodies in sublethal exposure. They become lean towards the abdomen position compared to the control fish and they seem to be under stress, but this is not fatal (10).

Toxicokinetics

Fish in general are exposed to pyrethroids through their gills, which are multifunctional and complex organs with which fish make intimate contact with their ambient water (39). Py-

rethroids are attracted to the non-water soluble components of cells due to their lipophilicity and permeate through the gills easily, even from water containing low levels of pyrethroids. This is a contributing factor in the sensitivity of the fish to aqueous pyrethroid exposures (40, 41).

When rainbow trout body was studied, the greatest amount of radiolabeled fenvalerate residues were found in the bile, then in the fat deposits and followed by the liver, gill, kidney and red blood cells. Concentration in the brain was lower than in most other tissues (42).

Common way of detoxification is hydrolysis in liver and plasma of animals. The acid and alcohol components of pyrethroids that result from ester hydrolysis are of minimal toxicity to any animals (1, 4). Hydrolysis is followed by hydroxylation and conjugation to glucuronides and sulphates, which are excreted in urine (4). But fish treated by pyrethroids do not show significant levels of ester hydrolysis products in urine or bile. It seems that permethrin elimination from fish is quantitatively different from that reported in mammals and birds, with oxidative degradation predominating and ester hydrolysis constituting a minor reaction (7). Oxidation products are most common, primarily due to ring hydroxylation and side chain oxidation reactions in fish (1, 7). Because of lack of hydrolysis detoxification, products of ester hydrolysis are rarely found (1) and only low levels could be confirmed (7).

Toxicokinetic experiments indicate that fenvalerate elimination rate in rainbow trout is much slower than in birds and mammals (1). The half-lives for elimination of several pyrethroids by trout are all greater than 48 h, while half-lives of elimination in birds and mammals range from 6 to 12 h (7).

Toxicodynamics

Pyrethroids bind to a receptors at the sodium gate of neuron and prevent it from closing fully. The resulting steady leakage of sodium ions into the neuron creates a less stable resting state and the neuron is susceptible to repetitive firing of nerve, which leads to hyperactivity, tremors and tetany (43, 44).

Effect of pyrethroids in mammals and insects depends on stereospecificity highly. Some isomers demonstrate strong potency and their mirror image isomers show almost no toxicity. The available data for fish are not so uniform (1, 7). Fish seems to be equally sensitive to both cis and trans isomers of permethrin (1). In contrast stereospecific influence of fenvalerate toxicity on fish is similar to that of mammals. The 2S pair of isomers is 3.3 times more toxic to fathead minnow (*Pimephales promelas*) than technical mixture with all four isomers (1, 45). Recent research indicates stereoselectivity in the estrogenic activity of permethrin, which results from stereoselective biotransformation of the parent compound to more estrogenic metabolites. 1S-cis-permethrin has a higher activity than the 1R-cis enantiomer (46).

Synthetic pyrethroids have deleterious influence on Ca-ATPases and other ATPases in vertebrates and invertebrates so additional toxic effect must be considered (1). Fish treated by cypermethrin show inhibition of gill Na+/K+ -ATPase activity which induce osmotic imbalance and influence maintenance of osmotic and ionic homeostasis (11).

It is difficult to differentiate between type I and type II syndromes in fish. Both types of pyrethroids cause similar neurological symptoms and fish generally become inactive before death (7).

Clinical symptoms of poisoning

The following clinical symptoms are observed during acute toxicity tests on rainbow trout and common carp: accelerated respiration, loss of movement coordination, fish lay down at their flank and move in this position. Subsequent short excitation stage (convulsions, jumps above the water surface, movement in circles) changes into a resting stage, and another short excitation period follows again. In the end fish fall into damp, move mainly at their flank. Respiration is slowed down, the damp phase and subsequent agony are very long (34, 47). Similar neurological symptoms could be observed after 2 weeks of exposure to subacute concentration of deltamethrin (1.46 µg/L) on monosex Nile Tilapia (*Oreochromis niloticus*). It is accompanied by colour darkening of the body surface, slight erosions and/or rotting of fins and tail, slimness, general loss of fish scales, eye cataract and sometimes exophthalmia. Internally, there is general congestion of the liver, kidneys, gills and blood in the abdominal cavity (37). Loss of equilibrium, vertically hanging, gill flailing, erratic swimming, swimming at the water surface, air gulping from the water surface or staying mo-

tionless on the aquarium bottom are observed during tests of acute toxicity of deltamethrin on the fry rainbow trout. The toxicity and presence of symptoms depends on increasing concentration and exposure time. Colour darkening is observed at concentrations higher than 8 µg/L (48). Study of acute cypermethrin toxicity on rainbow trout describes the almost identical neurological symptoms again (gill flailing, hyperactivity, loss of buoyancy and inability to remain upright) (27) and on common carp abnormalities of movement again and hyperactivity are described especially (49). Necropsy after acute toxicity tests on rainbow trout and common carp reveales watery mucus on body surface, excess fluids in body cavity and congestion of visceral vessels (2). Acute toxicity of cypermethrin in silver catfish (*Rhamdia quelen*) causes loss of equilibrium, vertical hanging in water, rapid gill movement, erratic swimming, sudden swimming motion in a spiral fashion after long periods of inactivity and sudden movement after prolonged inactivity in the tank bottom (50). Respiration and movement abnormalities are described mainly (30, 51).

Endocrine and reproductive disruption

Cypermethrin reduces the fertilization success in atlantic salmon (*Salmo salar*). It inhibites ability of male salmon parr to detect and respond to the female salmon priming pheromone PGF2α. The increase in expressible milt and the levels of plasma sex hormones are reduced in the presence of the pyrethroid as the result of impaired olfactory detection of the priming pheromone (32).

Biochemical and haematological profiles

Reduction in hepatic glycogen accompanied by increased level of plasma glucose is a common reaction of fish against xenobiotic insult followed by metabolic stress (51-54).

In rainbow trout cypermethrin causes significantly decreased concentration of ALP and significantly increased concentration of ammonia, AST, LDH, CK and lactate in blood plasma (34). In common carp bifenthrin causes increased concentration of ammonia, AST and CK too (54). In silver catfish cypermethrin causes increasing of levels Na^+, K^+, Mg^{2+}, P, urea, glucose, cholesterol, creatinine, AST and ALP, whereas total protein, triglyceride and ALT levels are reduced (50). In common carp deltamethrin causes decreased concentration of total protein in blood plasma (47).

An increase of plasma ammonia level is supposed due to an increase of amino acids catabolism and due to an inability to convert the toxic ammonia to less harmful substances and failure of ammonia excretion. Decrease of the levels of free amino acids accompanied by increase of the activities of AST, ALT and GDH in the vital organs is seen, because the amino acid catabolism is one of the main mechanisms, which ensure immediate energy demand to the fish (55). An increase of AST and CK indicates tissue impairment based on the stress (56). The increase of LDH level is connected with metabolic changes, i.e. the glycogen catabolism and glucose shift towards the formation of lactate in stressed fish, primarily in the muscle tissue (52). Metabolic stress induced by pyrethroids is accompanied by changes in levels of enzymes of antioxidant defense (57, 58).

Studies of haematological parameters are inconsistent. In catfish (*Heteropneustes fossilis*) deltamethrin causes a significant increase in RBC, but a small decrease in Hb, MCV, MCH and PCV (59). In common carp acute intoxication of deltamethrin causes decrease in RBC, Hb and PCV and has no effect on MCV, MCH, MCHC, total leukocyte count and relative as well as absolute counts of lymphocytes, monocytes, neutrophil granulocytes and their developmental forms (47). In rainbow trout cypermethrin causes a significant increase in the levels of RBC and a significant decrease in the Hb, MCH, MCHC, thrombocyte count and erythrocyte sedimentation rate (60). But only significant decrease in count of developmental forms of myeloid sequence and the segmented neutrophilic granulocytes is described in another acute toxicity test with cypermethrin and any effect on the haematological indicators such as RBC, Hb, PCV, MCV, MCHC, MCH and leukocytes (34). Elevation of the relative and absolute monocyte counts is described in common carp treated by bifenthrin (54). Deltamethrin causes decreased lymphocyte and basophile percentages and decrease of total leukocyte and erythrocyte counts, Hb and PCV simultaneously with serious hypoproteinaemia, hypoalbuminaemia, hypercholesterolaemia, hyperglycaemia in Nile tilapia exposed to subacute concentration for weeks (37).

Post-mortem findings

Severe teleangioectasiae are revealed in secondary lamellae of gills, with the rupture of pillar cells in 50% of fish treated by bifenthrin (54). The most common gill changes of fish treated by deltamethrin are desquamation and necrosis. It is followed by the lifting of the lamellar epithelium, oedema, aneurism, hyperplasia of epithelial cells and fusion of the secondary lamellae. These changes are results of direct responses of gill to the action of deltamethrin and simultaneously defense responses of organism against toxicant to make it more difficult to access to blood stream (61).

Bifenthrin causes degeneration of hepatocytes, especially in periportal zones, in 40% of treated fish. Affected hepatocytes show pycnotic nuclei and many small or single large vacuoles in the cytoplasm. Vacuole shape is typical for fatty degeneration of liver. It can imply the influence of pyrethroids in the digestive tract. (54).

Deltamethrin destructive effects in fish kidney are characterized by degeneration in the epithelial cells of renal tubules, pycnotic nuclei in the haematopoetic tissue, dilatation of glomerular capillaries, degeneration of glomeruli, intracytoplasmatic vacuoles in epithelial cells of renal tubules with hypertrophied cells and narrowing of the tubular lumen (61).

Factors influencing pyrethroids toxicity

A lot of factors can modulate the toxicity. Many synthetic pyrethroids have their 96 h LC50 values under 1µg/L, while chronic toxicity can be recorded at one to two orders of magnitude lower than that (5). Fish toxicity studies vary widely in their methodology (e.g., static conditions vs. flow-through exposures, nominal concentrations added to the water vs. measured concentrations). A lot of studies in standardized water demonstrate extraordinary toxicity, however field trials show the pyrethroids to be less potent than expected from laboratory studies. It is determined that pyrethroids, with their extremely low water solubility and high affinity for particulate matter in solution, do not remain bioavailable for uptake by the fish in the field ponds. When the pyrethroids molecules bind to the suspended solids or the sediment, the resultant toxicity is orders of magnitude less than predicted by the clean water assays (1).

Currently available formulations of pyrethroids are oil based, emulsifiable concentrates (EC). The emulsifiable formulation keeps the pyrethroids in solution longer compared to the technical chemicals and the pyrethroids adsorb to the glass quickly. Pyrethroids tend to bind to the glass and plastic (62). EC formulations are usually two to nine times more toxic than the technical grade forms, most likely due to synergistic interactions (63).

The ionic characteristics of the water can exert influence on the toxicity of pyrethroids to fish. Water hardness (summary Ca^{2+} + Mg^{2+}) is shown to be a factor in bluegill (*Lepomis macrochirus*) susceptibility to fenvalerate. The LC50 values are twofold higher in very soft water, compared to hard water. Increased toxicity on bluegill fry is recorded when salinity raises (64). Pyrethroids are more toxic at lower temperatures and conversely fish are more susceptible at lower temperatures (1, 5, 13, 44). There is a possible increase in the toxic impact of pyrethroids on reproduction during spawning season in the cold water (32).

Pyrethroids appear to be generally more toxic to smaller fish than larger ones (5, 13, 51). Fish embryos appear to be less sensitive to pyrethroids than larvae (12).

Toxicity of pyrethroids is dramatically influenced by the presence of particulate matter in the water column, probably through adsorbtion of the very lipophilic toxicant molecules to the suspended matter, sediment and dissolved organic matter (40, 65). That is why adsorbtion of pyrethroids is more quick in system like farm ponds with organic matter than in typical streams (12).

Piperonyl butoxide is commonly added to pyrethroid products to enhance the toxic effects of the active ingredient. Piperonyl butoxide inhibites a group of enzymes, which are involved in pyrethroid detoxification (12).

Conclusion

Pyrethroids are predominant class of insecticides. Their widespread use represents an increasing threat of water pollution. Investigation of their properties in connection with environment, acute and chronic effects and potential bioaccumulation must continue thoroughly. Research on non target species including fish should be really detailed.

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VPLIV PIRETROIDOV NA RIBE

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Povzetek: Piretroidi spadajo med najbolj pogosto uporabljene pesticide po vsem svetu. Njihova masovna uporaba ogroža naravno okolje, vključno z vodnimi ekosistemi. Čeprav se piretroidi v tleh in rastlinah hitro razgradijo, so za ribe zelo strupeni. Glede na svoje značilnosti se piretroidi delijo v dve skupini, tip I in II. Oba povzročata podobne nevrološke simptome. Piretroidi vplivajo na delovanje natrijevih kanalčkov v živčnih celicah, piretroidi tipa II poleg tega vplivajo tudi na kloridne in kalcijeve kanalčke. Ključnega pomena pri zastrupitvi rib s piretroidi je njihovo počasnejše izločanje kot pri pticah in sesalcih. Piretroidi se hitro absorbirajo preko škrg, po krvi pridejo v žolč, jetra, ledvice in rdeče krvne celice, kjer se presnavljajo s hidrolizo, hidroksilacijo in vezavo na glukuronide in sulfate. Akutna zastrupitev rib se kaže z motnjami v gibanju in dihanju ter smrtjo. Kronična izpostavljenost piretroidom pri ribah povzroči spremembe v obnašanju, krvni sliki, histopatološke spremembe, zmanjšano rast ter vpliva na imunski in endokrini sistem. V obeh primerih pa je tudi prizadeta reprodukcijska sposobnost. Toksičnost piretroidov je odvisna od številnih notranjih in zunanjih dejavnikov.

Ključne besede: piretroidi; nevrotoksičnost; občutljivost; fiziološke motnje