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The Aquatic Environment and Pharmaceutical Products- A Review

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ABSTRACT

In recent decades, more and more pharmaceutical products exist in the nature. In many parts of the Globe, and especially close to urban areas, medicines have been presented in surface waters, groundwaters and soils. This is related to the growth in the utilisation of medicine and the development of analytical detection techniques in order determination of these traces of compounds in the environment. Pharmaceuticals reach the nature through the discharge of effluents from urban waste water treatment plants, the discharge of effluents from hospitals and drug factories, the using of sewage sludge in agriculture, the breeding of herbivorous animals, the treatment of pets, the spreading of manure and aquaculture, the improper disposal in landfills of unused pharmaceutical substances and contaminated waste. Researches showed that pharmaceutical products and residues are mainly present in water bodies and that they are partly eliminated by conventional wastewater treatment plants, which currently cannot effectively filter all pharmaceuticals.

KEYWORDS: Aquatic ecosystems, Environment, Pharmaceutic contaminants, Toxicity

1. INTRODUCTION

Pharmaceuticals are a very heterogeneous group of chemicals used to treat, diagnose and prevent human and animal diseases (Collard et al., 2013; Gröner et al., 2015). Large amounts of chemicals are also used in current agricultural practices in order to stimulate the increase of the production in animal breeding (Zuccato et al., 2010; Liu et al., 2014 a).

The presence of such compounds in the environment was neglected until several decades, largely due to their extremely low levels in the wild, which made them almost undetectable in the aquatic environment until the 1960s (Burkina et al., 2015).

Research proved that pharmaceuticals are present worldwide in groundwater, surface water, wastewater, soil and biota (aus der Beek et al., 2016; Łukaszewicz et al., 2018; Patel et al., 2019).

In the last 50 years, a large number of new chemicals have been manufactured, some of them in large volume. Their use and consumption is constantly increasing because on the market appears continously new medicine, the population of the world is increased and the demand for animal proteins is enormous (Khan et al., 2020; Khan et al., 2021).

Among all the industries, the pharmaceutical one presents the highest developpement and innovation rhythm. In USA, in 2020, the economic experts evaluated pharmaceutical production at 1,12 trillion USD and they estimate that it will reach at 1,57 trillion USD in 2023. In the next years, it will estimate a mean growth rate of 6,5%. The drugs with the highest growth rate (12 %) are from the antitumors, antirheumatic and antidiabetics group.

The growth rate of pharmaceutical production and diversification exceeds that of most of the previously recognised agents of global change, such as the increase in the concentration of carbon dioxide in the atmosphere, nutrient pollution, habitat destruction and biodiversity loss (Bernhardt et al., 2017).

In Germany, the use of pharmaceuticals is expected to increase by 43-67% until 2045, from the 2015 reference value. Drug consumption is about 20 times higher in the older population than in the younger one. It is believed that an aging population is the main engine, since it is estimated that until 2045, 9 % of humans will reach the age of 60 and more (Civity, 2017). Currently, approximately 4000 medicines are available on the global place, with an annual global use of close 100,000 tons/year (Lindim et al., 2017). Among these, more than 3000 medicines are recorded in Europe (Taylor et al., 2014).

Until present, more than 250 antibiotics commonly used as human and veterinary drugs have been registered and used (Kovalakova et al., 2020; Zainab et al., 2020). The usage of antibiotics by people recorded a growth by 65% in the period 2000 - 2015, with consumption expected to growth to 200% until 2030 (Polianciuc et al., 2020; Scaria et al., 2021).

The proportion of veterinary antibiotics will reach 105,596 tons in 2030 (an increase of 67%), due to the growing demand of consumers for animal products (Van Boeckel et al., 2015).

Researches from the last decades proved that pharmaceuticals products are in the environment due to the widespread and continuous usage (Kümmerer, 2009; Ben et al., 2019). Several thousand tonnes of these medicines have been showed to be produced yearly, and they are entered into different ecosystems, including waters (Ji et al., 2012; Al Aukidy et al., 2012).

Also, it is estimated that 10% of pharmaceuticals pose a potential risk of pollution to the environment (Küster and Adler, 2014; Boxall et al., 2012; Carvalho and Santos, 2016). Their number is increasing every day around the world, which makes it quite difficult to establish rules. Only a small percentage of these pharmaceuticals undergoes rigorous safety and toxicity tests (Landrigan et al., 2018). The pollution with pharmaceutical products of the aquatic and terrestrial environment makes that these products to be assimilate by respective flora and fauna or to be bioaccumulate (Arnold et al., 2014).

The impact of these pollutions on the environment depends by a serie of factors like usage mode, toxicity, persistence and mobility, source and timing of pollution, sensitivity and stochastic environmental condition (OECD, 2019).

2. THE EXISTENCE OF PHARMACEUTICALS POLLUTION

Pharmaceuticals in the environment mainly include medicines administered to humans or animals, such as antibiotics, anti-inflammatories, their metabolites, as well as transformation products, which are either excreted in feces and urine, from domestic WWTP, clinics, hospitals, the pharmaceutical industry, aquaculture wastewater (Katsikaros and Chrysikopoulos, 2020; Li et al., 2020; Servadio et al., 2021; Jiang et al., 2021; Li et al., 2021; Yang et al., 2021).

The first research on the detection of pharmaceuticals in the environment began in the USA in the 1970s (Garrison et al., 1976). Then, in the sewage water of the Kansas City, was discovered clohidric acide, an metabolite of fibrates used for lowering lipids (Hignite and Azarnoff, 1977). Later in the 1990s, this is was evidenced in the wastewater from Germany (Heberer and Stan, 1997; Ternes et al., 1998). In the 1970s it was constated the presence of the synthetic hormones used in contraceptive drugs (Tabac and Bunch, 1970; Norpoth et al., 1973; Tabak et al., 1981; Aherne and Briggs, 1989).

In 1999, Daughton and Ternes described for the first time medicines from the environment as ″agents of subtle change″, being recognized the harmful impact on the environment (Daughton and Ternes, 1999).

The best-known and demonstrative example of the harmful effects of pharmaceuticals on wildlife was aimed at the dramatic decline in populations in eagle species in India and Pakistan, leading to localized extinctions (Oaks et al., 2004).

In the middle of 1990s , Ternes, Hirsch, Mueller and Heberer developed the methods for the determination of neutral drugs as betablockers in aquatic matrices using GC/MS (Gas chromatography/ Mass spectrometry) and LC/MS/MS (Liquid chromatography and two mass spectometry analyzers) (Ternes et al., 1998).

In 2006, Mitani and Kataoka make the first report related the determination of flouroquinolones in environmental water by in-tube solid phase microextraction coupled with liquid chromatography – tandem mass spectrometry (Mitani and Kataoka, 2009).

The existence and detection of active pharmaceutical ingredients (APIs) in the surroundings has, over the past 20 years, attracted the attention of the scientific community, and this has only been possible with the advent of sophisticated methodologies of analytical chemistry, high-resolution mass spectrometry (HRMS) with LC, especially environmental transformation products (Richardson and Bowron, 1985).

In present, the determination of medicines in waters by solid phase extraction, coupling of membrane filtration and advanced oxidative processes followed by identification and quantification using either liquid chromatography and/or gas chromatography, LC-MS and/or GC-MS (Ganiyu et al., 2015).

In recent decades, the unintentional existence of pharmaceutical pollutions in the surroundings around the world is bigger and it can have a noxious effects on surroundings (aus der Beek et al., 2016; Łukaszewiecz et al., 2018; Patel et al., 2019).

Pharmaceutical products from the environment pose a potential threat for the human health and for the ecosystems (La Farré et al., 2008).

Studies proved that pharmaceutical products come into the environment from human and veterinary use, through the excretion of both metabolised and non-metabolised medicines, the elimination of unused medicines (Fent et al., 2006; Carvalho and Santos, 2016; Ben et al., 2019).

Scientifically, it was proved that antibiotics from the surroundings determine the development of multi-resistant bacteria (Bruhn, 2003; Kümmerer, 2009; Pawlowski et al., 2016).

Most antibiotics can not be fully used by the human or animal body, the metabolism of pharmaceuticals is not more than 15% [43], the rest being excreted through by urine and feces (Zuccato et al., 2010; O′Brien and Dietrich, 2004).

These non-metabolized compounds are thrown into household effluents and discharged to WWTP. Wastewater treatment plants, hospitals and industrial effluents constitutes the main anthropic sources of pharmaceutical pollution in the environment (Barbosa et al., 2016; Rizzo et al., 2019).

Present technological processes are not adapted for total removing these pollutants and they arrive in the waters (Yao et al., 2021).

Researches realised at 3 WWTP from Switzerland highlited the fact that the mean elimination efficiency of clarithromycin was 81% and for thilosin it was 76% (McArdell et al., 2003).

Studies conducted at 2 plants from Hong Kong conclusioned that erythromycin was eliminated in a rate of 43%, ciprofloxacin in 66% of cases and Aureomycin in 83% of cases (Li and Zhang, 2011).

For the antiepileptic medicine carbamazepine the rate of elimination was only 8%. The clofibrate drug using for the cholesterol-reducing has a unsignificance rate (Nkoom et al., 2019; Kumar et al., 2019).

The presence of these compounds in wastewater demonstrates that pharmaceutical polution can not be eliminated totally in the WWTP (Jelic et al., 2011; Tran and Gin, 2017; Madikizela et al., 2020; Mousel et al., 2021; Rout et al., 2021; Shi et al., 2020), and they arrive in the waters being a ecological risks for organisms (Morosini et al., 2020).

Wastewater from clinics and hospitals (HWW) have in composition, in addition to antibiotics and analgesics, anti-inflammatories, psychiatric medicine, β-blockers, anesthetics, disinfectants, chemicals from laboratory activities and development and fixation solutions from the processing of photographic films and X-ray contrast media (Chartier et al., 2014).

They are typically thrown into sewers and transported to WWTP without any pretreatment (Dinh et al., 2017; Maheshwari et al., 2016). Studies showed that hospital wastewater have a big loading of pharmaceutical pollutants (Al-Maadheed et al., 2019) related to the municipal wastewater plants (Santos et al., 2010; Wang et al., 2014; Azuma et al., 2019).

Another important pollutant is pharmaceutical industry (Giri and Pal., 2014).

In wastewater from a chinese drug factory, important quantities of oxytetracycline (600mg/l) and oxalic acid (9100 mg/l) was determined, concentrations being by 106 times bigger than normally (Cadoso et al., 2014).

Another group of pharmaceutical pollutant are medicines which residues arrive in sewage or in rubbish (Ruhoy and Daughton, 2008).

Studies conducted showed that in the municipal solid waste was found big quantities of residues pharmaceutical pollutants (8,1 mg/kg) which affects the quality of groundwater (Musson and Townsend, 2009; Chung et al., 2018; You et al., 2018; Zhao et al., 2018).

Another important sector of economy which contribute to the pollution of the environment is agriculture through zootechny. This sector is characterised by a big consumption of medicine used in veterinary purpose and for stimulating production.

The pollution of the environment is done by urine and the feces of the animals, incorectly elimation of the unused medicine and animal’s food. In the rubbish was detected tens of μg/l of antibiotics (Zhi et al., 2018), antihelmintics and NSAIDs (Łukaszewicz et al., 2016; Petrie and Camacho-Munoz, 2020).

In aquaculture, several types of pharmaceutical products from the group of antibiotics, antiparasitics, hormones and stimulants are used, which are generally applied together with food (Pham-Duc et al., 2019; Hossain et al., 2017).

Considering that pharmaceuticals products are applied directly in water, some of them being partly metabolised or unmetabolised (Zhang and Li, 2007), the risk of pollution is big (Santos and Ramos, 2018).

A study conducted at a fish and shrimp pond from China showed that in the waters remained o big quantity of antibiotics, ranged between 65 and 7729ng/l (Zou et al., 2011).

A big quantity of fluoroquinolones (136ng/l) was detected in the rivers from Poland (Wagil et al., 2014; Wagil et al., 2015).

The risk is big for the environment if the water from the pond enters directly into the natural receptors, without being treated.

The accidental presence of pharmaceutical pollutants in rainwater may be caused by the illegal discharge of waste water and the overflow and leakage of surface due to leaky systems (Launay et al., 2016; Tran et al., 2015b; Yin et al., 2019).

An accident of this kind occurred in Poland in 2019, when a leak of more than 3.6 million m^3 of untreated wastewater was discharged into the Vistula River (Stepnowski et al., 2020).

Another problem is that of poorly developed countries that do not apply a wastewater treatment technology and they are discharged directly into rivers. Thus, the concentrations of pharmaceutical pollutants in rivers are similar to those in untreated waters in developed countries (Williams et al., 2019).

3. EFFECTS OF PHARMACEUTICAL POLLUTANT ON THE ECOSYSTEM

The accidental existence of medicines in water at quantities that have harmful effects on aquatic organisms is more and more relevant (Nunes, 2015a). These molecules have harmful effects and cause the behavior change of organisms such as phytoplankton (Grzesiuk etal. 2018), amphipods (Borgmann et al., 2007), crustaceans (De Lange et al., 2006), fish (Li and Zhang, 2011; Ogueji et al., 2018) and mammals (Winter et al., 2010).

Many groups of molecules are determined in different water bodies because of their use at humans and animals. These groups of molecules found in the nature include non-steroidal anti-inflammatories, antibiotics, anticonvulsants, antidepressants and oral contraceptives, and they are described in water quality reports.

The harmful components for animals of medicines are not well established, but proteomic responses and gene expression are much researched by specialists (Liu et al., 2016; Wang et al., 2017; Zhang et al., 2021).

In waters, the quantities of pharmaceutical pollutants are very small, with ranges from ng/L to µg/L, but having a permanent existence in nature, they cause undesirable impacts on non-target aquatic organisms. Toxicity varies depending on the trophic level of living things and the class of the pharmaceutical product. Low trophic species, cyanobacteria and algae, show a higher sensitivity than organisms with higher trophic levels, crustaceans and fish (Gonzáler-Pleiter et al., 2013).

Cyanobacteria and algae, are the most vulnerable aquatic species, since pharmaceutical contaminants can affect their development, feeding and antioxidant systems, and harmfulness is associated with the group, dose of the product and time of exposure. The development and feeding of the cyanobacteria Microcystis aeruginosa was supported by minute amounts of 0.001–0.1 µg/L of Erythromycin, but cancelled at amounts greater than 0.1 µg/L (Du et al., 2018).

Enrofloxacin and norfloxacin inhibited the growth of Chrysosporum ovalisporum cyanobacteria, but had a less inhibitory effect on Chlorella vulgaris green algae (Chen et al., 2020).

The antidepressant drug sertraline and the compounds testosterone and 4-hydroxyandrostendione were very harmful to the crustacean species Daphnia magna (Minagh et al., 2009), which induced strong changes in the population of this species (Barbosa et al., 2008).

Ibuprofen and paracetamol proved very dangerous for another crustacean, namely Neocaridine denticulate, causing its death (Sung et al., 2014).

Chronic exposure to anti-inflammatory drugs of marine mussels, Mytilus sp., altered energy metabolism′ characteristics (Schmidt et al., 2014). The respiratory activity of exposed organisms interferes with the mechanisms used by animals to have energy. Thus, hypolipidemic fibrates used in the treatment of people thus stimulates the less energy-efficient anaerobiotic pathway for aquatic organisms (Nunes et al., 2004).

Fish are the most evolved group of aquatic food chain creatures. Many particularities of their physiology do them to be vulnerable to pharmaceutical absorption and toxic consequences. The absorption of medicines by fish can take place both through the dermal surface and through the gills for pharmaceuticals associated with water/sediment, orally through diet or through the maternal route (Corcoran et al., 2010).

Widely used nonsteroidal anti-inflammatory drugs (NSAIDs) and some of their metabolites are very often detected both in WWTP and in water bodies at very small amounts (Ascar et al., 2014; Burkina et al., 2015).

Numerous studies report that traces of NSAIDs concentrations, such as diclofenac, can have a negative impact on different animals, affecting the reproductive and renal systems (Corcoran et al., 2010; Islas-Flores et al., 2013). Some researches proves that diclofenac has a negative impact on the organs of fish at important concentrations for nature (Schwaiger et al., 2004; Triebskorn et al., 2004).

Diclofenac may induce oxidative stress in Danio rerio (Diniz et al., 2015) and carp (Cyprinus carpio) (Islas-Flores et al., 2013; Saucedo-Vence et al., 2015) and it caused immunosuppression and genotoxicity on a primary culture of the monocytic line of the kidney prior to the hoplias malabaricus species (Ribas et al., 2014). It altered blood sugar and plasma proteins, ionoreglatory responses (Na+, K+ and Cl-1) and had a profound influence on thyroid hormones, hematological and enzymatic profile for Cyprinus carpio (Saravanan et al., 2014; Saravanan et al., 2011; Saravanan and Ramesh, 2013).

Diclofenac also affected gene expression in rainbow trout (Oncorhynchus mykiss) (Cuklev et al., 2011) and Japanese medaka (Oryzias latipes) (Gröner et al., 2015) and it changed Japanese medaka feeding behavior (Nassef et al., 2010). Histopathological alterations in the gills with epithelial lifting, necrosis of hair cells, hypertrophy and hyperplasia and kidneys, with induction of glomeruloneophritis, hyaline droplet degeneration and necrosis of endothelial cells was found in rainbow trout chronically exposed to this medicine (Schwaiger et al., 2004; Triebskorn et al., 2004).

NSAIDs can have harmful effects on reproduction in fish, indomethacin has been shown to change the ripening and ovulation process of oocytes in zebrafish (zebrafish – Danio rerio) to an amount of 100 mg/L (Lister and Van der Kraak, 2008). The highly prescribed drug paracetamol as analgesic and antipyretic has been shown to be toxic to fish. It can be hepatotoxic to overdose, a well-known situation in both animals and humans (McGill et al., 2021; Beger et al., 2015; Ramachandran and Jaeschke, 2017). Exposure of rainbow trout to this drug induced oxidative harmful effects and peroxidative damage (Ramos et al., 2014) and caused endocrine disorders with decreased testosterone levels and increased levels of estradiol, hepatotoxicity, genotoxicity of DNA damage and tissue damage at male fish Rhamdia quelen after subchronic exposure (Guiloski et al., 2017a).

Ketorolac has induced oxidative damage and changes in antioxidant status in carp and is a potential genotoxic agent due to the increased frequency of micronuclei in exposed individuals (Galar-Martinez et al., 2016). The subchronic exposure of zebra fish to acetylsalicylic acid caused a growth in biotransformation system and antioxidant enzymes and a decrease in lipid peroxidation, and at carp it had significant effects on hatchability, early ontogeny, morphology and morphometric and state characteristics, and also changes in oxidative stress parameters (Zivna et al., 2015).

Regarding antibiotics in water bodies, little data in specialized studies report the harmful impact of these drugs in fish. The existence of antibiotics in water has been researched in terms of their contribution to increasing bacterial resistance and effects on human health through the transfer of resistance to human pathogens. In fish, exposure to enrofloxacin can lead to disorders such as oxidative stress, lipid peroxidation and neuronal dysfunction for Pangasianodon hypophthalmus (Neil et al., 2009). Tetracycline can exert pro-oxidative activity by increasing CAT liver activity and significant histological damage in the gills for Gambusia holbrooki (Nunes et al., 2015c).

Yonar et al. (Yonar, 2012; Yonar et al., 2011) have researched the impact of oxytetracycline on rainbow trout for 14 days and showed oxidative effects. Oxytetracycline has also been shown to suppress specific and nonspecific immune system parameters such as hematocrit, leukocyte count, production of oxidative radicals, total plasma proteins and levels of immunoglobulins and phagocytic activity.

Some studies have reported that amoxicillin induced oxidative stress in several organs of Cyprinus carpio (Elizalde-Velázquez et al., 2017), causes changes in catalase and glutathione-S-transferases in Danio rerio (Oliveira etal., 2013) and determine genotoxicity by growth the frequency of micronuclei and the percentage of DNA in the tail of comets in the comet test (Anlas and Ustuner, 2016).

Norfloxacin, oxytetracycline and chlortetracycline (Ji et al., 2012; Liu et al., 2016) may affect vitelogenin in fish. Chlortetracycline demonstrated potential estrogenic activity because it increased estradiol levels in medaka men after 14 days of exposure (Ji et al., 2012; Burkina et al., 2015).

Rodrigues and others researchers (Rodrigues et al., 2016) reported genotoxicity occurence in blood cells, suggesting that harmful effects of erythromycin-induced DNA may be linked to observed oxidative damage, which has been demonstrate to appear at important amounts of erythromycin for the environment. Antiparasitic medicine might have a enormous toxicity related to antibiotics, thus is a damage for embryos of zebra fish (Carlsson et al., 2013).

Azoles interfere with steroid biosynthesis and therefore the equilibrium of sex hormones at non-target species, including fish (Matthiessen et al., 2002).Toxic effects of these chemicals include inhibition of brain activity and ovarian aromatase at trout exposed to fadrozole and prochloraz (Ankley et al., 2002) and rainbow trout exposed to clotrimazole (Hinfray et al., 2006; Burkina et al., 2015) and they can act as endocrine disruptors.

Another group of pharmaceutical compounds prioritized for environmental risk assessment are antilipidic drugs, mainly fibrates, whose main action is lowering plasma triglyceride levels and concentrations of total cholesterol and low density lipoprotein, as well as to produce a mild growth in high-density lipoprotein cholesterol (Burkina et al., 2015). Fibrates presented in the aquatic environment, even in the micromolar concentration range, can cause adverse changes to non-target organisms (Santos et al., 2010). Ecologically relevant concentrations of gemfibrozil (1.5 μg/L) affected testosterone levels in golden fish, providing important data that this molecule can act as an endocrine disruptor at this fish and induced nuclear abnormalities (ruptures and DNA micronuclei) in the erythrocytes of Sparus aurata (Barreto et al., 2017).

Clofibric acid also alters the hematological and enzymatic profiles of Cyprinus carpio freshwater fish and has harmful effects for the reproductive system, which reffered at decreased sperm counts, impaired spermatogenesis and a low quantity of androgens in plasma (Corcoran et al., 2010). Fish are very vulnerable to endocrine modulation, especially through exposure to estrogens, steroids excreted by women, either naturally or as a result of oral contraception (Crane et al., 2006).

Three sterols, 17β-natural estradiol (E2), natural estrone (E1) and synthetic 17α-ethinyl estradiol (EE2), used in contraceptives, constitute an important pollution source in the nature (Burkina et al., 2015). Some researches give data that exposure to these molecules may induce abnormal modulation or disruption of development and reproduction at fish species.

The estrogenic compound 17β-estradiol induced oxidative stress to various organs for common carp (Cyprinus carpio) (Gutierrez-Gomes et al., 2016), which causes endocrine disorders and affects normal reproduction (testicle development, spermiation and reproductive behavior), which can have dramatic consequences on the reproduction of this species (Bjerselius et al., 2001; Schoenfuss et al., 2002; Oshima et al.,2003). Exposure to pharmaceutical estrogen EE2 and the anabolic androgen 17β-trenbolone (Tb) for zebra fish (Danio rerio) induces an increased quantity of vitelogenin and the feminization of fish (Örn et al., 2006).

Decreased gonadal development, fecundity and/or low fertility (Xu et al., 2008) and changes in gonadal differentiation (Fenske and Senger, 2004) are among the most frequently showed impacts. Neuroactive compounds are drugs that act on the nervous system.

Antiepileptic drugs have effects on the central nervous system by decreasing general neuronal activity (Fent et al., 2006). Carbamazepine has various toxic effects on fish, including severe histological alterations in the kidneys and moderate/mild reactions in gills and livers (Triebskorn et al., 2007), being lethal to zebrafish at concentrations of 43μg/L (Tracker, 2005; Li et al., 2011).

Noxious impact of diazepam on the liver and gill tissues in Clarias gariepinus fish have been suggested by changes in the activities of antioxidant defense enzymes and lipid peroxidation (Ogueji et al., 2017). Oxidative effects and obvious behavioral changes in males Gambusia holbrooki (Nunes et al., 2008).

Antidepressants constitue an extremely important group of medicinal contaminants, many researches showed that these molecules may represent a big risk level to fauna from the water (Brodin et al., 2013; Melvin, 2017). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (IRSN) are used as drugs to treat conditions associated with depression, anxiety and other psychological disorders (Santos et al., 2010; Melvin, 2017). These psychoactive drugs have the ability to alter normal behavioral patterns (Melvin, 2017).

In the Japanese medaka it has been proven that serotonin induces the maturation of oocytes (Iwamatsu et al., 1993). This finding is important in aquaculture to increase fish production.

Another SSRIs, sertraline, exhibits very toxic properties, since it has the ability to bioaccumulate itself in different tissues of fish, especially in the liver and brain, and causes biochemical and behavioral changes in fish (Xie et al., 2015). Fish exposed to bigger amounts of this medicine presented a decrease in breathing and a loss of coordination of movements (Minagh et al., 2009; Santos et al., 2010).

In wild fish populations, detectable amounts of fluoxetine were found in the tissues of their bodies (Melvin, 2017). These drugs act on fish due to their bioaccumulation potential and exert toxic effects of changing reproductive parameters, including abnormalities of the testicles in exposed males (Dorelle et al., 2017), an increase in plasma levels of 17β. -estradiol (E2) in males of Carassius auratus (Mennigen et al., 2010) and females of Japanese medaka, Oryzias latipes (Foran et al., 2004).

At caras carp (Carassius auratus) significant improvements in enzymes involved in the antioxidant defense mechanism, neurotransmission, swimming activities and a decrease in the tendency to escape, the rate of feeding and the consumption of food were observed (Xie et al., 2015).

B-blockers are medicine with a noxious impact on the environment, even at very low amounts (Diniz et al., 2015). Propranolol causes a decrease in testosterone levels in the Japanese medaka (Huggett et al., 2002).

At fish exposed to metoprolol, histological changes were observed in cell areas adjacent to liver vessels for concentrations above 1μg/L (Triebskorn et al., 2007).

The discharge of ilegal medicine in water bodies produces addiction in fish and changes their habitat (Brodin et al., 2013).

Fish exposed to amounts of methamphetamine from the nature, will develop addiction and will be attracted to live near discharges of wastewater treatment effluents. Wastewater effluents contains many nutrients, giving additional energy to attract fish to spring in these areas (Boulêtreau et al., 2011).

Research papers on the subject have clearly showed the receptiveness of many species to numerous pharmaceutical products discharged in nature, highlighting the potential toxicity of many drugs, characterized to date for a large number of organisms.

4. CONCLUSIONS

The numerous researches carried out, so far, prove that the pharmaceutical products discharged in the aquatic environment are biologically active and persistent and are able to exert significant risk effects on many organisms, even in very low quantities.

The persistence of pharmaceuticals in the environment could not only harm ecosystems and wildlife, but also weaken the effectiveness of those pharmaceuticals, especially in the case of antibiotics, as they can lead to antibiotic resistance.

Studies are required for all pharmaceuticals on safety and toxicity for the environment. Government rules are also necesary to check the contribution of drugs in nature. The research of noxious impacts involves the development, implementation and validation of new analytical tools. Long-term research is needed to promote the bioaccumulation in important interval of the life cycle of organisms that will allow a good knowledge of the impact caused by pharmaceutical molecules.

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