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WATER CONTAMINATION BY DRUGS

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ABSTRACT

The presence of drugs in water bodies in the contemporary scenario is increasingly active causing problems both for marine biota, faunal biodiversity and floristic endemic. The evaluation of microbiological parameters is needed by withdrawal of several samples of fresh water from rivers and other water bodies of interest in order to identify and detect possible pathogens linked to inadequate release of drugs that cause water contamination and, therefore, in other living organisms. This review aims at diagnosing the susceptibility of these drugs released into water bodies, whether through inadequate disposal of wastewater and water contaminated by drugs of their own pharmaceutical industries, whether launched by the general population that, for lack of information and tax incentives, throw in water bodies all kinds of drugs through various home launched.

KEYWORDS: Drugs, contamination, water, pathogens.

1. INTRODUCTION

The natural resource "water" is one of the most important for humanity (perhaps the most important), since in addition to being fundamental for the maintenance of life, this resource is directly or indirectly linked to most of the productive processes of our Contemporary society[1].

Brazil is among the countries that have the most potable water in the world and it is therefore of the utmost importance that the State establishes and implements policies for the conservation of water resources. In Brazil, the legal framework for the entire water management process is Federal Law 9.433 / 97, which established the National Water Resources Policy, in effect creating the National System for Water Resources Management[2].

Federal Law No. 11,445 / 2007, known as the National Guidelines for Basic Sanitation (LNSB), regulated by Federal Decree No. 7,217 / 2010, which establishes, among its fundamental principles, the universalization of the provision of services (article 2) . The universalization is conceptualized as the progressive extension of the access of all occupied households to basic sanitation (article 3, item III)[3].

In the context of the sectoral regulatory framework, basic sanitation is defined (article 3, item I) as the set of services, infrastructures and operational facilities for water supply, sanitary sewage, urban cleaning and solid waste management and urban drainage. However, unfortunately in the country still does not exist in a specific way[4].

Waste management is addressed in specific regulations in sectors of the pharmaceutical production chain according to Moura (2013)[4], such as ANVISA's RDC nº 306/2004 and CONAMA Resolution nº 358/2005 (management and final destination of RSS), and DRC no. 17/2010 of ANVISA (Good Manufacturing Practices), but the current norms do not consider the shared responsibility of each entity in the pharmaceutical chain, nor do they consider household residues of medicines; therefore the disposal of expired drugs, out of specification, leftovers, incorrect packaging etc., is done by the majority of the population.

It is estimated that in Brazil, the volume of household waste of medicines will turn around from 4.1 thousand to 13.8 thousand tons per year[5].

The objective of this review is to carry out the bibliographic survey of studies on the contamination of drugs in water, as well as those that are the main ones affected by their effects and the types of contaminants with their respective degree of concentration and incidence.

The focus will still be on the major pathogens that may be caused by the release of certain drugs. We have also focused this review on the possible causes of incorrect drug delivery in water so that all local society benefits from the information and uses it as a tool for collecting a quality public service against water resources management, that is, as a common good of the people.

2. MATERIAL AND METHODS

The methodology used was to search for the main types of drugs that are present in water bodies in general, their respective concentrations and possible effects of the

presence of these drugs in the water. Through literature review, articles and research aimed at the launching of drugs in water bodies, this review seeks to inform about the harmful effects of water contamination by different types of drugs.

3. LITERATURE REVIEW

Launch of drugs in water: a problem to worry about

The processes that are considered conventional for the treatment of water and sewage, do not show significant degrees of efficiency for the removal of several drug residues, due to their biocidal action or complex chemical structures that cannot biodegrade, evidenced by several studies that show the presence of this type of contaminant in Sewage Treatment Plants effluents[6].

The first studies that were done, according to the authors, to detect the presence of drugs in the environment, and also where the presence of hydrochloric acid, metabolite of the anti-lipids, clofibrate and etofibrate, whose concentration range was around μg L^{-1}, studies done in Sewage Treatment Plants in the United States. The main route of drug launches in water is not other than by domestic sewage, whether treated or not, in water bodies[6].

Pharmaceutical industries and the rural sectors themselves are also undesirable drug launchers, where the latter, due to the residues of drugs present in animal manure, throw in both the use of this for soil fertilization and the natural way of the animal through its physiological processes[6].

For comparative purposes, we have another generating source as the main source for the launching of drugs in water, which comes from hospitals:

> Following its administration, a significant part of the original drug and its metabolites are excreted through urine and human and animal feces, reaching the sanitary sewers and effluents of Sewage Treatment Plants, through domestic sewage, but mainly hospital[7].

In the work of these authors, about mitigation measures regarding the disposal of drugs in water bodies made in Londrina in the State of Paraná, it is emphasized that several studies around the world have been drawing attention to the presence of drug residues in water bodies. Through improper disposal, shallow and deep water is becoming increasingly contaminated.

While the ANVISA Resolution - RDC / ANVISA no. 306, of December 7, 2004, in its point 13.3.1, recommends that:

> Liquid waste from sewage and wastewater from a health facility must be treated prior to release to the receiving body or to the sewage collection network, whenever there is no collective sewage treatment system serving the area where the service is located, as Defined in RDC ANVISA no. 50/2002.

Drugs of various therapeutic classes, such as antibiotics, hormones, anti-lipids, anti-inflammatories, analgesics etc., are detected in domestic sewage, as well as in surface and groundwater in concentrations ranging from ng L-1 to μg L-1 in various Parts of the Earth[6].

The food industry uses more and more water, significantly increasing human consumption of food, and naturally increases the use of water[9], and it is possible to infer, in fact, great possibilities of the use of contaminated water for irrigation and/ or any kind of use for human consumption. If treatment companies cannot contain all the drug contaminants present in the water, the more those who are small or medium-sized farmers.

Not only human consumption, but several other ecosystems are directly or indirectly affected by the incorrect introduction of drugs[10]. One can think of the contamination of rivers and lakes, and consequently, when in animal and floristic hydration, culminating in accumulation of Contaminants in the consumption of all these elements through, therefore, not only of hydration, but also of food. Rabelo (2014)[9] brings several quantitative and qualitative information about water contamination and its intake by pigs.

The two groups that present a higher degree of concern, according to Zapparoli *et al*. (2011)[8], are the antibiotics and the hormones, being the estrogen also quite emphasized.

It is therefore possible to identify high release of estrogen in water, especially by releasing the female hormone through the effects of contraceptives and contraceptive drugs.

> According to Routledge *et al.*, two species of fish, *Oncorhynchus mykiss* and *Rutilus rutilus*, were exposed for 21 days to concentrations of environmentally relevant 17b-estradiol and estrone (1, 10, 100 ng L^{-1}). According to these and other researchers, the results confirmed that the estrogens identified in domestic effluent are present in amounts sufficient to induce the synthesis of VTG in fish species. Effluents from Sewage Treatment Plants have been reported as the major cause of estrogenic effects in fish[11].

Some solutions of removal of these endocrine disruptors in the Treatment Stations are:

> In the case of DCF, drug with low-log K_d e K_{bio}<0,1 $L.g_{ss}^{-1}.d^{-1}$, is expected low sorption removal and low biodegradability, regardless of the age of the sludge. This assumption was confirmed by the low removal efficiencies found in the literature (medians <20%), apparently independent of the age of the sludge. However, it is important to observe the greater variability of the data and

the greater amount of DCF production results in activated sludge systems with sludge ages less than or equal to 10 days, which to a certain extent shows a small dependence on the removal of the DCF from this parameter Operational[12].

Other studies have proposed reactors from the most diverse compartments that significantly improve the removal of biodegradable compounds, when compared to a reactor in hydraulic regime of complete mixing[13].

There are also some results of ecotoxicological assays used to evaluate the effects of the relevant drugs, as in studies that found fluoxetine in *Vibrio fischeri* and in *H. azteca* aquatic organisms frequently exposed to environmental contaminants[14].

From these results, the researchers observed that "from 0.3 mg.L^{-1} of fluoxetine hydrochloride mortality occurred in *H. azteca*, while the inhibition of photoluminescence in *Vibrio fischeri* was obtained from 30 mg.L^{-1}". The lower values, in the latter case, of EC_{50}, showed higher toxicity in the assays with the generic product.

Types and concentrations of drugs released into water bodies

The mean concentrations of drugs detected in aquatic environments, where they are the most significant drugs presented in the concentrations that follow:

Table 1. Mean concentrations of drugs detected in aquatic environments (elements with a higher degree of significance).

Drug (therapeutic class)	Maan of Concentration (µg L^{-1})	Pattern
Atenolol (β-blocker)	0.49	Raw sewage / Italy
Bezafibrate (anti-lipids)	1.2	Gross Sewage (Brazil)
Carbamazepine (anticonvulsant)	1.7	Gross sewage (Sweden)
Ketoprofen (anti-inflammatory)	2.0	Gross sewage (Finland)
Ciprofloxacin (antibiotic)	0.37	Effluent from Sewage Treatment Plants (Switzerland)
Diclofenac (anti-inflammatory)	2.9	Gross Sewage (Brazil)
	4.0	Surface water (Brazil)
17α-Ethinylestradiol (contraceptive hormone)	5.8	Gross Sewage (Brazil)
Genfibrozil (antilipemic)	2.14	Effluent from Sewage Treatment Plants (Italy)
Ibuprofen (anti-inflammatory)	13.1	Gross sewage (Finland)
Ibuprofen (anti-inflammatory)	54.2	Gross Sewage (Brazil)
Propranolol (β-blocker)	0.17	Effluent from Sewage Treatment Plants (Germany)
Sulfametoxazol (antibiótico)	4.9	Gross sewage (Finland)
Sulfamethoxazole (antibiotic)	0.58	Gross sewage (Spain)
Tetracycline (antibiotic)	0.11	Surface water (USA)
Trimethoprim (antibiotic)	0.08	Gross sewage (Sweden)
	0.08	Effluent from Sewage Treatment Plants (Greece)
Trimethoprim (antibiotic)	0.32	Effluent from Sewage Treatment Plants (Germany)

Source: Melo *et al.* (2009)[6].

While in Borrely *et al.* (2012)[14] we can see:

Table 2. Concentrations of emergent pollutants (µg / L) in tributaries and effluents from sewage treatment plants.

Pharmaceutical compounds	Molecules	Affluent	Effluent	Removal rate (%)
Antibiotics	Erythromycin-H_2O	2.025	0.59	70.9
	Tetracycline	48	2.375	95.1
Antiepileptics	4-aminoantipyrine	1.517	0.676	55.4
Analgesics and anti-inflammatories	Ibuprofen	13.482	3.480	74.2
Lipid regulator	Bezafibrate	1.948	0.763	60.8
Betablockers	Metoprolol	1.535	0.679	55.8
Antidepressant	Fluoxetine	5.85	0.112	98.1

Source: Borrely *et al.* (2012)[14]

The release of drugs into the water is therefore an inconvenient environmental fact. Indeed, according to the tables above, it is possible to perceive high rates also of removal, however, not enough for accumulation in the human organism over the years.

It is also valid to highlight the main drugs launched by domestic routes, differentiating them in the hospital pathway and health systems. As important as it is to inform

that such postings are not necessarily specific to the hospital or domestic network.

Thus, based on the work of Borely (2012) are the drugs with greater use in hospitals:

a. *Antibiotics: Clarithromycin, Ciprofloxacin, Erythromycin - H2O;*
b. *Analgesics and anti-inflammatories: Codeine, Ketoprofen, Ketorolac*
c. *Antidepressant: Fluoxetine and Diazepan.*

While the ones with the highest degree of release in terms of the domestic route are the drugs that follow:*Antibióticos*: Ciprofloxacina, Metronidazol, Norfloxacina;

a. *Antiepileptics: Carbamazepine;*
b. *Analgesics and anti-inflammatory: Diclofenac, Ibuprofen, Ketoprofen, Naproxen;*
c. *Lipid Regulator: Bezafibrate;*
d. *Betablockers: Atenolol, Propranolol;*
e. *Antidepressant: Fluoxetine.*

In studies of the latter's (fluoxetine) impact on water, they have concluded that their research has demonstrated high concentrations of fluoxetine in water - what they call an SSRI: selective serotonin reuptake inhibitor - which has specific impact on behaviors that are linked to reproduction and problems with predators[15].

This research also points to the impacts of fluoxetine that are related to the fish's dependence on this drug, being more pronounced in males, in order to reach specific regions of the brain, considering that not all behaviors are impacted by the same dose and Exposure, therefore, certain that males and females do not demonstrate the same effects. Finally, the authors conclude that the removal of this drug and the consequent low fish exposure to fluoxetine, in large part, results in a return to normal behavior.

Aside from the drugs mentioned above, it is also possible to verify the degree of problematic that anxiolytics (pharmaceuticals used to treat anxiety) cause when released into effluents. These drugs are a class of drugs commonly prescribed by psychotherapists, with benzodiazepines being used the world over, according to researchers[16].

Anxiolytics persist in wastewater effluents, with concentrations ranging from 0.01 $\mu g.L^{-1}$ in the treated effluent. Several benzodiazepines are also very resistant to photodegradation, allowing their persistence in aquatic environments, being found by researchers with concentrations ranging from 0.001 to 0.4 $\mu g.L^{-1}$ in rivers and streams.

Like all researchers, Brodin *et al.* (2013)[16] also assert that because benzodiazepines are designed to alter behavior by binding to g-aminobutyric acid (receptors, which are found in a wide range of animal species), it is quite likely that organisms in aquatic environments are also experimenting Behavioral changes and modifications.

Finally, the researchers screened Swedish surface water by finding common benzodiazepine concentrations, such as oxazepam, of 0.73 $\mu g.L^{-1}$ in wastewater treated effluents, which is alarming, and still 0.58 $\mu g.L^{-1}$ in a medium-sized river (Fyris River, Upsala, Sweden) to which it receives the release of treated wastewater. The concentration of oxazepam in the European Sheep (*Perca fluviatilis*) muscle tissue of the Fyris River was more than six times higher than in water, clearly indicating a bioaccumulation of this drug in fish.

Therefore, pharmaceuticals, such as benzodiazepines, as well as several others presented, were designed precisely for behavior change, may have ecologically important evolutionary effect through changes in fish behavior which, and, over time, influence such behavior point the aquatic environment that arrives change the whole.

4. DISCUSSION

Contemporary scenario and drug withdrawal

> Environmental degradation demoralizes the so-called rule of law [...]. Among the underpinnings of the sustainability of underdevelopment, there is a low level of knowledge and blatant social insensitivity in most legislators [...], such facts do not free the Legislative and Judiciary from the damaging regime of clientelism that generates, in addition to unjust laws, Unconstitutional laws. In other words, illegal laws[17].

It is imperative that the globe goes through one of the biggest shortages of drinking water, suitable for human consumption, sanitation laws exist until, however, there is less and less access to quality water resources, ie without the severe intervention of man . In 2006, more than 2.5 billion people had no access to sanitary facilities[18].

Therefore, the anthropological action is directly linked to the causes of low water quality factors, diseases acquired by the consumption of contaminated water, since they alter the affected ecosystem physically, chemically and biologically, and it is still possible to include as aggravating the mismanagement Management of water resources by competent authorities and environmental bodies.

Currently, the Brazilian consumes on average 150 liters of water per day and 80% of the water consumed turns into sewage. In the country, the proportion of households with adequate sanitation increased from 45.3% in 1991 to 56.5% in 2000 and 61.8% in 2010. In cities with up to 5,000 inhabitants, these proportions increased from 9.7% in 1991 to 21.7% in 2000 and 30.8% in 2010. In cities with more than 500 thousand inhabitants, the percentages were 73.6% in 1991, 79.7% in 2000 and 82.5% in 2010[19].

The State Policy on Water Resources is a very innovative law regarding its structure and political guidelines, considering the systemic and integrated management of

this resource, with the direct and legitimate participation of the different social actors: States, Federal District and Municipalities - and Organized Civil Society. However, it is a bitch who can not guarantee that everything is under control when it comes to the launch of drugs in water bodies.

In fact, the release of medicine remnants, whether deliberately dumped or accidentally, represents a potential problem for water treatment both in Water Treatment Stations and in Effluent Treatment Stations.

Drugs can reach the sewage collection networks by dumping gray water (derived from showers, washbasins and laundries), black water (excreta from individuals who may contain oral medications and natural hormones) and dispose of in the sanitary facilities, of unused or expired expiry date. Sewage treatment plants usually employ biological processes as the main technology and, in a few cases, use complementary treatment techniques. Thus, sewage treatment plant units are designed to reduce the burden of organic pollutants and, possibly, pathogenic nutrients and microorganisms, not specifically targeting the removal of drugs present in sanitary sewage. Any removal of these compounds that may occur is incidental and inherent in the treatment process[12].

Escherichia coli is indicated as the main indicator of water quality and is associated with water contaminated with fecal material from humans and warm-blooded animals[20].

Removal of drugs and hormones that contaminate water in a rural region where effluents from such systems are typically discharged into receiving basins, leading to a potential transfer of medications and personal care products and steroid sewage hormones to the environment.

They also identified personal care products and steroids in rural sewage treatment ponds, clearly pointing to the ineffectiveness of this system, in several chemical compounds, by pond treatment plants (in rural cases). The authors identify septic tank systems as a potential source of emerging contaminants in groundwater, considering that septic tank and pond systems demonstrate little efficacy in the removal of contaminants, causing effluent from aerated lagoons to also retain metals Pathogens and organic pollutants, in addition to excessive amounts of nutrients[21].

5. CONCLUSION

This review aimed at discussing whether the presence of drug residues in the waters is respecting or altering the environment in which it is being launched, as well as considering its pathological relationships with the possible toxicological contact of some drugs, considering that all the works involving Drugs say yes. Also the main drugs launched in water bodies, their main types and in which concentrations. Clearly, there is a need for diversified research for each contaminant released, since the patenting of new drugs is frequent, which results in the study of a single focus for some specific pathogenesis, forgetting other organisms (including humans) that can be reached indirectly, To which little or nothing is known about the harmful and deleterious effects that can be caused to them.

REFERENCES

[01] Silva PRV, et al. Uma medida de sustentabilidade ambiental: pegada hídrica. Rev. bras. eng. agríc. ambient, Campina Grande 2013; 17 (1):100-105.

[02] Lira WS, Cândido, GA. Gestão sustentável dos recursos naturais: uma abordagem participativa [online]. Campina Grande: EDUEPB, 2013; 325p.

[03] Brasil. Decreto Federal nº 7.217 de 21 de junho de 2010. Regulamenta a Lei no 11.445, de 5 de janeiro de 2007, que estabelece diretrizes nacionais para o saneamento básico, e dá outras providências. [acesso 02 mai. 2016]. Disponível em: <http://www.planalto.gov.br/ccivil_03/_ato2007-2010/2010/decreto/D7217.htm>.

[04] Moura JC. Anvisa e a implantação da logística reversa de resíduos de medicamentos. 2013. [acesso 05 set. 2016]. Disponível em: <http://www.senado.leg.br/comissoes/CMA/AP/AP20120510_JAIME_OLIVEIRA.pdf>.

[05] ABDI, Agência Brasileira de Desenvolvimento Industrial. Logística reversa para o setor de medicamentos. 2013. [acesso 05 set. 2016]. Disponível em: <http://www.abdi.com.br/Estudo/Log%C3%ADstica%20Reversa%20de%20Medicamentos.pdf>.

[06] Melo SAS, et al. Degradação de fármacos residuais por processos oxidativos avançados. Quím. Nova, São Paulo, 2009; 32 (1):188-197.

[07] Garrison AW, Pope JD, Allen FR. Identification and Analysis of Organic Pollutants in Water; Keith, C. H., ed.; Ann Arbor Science Publishers: Ann Arbor, 1976; cap. 30.

[08] Zapparoli ID, Camara MRG, Beck C. Medidas mitigadoras para a indústria de fármacos Comarca de Londrina – PR, Brasil: impacto ambiental do despejo de resíduos em corpos hídricos. In 3. International Workshop Advanced in Cleaner Production. Cleaner Production Initiatives and Challenges for a Sustainable World. São Paulo, 2011.

[09] Rabelo, MHS, Silva EK, Peres AP. Análise de Modos e Efeitos de Falha na avaliação dos impactos ambientais provenientes do abate animal. Eng Sanit Ambient 2013; 19(1):79-86.

[10] Barcelos MN, Peres AP, Pereira IO, Chavasco LS, Freitas DF. Aplicação do método *Failure Mode and Effect Analysis* (FMEA) na identificação de impactos ambientais causados pelo descarte doméstico de medicamentos. Engenharia Ambiental 2011; 8(4):62-68.

[11] Bila DM, Dezotti M. Desreguladores endócrinos no meio ambiente: efeitos e conseqüências. Quím. Nova, São Paulo, 2007; 30(3):651-666. [acesso 06 mai. 2016] Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-40422007000300027&lng=en&nrm=iso>.

[12] Aquino SF, Brandt EMF, Chernicharo CAL. Remoção de fármacos e desreguladores endócrinos em estações de tratamento de esgoto: revisão da literatura. Eng. Sanit. Ambient 2013; 18(3):187-204. [acesso 06 mai. 2016]. Dispo-

nível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1413-41522013000300187&lng=en&nrm=iso>.
[13] Joss A, Zabczynski S, Göbel A, Hoffmann B, Löffler D, Mcardell CS, Ternes TA, Thomsen A, Siegrist H. Biological degradation of pharmaceuticals in municipal wastewater treatment: Proposing a classification scheme. Water Research,2006; 40:1686-1696.
[14] Borrely SI, Caminada, SML, Ponezi NA, Santos DR, Silva VHO. Contaminação das águas por resíduos de medicamentos: ênfase ao cloridrato de fluoxetina. O Mundo da Saúde, São Paulo 2012; 36(4):556-563.
[15] Weinberger II, Joel KR. Environmental concentrations of the selective serotonin reuptakeinhibitor fluoxetine impact specific behaviors involved inreproduction, feeding and predator avoidance in the fish Pimephalespromelas (fathead minnow). Aquatic Toxicology 2014; 151:77–83.
[16] Brodin T, Fick J, Jonsson M, Klaminder J. Dilute Concentrations of a Psychiatric Drug Alter Behavior of Fish from Natural Populations. Science, 2013; 339:814.
[17] Procópio A. Subdesenvolvimento sustentável. Curitiba: Juruá, 2008.
[18] UNICEF. UNICEF e OMS lançam relatório sobre diarreia, a segunda maior causa de mortalidade infantil. 2009. [acesso 02 mai. 2016]. Disponível em: <http://www.unicef.org/brazil/pt/media_16165.htm>.
[19] IBGE, 2010. Síntese de Indicadores Sociais: uma análise das condições de vida da população brasileira. Rio de Janeiro. [acesso 06 jun. 2015]. Disponível em: < http://www.ibge.gov.br/home/estatistica/populacao/condicaodevida/indicadoresminimos/sinteseindicsociais2010/SIS_2010.pdf>.
[20] Giowanella M, Bozza A, Dalzoto PR, Dionísio JÁ, Andraus S, Guimalhães EL. Gomes. Microbiological quality of water from the rivers of Curitiba, Paraná State, Brazil, and the susceptibility to antimicrobial drugs and pathogenicity of *Escherichia coli*. Environ Monit Assess. 2015; 187: 673.
[21] Li X; Zheng W; Kelly WR. Occurrence and removal of pharmaceutical and hormone contaminants in rural wastewater treatment lagoons. Science of the Total Environment. 2013; 445–446:22–28.