Algerian Journal of Environmental Science and Technology
September edition. Vol.6. Nº3. (2020)
ISSN : 2437-1114
www.aljest.org

A short review on use, presence and ecotoxicology of paracetamol in the aquatic environment

F. Medjdoub*, H. Aksas, K. Delci, S. Bougherara, K. Louhab.

Food Technology Research Laboratory (LRTA) Faculty of Sciences Engineer
University of M'hamed Bougara, Boumerdes, 35000 Boumerdes–Algeria

*Corresponding author: fatma.medjdoub@yahoo.fr.

ARTICLE INFO

Article History :

Received ***: 14/01/2019***
Accepted ***: 16/07/2019***

***Key Words*:**

Paracetamol ;
Use ;
Presence ;
Ecotoxicology.

ABSTRACT

Abstract: *Paracetamol are biologically active and persistent substance which is often detected in sewage treatment plant effluents while the soil pollution and groundwater is more limited .Chronic ecotoxicity data as well as information on the current distribution levels in different environmental compartments continue to be sparse and are focused on those therapeutic classes that are more frequently prescribed and consumed.This article reviewsthe different contamination sources as well as presence and and ecotoxicological effects on the environment.*

I. Introduction

Water pollution research using pharmaceutical residues is one of the important aspect of current environmental research due to their physiological effects on animals and people at very low concentrations [1, 2], It has been revealed that they can cause aquatic toxicity, develop resistance to pathogenic microbes and have genotoxicity and endocrine disruption [3].

Paracetamol (Figure 1) is one of the most widely used drugs in the world. It is a particularly well tolerated analgesic and antipyretic with few harmful secondary effects. As an example, Paracetamol is one of the fewer drugs authorized for use by pregnant women or young children [4,5]. The international common name recommended by the World Health Organization is "Paracetamol", but in the National Formulary13 (U.S.A.), the name "Acetaminophen" appears. It is also known in the literature as acetamidophenol, acetyl-aminophenol, parahydroxy-acetanilide or N-acetyl-para aminophenol.

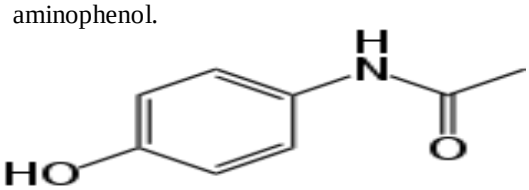

Figure 1 .*Chemical formula of paracetamol.*

From a chemical point of view, paracetamol has an aromatic cycle to which various nitrogenous, phenolic (Figure 1), or acidic functional groups are bonded. Table 1 summarizes the main physico-chemical properties of paracetamol.

Table1. *Physico-chemical properties of paracetamol.*

Physico-chemicalproperties	
Gross formula	$C_9H_8NO_2$
Molar mass	151.2 g/mol
Melting point	168-172°C
Solubility	Water: quite soluble. Alcohol: easily soluble. Ether and chloroform: very slightly soluble. [6].
Mass density	1.293g /ml at 21°C
Dissociationconstant	pKa = 9.5
Hydrophobicity	Log Kow = 0.46
Elementary analysis	C: 63.56%, H: 6%, N: 9.27%, O: 21.17% [7
Organoleptic characters	Is presented in the form of a white, odourless,crystalline powder [8].

II. Use and Consumption

Paracetamol, discovered more than a century ago, was first synthesized by Morse in 1878. It is the most frequently used analgesic and antipyretic[9-11], with or without a medical prescription[12] and certainly the most widely used by the population in different medicinal specialties in the world[13] for the fever treatment, headaches and some minor pains[14,15]. The most important harmful side effect of paracetamol is liver and kidney alteration by the formation of hepatotoxic metabolites such as N-acetyl-p-benzoquinone imine [16, 17] with a potential risk of hepatitis development[18].

More than 160 pharmaceutical specialities commercialized in France are based on paracetamol [19]. Paracetamol is available in different dosage forms such as pills, capsules, drops, elixirs, suspensions and suppositories. It is notably found in Doliprane, Efferalgan and Dafalgan, which occupy the top three places in terms of quantity sales. [20].

As a result, current world production of paracetamol is very high: nearly 150,000 t/year [21] with an annual increase of 2 to 3%[22], its consumption throughout the world has also increased. Rates in some developed countries have exceeded 20 g / person / year. The French people are very high consumers of paracetamol (47 g / person / year) with a total consumption of (3303 tons)[23] compared to the English people (16 g / person / year), German people (4.5 g / person / year) and Spanish people (3.6 g / person / year)[24]. In the United Kingdom, a more recent estimate of consumption, including paracetamol and the combination of paracetamol pills purchased without a prescription, was 3.5 billion 500 mg pills in 2000 [25].

Paracetamol was distributed in 2006 in Wales (population of about 3 million) at the level of more than 140 tons, more than 45 g / person / year [26]. In Italy, per habitant consumption is much lower, about 9 g / person / year, but total consumption is still considerable at 500 tonnes / year[27] and with a total consumption of 295 tonnes / year in Australia [28].

III. Origin and Presence

The presence of pharmaceutical products in the environment is due to different sources: human (the excretion of drugs or their metabolites that are not absorbed by the human body via the toilet) [47], agriculture (veterinary and aquaculture drugs)[30], and industry (pharmaceutical manufacturing residues)[31, 32]. Residues and metabolites are released to the environment through various transfer pathways as shown in Figure.2[33].

After use, pharmaceutical products are excreted in their native form or as metabolites form via urineand faeces [34, 35] and then directed into municipal wastewater treatment networks (and on the soil for most veterinary drugs)[36-40]. Effluents from hospitals and the pharmaceutical industry, as well as landfill leachate from landfills, are also a non-neglected source [41]. These pharmaceutical products are more or less eliminated by water treatment plants and are found in rivers, lakes, estuaries and even more rarely in groundwater and drinking water [42-45]. In addition, residues of veterinary drugs are released directly to the ground via animal excreta. They will then enter surface water by entrainment with runoff water or migrate deep into the soil. In the case of aquaculture, drug residues are directly placed in farm water [46].

There are also additional paths for the introduction of drug residues into the environment such as sewer leaks, spreading contaminated sewage sludge on the ground (for drug residues that would be trapped in such sludge) may also result in soil and surface water pollution through streaming (runoff) or the release of unused drugs with household waste that can thus pollute soil and groundwater in landfills [47,48]. The main source of surface water pollution by paracetamol comes from wastewater treatment plant effluents[49,50], when discharged or released to land and sewers, or when it is thrown into garbage, septic tanks or wastewater [51], polluting water bodies, while soil and groundwater pollution is more limited[52]

Presence of drugs in the aquatic environment became a global issue[53] with potential effects on living systems[54-58], not only because of pharmaceutical products volumes used, but also due to their persistence [59,60] and critical biological activity (high toxicity, potential effects on major biological functions, such as reproduction and bioaccumulation in the food chain)[61]. Surface and groundwater are the main resources for the production of drinking water in Europe and worldwide (for example, in France, 67% of the water distributed comes from groundwater and 33% from surface water [62]). Compound Paracetamol, is widely used, is found in all aquatic environments [63,64], including effluents from urban wastewater treatment plants, where it is still found in STPs inputs at high concentrations and more particularly from 32 ng/L to 127 µg/L in France[46], up to 150 µg/L in the United States[65] ; 218 µg/L in China[66] ; 246 µg/L in England[67] ; 85 µg / L in Sweden[68].

In wastewater treatment plant of effluents, paracetamol has important concentration variations: it is sometimes measured at a few tens of ng/L [69, 70, 71] but concentrations have been observed up to tens of µg/L[72, 73] or even hundreds of µg/L[74]. Detected in a Michigan wastewater treatment plant in the United States at a concentration of 670 µg/L [75] and up to 6 µg/L in wastewater treatment plant in Europe [49], as an example, a sampling at the STPTancarville in France in June 2011 is

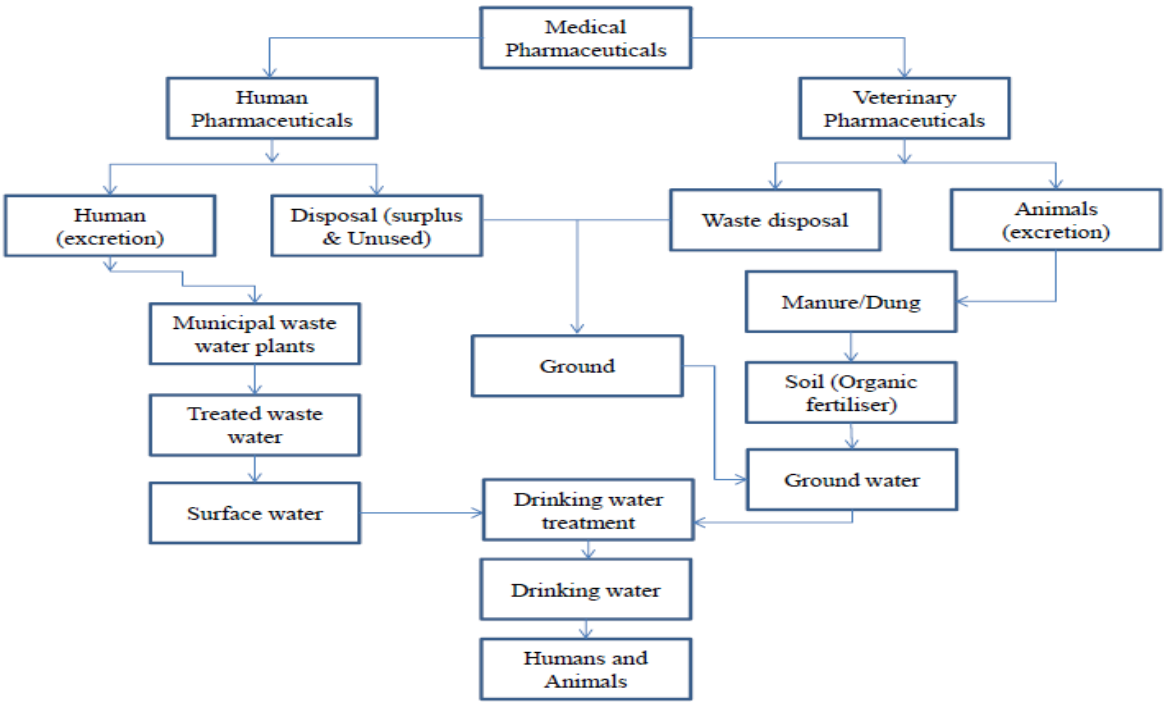

Figure 2. *Sources and pathways for the introduction of pharmaceutical product residues into the aquatic environment.*

exceptional because the cumulative concentration has a very high value. In addition, paracetamol concentration is particularly high: 70 µg/L. This indicates a malfunction of the station because these high concentrations are more encountered in the case of STP inlet water [45]. [72] and [74] also found paracetamol in STP outlet waters up to 250 µg/L and 201 µg/L.

According to published documents, paracetamol is found in surface waters at varying concentrations: 14.7 ng/L in France[62] (0.11 µg/L in French rivers water [76] and is also most frequently found in French rivers, with concentrations of 100 ng /L but up to 250 µg/L in the Mediterranean Sea around Marseille[77]) from 24 to 435 ng/L in Thailand [78], 1968 ng/L in Spain[74], 13.2 µg/L in Costa Rica[79] and up to 10 µg/L in the United States [76]. It is also detected in groundwater with a maximum concentration of 1890 ng/L in the United States [80] and 5.3 ng/L in France [81] and in the order of a few dozen ng/L in the Loire-Bretagne basin [72]. It is found in drinking water in the order of 210.1ng/L [72].

IV. Ecotoxicological Impact

In recent years, researchers have focused their efforts on a more comprehensive assessment of the risk that pharmaceutical residues can cause to theenvironment, taking into account drug metabolism, toxicity and biodegradability [82]. According to studies carried out in Denmark and England, paracetamol is among the molecules of greatest concern for the environment [83] which presents a danger to the aquatic environment [84].

The paracetamol processing efficiency in treatment plants varies from 38 to 100% with an average abatement of 87.3% [85], about 80% and 86% in hospital and municipal wastewater treatment plants respectively [86-88]. This justifies their occurrence in all aquatic environments at a lower concentration level [77].However, under the effect of improperly treated or untreated water in STPs [79, 89], their undesirable effects in different organisms were observed by high quantities of BOD_5, COD and COD/DBO_5 [90, 91].

Paracetamol, highly prescribed, is a weak inhibitor of the enzyme cyclo-oxygenase, whose high-dose side effects are mainly associated with the formation of hepatotoxic metabolites into sulfate metabolites and glucuronide [92] and induces the proliferation of cancer cell cultures via estrogen receptors, but has no estrogenic activity in rodents [93].

In secondary processing, where substances are transformed by biological degradation through activated sludge and secondary sedimentation, they can be transformed into toxic by-products viatertiary treatment [94, 95]. This is the case of paracetamol, which is biodegradable during water treatment [96] according to laboratory and plant studies [97, 98], it is transformed by chlorination of drinking water and effluents into N-acetyl-p benzoquinone and 1,4-benzoquinone imine form

when glutathione rate is diminished in liver cells [99], the first molecule is toxic to the liver while the second is suspected to be genotoxic and mutagenic[100,101]. Kinetic studies on the stability of paracetamol in Al-Quds activated sludge have proven that paracetamol biodegrades in less than a month to provide p-aminophenol at high efficiencies, it has been determined that Pseudomonas aeruginosainin is the most responsible bacteria for the biodegradation of paracetamol to p-aminophenol and hydroquinone[102].

In toxicity studies,[103] suggested that paracetamol at low concentrations below a few ng/L may disrupt vital systems such as the endocrine system (reduce/increase of fertility, increase incidence of hermaphrodial cases, disruptions of steroid metabolism) in aquatic organisms, tests were performed on algae, water flakes, fish embryos, luminescent bacteria and ciliates, the most sensitive species is crustaceans (Daphnia magna) for which the Lethal Dose values of 50% (LD_{50}) (is the lethal concentration that causes 50% of mortality in the exposed population of organisms[85]) of 30.1 mg/L[104], 50 mg/L[105] and 11.85 mg/L[106]. Also a Korean study confirms the potential ecological risks of paracetamol after tests on Vibrio fischeri and Daphnia magna[107].

A homologue of the COX 2 isoform is one of the targets of paracetamol that has been discovered in the macrophages of trout fish (Oncorhynchusmykiss) [108] and a receptor homology in rainbow trout indicates a sensitivity of fish to this molecule [109]. In another study, 0.05 M (7.5 mg.l-1) paracetamol prevents 50% of vitellogenin production in isolated trout liver cells[110], significant sublethal (sub-lethal) effects were observed on the zebra mussel (Dreissenapolymorpha) when exposed to a mixture of diclofenac, ibuprofen and paracetamol[110].

A study on the use of paracetamol as a poison against snakes leads to the exposure of non-target species to high concentrations via hidden pills in mice, consumed by snakes. Potentially affected non-target species are those that will consume contaminated carcasses of mice and dead snakes. Doses attributed to snakes show an accumulation of 30% of the ingested dose, i.e. between 200 and 600 µg/g of dry weight. Unfortunately, there have been no measurements in consumers (crows, crabs, lizards, etc.), but the mortality of these species does not seem to be significantly different between the treatment period and the period before paracetamolwas used as a poison[111], hence, paracetamol could pose a threat to non-target organisms[61].

Table 2. *Parameters ofthecolumnobtained at different flowrates.*

Country	Samples	Concentration (ng/l)	Ref	Taxon	Species	Ecotoxicitydata (mg/l)	Ref
Spain	• STP effluent	32-4300	[112]	Bacteria	V. fischeri	2.68	[113]
	• Hospital effluent	500-29000	[114]	Fish	O. latipes	267.5	[18]
	• Surface water	2-112	[115]	/	/	/	/
United kingdom	• STP effluent	< 50	[116]	Celiates	Tetrahymenapyriformis	112	[105]
	• Surface water	299	[67]	Fish	B. rerio (zebrafish)	378	
Serbia	• Danube River water	78.17	[117]	Bacteria	V.fischeri	650	[105]
France	• Surface water	10	[62]				
		103	[118]	/	/	/	/
	• Drinking water	45	[119]				
		210	[120]				
Taiwan	• Hospital effluent	62.25	[121]	Crustacean	D. magna	26.6	
	• Pharmaceutical production facility effluent	124					[18]
South korea	• Surface water	5-127	[121]				
		129	[45]				
		4.1-73	[122]	Crustacean	D. magna	50	
	• Han river water	< 5-9	[122]				
	• STP effluent	< 5-127	[70]	Algae	Scenedesmussubspicatus	134	[105]
		1.8-19					
Canada	• Drinking water	17	[123]	/	/	/	/
USA	• Surface water	380	[124]	Crustacean	D. magna	30.1	[18]
		10 µg	[125]				

• Groundwater	180	[80]

V. Conclusion

The presence of pharmaceuticals product in the environment is being reported world wide. Furthermore, newdata on the sources, presenceandeffects of paracetamol in the environment, seemstoindicatethepossibilityof a negative impact on different ecosystemsandimply a threattopublichealth.
Forthisassumption, datafromacuteandchronicecotoxicitytests on speciesbelongingto different trophiclevels such asbacteria, algae, crustaceansandfishamongothers, is relevant toillustratetheseveraladverseeffectsthat environmental exposuretomeasuredconcentrationsofthesecontaminantscanhave. The principaltoxicologicalendpoints/studiesthataredescribedaregrowth, survival, reproductionandimmobilizationofspecies.

VI. References

1. Oaks, J.L.; Gilbert, M.; Virani, M.Z.; Watson, R.T.;Meteyer, C.U.; Ridesut, B.A.; and al.Diclofenac residuesas the cause of vulture population decline in Pakistan.*Nature* 427 (2004) 630–633.
2. Winder, V.L.;Sapozhnikova,Y.;Pennington, P.L.;Wirth, E.F.Effects of fluoxetine exposure on serotonin related activity in the Sheep shead Minnow (Cyprinodonvariegatus) using LC/MS/MS detection and quantitation, Comp. Biochem. Phys. *(Part C)* 149 (2009) 559–565.
3. Rakic, V.; Rajic, N.; Dakovic, A.; Auroux, A.The adsorption of salicylic acid, acetylsalicylic acid and atenolol from aqueous solutions onto natural zeolites and clays: Clinoptilolite, bentonite and kaolin. *Microporous and Mesoporous Materials* 166(0) (2013) 185-194.
4. Roxan, J. Nouvelles voies de syntheses du paracetamol et de son precurseur catalyse. *Universite Claude Bernard - Lyon I,* (2014). Francais. <NNT2014LYO10295>. <tel01132399>
5. Paracétamol, Pharmacopée Européenne, *5éme edition*(2004).
6. DRIAD, Y.Stabilité du paracétamol : Application à un sachet produit en industrie pharmaceutique, faculté de pharmacie, *université HENRI POINCARE - NANCY 1* thèse de doctorat, (2009), France.
7. Lorphensri, O. ;Intravijit, J. ; Sabatini, D.A. ;Kibbey, T.C.G. ;Osathaphan, K. ;Saiwan, C. Sorption of acetaminophen, 17 a-ethynylestraiol, nalidixic acid, and norfloxacin to silica, alumina, and a hydrophobic medium.*Water Res* 40 (2006) 1481 –1491.
8. Pharmacopée Française. Monographie : Paracétamol. *10éme édition.*
9. Fernández,C.; González-Doncel, M.;Pro, J.;Carbonell, G.;Tarazona, J.V. Ocurrence of pharmaceutically active compounds in surface waters of the Henares-Jarama-Tajo river system (Madrid, Spain) and a potential risk characterization. *Sci. Total Environ*408 (2010) 543-551.
10. Khaskheli, A.R.; Fischer, J.;Barek, J.;Vyskoc, il.; Sirajuddin,V.;Bhanger, M.I. Differential pulse voltammetric determination of paracetamol in tablet and urine samples at a micro-crystalline natural graphite–polystyrene composite film modified electrode.*Electrochim. Acta* 101 (2013) 238–242.
11. Song, C.; Jian, W.;Hongying, X.;Jinhui, P.;ShiXing, W.;Libo, Z. Microwave-assisted regeneration of spent activated carbon from paracetamol wastewater plant using response surface methodology.*Desalination and Water Treatment* (2015). DOI: 10.1080/19443994.2015.1102766
12. Bertoldi, A.D.; Barros, A.J.D.; Hallal, P.C.; and Lima, R.C. Drug utilization in adults: Prevalence and individuals determinants. *Revista. Saúde .Pública*, vol. 38, no. 2(2004).
13. Bannwarth, B.; and Pehourcq, F. Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues. *Drugs* 63(2003). Spec No 2: p. 5-13.
14. Holm, J.V.; Ruegge, K.; Bjerg, P.L.; Christensent, H. Occurrence and distribution of pharmaceutical organic compounds in the groundwater down gradient of a landfill (Grindsted Denmark). *Environ. Sci.*Techno l29(5) (1995) 1415–1420.
15. Ikehata, K.; JodeiriNaghashkar, N.; Gamal El-Din, M. Degradation of Aqueous Pharmaceuticals by Ozonation and Advanced Oxidation Processes: A Review. *Science & Engineering* 38 (2006.) 353-414.
16. Johnson, K.; A. P, R. Investigating the human metabolism of acetaminophen using UPLC and exact mass oa-TOF MS. *Journal of Pharmaceutical and Biomedical Analysis*39 (2005) 805-810.
17. Rubenstein, J.H.; andLaine, L. The hepatotoxicity of non-steroidal anti-inflammatory drugs. *Alimentary Pharmacology and Therapeutics.* vol. 20, no. 4, (2004). p. 373-380.
18. Kim, Y.; Choi, K.; Jung, J.; Park, S.; Kim, P.-G.; and Park, J.; Aquatic toxicity of acetaminophen carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risKorea. *Environment International* vol. 33, no.3, p. 370-375 (2007).
19. Vona, A.; di Martino, F.;Garcia-Ivars, J.; Picò, Y.;Mendoza-Roca, J.; Iborra-Clar, M. Comparison of different removal techniques for selected pharmaceuticals. *Journal of Water Process Engineering* 5 (2015) 48-57.
20. Analyse des ventes de médicaments en France , année 2010, 2011 et 2013 publié par l'ANSM (ansm.sante.fr).
21. FilipaAleksandrova, V. Vers un procédé fenton hétérogène pour le traitement en continu d'eau polluée par des polluants pharmaceutiques. *Thèse De Doctorat* (2014).
22. www.bloomberg.com(www.bloomberg.com/apps/news?pid=newsarchive&sid=az9ShNouwC8U)
23. Besse, J.P.;Garric, J. Médicaments à usage humain: risque d'exposition et effets sur les milieux récepteurs. Proposition d'une liste de médicaments à usage humain à surveiller dans les eaux de surface continentales. *Agence de l'Eau R.M.C.* Lyon (2007) 241 p.
24. Sadezky, A.;Löffler, D.;&Ternes, T. Proposal of an environmental indicator and classification system of

pharmaceutical product residues for environmental management. In ProjetEuropéen KNAPPE, Deliverable D12 (2008). p92. *European Commission, 6th Framework Program.*
25. Sheen, L.; Dillon, J.F.; Bateman, D.N.; Simpson, K.J.; Macdonald, T.M.Paracetamol toxicity: epidemiology, prevention and costs to the health-care system. *QJM* 95 (2002).609–619.
26. Kasprzyk-Horderna, B.; Dinsdale, R.M.; Guwy, A.J. The occurrence of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs in surface water in South Wales, UK. *Water Research* 42 (2008) 3498–3518.
27. DelFarmaco, A.I. Bollettino di informazione. *Ministerodella Salute* (2005), Roma.
28. Khan, S.J.; andOngerth, J.E. Modelling of pharmaceutical residues in Australian sewage by quantities of use and fugacity calculations. *Chemosphere* 54(3), (2004) 355-367.
29. Rivera-Utrilla, J.;Sánchez-Polo, M.; Ferro-GarcìaM. Á. ; Prados-Joya, G. ; Ocampo-Pèrez, Raúl. Pharmaceuticals as emerging contaminants and their removal from water. *A review Chemosphere* 93 (2013) 1268-1287
30. Quero-Pastor, M.; Valenzuela, A.; Quiroga, J.M.;Acevedo, A. Degradation of drugs in water with advanced oxidation processes and ozone. *Journal of Environmental Management* 137 (2014) 197-203
31. Collado, N. ; Buttiglieri, G. ; Ferrando-Climent, L.; Rodriguez-Mozaz, S. ; Comas, J. ; Rodriguez-Roda, I. ; Barcelò, D. Removal of ibuprofen and its transformation products: Experimental and simulation studies. *Science of the Total Environment* 433 (2012) 296-301
32. Heberer, T. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicol. Lett.*131 (2002)5–17. doi:10.1016/S0378-4274(02)00041-3.
33. Balch, K. The Silent Killer in your Medicine Cabinet. *Columbia News Service (*2010).
34. Andreozzi, R.; Raffaele, M.; Nicklas, P. Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment. *Chemosphere* 50 (2003)1319-1330.
35. Bahlmann, A.; Brack, W.; Schneider, R.J.; Krauss, M. Carbamazepine and its metabolites in wastewater: Analytical pitfalls and occurrence in Germany and Portugal. *Water Res* 57 (2014) 104–114. doi:10.1016/j.watres.2014.03.022.
36. Calisto, V.; Ferreira, C.I.A.; Santos, S.M.; Gil, M. V.; Esteves, V.I.; Otero, M.Production of adsorbents by pyrolysis of paper mill sludge and application on the removal of citalopram from water. *Bioresource* Technology 166 (2014) 335-344
37. Yan, Q.;Gao, X.; Peng Chen, Y.; Peng , X.Y.; XinZhang, Y.; Gan, X.M.; Zi, Ch.F.; Guo, J.S. Occurrence, fate and ecotoxicological assessment of pharmaceutically active compounds in wastewater and sludge from wastewater treatment plants in Chongqing, the Three Gorges Reservoir Area. *Science of the Total Environment*470-471 (2014) 618630.
38. Yan, Q.; Gao, X.; Huang, L.; Gan, X.M.; Zhang, Y.X.; Chen, Y.P.; Peng, X.Y. Occurrence and fate of pharmaceutically active compounds in the largest municipal wastewater treatment plant in Southwest China: Mass balance analysis and consumption back-calculated model. *Chemosphere* 99 (2014) 160-170
39. MeritxellGros, Mira Petrovic, AntoniGinebreda, DamiâBarcelò. Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. Environment International 36 (2010) 15-26
40. Cardoso, O.; Porcher, J.M.; Sanchez, W. Factory-discharged pharmaceuticals could be a relevant source of aquatic environment contamination: Review of evidence and need for knowledge. *Chemosphere* 115 (2014) 20-30.
41. Larsson, D.G.J. Pollution from drug manufacturing: review and perspectives. *Philos. Trans. R. Soc. Lond. B Biol. Sci* 369 (2014). 20130571. doi:10.1098/rstb.2013.0571.
42. Guerra, P.; Kim, M.; Shah, A.;Alaee, M.;Smyth, S.A. Occurrence and fate of antibiotic, analgesic/anti-inflammatory, and antifungal compounds in fivewastewater treatment processes.*Science of the Total Environment* 473-474 (2014) 235-243
43. Richard, H.; berg, L.; Ostman, M.; Olofsson, U.; Grabic, R.; Fick, J. Occurrence and behaviour of 105 active pharmaceutical ingredients in sewage waters of a municipal sewer collection system.*Water research 58* (2014) 221-229
44. Dai, Ch.M.;Zhang, J.; Zhang, Y.L.; Zhou, X.F.; Duan, Y.P.;Liu, Sh.G. Selective removal of acidic pharmaceuticals from contaminated lake water using multitemplates molecularly imprinted polymer. *Chemical Engineering Journal* 211-212 (2012) 302-309.
45. Sim,WJ.; Kim, H.Y.; Choi, S.D.; Kwon, J.H.; Oh, J.E; Evaluation of pharmaceuticals and personal care products with emphasis on anthelmintics in human sanitary waste, sewage, hospital wastewater, livestock wastewater and receiving water. *Journal of hazardous materials* (2013) .219-227.
46. BUI Van Hoi, contribution a l'étude de la présence et du devenir des résidus de médicaments dans les compartiments aquatiques. Université Bordeaux 1, thèse de doctorat, chimie analytique et environnement, (2013), France.
47. Hollender, J., Singer, H.; Mcardell, C. Polar organic micropollutants in the water cycle. *Springer Netherlands* (2008) (103-116).
48. Fent, K.; Weston, A.; Caminada D. Ecotoxicology of human pharmaceuticals. Aquatic Toxicology 76, (2006). 122-159.
49. Ternes, T. A. Occurrence of drugs in German sewage treatment plants and rivers. *Water Research* 32 (1998)3245-3260.
50. Thomas, H. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *ToxicologyLetters*131 (2002). 5-17.
51. Kümmerer, K. Pharmaceuticals in the Environment – A Brief Summary. *Springer Berlin Heidelberg* (2008) (3-21).
52. Andreozzi, R.; caprio, V.; marotta, R.; vogna, D. Paracetamol oxidation from aqueous solutions by means of ozonation and H2O2/UV system. *Water Research* 37(2003) 993-1004.
53. Kimura, K.; Iwase, T.;Kita, Sh.;Watanabe, Y. Influence of residual organic macromolecules produced in biological wastewater treatment processes on removal of pharmaceuticals by NF/RO membranes. *Water research* 43 (2009) 3751-3758.
54. Quesada-Penate, I.;Julcour-Lebigue, C.;Jáuregui-Haza, U.J.;Wilhelm, A.,M.;Delmas, H. Degradation of paracetamol by catalytic wet air oxidation and sequential adsorption – Catalytic wet air oxidation on activated carbons. *Journal of Hazardous Materials* 221-222 (2014) 131-138.
55. Carmona, E.; Andreu, V.; Picò,Y. Occurrence of acidic pharmaceuticals and personal care products in Turia River Basin: From waste to drinking water. *Science of the Total Environment* 484 (2014) 53-63.
56. Yuan, X.; Qiang, Z.; Ben, W.; Zhu, B.; Liu, J. Rapid detection of multiple class pharmaceuticals in both municipal wastewater and sludge with ultra high performance liquid chromatography tandem mass spectrometry. *Journal of Environmental Sciences* 26 (2014) 1949-1959.

57. Maeng, S.K.; Ameda, E.; Sharma, S.K.; Grützmacher, G.; Amy, G.L. Organic micropollutant removal from wastewater effluent-impacted drinking water sources during bank filtration and artificial recharge.*Water Res* 44(2010). 4003–4014.
58. Ortiz de García, S.; Pinto Pinto, G.; GarcíaEncina, P.; Irusta Mata, R. Consumption and occurrence of pharmaceutical and personal care products in the aquatic environment in Spain. *Sci Total Environ* 444 (2013) 451-465.
59. Wang, L.;Ying, G.G.;Zhao, J.L.;Yang, X.B. Chen, F.;Tao, R.;Liu, Sh.; Zhou. L-J. Occurrence and risk assessment of acidic pharmaceuticals in the Yellow River, Hai River and Liao River of north China. *Science of the Total Environment* 408 (2010) 3139-3147
60. Katritzky, A.R.; Kasemets, K.; Slavov, S.; Radzvilovits, M.Tamm, K.; Karelson, M. Estimating the toxicities of organic chemicals in activated sludge process. *Water research* 44 (2010) 2451-2460
61. Santos, Lúcia H.M.L.M.;Araújo, A.N.;Fachini, A.; Pena,A.; DelerueMatos,C.; Montenegro, M.C.B.S.M. Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. *Journal of Hazardous Materials* 175 (2010) 45-95
62. Vulliet, E.;Cren-Olivé, C.;Grenier-Loustalot, MF. Occurrence of pharmaceuticals and hormones in drinking water treated from surface waters. *Environ ChemLett*9 (2011)103 – 14.
63. Bila, D.M.; and Dezotti, M. Pharmaceutical drugs in the environment. *Química Nova* (2003) vol. 26, no. 4.
64. Jeff,D.; Mendoza, M.; Pritchard, J. Pharmaceuticals Found in Drinking Water.*AN AP INVESTIGATION: Associated Press Writers* (2012).
65. Blair, B.D.; Crago, J.P.; Hedman, C.J.; Treguer, R.J.F.;Magruder, C.; Royer, L.S.; Klaper, R.D.; Evaluation of a model for the removal of pharmaceuticals, personal care products, and hormones from wastewater. *Science of the Total Environment* 444 (2013)515–521.
66. Yu, Y.; Wu, L.; Chang, A.C. Seasonal variation of endocrine disrupting compounds, pharmaceuticals and personal care products in wastewater treatment plants. *Science of the Total Environment* 442 (2013) 310–316.
67. Kasprzyk-Hordern, B.; Dinsdale, R.M.; Guwy, A.J. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Research* 43 (2009)363–380.
68. Wahlberg, C.; Björlenius, B.; Paxéus, N. LäkemedelsresteriStockholmsvattenmiljö - Förekomst, förebyggandeåtgärderochreningavavloppsvatten. *(Report nr:2010-16).Stockholm: Stockholm Vatten* (2010).
69. Selma dos Santos Melo, Joel Estevão de Melo Diniz, Jonilson Heslei Guimarães,Josivan da Silva Costa. Production and characterization of absorbent heat from the bark of residual Brazil nut bark (BertholletiaExcelsa l.). *Chemistry Central Journal* (2015) 9-36 DOI 10.1186/s13065-015-0114-3.
70. Kim, S.D.; Cho, J.; Kim, I.S.; Vanderford, B.J.; Snyder, S.A. Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. *Water Research* 41(2007)1013–1021.
71. Verlicchi, P.; Al Aukidy, M.; Zambello, E. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review. *Science of the Total Environment* 429 (2012a) 123–155.
72. Togola, A.; Budzinski, H. Multi-residue analysis of pharmaceutical compounds in aqueous samples. *Journal of Chromatography a 1177* (2008). 150–158.
73. Gros, M.; Petrovic, M.; Barceló, D. Development of a multi-residue analytical methodology based on liquid chromatography–tandem mass spectrometry (LC–MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters. *Talanta* 70 (2006)678–690.
74. Gracia- Lor, E.; Sancho, J.V.; Hernández, F. Multi-class determination of around 50 pharmaceuticals, including 26 antibiotics, in environmental and wastewater samples by ultrahigh performance liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A 1218 (*2011) 2264–2275.
75. Gao, P.; Ding, Y.; Li, H.; Xagoraraki, I. Occurrence of pharmaceuticals in a municipal wastewater treatment plant: Mass balance and removal processes. *Chemosphere*88 (2012)17-24.
76. Kolpin,D.W.; Furlong, E.T. ; Meyer, M. ; Thurman, E.M. ;Zaugg, S.D.; Barber, L.B.; Buxton, H.A.T. "Pharmaceuticals, hormones and other organic wastewater contaminants in US streams.1999-2000: *A national reconnaissance" Environmental Science &Technology*36 (2002)1202-1211.
77. COETSIER Clémence, Approche intégrée de la gestion environnementale des produits pharmaceutiques dans des rejets de stations d'épuration urbaines et leur milieu récepteur : occurrence, impact et traitements tertiaires d'élimination. *Thèse de l'Université Montpellier II Sciences et Techniques du Languedoc*(2009) France.
78. Tewari, S.; Jindal, R.; Kho, Y.L.; Eo, S.; Choi, K.;Major, N.D. pharmaceutical residues in wastewater treatment plants and receiving waters in Bangkok, Thailand, and associated ecological risks. *Chemosphere* (2013).
79. Spongberg, A.L.; Witter, J.D.; Acuña, J.; Vargas, J.; Murillo, M.; Umaña, G.; Gómez, E.; Perez, G. Reconnaissance of selected PPCP compounds in Costa Rican surface waters. *Water Research* 45 (2011)6709–6717.
80. Fram, M.S.; Belitz, K. Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California. *Science of the Total Environment* 409 (2011)3409–3417.
81. Marion Rabiet, Contamination de la ressource en eau par les eaux usées dans un bassin versant Méditerranéen - Apport des éléments majeurs, traces et terres rares.*Université Montpellier II - Sciences et Techniques du Languedoc*(2006) French.
82. Marco-Urrea, E.; Radjenovic, J.; Caminal, G.; Petrovic, M.; Vicent, T.; & Barceló, D. Oxidation of atenolol, propranolol, carbamazepine and clofibric acid by a biological Fenton-like system mediated by the white-rot fungus Trametesversicolor. *Water Research* 44(2) (2010)521-532.
83. Stuer-Lauridsen, F.; Birkved, M.; Hansen, L.P.; Holten, H.C.; Halling-Sorensen, B. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere* 40 (2000) 783-793.
84. SMPA, Environmental impact from medicinal products and cosmetic and hygiene products. *Report of Swedish Medical Products Agency* (2004).
85. Thomas Thiebault, L'adsorption des produits pharmaceutiques par interactions organominerales : processus et applications environnementales. *Sciences de la Terre. Universite d'Orleans*(2015). France.

86. Radjenovic, J.;Petrovic, M.;Barcelo, D. Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment. *Water research* 43 (2009)831-41.
87. Rosal, R.; Rodriguez, A.;Perdigon-Melon, J.A. ; Petre, A. ; Garcia-Calvo, E. ; Gomez, MJ. ;Aguera, A. ; Fernandez-Alba, AR. Occurrence of emerging pollutants in urban wastewater and their removal through biological treatment followed by ozonation. *Water research*44 (2010)578-88.
88. Sim, WJ.; Lee JW.; Oh, JE. Occurrence and fate of pharmaceuticals in wastewater treatment plants and rivers in Korea. *Environ Pollut*158 (2010)1938-47.
89. Pailler, J.-Y.; Krein, A.; Pfister, L.; Hoffmann, L.; Guignard, C. Solid phase extraction coupled to liquid chromatography-tandem mass spectrometry analysis of sulfonamides, tetracyclines, analgesics and hormones in surface water and wastewater in Luxembourg. *Science of the Total Environment* 407 (2009)4736–4743.
90. GamzeDalgic, F.; TurkdoganKaan, I.;Yetilmezsoy, E.K. treatment of real paracetamol wastewater by fenton process.*Chem. Ind. Chem. Eng. Q.* 23 (2) 177-186 (2017).
91. Melero, J.; Martínez, F.; Botas, J.A.; Molina, R.; Pariente, M.I. Heterogeneous catalytic wet peroxide oxidation systems for the treatment of an industrial pharmaceutical wastewater. *Water Res* 43(2010) 4010-4018.
92. Johnson, K.A.; Plumb, R. Investigating the human metabolism of acetaminophen using UPLC and exact mass OA-TOF MS. *J. Pharmaceut. Biomed.*39 (2005) 805–810.
93. Harnagea-Theophilus, E.;Gadd, S.L.; Knight-Trent, H.A.; DeGeorge, G.L.; Michael, R.M. Acetaminophen-induced proliferation of breast cancer cells involves estrogen receptors. *Toxicol. Appl. Pharm* 155(1999) 273–279.
94. Falås, P.; Baillon-Dhumez, A.; Andersen, H. R.; Ledin, A.;& la Cour Jansen, J. Suspended biofilm carrier and activated sludge removal of acidic pharmaceuticals. *Water Research* 46(2012) 1167–1175.
95. Salgado, R.; Marques, R.; Noronha, JP.;Carvalho, G.Oehmen, A.; Reis, M.A.M. Assessing the removal of pharmaceuticals and personal care products in a full-scale activated sludge plant . *Environ SciPollut Res* 19(2012) 1818–1827.
96. Benotti,M.J.;Trenholm,R.A.;Vanderford,B.J.;Holady, J.C.; Stanford, B.D.; Snyder, S.A. Pharmaceuticals and endocrine disrupting compounds in U.S. *drinking water, Environ. Sci. Technol.* 43 (2009) 597–603.
97. Joss, A.;Zabczynski, S.; Gobel, A.; Hoffmann, B.; Loffler, D.;McArdell, C.;Ternes, T.; Thomsen, A.; Siegrist,H. Biological degradation of pharmaceuticals in municipal wastewater treatment: Proposing a classification scheme. *Water Res* 40(2006) 1686-1696.
98. Yu, J.T.; Bouwer, E.;Coelhan, M. Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent. *Agricultural Water Management* 86 (2006) 72-80.
99. Timbrell, J. Principles of Biochemical Toxicology. *Thirded,Taylor& Francis* (2002) London.
100. Bedner, M.; Maccrehan, W. Transformation of acetaminophen by chlorination produces the toxicants 1,4-benzoquinone and N-acetyl-p-benzoquinone imine. *Environ. Sci. Technol.* 40 (2006). 516-522.
101. Deborde, M.; von Gunten, U. Reactions of chlorine with inorganic and organic compounds during water treatment-Kinetics and mechanisms: a critical review. *Water Res* 42 (2008), 13-51.
102. Karaman, R.;KhamisM.; Abbadi, J.; Amro, A.; Qurie, M.;Ayyad, I.;Ayyash, F.; et al,. Paracetamolbiodegradationbyactivated sludge and photo-catalysis and its removal by a micelle-clay complex, activated charcoal and reverse osmosis membranes. *Environmental Technology* (2016). ISSN: 0959-3330.
103. Kidd, K. Collapse of a fish population after exposure to a synthetic oestrogen. *PNAS* 104(2007) 8897-8901.
104. Kim, Y.;Choi, K.;Jung, J.;Park, S.;Kim, P.-G.;Park, J. Aquatic toxicity of acetaminophen, carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risks in Korea.*Environ. Int.* 33 (2007) 275–370.
105. Henschel, K.P.; Wenzel, A.; Diedrich, M.; Fliedner, A. Environmental hazard assessment of pharmaceuticals. *Regul. Toxicol. Pharm*25(1997)220–225.
106. Kim, P.; Park, Y.; Ji, K.; Seo, J.; Lee, S.; Choi, K.; Kho, Y.; Park, J.; Choi, K. Effect of chronic exposure to acetaminophen and lincomycin on Japanese medaka (Oryziaslatipes) and freshwater cladocerans Daphnia magna and Moinamacrocopa, and potential mechanisms of endocrine disruption. *Chemosphere* 89 (2012) 10–18.
107. Younghee, K.;Kyungho, C.;Jinyong, J.;Sujung, P.; Pan-Gyi, K.;Jeongim, P. Aquatic toxicity of acetaminophen, carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risks in Korea. *Environ. Int.*33(2007) 370-375.
108. Zou, J.; Neumann, N.F.; Holland, J.W.; Belosevic, M.; Cunningham, C.; Secombes, C.J.; & Rowley, A.F. Fish macrophages express a cyclooxygenase-2 homologue after activation. *Biochem.J* 340 (Pt1) (1999) 153-9.
109. Collette-Bregand, M. Contamination des milieux aquatiques par les substances pharmaceutiques et cosmétiques - Etat des lieux et perspectives. *Archive Institutionnelle de l'Ifremer*(2009).
110. Parolini, M.;&Binelli, A. Sub-lethal effects induced by a mixture of three non-steroidal anti-inflammatory drugs (NSAIDs) on the freshwater bivalve Dreissenapolymorpha. Ecotoxicology 21 (2012) 379-92.
111. Johnston, et al.;(2002).
112. Gómez, M.J.;Martínez Bueno, M.J.;Lacorte, S.;Fernández-Alba, A.R.;Agüera, A. Pilotsurvey monitoring pharmaceuticals and related compounds in a sewage treatment plant located on the Mediterranean coast.*Chemosphere* 66 (2007) 993–1002.
113. Quinn, B.; Gagné, F.;Blaise, C. An investigation into the acute and chronic toxicity of eleven pharmaceuticals (and their solvents) found in wastewater effluent on the cnidarian, Hydra attenuate.*Sci. Total Environ*389 (2008) 306–314.
114. Gómez, M.J.; Petrovi ´c, M.; Fernández-Alba, A.R.; Barceló, D. Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction andliquidchromatographytandemmassspectrometryan alysisinhospitaleffluent wastewaters.*J. Chromatogr.A* 1114 (2006) 224–233.
115. Vazquez-Roig, P.; Andreu, V.; Blasco, C.; Picó, Y. Risk assessment on the presence of pharmaceuticals in sediments, soils and waters of the Pego–Oliva Marshlands (Valencia, eastern Spain). *Science of the Total Environment* 440 (2012). 24–32.
116. Hilton, M.J.; Thomas, K.V. Determination of selected human pharmaceutical compoundsineffluentandsurfacewatersamplesbyhigh-performanceliquid chromatography-electrospray tandem mass spectrometry.*J. Chromatogr. A* 1015(2003) 129–141.
117. Gruji ´ c, S.; Vasiljevi ´ c, T.; Lau ˇ sevi ´ c, M. Determination of multiple pharmaceutical classes in surface and ground waters by liquid chromatography-

ion trap-tandem mass spectrometry.*J. Chromatogr. A 1216* (2009) 4989–5000.
118. AFFSA, Synthèse des résultats de campagnes d'analyses de résidus de médicaments dans les eaux effectuées par les drass dans trois bassins pilotes. (2009), p.95.
119. Vulliet, E.; Cren-Olivé, C.; Grenier-Loustalot, M.-F. Occurrence of pharmaceuticals and hormones in drinking water treated from surface waters. *Environmental Chemistry Letters* 9(1) (2009) p.103-114.
120. Jean-Sébastien Derauw, Pollution médicamenteuse des eaux, Chimie organique environnementale, Institut*Meurice*.
121. Lin, A.Y.-C.; Tsai, Y.-T. Occurrence of pharmaceuticals in Taiwan's surface waters: impact of waste streams from hospitals and pharmaceutical production facilities.*Sci. Total Environ* 407(2009) 3793–3802.
122. Choi, K.;Kim, Y.;Park, J.;Park, C.K.;Kim, M.;Kim, H.S.;Kim, P. Seasonal variations of several pharmaceutical residues in surface water and sewage treatment plants of Han River, Korea.*Sci. Total Environ 405* (2008) 120–128.
123. Kleywegt, S.; Pileggi, V.; Yang, P.; Hao, C.; Zhao, X.; Rocks, C.; Thach, S.; Cheung, P.; Whitehead, B. Pharmaceuticals, hormones and bisphenol A in untreated source and finished drinking water in Ontario, Canada — Occurrence and treatment efficiency. *Science of the Total Environment* 409 (2011)1481–1488.
124. Barnes, K.K.;Kolpin, D.W.;Furlong, E.T.;Zaugg, S.D.;Meyer, M.T.;Barber, L.B. A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States—I) Groundwater. Sci. Total Environ 402 (2008) 192–200.
125. Roberts, P.H.; Thomas, K.V. The occurrence of selected pharmaceuticals in wastewater effluent and surface waters of the lower Tyne catchment. *Science of the Total Environment* 356 (1 e 3) (2006). 143 e 153.

Please cite this Article as:
Medjdoub F., Aksas H., Delci K., Bougherara S., Louhab K.,A short review on use, presence and ecotoxicology of paracetamol in the aquatic environment, ***Algerian J. Env. Sc. Technology***, ***6*:3(2020) 1408-1416.**