IJBPAS, May, 2014, 3(5): 624-638

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EMERGING POLLUTANTS IN AQUEOUS MEDIA: NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) AND THEIR POTENTIAL TOXIC RISK

CONTAMINANTES EMERGENTES EN MEDIO ACUOSO: FÁRMACOS ANTIINFLAMATORIOS NO ESTEROIDEOS (AINES) Y SU POTENCIALIDAD DE RIESGOS TÓXICOS

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of chemicals used for therapeutic purposes, involving large amounts of different active compounds administered to treat, cure or prevent diseases that afflict humans or used in agribusiness to increase growth and livestock health care. Thousands of tons of drugs are used annually in a disorderly manner. Since 1980, scientific research has shown the presence of drugs in the environment that are mainly introduced through excretion in its original form and/or its metabolites. In this paper, we review the general characteristics of NSAIDs, concentrations found in the environment of aspirin (acetylsalicylic acid), diclofenac, ibuprofen, naproxen and acetaminophen, five of the most

commonly used NSAIDs and toxicity present in some aquatic organisms. There are minimal studies conducted in Mexico around this issue and it is necessary to know the concentrations of drugs in surface water and groundwater.

Keywords: NSAIDs, Diclofenac, Ibuprofen, Naproxen, Acetaminophen, Acetylsalicylic Acid

RESUMEN

Los fármacos antiinflamatorios no esteroideos (AINEs) son un grupo de sustancias químicas y biológicas utilizadas para tratar, curar o prevenir enfermedades que aquejan al ser humano. También son utilizados en la agroindustria para incrementar la masa muscular y cuidar la salud del ganado. Miles de toneladas de medicamentos se utilizan anualmente en forma desordenada. Desde 1980 investigaciones científicas muestran la presencia en el ambiente de medicamentos que son principalmente introducidos a través de la excreción del ser humano y animales sometidos a algún tipo de tratamiento (ganado) en su forma original y como metabolitos. En este trabajo se revisan las características generales de los AINEs, algunas de las concentraciones que se han encontrado en el ambiente del ácido acetilsalicílico, diclofenaco, ibuprofeno, naproxeno, y paracetamol, cinco de los AINEs más utilizados, así como la toxicidad para los organismos acuáticos. En México son mínimos los estudios que se realizan en torno a esta temática y es necesario saber las concentraciones de dichos fármacos en aguas superficiales y subterráneas para tomar las medidas necesarias para finalmente crear límites permisibles y mantener un equilibrio.

Palabras clave: AINEs, Diclofenaco, Ibuprofeno, Naproxeno, Acido Acetil Salicílico, Paracetamol, Toxicidad

INTRODUCTION

Drugs are a group of chemical and biological substances which involves large amounts of different active compounds administered to treat, cure or prevent diseases that afflict humans. They are also used in agribusiness to increase growth and livestock health **[1, 2]**. Pharmaceuticals are important for the world economy because the demand is constant and each year sales increase by 2.4% approximately. In 2012, global sales of drugs left a total gain of $ 962 billion **[3]**. Currently, one of the concerns of environmental pollution is the presence of drugs in the aquatic media and its negative effects **[1]**. Since 1980, scientific research has shown the presence in environment of drugs

introduced mainly through excretion in its original form and metabolites via continuous wastewater discharges in hospitals, homes and places where a potential number of people are agglomerated, as well as in drug factories, agribusiness and fisheries. Poor disposal of expired drugs and final effluent wastewater treatment plants represent major sources of the presence of pharmaceutical substances in wastewater, surface water and underground water **(Figure 1) [2, 4-7]**.

The concentrations in which these contaminants are normally found in the water are at concentrations ng/l or µg/l **[5]**. Different drugs produce chronic toxic effects (estrogenic, genotoxic, carcinogenic and teratogenic) and acute toxicity during exposure because a large number of species are more sensitive to the effects of a drug compared to the human or animal parenting **[8]**. Drugs have been reported and its metabolites at trace concentrations in drinking water systems. This means that the exposure of humans to pharmaceutical residues is latent, however there are no studies showing adverse effects on human health arising from the presence of drugs in drinking water or eating fish that have accumulated these pharmaceutical residues **[9]**.

Inside the identification and quantification of drugs in the environment, several therapeutic classes are highlighted, mainly nonsteroidal anti-inflammatory drugs (NSAIDs), which predominate in the analysis of environmental samples, as well as in prescription lists **[4-10]**. In this paper we review the general characteristics of NSAIDs, some of the concentrations found in the environment of acetylsalicylic acid**,** diclofenac, ibuprofen, naproxen, and acetaminophen, five of the most commonly used NSAIDs, as well as the toxicity present in organisms.

Emerging Contaminants

Freshwater bodies face the load chemicals 100,000 incorporated with the use of about 300 million tons of synthetic compounds, which are used annually in the manufacture of various products **[11]**. The presence of these products in the environment is a major problem for many researchers. The most problematic pollutants are: pharmaceuticals, personal care and cleaning products. These chemicals of various kinds are known as emerging contaminants. The list of emerging contaminants is extensive, diverse and different chemical nature **(Table 1)**; today is still insufficient information about the impact on the environment and health damages. The main features of these pollutants are the constant presence in the environment,

continuous income aquatic systems, high consumption market, rapid change in products and high degree of removal **[12]**.

NSAIDs: NSAIDs (Non-steroidal antiinflamatory drugs: NSAIDs for short) are the most reported drugs by doctors. These are weak organic acids which have high affinity for lipids in acidic media and plasma proteins, sharing therapeutic actions for controlling a varying degree of pain (analgesic), inflammation (anti-inflammatory) and fever (antipyretics) **[13]**. NSAIDs act by reversible or irreversible inhibition of the enzyme cyclooxygenase (COX) in the COX-1 isoform (constitutive) and COX-2 (pro-inflammatory) or both. These cyclooxygenases are responsible for the synthesis of different fast acting prostaglandins. They are frequently used in the area rheumatology, dentistry, orthopedics and primary care **[14, 15]**.

NSAIDs can be classified by their main chemical group **(Table 2)**. Among the variety of NSAIDs, there are some of the greatest interest in contained acetylsalicylic acid in its oral presentation of 100 and 500 mg total dose per day for two to three grams, ibuprofen oral presentation 200, 400, 600, 800 mg total dose per day for two to four grams, naproxen oral presentation 200, 250, 500, 750 mg total dose per day of a gram, diclofenac oral presentation 50, 75, 100 mg total dose of 200 mg daily and paracetamol in oral presentation of 100 and 500 m **[14]**. **Table 3** shows characteristics of NSAIDs of interest to this study. These drugs are essential in Mexico as they are in the basic box of the Mexican Social Security Institute (IMSS).

Concentrations of NSAIDs in the Aquatic Environment

The main causes of pollution are due to anthropogenic activities. Water pollution is defined as the alteration of water quality caused by the presence of pollutants from different origins. These pollutants come mainly from the urban, industrial, agricultural and pharmaceutical areas. The presence in the environment causes effects on living beings as toxic, carcinogenic, mutagenic, teratogenic, among others **[16]**.

The exact quantification of pharmaceuticals, especially in aquatic environmental samples, may be an analytical challenge, due to their low occurrence. The gas chromatography in combination with liquid extraction and cleaning methods provides the ability to quantify many pharmaceuticals and metabolites concentrations below the ng/l. Capillary electrophoresis (CE) and has the advantage that the operation is less complex and costly but with detection limits ug/l **[17]**.

At the global level, NSAIDs are the sixth of sales. NSAIDs, such as acetylsalicylic acid diclofenac, ibuprofen, naproxen, diclofenac and paracetamol are usually found in significant amounts in the water **[7, 18, 19]**. **Table 4** presents the concentrations of NSAIDs found in different aquatic environments across several different analytical procedures.

Most wastewater from Mexico City is sent untreated to the Valley of Tula, Hidalgo. The concentration of organic micropollutants in wastewater in the Mezquital Valley such as the detection of ibuprofen (0.742-1.406 µg/l), naproxen (7.267-13.589 µg/l) and diclofenac (2.052-4.824 µg/l) concentrations reflect that the employment rate is relatively high. These contaminants are polar pharmaceuticals which gives them the capacity to move through the soil profile (environmental kinetics) and persistent enough to contaminate the aquifer **[20]**. Concentrations of ibuprofen, naproxen, diclofenac greater than 1 µg/l are a risk for groundwater contamination resulting from the wastewater irrigation **[21]**.

Bioassays to Assess Toxicity of NSAIDs

The bioassay consists of exposing organisms to different concentrations of the test compounds or percentage dilutions of effluents and water samples problem **[22]**. Bioassays are commonly used organisms ranging from the simplest to the closest to the human evolutionary scale. They are kept under controlled conditions and offer multiple advantages: providing answers to molecular, biochemical and physiological phenomena that occur due to the presence of a pollutant in an organism determined and these responses can extrapolate the results to humans **[23]**. At present, the acute toxicity proves pharmaceuticals substances in organisms belonging to various levels of biological organization, such as algae, cnidarians, crustaceans, mussels and fish. These studies focus on short-term effects and play an important role via environmental risk assessment, but are generally used to consider potential toxic action of pharmaceuticals **[18]**. To determine whether a particular drug may or may not generate impacts on an ecosystem a series of laboratory studies and toxicity studies are generated with a number of agencies **(Table 5)**.

Toxicity parameters most commonly used are the median lethal concentration (LC_{50}), the median effective concentration (EC_{50}) and median inhibition concentration (LC_{50}).

One of the mostly used bioassays is the *Danio rerio* (Zebrafish) as it is a powerful kind to deepen human pathologies. Its genome shows a high degree of genetic and

physiological similarity to humans in fundamental processes. With this organism, candidate genes to diseases or abnormalities in human chromosomal regions can be searched.

Morphological alterations in the embryonic development of zebrafish have been used for years to study the effects of pollutants **[24]**. In recent years the fish embryo tests are tests most promising animals and are a viable alternative for environmental toxicology. The embryos provide a model ethically acceptable and bioassays show these types of embryos correspond to high yield **[25]**.

Bioassays have been performed with NSAIDs in zebrafish, which have been exposed to concentrations greater than 10µg/l of ibuprofen and have caused cardiac abnormalities, curvature of the spinal cord and alterations in embryonic pectoral fin **[26]**. Diclofenac concentrations of 1000-2000 mg/l in zebrafish cause delay in hatching **[27]**.

CONCLUSION

The use and sale of drugs increase every year. New pharmaceuticals appear according to the new diseases. Acetylsalicylic acid, diclofenac, naproxen, ibuprofen and acetaminophen are group of drugs belonging to high consumption of NSAIDs and can be purchased without a prescription. After consumption, these drugs are excreted without knowing the negative impact that these compounds may have on ecosystems and public health. It is necessary to conduct further studies around NSAIDs and any other type of drug to establish its potential risk to the environment and the possibility of causing damage to human health. It is important to raise awareness of the damage are causing these chemicals are causing in the biotic and abiotic environment, to raise awareness among the population of often unnecessary drug overuse. Clearly there is presence of drugs in different concentrations in surface water systems but even more disturbing is the existence of groundwater concentrations, making it clear that hospitals are the biggest contributors of the introduction of these substances. Bioassays are powerful tools for information about the damage this type of emerging contaminants are inflicting on the environment, conducting experiments with different concentrations and mixtures thereof. Among the highlights of bioassays, zebrafish is an excellent model to extrapolate the results to human health since the genome of this fish shows a high degree of genetic and physiological similarity to humans in fundamental processes; other advantages are that high fertility has to put many embryos, organogenesis of 78-42 hours and the maintenance is economical which

allows large number of experiments; other advantage are: the high fertility rate with put many embryos, organogenesis of 78-42 hours and the maintenance is economical which allows large number of experiments Future investigations must continue to be generated to create regulations around the presence of contaminants in water bodies. In Mexico, there are minimal studies conducted around this issue and it is necessary to know the concentrations of drugs in surface water and groundwater in this country in order to take the necessary steps and establish permissible limits to maintain a balance.

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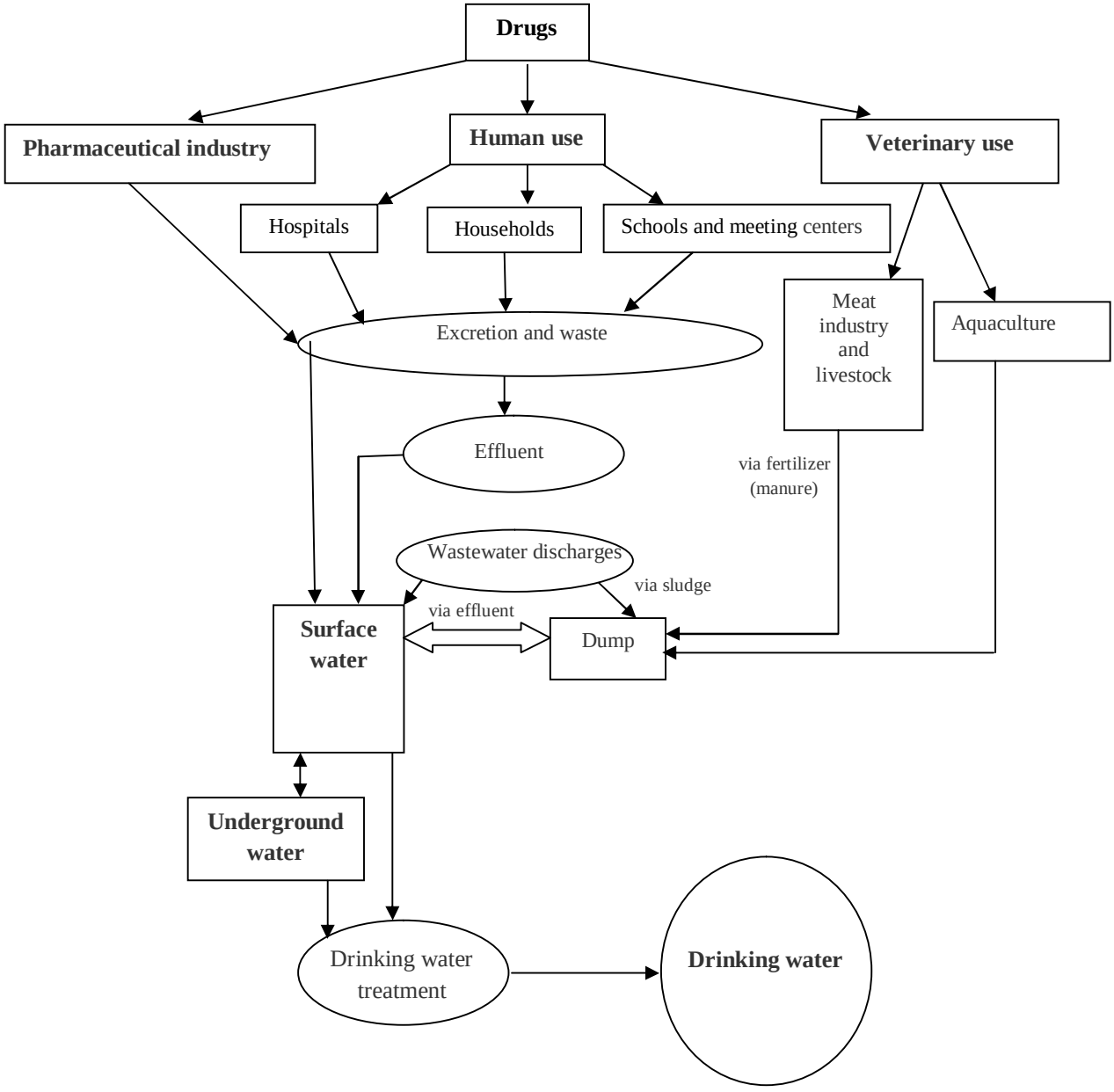

Figure 1: Routes of Entry of Drugs Into the Aquatic Environment (Adapted From Kümmerer, 2010, [5])

Table 1: Emerging Contaminants and Examples (Adapted From Barceló 2003, [12])

Compound groups	Examples
PHARMACEUTICALS	
Antibiotics (veterinary and medical)	**Erythromycin, Lincomycin, Sulfamethoxazole**
Analgesics Anti-inflammatories	**Acetaminophen Acetylsalicylic acid, Codeine, Diclofenac, Fenoprofen, Ibuprofen**
Psychiatric use	**Carbamazepine, Diazepam, Fluoxetine**
Lipid regulating	**Clofibric acid, Fenofibric acid, Atorvastatin, Bezafibrate**
Beta-blockers	**Atenolol, Metoprolol, Propranolol, Timolol**
X-rays (contrast media)	**Diatrizoate, Iopamidol, Iopromide**
Steroids and hormones (contraceptives)	**Estradiol, estriol, estrone, diethylstilbestrol**
PERSONAL CARE PRODUCTS	
Perfumes	**Fragrances, polycyclic and macrocyclic**
Sunscreens	**Benzophenone**
Insect repellents	**N, N-diethyltoluamide**
Antiseptics	**Triclosan, Chlorophene**
SURFACTANT DETERGENT AND ITS METABOLITES	**Alkylphenol ethoxylates, Alkylphenols (nonylphenol and octylphenol), Alkylphenol carboxylates**
FLAME RETARDANT	**Difenil ethers, Polybrominated diphenyl ethers (PBDEs), Tetrabromobisphenol A, tris(2-cloroetil)fosfato**
ADDITIVES AND INDUSTRIAL AGENTS	**Chelating agents (EDTA), Aromatic sulfonates**
GASOLINE ADDITIVES	**Dialkyl ethers, Methyl t-butyl ether(MTBE)**
DISINFECTION BY-PRODUCTS	**Bromate, Bromide acetonitriles, Bromo acids, Aldehydes bromine, cyano formaldehyde NDMA, iodine-THMs,**

Table 2: Classification of NSAIDs by its Active Component (Modified From Pérez-Ruiz *et al*., 2002, [14])

Chemical group	Active compound
Salicylates	**ASA (acetylsalicylic acid)**
Pyrazolone derivative	**Aminophenazone (dipyrone or metamizol); Phenylbutazone; Azaprofazona**
Para-aminophenol derivatives	**Acetaminophen (paracetamol or tylenol)**
Acetic acid derivatives.	**Indomethacin; Sulindac; Glucametacina**
Carboxylic and pyrrol pyrrolic derivatives	**Etodolac; Ketorolac**
Phenylacetic acid derivatives	**Diclofenac (voltaren); Tolmetin**
Acid derivatives n-Acetylanthranilic	**Mefenamic acid; Niflumic acid; Meclofenamic; lysine clonixinate**
Propionic acid derivatives	**Ibuprofen; Naproxen; Ketoprofen; Flurbiprofen; Fenoprofen; Oxaprozin**
Enolic derivatives	**Piroxicam; Meloxicam; Tenoxicam**
Nimesulide, sulphonanilide	**Nimesulide; Sulphonanilide**
Naphthylalkanones group	**Nabumetone**

Table 3: NSAIDs of Interest for the Present Work (Adapted from IMSS 2011; FACMED UNAM 2013, [47])

Pharmaceutical name	Chemical Group (NSAIDs)	Therapeutic indications	Pharmacokinetics	Administration
Acetylsalicylic acid	Salicylates	Indicated as an antipyretic, anti-inflammatory and antiplatelet. Useful for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute rheumatic fever.	Salicylates are eliminated from the body by renal excretion.	Oral
Diclofenac	Phenylacetic acid derivatives	It has analgesic and antipyretic activity and is indicated for the treatment of acute rheumatic diseases, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, back pain, gout acute phase, post-traumatic and postoperative inflammation, renal and biliary colic, migraine headaches, and prophylaxis for postoperative pain and dysmenorrhea	The metabolites are excreted in urine and bile 65%, 35% respectively.	Oral and intramuscular
Ibuprofen	Propionic acid derivative	Used for the treatment of painful states accompanied by significant inflammation such as rheumatoid arthritis and musculoskeletal mild (osteoarthritis, lumbago, bursitis, tendinitis, shoulder pain, sprains, strains, etc.). It is used for the treatment of moderate postoperative pain in dental pain, episiotomy, primary dysmenorrhea and headache.	Over 90% of an ingested dose is excreted in the urine as metabolites.	Oral
Naproxen	Propionic acid derivative	Treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and juvenile arthritis. It is also indicated for treatment of tendinitis, bursitis, sprains and postoperative pain management.	Naproxen Approximately 95% is excreted in the urine.	Oral
Paracetamol	Para-aminophenol derivatives	Joint disorders, otalgia, headache, sore odontogenic, neuralgia, minor surgical procedures and so on. treatment of fever.	Excreted in the urine unchanged between 1 and 2% of dose.	Oral and ophthalmological

Table 4: Concentrations of Some NSAIDs in Aquatic Environments

Drug	Location	Analytical procedure	Levels found µg//l	Reference
*ASA	In rivers of Romania	*SPE-GC–MS	0.030–0.037	[28]
*ASA	WWTP affluent in Japan	*SPE-GC–MS	0.47-19.4	[29]
Diclofenac	Groundwater in Germany	*SPE-GC–MS	0.59	[30]
Diclofenac	WWTP affluent in Switzerland	*SPE-GC–MS	1.3-2.9	[31]
Diclofenac	Hospital effluent in Spain	*SPE-HPLC–MS/MS	0.06-1.9	[32]
Ibuprofen	WWTP affluent U.K	*SPE-HPLC-MS/MS	7.741 -33.764	[33]
Ibuprofen	WWTP influent in Spain	* SPE-GC–MS	34-168	[34]
Ibuprofen	U.S.A Groundwater	*SPE-HPLC–MS/MS	3.11	[35]
Naproxen	WWTP Affluent in Sweden	*SPE-HPLC-MS/MS	3.65	[36]
Naproxen	WWTP effluent Canada	*SPE-GC–MS/MS	0.2714–7.9623	[37]
Naproxen	Germany river water	*HPLC–MS/MS	0.07	[38]
Paracetamol	Hospital effluent Spain	*SPE-HPLC-MS/MS	0.5–29	[32]
Paracetamol	WWTP Affluent in Spain	* SPE-GC–MS	29–246	[34]
Paracetamol	Groundwater in the U.S.A	*SPE-LC–MS	0.38	[35]

***Acetylsalicylic Acid (ASA), Solid Phase Extraction (SPE), gas chromatography with mass spectrometric detection (GC-MS), high performance liquid chromatography with detection by tandem mass spectrometry (HPLC-EM/EM), gas chromatography spectrometry with detection by tandem mass spectrometry, liquid chromatography with mass spectrometry detection (LC-MS).**

Table 5: Effects Some NSAIDs with Different Bioassays

Pharmaceutical	Specie	Toxicological point	Effect	Reference
ASA	*Dafnia magn*	EC_{50} (48 h)= 88.1mg/l	Immobilization	[39]
Diclofenac	*D. magna* *Desmodesmus subspicatus* *Lemna minor*	EC_{50} (48 h)= 68.0 mg/l EC_{50} (3 d)= 72 mg/l EC_{50} (7 d)= 72 mg/l	Immobilization, Growth inhibition rate	[40]
Diclofenac	*Oncorhynchus Mykiss*	LOEC 1, 5, 20, 100 and 500 µg/l (28 d)	Cytological abnormalities in the liver, kidney and gills	[41]
Diclofenac	*Salmo trutta f. fario*	NOEC 0.5, 5 and 50 µg/l (21 d)	Histopathological alterations	[42]
Ibuprofen	*D. magna* *D. subspicatus* *L. minor*	EC_{50} (48 h)= 108 mg/l EC_{50} (3 d)= 315 mg/l EC_{50} (7 d)= 22 mg/l	Immobilization, Growth inhibition rate	[40]
Ibuprofen	*Oryzias latipes* *Thamnocephalus platyurus*	LC_{50} (96 h)= >100 mg/l LC_{50} (24 h)= 19.59 mg/l	Mortality	[43]
Naproxen	*D. magna* *D. subspicatus* *L. minor*	EC_{50} (48 h)= 174 mg/l EC_{50} (3 d)= >320 mg/l EC_{50} (7 d)= 24.2 mg/l	Immobilization, Growth inhibition rate	[40]
Naproxen	*Brachionus calyciflorus* *Ceriodaphnia dubia*	E_{50} (48 h)= 0.56 mg/l EC_{50} (48 d)= 0.33 mg/l	Growth inhibition rate the population, Growth inhibition rate	[44]
Paracetamol	*D. Magna*	EC_{50} (48h)= 50 mg/l	Immobilization	[45]
Paracetamol	*D. Magna*	EC_{50} (48h)= 30.1 mg/l	Immobilization	[46]

(ASA) Acetylsalicylic acid; (h) hours; (d) days; (LC_{50}) Median Lethal concentration; (CE_{50}) Effective Concentration; (NOEC) No Observed Effect Concentration; (LOEC) Low Concentration Observed Effect