ANEXOS

Anexo 1- Artigo "*Emerging Pollutants: Environmental Impact of Disposal of Drugs*" e Tradução

Pharmaceutica Analytica Acta

Erzinger, Pharmaceut Anal Acta 2013, 4:9
DOI: 10.4172/2153-2435.1000e155

Research Article Open Access

Emerging Pollutants: Environmental Impact of Disposal of Drugs

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Introduction

The term "pollutant emergent" refers to any type of contaminant originated from previously undetected or products that were not problematized in health and environment [1]. In this group of pollutants has a product for veterinary use, personal care products, and pesticides. The pharmaceuticals in the aquatic environment should be highlighted by reaching the environment through discharges or excretion in unaltered form by the animal organism. The greater attention to this emerging type of pollutant occurs both by the increasing incidence of these concentration in the environment, as well as the increase of studies that show the health risks that these products can cause in cases of long-term exposure [2]. The emerging pollutants are found in soil, rivers, surface water and even groundwater, which in principle would require no specific treatments for its drinkability [3].

Analytical Techniques

According to Boxall [4] although pharmaceuticals are released into the environment for decades, researchers have only recently begun to quantify their levels in the environment. Using information from different countries and different usage patterns, prioritization exercises identified several drugs that are most likely to be released into the environment. For example, data from the UK on the annual use of veterinary drugs was combined with information on routes of administration, metabolism and ecotoxicity to identify drugs that should be monitored on a national recognition program [5]. Hilton et al. [6] conducted a similar exercise for human medicines, using information about the use and annual dose therapy with predictive models. Although these studies are usually based on country-specific information, they still give an indication of these substances to be investigated at the international level. New analytical techniques such as liquid chromatography coupled with mass spectrometry (LC-MS-MS), have enabled us to develop a better understanding of how drugs behave in the environment and to determine the concentrations in plants, waste water treatment, soils, surface water and groundwater [5].

Ecotoxicological Test

The qualitative and quantitative determination by instrumental analyzes are of utmost importance, but currently this is also emphasizing what the environmental impacts in the medium and long term to living beings obtained by ecotoxicological test. Pharmaceuticals are biologically active substances that were persistent and recognized as a permanent threat to environmental stability. Chronic x data as well as information on current distribution levels in different environmental compartments remain scarce and are focused on these therapeutic classes that are most often prescribed and consumed. However, they indicate that the negative impact of these chemical contaminants can have on living organisms, ecosystems and, ultimately, public health [7].

The analysis ecotoxicological to detect the toxicity of the sample as whole combined effects of the different constituents of the sample, while only the chemical analysis allows quantifying compounds isolated from a sample. This fact is of the utmost importance in the case of waste water, which exhibit great complexity, wherein the overall effect cannot correspond to the addition of the effects of the different components present may be synergistic (greater than the sum of the toxicity values of different constituents analyzed) or antagonistic (less than the sum of the toxicity values of analyzed separately).

The test measures the ecotoxicological effects of different concentrations of a sample in individuals of a given species. The effect concentration EC_{50} or LC_{50} lethal concentration corresponds to the concentration of the sample responsible for the effect in 50% of the organisms tested.

These tests can be acute or chronic depending on its duration and the observed effect. In the case of acute tests evaluated the effect is related mortality rates, immobilization or inhibition of growth and the lower this value, the higher is the toxicity of the sample, which often leads to misinterpretation of results achieved. Thus, began to use UT unit (toxicity) which corresponds to ($1/CE_{50}$ *100) for expression of results. The tests can measure the chronic effects on reproduction and genetic damage on the particular species.

The ecotoxicological tests may be performed using aquatic organisms or terrestrial depending on the type of study to be performed. These studies may be developed at the individual, population, community and even the ecosystem and may in some cases extend for several years.

In the process of evaluation of toxicity is to highlight the need to conduct a battery of tests with various organisms belonging to different trophic levels since these organisms have a different sensitivity to various types of toxic. Examples of organisms used in ecotoxicological tests, bacteria, fish, algae, amphibians, micro crustaceans and higher plants.

Advantages of toxicity tests provide an estimate of lethal and sub lethal toxicity when measuring the toxic agent is not chemically identified. These tests may provide an alarm signal or predict the potential environmental damage account for the effects of mixtures toxic an effluent chemically complex can be assessed generally as single pollutants and the results of these tests are more easily understood and accepted by the industrial and governmental in general.

How Limitations toxicity testing for toxic substances are not identified and the bodies-being tests that majorities of tests happen through visual analysis. Faced with these problems two devices

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Received September 26, 2013; **Accepted** September 30, 2013; **Published** October 03, 2013

Citation: Erzinger GS (2013) Emerging Pollutants: Environmental Impact of Disposal of Drugs. Pharmaceut Anal Acta 4: e155. doi: 10.4172/2153-2435.1000e155

were developed in which one obtains an automated way these tests. The Microtox® [8] using the marine bacterium *Vibrio fischeri* non-pathogenic naturally emitting light. The metabolism of the body is affected by low concentrations of toxic, affecting the intensity of the light emitted. It's greater the toxicity, greater the degree of inhibition of light production. Other equipment available on the market is the NGTOX® (New Generation ECOTOX) than through a system of image analysis and real time points up to 10 possible physiological variations algae *Euglena gracilis* [9].

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Pharmaceutica Analytica Acta

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DOI: 10.4172/2153-2435.1000e155

Artigo de Investigação Acesso Livre

Poluentes Emergentes: Impacto Ambiental da Eliminação de Medicamentos

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Introdução

O termo "poluente emergente" refere-se a qualquer tipo de contaminantes com origem em produtos que não foram previamente detetados ou que não foram considerados problemáticos no âmbito da saúde e do ambiente [1]. Neste grupo de poluentes encontram-se produtos para uso veterinário, de higiene pessoal e pesticidas. Os produtos farmacêuticos presentes no ambiente aquático deveriam ser salientados ao atingirem o meio ambiente através de descargas ou excreções inalteradas provenientes de organismos animais. O aumento de atenção dado a este tipo de poluentes emergentes deve-se quer ao aumento da incidência das suas concentrações no ambiente, assim como pelo aumento de estudos que advertem dos riscos para a saúde que esses produtos podem causar em situações de exposição a longo prazo [2]. Os poluentes emergentes podem ser encontrados nos solos, rios, água superficial e mesmo na água subterrânea, que em princípio não deveriam requerer qualquer tratamento específico para serem consideradas potáveis [3].

Técnicas Analíticas

De acordo com Boxall [4] apesar dos produtos farmacêuticos terem sido eliminados para o meio ambiente durante décadas, só recentemente os investigadores começaram a quantificar os níveis destes compostos no meio ambiente. Utilizando informação de diferentes países e diferentes padrões de utilização, testes de prioridade identificaram vários medicamentos com maior probabilidade de serem libertados para o meio ambiente. Por exemplo, dados do Reino Unido sobre o uso anual de medicamentos veterinários foram combinados com a informação sobre a forma de administração, metabolismo e ecotoxicidade para identificar medicamentos que deveriam ser monitorizados através de um programa nacional de identificação [5]. Hilton et al. [6] realizaram um estudo semelhante para medicamentos para seres humanos, utilizando informação sobre o uso e as quantidades terapêuticas anuais com modelos preditivos. Apesar destes estudos se basearem normalmente em informações específicas de um país, dão indicações sobre essas substâncias para serem investigadas a uma escala internacional. Técnicas analíticas novas tais como a cromatografia líquida acoplada com a espectrometria de massa (LC-MS-MS), permitiram desenvolver uma melhor compreensão sobre o comportamento dos medicamentos no meio ambiente e para determinar as concentrações em plantas, águas residuais tratadas, solos, águas superficiais e subterrâneas [5].

Análise Ecotoxicológica

As determinações qualitativas e quantitativas recorrendo à análise instrumental é de extrema importância, mas atualmente estas determinações também são enfatizadas recorrendo a análises ecotoxicológicas que indicam qual impacto ambiental a médio e longo prazo nos seres vivos. Os produtos farmacêuticos são substâncias biologicamente ativas persistentes e reconhecidas como uma ameaça permanente à estabilidade ambiental. Dados de rotina x assim como a informação sobre os níveis de distribuição atuais em diferentes tipos de ambientes continuam a ser escassos e dirigidos às classes terapêuticas que são mais frequentemente prescritas e consumidas. Contudo, indicam o impacto negativo que estes contaminantes químicos podem ter nos organismos vivos, ecossistemas e, em última análise, na saúde pública [7].

A análise ecotoxicológica deteta a toxicidade da amostra assim como a combinação dos efeitos dos diferentes constituintes da amostra, ao passo que a análise química só permite quantificar os compostos isolados de uma amostra. Este facto é extremamente importante no caso das águas residuais, que apresentam uma grande complexidade, em que o efeito total pode não corresponder à soma dos efeitos dos diferentes componentes presentes que podem ser sinérgicos (maiores do que a soma dos valores de toxicidade dos diferentes constituintes analisados) ou antagonistas (menores do que a soma dos valores de toxicidade analisados separadamente).

A análise quantifica os efeitos ecotoxicológicos de amostras de diferentes concentrações em indivíduos de uma determinada espécie. O efeito da concentração EC_{50} ou da concentração letal LC_{50} corresponde à concentração da amostra responsável pelo efeito em 50% dos organismos analisados.

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Recebido a 26 de setembro de 2013; **aceite** a 30 de setembro de 2013; **publicado** a 03 de outubro de 2013

Citação: Erzinger GS (2013) Poluentes Emergentes: Impacto Ambiental da Eliminação Incorreta de Medicamentos. Pharmaceut Anal Acta 4: e155. doi: 10.4172/2153-2435.2435.1000e155

doi: 10.4172/2153-2435.2435.1000e155

Estas análises podem ser urgentes ou de rotina dependendo da sua duração e dos efeitos observados. No caso de análises urgentes o efeito está relacionado com taxas de mortalidade, imobilização ou inibição de crescimento e quanto menor for este valor, maior é a toxicidade da amostra, o que frequentemente resulta na interpretação errada dos resultados obtidos. Assim, começou-se a usar a unidade UT (toxicidade) que corresponde a ($1/CE_{50}$ *100) para expressar os resultados obtidos. As análises podem medir os efeitos crónicos na reprodução e nas alterações genéticas de determinadas espécies.

As análises ecotoxicológicas podem ser realizadas utilizando organismos aquáticos ou terrestres dependendo do tipo de estudo a ser efetuado. Estes estudos podem ser efetuados a nível individual, populacional, comunitário e inclusivamente no ecossistema, podendo em alguns casos prolongar-se durante vários anos.

No processo de avaliação da toxicidade é de destacar a necessidade de realizar um conjunto de análises com vários organismos pertencentes a diferentes níveis tróficos, visto que estes organismos possuem uma sensibilidade diferente a diversos tipos de compostos tóxicos. Alguns exemplos de organismos utilizados em análises ecotoxicológicas incluem bactérias, peixes, algas, anfíbios, micro crustáceos e plantas mais complexas.

As análises de toxicidade têm como vantagem proporcionar uma estimativa da toxicidade letal e sub letal quando a quantificação do agente tóxico não é identificada quimicamente. Estas análises podem proporcionar um sinal de alarme ou prever a potencial deterioração ambiental tendo em conta que o efeito de misturas tóxicas presentes num efluente quimicamente complexo pode ser geralmente avaliado como sendo um poluente individual e os resultados destas análises são compreendidos e aceites mais facilmente pelas indústrias e governos, em geral.

Como o limite das análises de toxicidade para substâncias tóxicas nos organismos testados não é identificado a maioria das análises é efetuada visualmente. Confrontados com estes problemas foram desenvolvidos dois aparelhos que realizam de forma automática estas análises. O Microtox® [8] utiliza a bactéria marinha não patogénica *Vibrio fischeri* que emite luz de forma natural. O metabolismo do organismo é afetado por baixas concentrações de compostos tóxicos, que afetam a intensidade da luz emitida. Quanto maior for a toxicidade, maior será o grau de inibição de produção de luz. Existe outro equipamento disponível no mercado, o NGTOX® (ECOTOX de nova geração) que através de um sistema de análise imagiológica em tempo real consegue detetar até 10 possíveis variações fisiológicas da alga *Euglena gracilis* [9].

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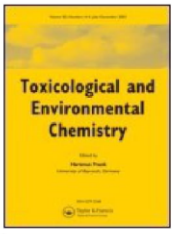
Anexo 2 – Artigo "*Pharmaceuticals as priority water contaminants*" e Tradução



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Toxicological & Environmental Chemistry

ISSN: 0277-2248 (Print) 1029-0486 (Online) Journal homepage: https://www.tandfonline.com/loi/gtec20

Pharmaceuticals as priority water contaminants

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To cite this article: P. Bottoni , S. Caroli & A.Barra Caracciolo (2010) Pharmaceuticals as priority water contaminants, Toxicological & Environmental Chemistry, 92:3, 549-565, DOI: 10.1080/02772241003614320

To link to this article: https://doi.org/10.1080/02772241003614320

Published online: 12 Mar 2010.

Toxicological & Environmental Chemistry
Vol. 92, No. 3, March 2010, 549–565

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REVIEW ARTICLE

Pharmaceuticals as priority water contaminants

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(*Received 4 January 2010; final version received 12 January 2010*)

Pharmaceuticals and their metabolites can reach water bodies through sewage systems, industrial discharges, effluents from sewage treatment plants (STPs), aquaculture, and livestock farming. Pharmaceuticals include a hundred substances which are very different as regards chemical–physical properties and environmental behavior, although they may have strong biochemical activities. At present, pharmaceuticals can reach water concentrations of ng L^{-1} to mg L^{-1} and some are considered ubiquitous.

Nevertheless, their presence in the aquatic environment and impact on aquatic biota and on human health have not yet been studied adequately. Experimental evidence indicates that pharmaceuticals may cause harmful effects, such as morphological, metabolic and sex alterations on aquatic species, induction of antibiotic resistance in aquatic pathogenic micro-organisms, and disruption of biodegradation activities in STPs. Risk assessment studies and evaluations are in progress. Yet, the available scientific data are consistent with the introduction of some pharmaceutical indicators in extensive water monitoring to better define their actual impact on aquatic organisms and humans. Under these perspectives, the inclusion of emerging pharmaceuticals in the revision of EU List of Priority Substances under the Water Framework Directive 2000/60/EC should be implemented as well as the definition of respective environmental quality standards.

Keywords: pharmaceuticals; metabolites; water contamination; surface water; drinking water

Introduction

The relevance of pharmaceuticals, for human and veterinary use as well as of their biologically active transformation products, as environmental micropollutants has caught more and more attention in recent years due to the growing understanding of their impact on water bodies (Halling-Sorensen et al. 1998).

Pharmaceuticals are molecules designed to produce a therapeutic effect on the body, usually active at very low concentrations, can pass through biological membranes and persist in the body long enough to avoid being inactivated before having an effect. These compounds are excreted through feces and urine as a mixture of metabolites and substances which are often unchanged.

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ISSN 0277–2248 print/ISSN 1029–0486 online

DOI: 10.1080/02772241003614320
http://www.informaworld.com

The primary sources of pharmaceutical contamination are represented by domestic, urban, hospital, and industrial wastewater, as well as by effluents from sewage treatment plants (STPs), aquaculture, and intensive livestock farming. Moreover, re-use of solid and liquid livestock manure and sewage sludge in agriculture, in order to recycle nitrogen compounds as fertilizers, can contribute to the dispersion of pharmaceuticals into soil and, under certain conditions, into water bodies. At present, the presence of antibiotics, steroids, blood lipid regulators, estrogens, painkillers, anti-inflammatories, antiseptics, antihypertensive drugs, antiepileptics, antineoplastic agents, and other substances in surface water bodies is well-documented. Percolation of pharmaceuticals into groundwater and their presence in sea coastal water have been detected as well.

The scientific community has focused mainly on the class of antibiotics which contaminate the water environment and food with relation to the possibility of helping formation of antibiotic-resistant bacteria and to the associated health risks (Austin 1985; Miranda and Castillo 1998; Boon and Cattanach 1999). Another important issue pertains to steroidal drugs that may cause the metabolic and structural alterations observed in aquatic organisms (Routledge et al. 1998; Larsson et al. 1999). Due to water resources and their effects, also the possible suppressant effects on degrading microorganisms in wastewater treatment plants, study of pharmaceuticals is a matter of keen interest (WHO 1999).

People can be exposed to pharmaceuticals that pollute the water environment through drinking water or consumption of aquatic organisms. Risk assessment studies for aquatic species and humans are in progress. Nevertheless, the risk of exposure to pharmaceuticals has proven higher for aquatic species than for humans, and some substances such as ibuprofen, acetylsalicylic acid, paracetamol, amoxicillin, oxytetracycline, and mefenamic acid are thought to be present in water at a risk level that is not negligible for water biota (Christensen 1998; Stuer-Lauridsen et al. 2000; Jones, Voulvoulis, and Lester 2002; Grung et al. 2008). In this context, the known pressures of pharmaceuticals on water ecosystems and their potential impacts on aquatic organisms have been documented and this evidence could lead to their inclusion among new priority candidates in the current or future revision of the EU List of Priority Substances relevant to the Water Framework Directive 2000/60/EC.

Sources of contamination

The primary source of release of pharmaceuticals into the aquatic environment is represented by domestic and hospital sewage disposal, due to the widespread use of drugs for treatment of human diseases. In fact, most pharmaceuticals are only partially transformed or retained in the body and they are excreted through urine as mostly active metabolites of compounds that can remain unchanged or be conjugated to polar molecules (Reddersen, Heberer, and Dunnbier 2002).

Another major source of pharmaceuticals, which is equally important but restricted to specific areas of countries, is the disposal of sewage from intensive livestock farming sites and effluents from intensive aquaculture systems, where the use of veterinary drugs is ordinary and necessary.

Many studies demonstrate that, when sewage drain lines converge into treatment plants, effluents from such plants can still contain remarkable amounts of

Table 1. Theoretical percentages of pharmaceuticals concentration and removal in some treatment phases into a conventional STP.

Name	Influent water	Primary sludge	Discharge sludge	Volatilization (total)	Bio-degradation (total)	Effluent water	Removal (total)
Mefenamic acid	100	50.4	30.07	0	0.7	18.84	81
Allopurinol	100	0.25	1.25	0	0.09	98.15	1.85
Amoxicillin	100	0.27	1.52	0	0.09	98.12	1.88
Aspirin	100	0.29	1.53	0	0.09	98.09	1.91
Atenolol	100	0.25	1.51	0	0.09	98.15	1.85
Carbamazine	100	0.92	1.95	0	0.1	94.04	2.96
Cimetidine	100	0.26	1.51	0	0.09	98.14	1.86
Diclofenac sodium	100	0.26	1.51	0	0.09	98.13	1.87
Diltiazem hydrocloride	100	1.42	2.28	0	0.11	96.19	3.81
Erythromycin	100	2.87	3.23	0	0.13	93.77	6.23
Fenoxymethyl-penicillin	100	0.54	1.7	0	0.1	97.66	2.34
Gliclazide	100	0.56	1.71	0	0.1	97.63	2.37
Ibuprofen	100	16.48	11.92	0	0.31	71.28	28.72
Mebevarin hydrocloride	100	12.73	9.58	0	0.26	77.43	22.57
Mesalazine	100	0.27	1.52	0	0.09	98.12	1.88
Metmorphine hydrocloride	100	0.25	1.5	0	0.09	98.15	1.85
Naproxene	100	3.66	3.75	0	0.14	92.45	7.55
Oxytetracycline	100	0.25	1.51	0	0.09	98.15	1.85
Paracetamol	100	0.26	1.51	0	0.09	98.14	1.8
Quintin sulfate	100	54.5	31.64	0	0.74	13.12	86.88
Sodium valproate	100	0.25	1.5	0.08	0.09	97.99	2.01
Sulfate iron (III)	100	0.25	1.51	0	0.09	98.15	1.85
Sulfasalazine	100	12.51	9.44	0	0.26	77.8	22.2

Source: Modified and adapted from Jones, Voulvoulis, and Lester (2002).

pharmaceuticals and metabolites, because ordinary degradation systems are often characterized by low efficiency caused by inhibition or alteration of efficacy of degrading microorganisms, as well as by their poor adaptation to drugs contained in affluents of plants. Table 1, where some cases of modeled degradation rates in a standard treatment plant are given, shows an example for such a phenomenon (Jones, Voulvoulis, and Lester 2002). The authors were able to assess, for each compound contained in affluents and effluents, the overall amount of degradation through the plant, including standard processes of biodegradation, sorption to sludge, and stripping to air. This study has revealed that most pharmaceuticals are unlikely to be degraded in a treatment plant and may be, therefore, released into rivers.

Other sources of contamination are indirect, such as reclaimed wastewater from treatment plants, used, as an example, for irrigation, sludges used in agriculture to reclaim inorganic nutrients, sewage from livestock farming sites applied on farmland, manufacturing waste from pharmaceutical industries, hospital wastewater and improper disposal of out-of-date medicines.

In these cases, an impact on the terrestrial and hypogeal environment is expected as well, but only a small number of study topics are available on this at present. Among them, studies to assess toxic effects of some veterinary drugs on plants (Migliore, Cozzolino, and Fiori 2003) deserve mention.

Close attention must be paid to hospital wastewater. The World Health Organization (WHO) has devoted a treatise on this topic (WHO 1999). Unlike domestic wastewater, wastewater from hospital centers contains various potentially hazardous substances and precisely:

(1) microbiological pathogens: enteric pathogens easily spread through water, they include bacteria, viruses, and helminths;
(2) hazardous chemical compounds: chemical substances used for cleaning and disinfection (e.g., formaldehyde);
(3) pharmaceutical products: usually discarded by hospital pharmacies and hospital wards. They are mostly antibiotics and genotoxic drugs. Genotoxic waste also includes cytotoxic and antineoplastic agents, which are used in cancer chemotherapy and as immunosuppressants (organ transplants and immunologic diseases). Cytotoxic pharmaceuticals can be classified as follows:
    - alkylant agents: they are responsible for alkylation of DNA nucleotides and cross-linking phenomenon;
    - antimetabolites: they inhibit biosynthesis of nucleic acids in cells;
    - mitotic inhibitors: they prevent cell replication.
(4) radioactive isotopes: they are mostly produced by oncology wards (following diagnosis, therapy, diagnostic imaging, research, etc.).

As to their disposal, all residues from handling of antiblastic chemotherapic substances (individual and disposable safety apparel, disposable absorbent sheets, basins, gauzes, cotton wool, phials, medicine bottles, syringes, etc.) must be considered as special hospital waste and must be chemically inactivated and incinerated. A considerable problem is represented by treated patients' urine, which typically contains high concentrations of active ingredients and does not get inactivated.

Main pharmaceuticals used in Italy and other countries

The classic method to initially assess the impact on the environment from a certain type of contamination consists of quantifying release modes and rates of contaminants.

The collection of data about use, production, and selling of individual compounds or classes of compounds allows an initial identification of most significant molecules or groups in order to direct possible research activities and investigations to environmental areas potentially or actually affected by contamination.

In the case of pharmaceuticals this issue proves particularly important, since molecules allowed to be used in different countries add up to several thousands. In spite of that, neither direct data about production and selling nor information about consumption is available. As to Italy, as well as to other countries, obtaining this kind of information consists of examining therapeutic medical prescriptions and

Table 2. Active principles highly used in Italy, the UK, and the USA in decreasing order.

Italy (2001)[a]	UK (2000)[b]	USA (2005)[c]
Omeprazol	Paracetamol	Azithromycine
Amlodipina	Metformine hydrochloride	Amoxicillin
Enalapryl	Ibuprofen	Furosemide
Simvastatin	Amoxicillin	Hydrochlorotiazide
Epoetine alfa	Sodium valproate	Amlodipine
Claritrhomycin	Sulfasalazine	Lisinopril
Nitroglycerin	Mesalazine	Alprazolam
Amoxicillin þ clavulanic	Carbamazepine	Sertraline
Doxazosin	Ranitidine hydrochloride	Metoprolol
Ranitidine	Cimetidine	Simvastatin
Celecoxib	Naproxen	Estrogen conjugates
Cefitraxone	Atenolol	Lansoprazol
Hydrochlorotiazide þ enalapryl	Oxitetracycline	Ceritizine
Fluticason	Erithromicine	Ibuprofen
Nimesulid	Diclofenac	Levothyroxine
Paroxetin	Flucloxacilline	Propoxyphene n/apap
Somatropin	Fenoxymetilpenicilline	Triamterene hydrochlortiazide
Cyclosporin	Allopurinol	Celecoxib
Tamsulosin	Diltiazem chloridrate	Zolpidem
Finasteride	Gliclazide	Fexofenadine
Beclometason	Aspirin	Cefalexine
Rofecoxib	Quinine sulfate	Esomeprazolo
Pravastatin	Mebeverin hydrochloride	Alendronate
Nifedipine	Mefenamic acid	Rofecoxib
Azithromicyn		Montelukast
Cefonicid		Norgestimate/ethinyl-estradiol
Lansoprazol		Prednison
Cyprofloxacin		Metoprolol

Notes: [a]Italian Ministry of Health, 2001.
[b]Jones, Voulvoulis, and Lester, 2002.
[c]RxList, The Internet Drug Index, 2005.

extrapolating the amounts of sold, used, or administered individual active ingredients by various computation methods.

On this subject, we give here an account of some data from the Department of Health (Italian Ministry of Health 2001) concerning 30 most expensive compounds charged to National Health Service (SSN) over the first 9 months of 2001 (Table 1, first column). Furthermore, each active ingredient reported in the first column of Table 2 exceeded the expense threshold of 51 million euros. For example, the expense for just one substance, omeprazole, exceeded 289 million euros, while the overall expense for the 30 compounds (about 3,283,000,000 euros) added up to about 36% of the total national expense charged to SSN over that period (about 9,109,000,000 euros).

On the other hand, in the first semester of 2001, the biggest expenses charged to SSN were related to the following therapeutic groups which are listed in descending order according to costs:

- cardiovascular system;
- systemic antimicrobials;

- gastrointestinal apparatus and metabolism;
- respiratory system;
- nervous system;
- musculoskeletal system;
- blood and hematopoietic organs;
- urogenital system and sex hormones.

Ministerial sources confirm what was mentioned above about the upward trend in pharmaceutical costs. An increase in sales of pharmaceuticals has been observed in all developed countries. In 2000, an average 9% increase was registered in European countries and, among them, Italy was characterized by the largest increase (14%) in comparison to, for example, the UK (5%). In the US, the increase was around 19% (Italian Ministry of Health 2001).

As a comparison, Table 2 also reports a list of the 25 most used drugs in the UK in 1998 (Jones, Voulvoulis, and Lester 2002) and one of the 30 most prescribed substances in the US in 2003 (RxList, The Internet Drug Index 2005).

Such examples demonstrate that pharmaceuticals and their associated categories are quite comparable, at least in western countries. The above data immediately suggest how high an impact hormonal and antibiotic compounds can have on the aquatic environment and, for this reason, environmental and ecotoxicological research has focused on these main categories, also in terms of exposure and risk for both aquatic species and humans.

Back to the problem of identifying the most significant substances according to their possible impact on the environment, it must be said that, according to various researchers, data about medicine consumption are important, but might be insufficient. In fact, many occasionally used, but highly toxic compounds, such as, anticancer agents, which could have cytotoxic, mutagenic, and genotoxic effects also on environments (and, therefore, on organisms) different from their therapeutic targets, might be found at high concentrations in areas close to release points or in small water bodies, where dilution might be less effective at lowering pollution load.

Concerning this, a list of anticancer pharmaceuticals, which have been classified by the International Agency for Research on Cancer (IARC), according to their carcinogenic potential (IARC 2005), is as follows:

- Group 1A (human carcinogens): butanediol dimethylsulfonate (busulfan, myleran), cyclophosphamide, chlorambucil, 1-(2-chloroethyl)- 3(4-methylcyclohexyl)-1-nitrosurea, melphalan, MOPP (mixture of mustar- gen, oncovin, procarbazine and prednisone) and other combinations of alkylant agents, 2-naphthylamine, tamoxifen, TIOTEPA (triethylentiophosphoramide);
- Group 2A (probable human cancerogens): adriamycin, azacitidine, cisplatin (CDDP), carmustine (BCNU), chlorozotocin, etoposide, lomustine (CCNU), nitrogen mustard, procarbazine, teniposide;
- Group 2B (possible human cancerogens): amsacrine, aziridine, bleomycin, dacarbazine, daunomycin, mitomycin C, mitoxantrone, streptozotocin, zidovudine;
- Group 3 (not classified as human carcinogens): acyclovir, 6-mercaptopurine, methotressate, prednimustine, prednisone, vinblastine sulfate, vincristine sulfate.

Finally, the main classes of veterinary compounds must be mentioned. As to beef farming, in Italy the commonly used drugs are antibacterials administered with feed and water. Among them are (Busani et al. 2003):

- cephalosporins (from 1st to 4th generation), enhanced aminopenicillins and penicillin G, commonly used to treat mastitis;
- 3rd generation aminosides (gentamycin, apramycin) and fluoroquinolones, used to treat neonatal enteritises and for weaned cattle;
- Fluoroquinolones, macrolides and phenicols to treat respiratory infections.

Antibiotics are the most used drugs in aquaculture sites as well, in order to treat most common fish diseases. As to Italy, we must mention (Lalumera et al. 2004):

- Amoxicillin, flumequine, oxytetracycline, sulfamerazine, thiamphenicol.

In other countries, such as the Netherlands and the UK, the most used veterinary pharmaceuticals are (Boxall et al. 2003):

- antimicrobials: amoxicillin, dihydrostreptomycin, enrofloxacin, lincomycin, oxytetracycline, sulfadiazine, tylosin;
- antiparasitic agents: ivermectin, pyrantel, triclabendazole;
- Coccidiostatic drugs – antiprotozoans: amprolium, clopidol, dimetridazole, narasin, nicarbazin;
- antifungal agents: chlorhexidine, griseofulvine, miconazole;
- hormones: altrenogest, estradiol benzoate, ethinylestradiol, methyltestosterone, melatonin, progesterone;
- growth promoters: flavophospholipol, monensin, salinomycin;
- anesthetics: alotan, isoflurane, procaine, lidocaine/lignocaine;
- Sedatives: phenobarbitone.

Following the collection and the evaluation of information about used/sold amounts of medicines, animal metabolism, and the mode of release into the environment, this study also presents a list of veterinary drugs which are thought to possibly contaminate the environment (Boxall et al. 2003). Compounds written in capital letters have been actually searched for and found in water bodies:

- amitraz, amoxicillin, amprolium, antiseptics, baquiloprim, cephalexim, CHLOROTETRACYCLINE, clavulanic acid, clindamycin, clopidol, CIPERMETRINE, cyromazine, decoquinate, deltametrine, DIAZINON, dihydrostreptomycin, dimethicone, EMAMECTIN BENZOATE, enrofloxacin, fenbendazole, flavomycin, flavophospholipol, florphenicol, flumetrine, fosmet, immunologic agents, IVERMECTIN, lasalocid, levamisole, lidocaine, LINCOMYCIN, maduramycin, monensin, morantel, neomycin, nicarbazin, nitroxinil, OXOLINIC ACID, OXYTETRACYCLINE, piperonyl butoxide, poloxalene, procaine, benzilpenicillin, procaine penicillin, robenidine hydrochloride, salinomycin, SARAFLOXACIN, sulfadiazine, TETRACYCLINE, tiamulin, tilmicosin, toltrazuril, triclabendazole, TRIMETOPRIM, TYLOSIN (Boxall et al. 2003).

Chemical–physical properties

Very little data are available about the environmental fate of pharmaceuticals and their chemodynamic and chemical–physical properties. In particular, we can find

solubility and pKa data and, with more difficulty, Kow (octanol/water partition constant), Kd (soil-water partition constant), Koc (soil organic carbon/water partition constant) and DT50 (degradation half-life) data for soil and water. Altogether, these parameters can give information about the environmental behavior of drugs. Some of them are typically used to compute their theoretically predicted concentrations in surface and ground water, as well as in soil and sediments (PECs), or they allow us to define screening indexes that could assess their ability to percolate into groundwater, as well as more complex mathematical distribution models, as is customary for various categories of contaminants such as phytosanitary products.

In general, the heterogeneity of chemical classes of pharmaceuticals is clear, which, in turn, implies heterogeneity of associated chemical–physical properties. Many pharmaceuticals are water soluble and nonvolatile, others are polar and not easily adsorbable, while some others are lipophilic and show a certain tendency to bioaccumulation and adsorption on sediments. Following metabolic processes, other drugs can produce metabolites conjugated to soluble polar molecules, which, under conditions treatment, can be biologically hydrolyzed and transformed back into active molecules.

Some pharmaceuticals, such as oxolinic acid, cyclophosphamide, flumequine, ivermectin, oxytetracycline and clofibric acid, are known for their persistence in the aquatic environment, as well as in soil and sediments, and/or for their resistance to biologic degradation in treatment plants. Such compounds have shown, in various matrices and under different experimental conditions, degradation half-lives which are longer than 100 days and sometimes as long as several years (Steger-Hartmann, Kummerer, and Hartmann 1997; Halling-Sorensen et al. 1998; Steger-Hartmann, Lange, and Schweinfurth 1999; Winkler, Lawrence, and Neu 2001). As to their persistence, since many pharmaceuticals are designed to be orally administered, they prove insensitive to degradation processes by chemical hydrolysis or mediated by enzymes, which, in the aquatic environment and in soil, represent some of the primary degradation modes of xenobiotics, such as phytopharmaceuticals. According to some researchers, this means that, at least in the aquatic environment, photodegradation processes should prevail. Consequently, various studies on this specific topic have been performed with the aim to define boundary conditions that can influence and enhance such processes, especially in treatment plants (Andreozzi, 2003; Raffaele, and Nicklas 2003).

Table 3 shows a list of chemical–physical and mobility parameters (such as Kd, Koc, and DT50), which have been extracted from a large number of studies and databases (The Merck Index 1996; Koschorreck, Koch, and Ro¨nnefahrt 2002; Andreozzi, Raffaele, and Nicklas 2003; Tixier et al. 2003; TOXNET Toxicology Data Network – Hazardous Substances Data Bank (HSDB) 2009).

As is clear from this table, data about degradation in soil are extremely deficient. In some cases, in the absence of specific studies, research was aided by algorithms which correlate partition constants, including the bioconcentration factor (BCF), with each other and allow extrapolation of unknown values. Parameters for some compounds included in Table 3 have been computed this way (Jones, Voulvoulis, and Lester 2002).

Table 3. Chemical–physical properties of some pharmaceuticals.

Compound	Water solubility[a]	pKa[b]	Koc	log Kow	Kd (L kg^{-1})	DT50 (days)	
						Water	Soil
Clofibric acid	Insoluble			2.57[c]		4.63[c]	
Mefenamic acid	0.0041 g/100 mL at 25°C pH 7.1	4.2[g]	461.0	5.12	18917		
Allopurinol	0.48 mg mL^{-1} at 25°C	9.3	19.4	—0.55	0.04		
Amoxycillin	4.0 mg mL^{-1}		865.0	0.87	1.06		
Aspirin	4600 mg L^{-1} at 25°C	3.5	10.0	1.19	2.22		
Atenolol	Slightly soluble	9.2	148.0	0.16	0.21		
Carbamazepine	Insoluble	13.9[g]		2.45[c]		63[c]; 100[d]	
Benzimidazole	Slightly soluble	5.48[a]	110[g]	1.32[g]; 6.2[c]			15[c]
Carbamazine	Insoluble	13.9[g]	3.87e þ 03	2.25	25.5		
Cimetidine	1.14% at 37°C	6.8[g]	690.0	0.40[g]	0.36	8[c]	
Diclofenac	4.9 mg mL^{-1} in deionized water at 25°C	4.2	833.0	0.70 – 4.51	0.72	5.0[d]	
		7.7	9.5e þ 03	2.70	72		
Diltiazem hydrochloride	Soluble	8.9	10.0	3.06	165		
Erythromycine	2 mg mL^{-1}						
Fenoxymethylpenicilline	5.88 mg L^{-1}[f]		177.0	2.09[f]	17.6		
Gliclazide			1.27e þ 4	2.12	19		
Ibuprofen	21 mg L^{-} at 25°C[g]	4.91[g]	394.0	3.97; 4.13–4.9[c]	454	20; 32[c]	
Mebeverine hydrochloride			6.66e þ 05	3.82	948		
Mesalazine			10.0	0.98	1.37		
Metformin hydrochloride	Soluble	12.4[g]		—1.43[g]	0.0003		
Naproxene	Insoluble	4.15[g]	349.0	3.18; 3.24[c]	217	14[c]	
Oxytetracycline	Slightly soluble[g]	3.3	97.2	—0.90	0.02		
Ofloxacine						10.6[d]	
Paracetamol (acetaminofen)	Slightly soluble[g]	9.4	61.7	0.46	0.41		
Propanolol	Soluble	9.45		—0.45 (pH 2)		16.8[d]	
Quinine sulfate	1 gr/810 mL	5.07[g] 3.5	1.85e þ 08	5.40	36045		
Ranitidine hydrochloride	Soluble						
Sodium valproate	Slightly soluble in the acid form		24.1	—0.85 0.37	0.02		
Sulfasalazine	Insoluble		1.84e þ 03	3.81	926		

Notes: Where not indicated, parameters were calculated as reported in Jones, Voulvoulis, and Lester (2002). [a]The Merck Index, 1996; [b]Jones, Voulvoulis, and Lester, 2002; [c]Tixier et al. 2003; [d]Andreozzi, Raffaele, and Nicklas, 2003; [e]Koschorreck, Koch, and Ro¨nnefahrt, 2002; [f]Christensen, 1998; [g]TOXNET Toxicology Data Network – Hazardous Substances Data Bank (HSDB) 2009.

Presence of pharmaceuticals in the aquatic environment

A vast amount of data are available on this subject in the scientific literature, even though they usually refer to small-scale investigations on a restricted number of drugs.

The results are obtained from many factors, such as uneasy identification of the most significant substances to be studied, complexity of analytical methods used to investigate very different molecules, which often request knotty procedures, and uneasy getting of certified analytical standards. Moreover, since concentrations of commonly water-dispersed pharmaceuticals are in the range ng L^{-1} to mg L^{-1}, sophisticated measuring instruments are needed. It must be said that detailed monitoring campaigns have been started only recently, in spite of substantial evidence of aquatic contamination by pharmaceuticals over the past 20 years.

The first known case of contamination of water resources dates back to the 1980s, following various investigations mainly performed in North European countries, such as Germany. Later, research spread to other European countries, as well as to the US and Canada. Some investigations on river water quality were based in Italy as well (Zuccato et al. 2000; Calamari et al. 2003).

At present, the presence of antibiotics, steroids, blood lipid regulators, estrogens, painkillers, anti-inflammatories, antiseptics, antihypertensive drugs, antiepileptics, antineoplastic agents, and other substances is well-documented in rivers, lakes, groundwater, drinking water, sea coastal water, urban effluents, and treatment plants (Steger-Hartmann, Kummerer, and Hartmann 1997; Buser and Muller 1998; Daughton and Ternes 1999; Stumpf et al. 1999; Sacher et al. 2001; Reddersen, Heberer, and Dunnbier 2002; Andreozzi, Raffaele, and Nicklas 2003; Atkinsons, Atkinsons, and Tarrant 2003; Tixier et al. 2003).

Some examples of detected concentrations (rounded data) are reported here. Maximum concentrations of 27–70 ng L^{-1} for lipid regulators (clofibric acid, bezafibrate) (Webb et al. 2003), 400 ng L^{-1} for phenazone (analgesic), 900 ng L^{-1} for one of its metabolites (AMDOPH) (Reddersen, Heberer, and Dunnbier 2002), 79–86 ng L^{-1} for RX contrast agents (iopamidol, diatrizoate) (Webb, Ternes, and Gibert 2003), and up to 24 ng L^{-1} for sedatives (diazepam) (Zuccato et al. 2000) have been detected in surface drinking water.

The most significant concentration levels, or ranges, of drugs in surface water pertains to furosemide (up to 88 ng L^{-1}) (Stumpf et al. 1999), ibuprofen (up to 92 ng L^{-1}) (Zuccato et al. 2000), bezafibrate (134–203 ng L^{-1}) (Zuccato et al. 2000), and atenolol (170–242 ng L^{-1}) (Zuccato et al. 2000), while lincomycin, erythromycin, and spiramycin antibiotics are characterized by levels up to 14, 17, and 68 ng L^{-1}, respectively (Zuccato et al. 2000). For sediments, the higher concentration levels are: 130 ng kg^{-1} for bezafibrate and lincomycin and 220, 410, 630, 2900 ng kg^{-1} for ibuprofen, ranitidine, erythromycin, and spiramycin, respectively (Zuccato et al. 2000).

Furthermore, in an investigation performed in the US concerning 139 water bodies downstream of urban centers or close-to-livestock farming sites, thus representing worst-case polluted sites, more than 90 organic contaminants were searched for, among which 21 substances were human and veterinary antibiotics, 19 were prescription medicines, and 14 steroids and hormones (Kolpin et al. 2002). Contamination frequencies have proven larger than 10% for 20 substances and their metabolites, in particular, 450% for cholesterol, trichlosan, coprostanol, and

caffeine. For more than 30 drugs, maximum concentrations larger than 0.1 mg L^{-1} have been found and some compounds, such as codeine and ibuprofen (1 mg L^{-1}), erythromycin-H20 (1.7 mg L^{-1}), sulfamethoxazole (1.9 mg L^{-1}), 1,7-dimethylxanthine (3.1 mg L^{-1}), stigmastanol (4 mg L^{-1}), caffeine (6 mg L^{-1}), acetaminophen (10 mg L^{-1}), cholesterol (up to 60 mg L^{-1}), and coprostanol (up to 150 mg L^{-1}), have shown max levels 1 mg L^{-1}. In the course of the above-mentioned study, different compounds have been detected in the same sample. In particular, also taking into account their effects, an overall maximum concentration of 53.7 mg L^{-1} for active hormonal agents
was observed, among which are a large number of pharmaceuticals (Kolpin et al. 2002).

As to contamination of groundwater, only a few studies are available, but substantial evidence exists for the presence of mainly polar drugs and metabolites. In a study performed in Germany, many medicinal products have been detected in groundwater probably polluted by wastewater (Sacher et al. 2001). Researchers analyzed more than 105 samples of well water and searched for 60 drugs. Thirty-nine compounds have been detected at concentrations ranging from 10 to 100 ng L^{-1}. For six compounds (iopamidol, sulfamethoxazole, sotalol, dichlophenac, carbamazepine, and amidotrizoic acid, in ascending order according to concentration), maximum levels in the range 300–1100 ng L^{-1} have been found.

This short summary of available data suggests the existence of diffuse contamination of water resources, in most developed countries, evidenced by some molecules which can be considered ubiquitous, such as acetylsalicylic acid, caffeine, nicotine, fluoroquinolone antibiotics, carbamazepine, and clofibric acid, with the almost constant presence of more than one drug in single water samples. Additionally, it is interesting to note that the presence of drugs in surface water does not show seasonal fluctuations, as in the case of phytosanitary products. Instead, the trend seems to be constant because of the uninterrupted release of pharmaceuticals into the environment and this configures, a problem of long-term multiple exposure to low concentrations of individual compounds especially for aquatic species (Daughton and Ternes 1999).

Effects on environmental organisms and risk assessment

As to the ecotoxicological effects of pharmaceuticals on nontarget organisms, a large number of studies have focused on antibiotics in terms of possible formation of both exogenic and natural antibiotic-resistant pathogenic microorganisms, possible associated risks for humans and problems concerning treatment plants, due to inhibition and disappearance of degrading microorganisms. Other investigations have dealt with steroids and sex hormones, due to metabolic and structural alterations observed in aquatic species.

What makes it difficult to assess the effects of other types of pharmaceuticals on organisms, which are different and can be phylogenetically very far, for example, from humans, is that metabolic, enzymatic, clinical, and behavioral targets are not easily identifiable.

Besides, also classic acute and chronic ecotoxicological tests present both practical and theoretical difficulties, since concentrations of individual pharmaceuticals in the aquatic environment are far lower than effective doses and, therefore, would seem not able to produce acute effects.

Moreover, standard tests on shellfish, algae, etc., might be not sensitive enough to highlight effects of molecules designed, in terms of amount and structure, not to appear as ''xenobiotic''. For this reason, alternative tests on possibly more sensitive organisms and groups of organisms are being developed. Finally, it must be said that ordinary studies usually focus on the analysis of individual compounds, while monitoring data concerning surface water bodies suggest to investigate effects of mixtures of drugs.

In the open scientific literature, available data about acute toxicity pertain to few molecules and data about chronic toxicity are even scarcer. EC50 and LC50 values concerning some human pharmaceuticals and spanning over six orders of magnitude have been observed for different aquatic species. Among such drugs, at least 10 are very toxic or extremely toxic (acute ecotoxicity endpoints of 0.1–1 mg L^{-1} and 0.1 mg L^{-1}, respectively):

- Alendronate, amitriptyline, carvedilol, ethinylestradiol, fluticasone, fluoxetin, fluvoxamine, midazolam, paclitexel, thioridazine (CSTEE 2001).

Environmental risk assessment (ERA) studies for aquatic species are in progress. This kind of study is usually based on the computation of risk quotient, which is defined, for any single substance, as the ratio of predicted or measured concentration in water (PEC, MEC) to no-effect concentration (PNEC), the latter being extracted from medium- and long-term toxicity data for aquatic organisms. Such procedures refer to general rules established by the European Commission to perform risk assessment for the environment and for humans in the EU Technical Guidance Documents (TGD) (European Chemical Bureau 2003) following expo- sure to new and existing chemical substances and to biocides. These same general rules shape the guidelines for environmental risk assessment of human pharmaceuticals, which have been recently delivered by the European Agency for the Evaluation of Medicinal Products (EMEA) in the context of marketing authorization (EMEA – CHMP 2006). It should be noted that, in this context, any potential risk to the environment, and particularly the aquatic environment, does not imply a refusal or a withdrawal of a marketing authorization but the possibility to adopt precautionary and safety measures to mitigate water pollution, as warning labeling of the end products and appropriate disposal of unused and expired ones (EMEA – CHMP 2006).

Regardless of the small amount of ecotoxicological data, some researchers have been able to establish that human pharmaceuticals such as:

- ibuprofen,
- acetylsalicylic acid,
- mefenamic acid,
- amitriptyline,
- amoxicillin,
- destropropoxyphene,
- fluoxetin,
- oxytetracycline,
- paracetamol/acetaminophen,
- propanolol,
- thioridazine

could be present in surface water at risk levels that are not negligible for aquatic organisms (Christensen 1998; Stuer-Lauridsen et al. 2000; Jones, Voulvoulis, and Lester 2002).

More recently, an environmental assessment study on 11 priority pharmaceuticals which were relevant for Norway water resources (cefuroxime, cyclophosphamide, cyprofloxacin, diclofenac, ethinylestradiol, ibuprofen, metoprolol, paracetamol, sulfamethoxazole, tetracycline, trimetoprim) was conducted by researchers of the Norwegian Institutes for Water Research and of Public Health (Grung et al. 2008) on the basis of EMEA protocols (EMEA – CHMP 2006). Also in this survey, risk quotients were derived based on acute toxicity effects on algae, aquatic invertebrates, and fish, and five substances showed alerting results (PEC/PNEC$\geq$1):

- cyprofloxacin,
- diclofenac,
- ethinylestradiol,
- sulfamethoxazole,
- Tetracycline.

A tentative comparison with MECs measured in effluents of an urban STP (Oslo area) confirmed an unfavorable risk quotient at least for cyprofloxacin, while further monitoring has been suggested by the authors for ethinylestradiol.

As to the risk of indirect human exposure to pharmaceuticals via drinking water, a study on 64 pharmaceutical products (Webb, Ternes, and Gibert 2003) must be mentioned, investigating concentrations of drugs detected in water (either max levels or, in the case of small traces, levels defined through limits of quantitation (LOQ)). These concentrations, once turned into daily intake doses, were compared to minimal daily therapeutic doses. Ten compounds (clofibrate, ibuprofen, dichlophenac, fenofibric acid, bezafibrate, phenazone, carbamazepine, iopamidol, iopromide, and diatrizoate) have shown concentrations higher than LOQ (1–50 ng L^{-1}), ranging from 3 to 86 ng L^{-1}. For all examined compounds, daily assumption doses, ranging from values $\geq$ ng day^{-1} to 172 ng day^{-1}, have proven at least three orders of magnitude lower than daily therapeutic doses, in the range 0.010–20000 mg day^{-1}, and, for 90% of them, the ratio has been found equal to 1/150,000. According to monitoring data and the applied methodology, the risk of human exposure via drinking water has proven negligible even extending risk assessment to the case of a long-term exposure (70 years). An interesting approach to human risk assessment (HRA) due to direct/indirect exposure (e.g., drinking water/fish consumption) to pharmaceuticals and metabolites was also applied to 26 compounds commonly detected in the US water bodies (Schwab et al. 2005). Briefly, the study implied the calculation of acceptable daily intakes (ADIs) starting mainly from lowest observed effects (LOELs) for therapeutic endpoints (points of departure or PODs) corrected with appropriate sets of uncertainty factors (UFs). PODs ranged from a minimum 0.0007 (digoxin and digoxigenin) to a maximum of 100 mg kg^{-1} day^{-1} (dehydronifedipine) and combined UFs from 1 up to 1000. Secondly, PNECs for drinking water alone, drinking water/fish, and fish alone exposures were derived both for adults and children and compared with measured or estimated surface water concentrations. Then, risk quotients were derived resulting considerably less than 1 for all the compounds under the three exposure scenarios for children (worst cases),

thus indicating no appreciable risks at the reported/estimated water concentrations. Still, this approach was not applied to hormones, estrogens or cytotoxic agents.

Nonetheless, it must be said that the above methods cannot be applied to genotoxic or generally cancerogenic molecules, since no threshold values can be defined in such cases. Moreover, the presence of pharmaceuticals in water at sub-therapeutic levels, especially when long-term, may cause nonpredictable effects which have not yet been studied (Webb, Ternes, and Gibert 2003).

Legislative aspects on ambient water protection

The European legislation concerning the protection of aquatic environments and related organisms is mainly represented by the Water Framework Directive 2000/60/EC (WFD), by the daughter Directive 2006/118/EC (GWD) for the protection of groundwater, and by the daughter Directive 2008/105/EC (PSD) which states the EU List of Priority Substances (also known as Annex X to WFD) for surface waters and related Environmental Quality Standards (EQSs). According to WFD, GWD, and PSD, all the European water bodies shall reach a ''good'' ecological and chemical status within 2015, through the adoption of measures aimed at reducing, limiting, and preventing pollution, and at reversing increasing contamination trends for all those contaminants which, at that date, are/will be at risk to be not compliant with their pertaining EQSs for surface water (PSD/WFD), Groundwater Quality Standard (GWD), Minimum List of pollutants and indicators for groundwater (GWD), Threshold Values for groundwater pollutants (GWD), etc.

In this context, pharmaceuticals whose pressures on water ecosystems and on aquatic organisms have been documented since more than 20 years in several EU countries should be considered as new priority candidates in the ongoing revision of the EU List of Priority Substances. The revision of the EU list and the subsequent definition of pertinent new EQSs are based on significant risks to or via aquatic environment in compliance with Art. 16 of the WFD. A simplified and pragmatic methodology was developed under the WFD Common Implementation Strategy (CIS) taking into consideration both monitoring data and modeling data. Among the possible priority pharmaceuticals, it should be noted that some cytotoxic/genotoxic/reprotoxic substances (tamoxifen, cyclophosphamide, etc.) synthetic estrogens and hormones, may be already intended as pertaining to the Point 4, Annex VIII WFD, (Indicative List of Main Pollutants: ''*Substances and preparations, or the breakdown products of such, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect steroidogenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment.*'') On the other hand, the inclusion of key pharmaceuticals in the EU List of Priority Substances should lead to extensive monitoring of ambient water, sediment, and biota in EU countries, in this supported by the last Daughter Directive 2009/90/EC which defines the minimum performance criteria for methods of chemical analysis in monitoring activities relevant to WFD and GWD.

Conclusions

The problem concerning the presence of pharmaceuticals in the aquatic environment appears extremely significant, since results from various investigations on surface and

ground water bodies in many countries in recent years, as well as some data emerging from ecotoxicological studies on nontarget species, identify such compounds as new environmental contaminants, which may alter aquatic ecosystems equilibria. In fact, the larger and larger use of both human pharmaceuticals and veterinary drugs (livestock and aquatic farming) in the developed countries is bound to produce an increase in release of drugs into water and, therefore, in their presence as contaminants, taking into account the limits of technologies currently exploited in treatment plants for removal and reduction of pharmaceuticals and their metabolites. Besides, the main environmental laws in force in Europe at present, as well as those ones concerning protection and production of water for human consumption, do not provide for parameters or recommendations to direct the attention of health authorities toward pharmaceuticals as contamination agents, also because the role of such authorities is unavoidably and primarily associated with protection, well-being and development of human population. Nevertheless, an inclusion of priority pharmaceuticals (e.g., cytotoxic/genotoxic substances, estrogens and hormones, persistent drugs in water and sediment, etc.), due to their potential environmental risks should be conducted in the ongoing and future reviews of the Priority Substances List under WFD. Consequently, taking into account potential risks due to the presence of pharmaceuticals in water, more work is needed to expand knowledge on this kind of contamination, especially in the areas of monitoring environmental behavior of ecotoxicological investigations in aquatic biota and sediments and of treatment technologies designed to limit the release of drugs into the aquatic environment.

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Química Toxicológica & Ambiental

ISSN: 0277-2248 (Print) 1029-0486 (Online) Página inicial da revista: https://www.tandfonline.com/loi/gtec20

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Para citar este artigo: P. Bottoni, S. Caroli & Barra Caracciolo (2010) Fármacos como principais contaminantes de água, Química Toxicológica e Ambiental, 92:3, 549-565, DOI: 10.1080/02772241003614320

Para aceder a este artigo: https://doi.org/10.1080/02772241003614320

Publicado online: 12 Março, 2010.

Química & Toxicologia Ambiental
Vol. 92, No. 3, Março 2010, 549–565

Taylor & Francis
Taylor & Francis Group

ARTIGO DE REVISÃO

Fármacos como principais contaminantes de água

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(*Recebido a 4 de Janeiro 2010; versão final recebida a 12 de Janeiro 2010*)

Os fármacos e os seus metabolitos podem alcançar os recursos hídricos através de sistemas de esgotos, descargas industriais, efluentes provenientes de estações de tratamento de esgotos (ETE), aquacultura, e criação de gado. Os fármacos incluem centenas de substâncias que são muito diferentes no que diz respeito às suas propriedades físico-químicas e comportamento ambiental, embora possam ter forte atividade bioquímica. Atualmente, os fármacos podem alcançar concentrações na água de nano gramas por litro e microgramas por litro, sendo que alguns são considerados universais.

Contudo, a sua presença no ambiente aquático e o impacto na biota aquática e na saúde humana não foram ainda adequadamente estudados. Estudos experimentais indicam que os fármacos podem causar efeitos prejudiciais, tais como alterações morfológicas, metabólicas e sexuais em espécies aquáticas, a indução de resistência a antibióticos em micro-organismos patogénicos aquáticos e a interrupção dos processos de biodegradação nas ETE. Existem estudos e avaliações de análise de risco a serem desenvolvidos. Contudo, os dados científicos disponíveis são consistentes com a introdução de alguns indicadores farmacêuticos na monitorização extensiva de água para melhor definir o seu atual impacto em organismos aquáticos e seres humanos. Dentro destas perspetivas, a inclusão de fármacos emergentes na revisão da Lista de Substâncias Prioritárias da União Europeia enquadrada na Diretiva 2000/60/CE do Quadro de Ação da Água deverá ser implementada, juntamente com a definição dos respetivos padrões de qualidade ambiental.

Palavras-chave: fármacos; metabolitos; contaminação da água; água superficial; água potável

Introdução

A relevância dos fármacos para o ser humano e para uso veterinário, assim como os seus produtos de transformação biologicamente ativos, como micropoluentes ambientais tem captado uma atenção cada vez maior nos últimos anos devido ao crescente reconhecimento do seu impacto nos recursos hídricos (Halling-Sorensen et al. 1998).

Os fármacos são moléculas concebidas para produzirem efeitos terapêuticos no organismo, normalmente ativos em concentrações muito reduzidas, capazes de penetrar nas membranas biológicas e permanecer no organismo o tempo suficiente para evitarem ser inativadas antes de causarem um efeito. Estes compostos são excretados através das fezes e urina numa mistura de metabolitos e substâncias que normalmente permanecem inalteradas.

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ISSN 0277–2248 print/ISSN 1029–0486 online

DOI: 10.1080/02772241003614320
http://www.informaworld.com

As principais fontes de contaminação farmacêutica incluem águas residuais domésticas, urbanas, hospitalares e industriais, e igualmente efluentes provenientes das estações de tratamento de esgotos (ETE), aquacultura, e criação de gado intensiva. Para além disso, a reutilização de estrume animal sólido e líquido e de lamas de esgotos na agricultura, de modo a reciclar compostos de azoto como fertilizantes, pode contribuir para a dispersão de fármacos no solo e, dentro de certas circunstâncias, nos cursos de água. Atualmente, a presença de antibióticos, esteroides, reguladores de lípidos no sangue, estrogénios, analgésicos, anti-inflamatórios, antissépticos, medicamentos para a hipertensão, antiepiléticos, agentes antineoplásicos, e outras substâncias nos cursos de água superficiais está bem documentada. A percolação de fármacos na água subterrânea e a sua presença na água costeira marinha foram igualmente detetadas.

A comunidade científica concentrou-se principalmente na classe de antibióticos que contaminam o ambiente aquático e alimentos, devido à possibilidade de proporcionarem a formação de bactérias resistentes a antibióticos e aos riscos de saúde associados (Austin 1985; Miranda and Castillo 1998; Boon and Cattanach 1999). Um outro assunto importante diz respeito a medicamentos esteróides que podem causar as alterações metabólicas e estruturais observadas em organismos aquáticos (Routledge et al. 1998; Larsson et al. 1999). Devido aos recursos hídricos e aos seus efeitos, também os possíveis efeitos supressores na degradação de microrganismos nas estações de tratamento de águas residuais é um assunto de grande interesse (WHO, 1999).

O ser humano pode ser exposto a fármacos que poluem o ambiente aquático ao beber água ou ao consumo de organismos aquáticos. Estão a serem desenvolvidos estudos de avaliação de risco para espécies aquáticas e seres humanos. Não obstante, foi comprovado que o risco de exposição a fármacos é superior para espécies aquáticas do que para o ser humano, e algumas substâncias tais como o ibuprofeno, ácido acetilsalicílico, paracetamol, amoxicilina, oxitetraciclina e ácido mefenâmico são considerados como estando presentes na água a um nível de risco que não é insignificante para a biota aquática (Christensen 1998; Stuer-Lauridsen et al. 2000; Jones, Voulvoulis, and Lester 2002; Grung et al. 2008). Neste contexto, as pressões conhecidas dos fármacos nos ecossistemas aquáticos e o seu potencial impacto nos organismos aquáticos foi documentado e esta evidência poderá levar à sua inclusão entre novos candidatos prioritários na atual ou futura revisão da Lista Europeia de Substâncias Prioritárias relevantes para a Diretiva 2000/60/CE do Contexto das Águas.

Fontes de Contaminação

As principais fontes de libertação de produtos farmacêuticos no ambiente aquático incluem as descargas de resíduos domésticos e hospitalares, devido ao consumo generalizado de medicamentos para o tratamento de doenças humanas. De facto, a maioria dos produtos farmacêuticos são apenas parcialmente transformados ou retidos no organismo e são excretados através da urina como metabolitos maioritariamente ativos ou compostos que podem permanecer iguais ou serem conjugados como moléculas polares (Reddersen, Heberer, and Dunnbier 2002).

Outra fonte principal de produtos farmacêuticos, que é igualmente importante, mas restrita a áreas específicas de países, incluem as descargas de resíduos provenientes de locais de criação de gado intensiva e efluentes provenientes de sistemas de aquacultura intensivos, onde o uso de medicamentos veterinários é normal e necessário.

Muitos estudos demonstram que, quando as linhas de descarga dos esgotos convergem para as estações de tratamento, os efluentes dessas estações de tratamento podem ainda conter quantidades extraordinárias de

Tabela 1. Percentagens teóricas da concentração de fármacos e a sua remoção em algumas fases de tratamento numa estação de tratamento de esgotos convencional.

Nome	Influente de Água	Lama Primária	Descarga de lama	Volatilização (total)	Bio-degradação (total)	Efluente de Água	Remoção (total)
Ácido mefenâmico	100	50,4	30,07	0	0,7	18,84	81
Alopurinol	100	0,25	1,25	0	0,09	98,15	1,85
Amoxicilina	100	0,27	1,52	0	0,09	98,12	1,88
Aspirina	100	0,29	1,53	0	0,09	98,09	1,91
Atenolol	100	0,25	1,51	0	0,09	98,15	1,85
Carbamazina	100	0,92	1,95	0	0,1	94,04	2,96
Cimetidina	100	0,26	1,51	0	0,09	98,14	1,86
Diclofenac sódico	100	0,26	1,51	0	0,09	98,13	1,87
Cloridrato de diltiazem	100	1,42	2,28	0	0,11	96,19	3,81
Eritromicina	100	2,87	3,23	0	0,13	93,77	6,23
Fenoximetil-penicilina	100	0,54	1,7	0	0,1	97,66	2,34
Gliclazida	100	0,56	1,71	0	0,1	97,63	2,37
Ibuprofeno	100	16,48	11,92	0	0,31	71,28	28,72
Cloridrato de mebevarina	100	12,73	9,58	0	0,26	77,43	22,57
Messalazina	100	0,27	1,52	0	0,09	98,12	1,88
Cloridrato de metmorfina	100	0,25	1,5	0	0,09	98,15	1,85
Naproxeno	100	3,66	3,75	0	0,14	92,45	7,55
Oxitetraciclina	100	0,25	1,51	0	0,09	98,15	1,85
Paracetamol	100	0,26	1,51	0	0,09	98,14	1,8
Sulfato de Quinina	100	54,5	31,64	0	0,74	13,12	86,88
Valproato de sódio	100	0,25	1,5	0,08	0,09	97,99	2,01
Sulfato de ferro (III)	100	0,25	1,51	0	0,09	98,15	1,85

Sulfassalazina	100	9,44	0	0,26	77,8	
		12,51				22,2

Fonte: Modificado e adaptado de Jones, Voulvoulis, and Lester (2002).

fármacos e metabolitos, porque aos sistemas de degradação comuns são frequentemente caraterizados por uma baixa eficiência causada pela inibição ou alteração da eficácia de microrganismos degradadores, e igualmente pela sua baixa adaptação a medicamentos presentes nos efluentes provenientes de estações de tratamento. Na Tabela 1, onde foram apresentados alguns casos de degradação modelo numa estação de tratamento normal, mostram um exemplo para este fenómeno (Jones, Voulvoulis, and Lester 2002). Os autores conseguiram determinar, para cada composto presente em afluentes e efluentes, a quantidade total de degradação ocorrida na estação, incluindo os processos padrão de biodegradação, adsorção a lamas e exposição ao ar. Este estudo demonstrou que é improvável que a maioria dos fármacos sejam degradados numa estação de tratamento, e como tal, poderão ser libertados para os rios.

Outras fontes de contaminação são indiretas, tais como as águas residuais recuperadas de estações de tratamento, usadas, por exemplo, para irrigação, lamas utilizadas na agricultura para aproveitar os nutrientes inorgânicos, efluentes provenientes de locais de criação de gado aplicadas em solo arável, resíduos industriais provenientes da indústria farmacêutica, águas residuais hospitalares e eliminação imprópria de medicamentos fora de prazo.

Nestes casos, é igualmente expectável um impacto no ambiente terrestre e ambiente hipogeico, mas apenas alguns tópicos de estudo encontram-se atualmente disponíveis. Entre eles, encontram-se estudos que avaliam os efeitos tóxicos de alguns medicamentos veterinários nas plantas (Migliore, Cozzolino, e Fiori 2003), dignos de menção.

Deve-se prestar atenção especial às águas residuais hospitalares. A Organização Mundial da Saúde (WHO) dedicou um tratado acerca deste tópico (WHO, 1999). Ao contrário das águas residuais domésticas, as águas residuais provenientes de centros hospitalares contêm várias substâncias potencialmente perigosas, sendo estas precisamente:

(1) Patogénicos microbiológicos: patogénicos entéricos que se propagam facilmente através da água, que incluem bactérias, vírus e helmintos;
(2) Compostos químicos perigosos: substâncias químicas utilizadas para limpeza e desinfeção (por exemplo, formaldeído);
(3) Produtos farmacêuticos: frequentemente descartados por farmácias e alas hospitalares. São maioritariamente antibióticos e medicamentos genotóxicos. Os resíduos genotóxicos também incluem agentes citotóxicos e antineoplásicos, que são utilizados em quimioterapia e em imunossupressores (órgãos transplantados e doenças imunológicas). Os medicamentos citotóxicos podem ser classificados da seguinte forma:
    . Agentes alquilantes: são responsáveis pela alquilação dos nucleótidos do ADN e de fenómenos de ligação-cruzada;
    . Antimetabolitos: inibem a biossíntese de ácidos nucleicos nas células;
    . Inibidores mitóticos: impedem a reprodução celular.
(4) Isótopos radioativos: São maioritariamente produzidos nas alas de oncologia (após o diagnóstico, tratamento, imagiologia de diagnóstico, pesquisa, etc.).

Quanto à sua eliminação, todos os resíduos provenientes do manuseio de substâncias quimioterapêuticas antiblásticas (vestuário de segurança individual e descartável, lençóis absorventes descartáveis, bacias, gazes, algodão hidrófilo, ampolas, embalagens de medicamentos, seringas, etc.) devem ser considerados como resíduos hospitalares especiais e devem ser quimicamente inativados e incinerados. Um problema considerável inclui a urina dos pacientes que contem tipicamente concentrações elevadas de ingredientes ativos e que não são inativados.

Principais produtos farmacêuticos em Itália e noutros países

O método tradicional para avaliar inicialmente o impacto no ambiente de um certo tipo de contaminação consiste em quantificar modos de descarga e níveis de contaminantes.

A recolha de informação acerca da utilização, produção e venda de compostos individuais ou classes de compostos permite uma identificação inicial da maioria das moléculas significativas ou grupos com o objetivo de direcionar possíveis atividades de pesquisa e investigações para áreas ambientais potencialmente ou atualmente afetadas por contaminação.

No caso dos fármacos, este ponto demonstra uma importância particular, visto que as moléculas que podem ser utilizadas em diferentes países somam um total de vários milhares. Apesar disso, não estão disponíveis estudos diretos sobre a produção e venda nem informações sobre o consumo. No que diz respeito a Itália, tal como a outros países, a obtenção deste tipo de informação consiste em examinar as receitas médicas terapêuticas e

Tabela 2. Princípios ativos muito utilizados em Itália, no Reino Unido e nos Estados Unidos da América (EUA) por ordem decrescente

Itália (2001) [a]	Reino Unido (2000) [b]	Estados Unidos da Améria (2005) [c]
Omeprazol	Paracetamol	Azitromicina
Amlodipina	Cloridrato de metformina	Amoxicilina
Enalapril	Ibuprofeno	Furosemida
Simvastatina	Amoxicilina	Hidroclorotiazida
Epoetina alfa	Valproato de sódio	Amlodipina
Claritromicina	Sulfassalazina	Lisinopril
Nitroglicerina	Messalazina	Alprazolam
Amoxicilna + ácido clavulânico	Carbamazepina	Sertralina
Atorvastina de cálcio	Sulfato de ferro (III)	Albuterol
Doxazosina	Cloridrato de ranitidina	Metoprolol
Ranitidina	Cimetidina	Sinvastatina
Cefitraxona	Atenolol	Lansoprazol
Hidroclorotiazida + Enalapril	Oxitetraciclina	Ceritizina
Fluticasona	Eritromicina	Ibuprofeno
Nimesulida	Diclofenac	Levotiroxina
Paroxetina	Flucloxacilina	Propoxifeno n/ aplicável
Somatropina	Fenoximetilpenicilina	Hidroclorotiazida de Triamtereno
Ciclosporina	Alopurinol	Celecoxib
Tansulosina	Cloridrato de Diltiazem	Zolpidem
Finasterida	Gliclazida	Fenofenadina
Beclometasona	Aspirina	Cefalexina
Rofecoxib	Sulfato de quinina	Esomeprazol
Pravastina	Cloridrato de mebverina	Alendronato
Nifedipina	Ácido mefenâmico	Rofecoxib
Azitromicina		Montelucaste
Cefonicidal		Norgestimato / Etinilestradiol
Lansoprazol		Prednisona
Ciprofloxacina		Metoprolol

Notas: [a] Ministério de Saúde Italiano, 2001
[b] Jones, Voulvoulis e Lester, 2002.
[c] RxList, Índice de fármacos na internet, 2005.

extrapolar as quantidades vendidas, utilizadas, ou ingredientes ativos administrados individualmente através de vários métodos de computação.

Acerca deste tópico, apresentamos aqui uma descrição de alguns dados provenientes do Departamento de Saúde (Ministério de Saúde Italiano, 2001) relativos aos 30 compostos mais caros cobrados ao Serviço Nacional de Saúde (SSN) durante os primeiros 9 meses de 2001 (Tabela 2, primeira coluna). Além disso, cada ingrediente ativo descrito na primeira coluna da Tabela 2 excedeu o limiar de despesas de 51 milhões de euros. Além disso, a despesa para apenas uma substância, omeprazol, excedeu 289 milhões de euros, enquanto a despesa global para os 30 compostos (cerca de 3.283.000.000 euros) somou um total de 36% da despesa nacional total cobrada ao SSN, durante aquele período (cerca de 9.109.000.000 euros).

Por outro lado, no primeiro semestre de 2001, as maiores despesas cobradas ao SSN estavam relacionadas com os seguintes grupos terapêuticos que são apresentados em ordem decrescente de acordo com os seus custos:

- Sistema cardiovascular;
- Antimicrobianos sistémicos;
- Aparelho gastrointestinal e metabolismo;
- Sistema respiratório;
- Sistema nervoso;
- Sistema músculo-esquelético;
- Sangue e órgãos hematopoiéticos;
- Sistema urogenital e hormonas sexuais.

Fontes ministeriais confirmam o que foi acima mencionado sobre a tendência do aumento dos custos farmacêuticos. Um aumento na venda de fármacos foi observado em todos os países desenvolvidos. Em 2000, foi registado um amento médio de 9% em países europeus, e entre eles, Itália foi caraterizada pelo maior aumento (14%) em comparação, por exemplo, com o Reino Unido (5%). Nos EUA, o aumento foi aproximadamente de 19% (Ministério de Saúde Italiano 2001).

Como forma de comparação, a Tabela 2 também apresenta uma lista dos 25 fármacos mais utilizados no Reino Unido em 1998 (Jones, Voulvoulis, e Lester 2002) e uma lista das 30 substâncias mais receitadas nos EUA em 2003 (RxList, Indice de fármacos na internet 2005).

Estes exemplos demonstram que os fármacos e as suas categorias associadas são bastante comparáveis, pelo menos em países ocidentais. Os dados acima mencionados sugerem de forma imediata o quão elevado um impacto hormonal e compostos antibióticos podem ter no ambiente aquático e, por este motivo, tem havido um aumento de investigação ambiental e ecotoxicológica nestas principais categorias, e também relativamente à exposição e risco para as espécies aquáticas e humana.

Voltando ao problema de identificar as substâncias mais significativas de acordo com o seu possível impacto no meio ambiente, deve ser dito que, de acordo com vários investigadores, os dados sobre o consumo de medicamentos são importantes, mas provavelmente insuficientes. De facto, muitos compostos ocasionalmente utilizados, mas altamente tóxicos, tais como agentes anticancerígenos, que podem ter efeitos citotóxicos, mutagénicos e genotóxicos também no ambiente (e, portanto, em organismos) diferentes do que teriam nos seus alvos terapêuticos, podem ser encontrados em elevadas concentrações em áreas próximas aos pontos de libertação ou em pequenos cursos de água, onde a diluição pode ser menos eficaz na redução da carga poluente.

Relativamente a esta preocupação, uma lista de fármacos anticancerígenos, que foram classificados pela *Agência Internacional para a Investigação do Cancro* (IARC), de acordo com o seu potencial carcinogénico (IARC, 2005), é a seguinte:

- Grupo 1A (carcinogéneos humanos): butanodiol dimetilsulfonato (bussulfano, myleran), ciclofosfamida, clorambucilo, 1-(2-cloroetil) -3(4-metilciclo-hexil)-1-nitrosureia, melfalano, MOPP (mustargen, oncovin, procarbazina e prednisona), e outras combinações de agentes alquilantes, 2-Naftilamina, tamoxifeno, TIOTEPA (Trietilenotiosfosforamida);
- Grupo 2A (carcinogéneos humanos prováveis): adriamicina, azacitidina, cisplatina (CCDP), carmustina, clorozotocina, etoposido, lomustina (CCNU), mostarda nitrogenada, procarbazina, teniposido;
- Grupo 2B (possíveis carcinogéneos humanos): amsacrina, aziridina, bleomicina, dacarbazina, daunomicina, mitomicina C, mitoxantrona, estreptozotocina, zidovudina;
- Grupo 3 (não classificados como carcinogéneos humanos): aciclovir, 6-Mercaptopurina, metotrexato, prednimustina, prednisona, sulfato de vinblastina, sulfato de vincristina.

Finalmente, as principais classes de compostos veterinários devem ser mencionadas. Relativamente à criação bovina, em Itália os fármacos normalmente utilizados são antibacterianos administrados juntamente com ração e água. Entre eles encontram-se (Busani et al. 2003):

- Cefalosporinas (desde a 1ª à 4ª geração), aminopenicilinas enriquecidas e penicilina G, frequentemente utilizadas para tratar mastite;
- Aminosídeos de 3ª geração (gentamicina, apramicina) e fluoroquinolonas, utilizadas para tratar enterite neonatal e para gado enfraquecido;
- Fluoroquinolonas, macrólidos e fenicóis para tratar infeções respiratórias.

Os antibióticos são igualmente os fármacos mais utilizados em locais de aquacultura, de modo a tratar a maioria das doenças mais comuns dos peixes. Em relação a Itália, devemos mencionar (Lalumera et al. 2004):

- Amoxicilina, flumequina, oxitetraciclina, sulfamerazina, tiamfenicol.

Noutros países, tais como os Países Baixos e o Reino Unido, a maioria dos medicamentos veterinários utilizados são (Boxall et al. 2003).

- Antimicrobianos: amoxicilina, di-hidroestreptomicina, enrofloxacina, lincomicina, oxitetraciclina, sulfadiazina, tilosina;
- Agentes antiparasitários: ivermectina, pirantel, triclabendazol;
- Medicamentos coccidiostáticos - antiprotozoários: amprólio, clopidol, dimetridazol, narasina, nicarbazina;
- Agentes antifúngicos: cloro-hexidina, griseofulvina, miconazol;
- Hormonas: altrenogest, benzoato de estradiol, etinilestradiol, metiltestosterona, melatonina, progesterona;
- Promotores de crescimento: flavofosfolipol, monensina, salinomicina;
- Anestésicos: halotano, isoflurano, procaína, lidocaína/lignocaína;
- Sedativos: fenobarbitona.

Após a recolha e avaliação da informação sobre a quantidade de medicamentos utilizados/vendidos, metabolismo animal e a forma de libertação para o ambiente, este estudo também apresenta uma lista de medicamentos veterinários que se pensa poderem contaminar o ambiente (Boxall et al. 2003). Os compostos escritos em maiúsculas foram procurados e encontrados em cursos de água:

- amitraz, amoxicilina, amprólio, baquiloprima, cefalexina, CLOROTETRACICLINA, ácido clavulânico, clindamicina, clopidol, CIPERMETRINA, ciromazina, decoquinato, deltametrina, DIAZINON, Di-hidroestreptomicina, dimeticona, BENZOATO DE EMAMECTINA, enrofloxacina, fenbendazol, flavomicina, flavofosfolipol, florfenicol, flumetrina, fosmete, agentes imunológicos, IVERMECTINA, lasalocida, levamisol, lidocaína, LINCOMICINA, maduramicina, monensina, morantel, neomicina, nicarbazina, nitroxinil, ÁCIDO OXOLÍNICO, OXITETRACICLINA, butóxido de piperonilo, poloxaleno, procaína, benzilpenicilina, penicilina procaína, cloridrato de robenidina, salinomicina, SARAFLOXACINA, sulfadiazina, TETRACICLINA, tiamulina, tilmicosina, toltrazuril, triclabendazol, TRIMETOPRIM, TILOSINA (Boxall et al. 2003).

Propriedades físico-químicas

Existem muito poucos dados disponíveis sobre o destino ambiental dos fármacos e das suas propriedades quimiodinâmicas e físico-químicas. Em particular, conseguimos encontrar

dados sobre solubilidade e pKa e, com maior dificuldade, informações sobre o Kow (constante de partição octanol / água), Kd (constante de partição solo / água), Koc (constante de partição carbono em solo orgânico/água) e DT50 (tempo de meia-vida de degradação) para o solo e água. Todos juntos, estes parâmetros podem dar informação sobre o comportamento ambiental dos fármacos. Alguns deles são tipicamente usados para calcular as suas concentrações previstas teoricamente na água superficial e subterrânea, e igualmente no solo e sedimentos (PEC's), ou permitem-nos definir testes de despistagem que poderão avaliar a sua habilidade de infiltração na água subterrânea, assim como para modelos de distribuição matemáticos mais complexos, como é habitual para várias categorias de contaminantes, tais como produtos fitossanitários.

No geral, a heterogeneidade das classes químicas dos fármacos é clara, o que por sua vez, implica heterogeneidade das propriedades físico-químicas associadas. Muitos fármacos são solúveis em água e não voláteis, outros são polares e dificilmente adsorvidos, enquanto outros são lipofílicos e demonstram uma certa tendência para a bioacumulação e adsorção de sedimentos. Após os processos metabólicos, outros fármacos podem produzir metabolitos conjugados com moléculas polares solúveis, que em condições de tratamento, podem ser biologicamente hidrolisadas e transformadas de novo em moléculas ativas.

Alguns fármacos, tais como o ácido oxolínico, ciclofosfamida, flumequina, ivermectina, oxitetraciclina e ácido clofíbrico são conhecidos pela sua persistência no ambiente aquático, e igualmente no solo e nos sedimentos, e/ou pela sua resistência à degradação biológica nas estações de tratamento. Estes componentes demonstraram, em várias matrizes e ao serem submetidas a diferentes condições experimentais, degradações de meia-vida que são superiores a 100 dias e algumas vezes chegam a durar vários anos (Steger-Hartmann, Kummerer, e Hartmann 1997; Halling-Sorensen et al. 1998; Steger-Hartmann, Lange, e Schweinfurth 1999; Winkler, Lawrence, e Neu 2001). Quanto à sua persistência, visto que muitos produtos farmacêuticos são designados para serem administrados por via oral, demonstram ser insensíveis a processos de degradação através de hidrólise química ou mediados por enzimas, que no ambiente aquático e no solo, representam alguns dos principais modos de degradação de xenobióticos, tais como os fitofármacos. De acordo com alguns investigadores, isto significa que, pelo menos no ambiente aquático, os processos de fotodegradação devem prevalecer. Consequentemente, vários estudos sobre este tópico específico foram desenvolvidos com o objetivo de definir as condições limite que podem influenciar e melhorar tais processos, especialmente nas estações de tratamento (Andreozzi, 2003; Raffaele, e Nicklas 2003).

A Tabela 3 mostra uma lista de parâmetros físico-químicos e de mobilidade (tais como o Kd, Koc e DT50), que foram extraídos de um vasto número de estudos e bases de dados (The Merck Index 1996; Koschorreck, Koch, e Rönnefahrt 2002; Andreozzi, Raffaele, e Nicklas 2003; Tixier et al. 2003; TOXNET Toxicology Data Network – Hazardous Substances Data Bank (HSDB).

Como se pode verificar nesta tabela, as informações sobre a degradação no solo são extremamente pobres. Em alguns casos, na ausência de estudos específicos, a investigação foi auxiliada por algoritmos que correlacionam constantes de partição, incluindo o fator de bio concentração (FBC), entre si e permitem a extrapolação de valores desconhecidos. Os parâmetros para alguns destes compostos incluídos na Tabela 3 foram calculados desta forma (Jones, Voulvoulis, e Lester 2002).

Tabela 3. Propriedade físico-químicas de alguns fármacos.

Composto	Solubilidade da água[a]	pKa[b]	Koc	log Kow	Kd (Lkg^{-1})	DT50 (dias) Água	DT50 (dias) Solo
Ácido clofíbrico	Insolúvel			2,57[c]		> 63[c]	
Ácido mefenâmico	0,0041 g/100 mL a 25°C pH 7,1	4,2[g]	461,0	5,12	18917		
Alopurinol	0,48 mg mL^{-1} a 25°C	9,3	19,4	-0,55	0,04		
Amoxicilina	4,0 mg mL^{-1}		865,0	0,87	1,06		
Aspirina	4600 mg mL^{-1} a 25°C	3,5	10,0	1,19	2,22		
Atenolol	Ligeiramente solúvel	9,2	148,0	0,16	0,21		
Carbamazepina	Insolúvel	13,9[g]		2,45[c]		63[c]; 100[d]	
Benzimidazol	Ligeiramente solúvel	5,48[g]	110[g]	1,32[g];6,2[c]			15[c]
Carbamazina	Insolúvel	13,9	3,87e + 03	2,25	25,5		
Cimetidina	1,14 a 37°C	6,8	690,0	0,40	0,36	8	
Diclofenac	> 9 mg mL^{-1} em água desionizada a 25°C	4,2	833,0	0,70 – 4,51	0,72	5,0[d]	
Cloridrato de diltiazem	Solúvel	7,7	9,5e +03	2,70	72		
Eritromicina	2 mg mL^{-1}	8,9	10,0	3,06	165		
Fenoximetilpenicilina	5,88 mgL^{-1}[f]		177,0	2,09[f]	17,6		
Glicazida			1,27e + 04	2,12	19		
Ibuprofeno	21 mgL^{-1} a 25°C[g]	4,91[g]	394,0	3,97; 4,13-4,9[c]	454	20; 32[c]	
Cloridrato de mebeverina			6,66e + 05	3,82	948		
Messalazina			10,0	0,98	1,37		
Cloridrato de metformina	Solúvel	12,4[g]		-1,43[g]	0,0003		
Naproxeno	Insolúvel	4,15[g]	349,0	3,18; 3,24[c]	217	14	
Oxitetraciclina	Ligeiramente solúvel[g]	3,3	97,2	-0,90	0,02		
Ofloxacina						10,6[d]	
Paracetamol (acetaminofeno)	Ligeiramente solúvel[g]	9,4	61,7	0,46	0,41		
Propanolol	Solúvel	9,45		-0,45 (pH2)		16,8[d]	
Sulfato de quinina	1 gr/810 ml	5,07[g]	1,85e + 08	5,40	36045		
Cloridrato de ranitidina	Solúvel	3,5					
Valproato de sódio	Ligeiramente insolúvel na sua forma ácida		24,1	-0,85	0,02		
Sulfato de ferro (III)	156,5 g L^{-1} a 20°C		14,6	-0,37	0,06		
Sulfassalazina	Insolúvel		1,84e + 03	3,81	926		

Notas: Onde não foram indicados, os parâmetros foram calculados conforme descrito em Jones, Voulvoulis, and Lester (2002). [a]The Merck Index, 1996; [b]Jones, Voulvoulis, e Lester, 2002; [c]Tixier et al. 2003; [d]Andreozzi, Raffaele, aend Nicklas, 2003; [e]Koschorreck, Koch, e Rönnefahrt, 2002; fChristensen, 1998; [g]TOXNET Toxicology Data Network – Hazardous Substances Data Bank (HSDB) 2009.

Presença de produtos farmacêuticos no ambiente aquático

Uma vasta quantidade de informação sobre este tópico está disponível na literatura científica, apesar de normalmente se referir a estudos de pequena escala sobre um número restrito de fármacos.

Os resultados são obtidos através de muitos fatores, tais como a difícil identificação das substâncias mais significativas a serem estudadas, a complexidade dos métodos analíticos utilizados para investigar moléculas muito diferentes, que frequentemente requerem procedimentos complexos, e a dificuldade em obter padrões analíticos certificados. Aliás, desde que as concentrações de fármacos dispersos de forma comum na água estejam na faixa de ng L^{-1} a μg L^{-1}, são necessários instrumentos de medição sofisticados. Deve constar que iniciativas de monitorização detalhada só tiveram início recentemente, apesar da substancial quantidade de provas de contaminação aquática por produtos farmacêuticos ao longo dos últimos 20 anos.

O primeiro caso conhecido de contaminação dos recursos hídricos remonta a 1980, após várias investigações maioritariamente realizadas em países do Norte da Europa, tais como a Alemanha. Posteriormente, as pesquisas foram alargadas a outros países europeus, e igualmente aos EUA e Canadá. Algumas investigações na qualidade da água dos rios foram igualmente realizadas em Itália (Zuccato et al. 2000; Calamari et al. 2003).

Atualmente, a presença de antibióticos, esteroides, reguladores de lípidos no sangue, estrogénios, analgésicos, anti-inflamatórios, antissépticos, medicamentos para a hipertensão, antiepiléticos, agentes antineoplásicos e outras substâncias está bem documentada em rios, lagos, água subterrânea, água potável, água costeira marinha, efluentes urbanos e em estações de tratamento (Steger-Hartmann, Kummerer, e Hartmann 1997; Buser e Muller 1998; Daughton e Ternes 1999; Stumpf et al. 1999; Sacher et al. 2001; Reddersen, Heberer, e Dunnbier 2002; Andreozzi, Raffaele, e Nicklas 2003; Atkinsons, Atkinsons, e Tarrant 2003; Tixier et al. 2003).

Alguns exemplos das concentrações detetadas (valores arredondados) são aqui mencionados. Concentrações máximas de 27–70 ng L^{-1} para reguladores de lípidos (ácido clofíbrico, bezafibrato) (Webb et al. 2003), 400 ng L^{-1} para fenazona (analgésico), 900 ng L^{-1} para um dos seus metabolitos (AMDOPH) (Reddersen, Heberer, e Dunnbier 2002), 79–86 ng L^{-1} para agentes de contraste RX (iopamidol, diatrizoato) (Webb, Ternes, e Gibert 2003), e até 24 ng L^{-1} para sedativos (diazepam) (Zuccato et al. 2000) foram detetados na água potável superficial.

Os níveis de concentrações mais significativos, ou intervalos, de fármacos na água superficial pertencem à furosemida (até 88 ng L^{-1}) (Stumpf et al. 1999), ibuprofeno (até 92 ng L^{-1}) (Zuccato et al. 2000), bezafibrato (134–203 ng L^{-1}) (Zuccato et al. 2000), e atenolol (170–242 ng L^{-1}) (Zuccato et al. 2000), enquanto os antibióticos lincomicina, eritromicina e espiramicina são caraterizados por níveis até 14, 17, e 68 ng L^{-1}, respetivamente (Zuccato et al. 2000). Para os sedimentos, os níveis de concentração mais elevados são: 130 ng kg^{-1} para bezafibrato e lincomicina e 220, 410, 630, 2900 ng kg^{-1} para ibuprofeno, ranitidina, eritromicina e espiramicina, respetivamente (Zuccato et al. 2000).

Para além disso, num estudo realizado nos EUA em 139 recursos hídricos a jusante de centros urbanos ou de locais de criação de gado, representando assim os locais mais poluídos, foram estudados mais de 90 contaminantes orgânicos, entre os quais 21 substâncias eram antibióticos humanos e veterinários, 19 eram medicamentos prescritos e 14 eram esteroides e hormonas (Kolpin et al. 2002). A frequência de contaminação foi provada como sendo superior a 10% para 20 substâncias e os seus metabolitos, e em particular, >50% para colesterol, triclosan, coprostanol e

cafeína. Para mais de 30 fármacos, foram encontradas concentrações máximas superiores a 0,1 μ L^{-1} e alguns compostos, tais como a codeína e ibuprofeno (1 μ L^{-1}), eritromicina-H20 (1,7 μ L^{-1}), sulfametoxazol (1,9 μ L^{-1}), 1,7-dimetilxantina (3,1 μ L^{-1}), estigmastanol (4 μ L^{-1}), cafeína (6 μ L^{-1}), acetaminofeno (10 μ L^{-1}), colesterol (até 60 μ L^{-1}) e coprostanol (até 150 μ L^{-1}), apresentaram níveis máximos de 1 μ L^{-1}. No decurso do estudo acima mencionado, foram detetados compostos diferentes na mesma amostra. Em particular, tendo igualmente em consideração os seus efeitos, foi observada uma concentração global máxima de 53,7 μ L^{-1} para os agentes hormonais ativos, entre os quais existe um vasto número de produtos farmacêuticos (Kolpin et al. 2002).

Relativamente à contaminação da água subterrânea, apenas alguns estudos estão disponíveis, mas existem provas substanciais para a presença de principalmente fármacos polares e metabolitos. Num estudo desenvolvido na Alemanha, muitos produtos medicinais foram detetados na água subterrânea, provavelmente poluída por efluentes (Sacher et al. 2001). Mais de 105 amostras de água de poço foram analisadas e inspecionadas para 60 fármacos por investigadores. Trinte e nove compostos foram detetados em concentrações que variam entre 10 a 100 ng L^{-1}. Para seis compostos (iopamidol, sulfametoxazol, sotalol, diclofenac, carbamazepina e ácido amidoxibenzóico, em ordem crescente de acordo com a sua concentração), foram encontrados níveis máximos no intervalo de 300–1100 ng L^{-1}.

Este pequeno resumo da informação disponível sugere a existência de uma contaminação difusa dos recursos hídricos, na maioria dos países desenvolvidos, sendo isto comprovado por algumas moléculas que podem ser consideradas universais, tais como o ácido acetilsalicílico, cafeína, nicotina, fluoroquinolonas, antibióticos, carbamazepina e ácido clofíbrico, com uma presença quase constante de mais do que um fármaco em amostras de água individuais. Adicionalmente, é interessante notar que a presença de fármacos na água superficial não apresenta flutuações sazonais, como no caso dos produtos fitossanitários. Contudo, a tendência parece ser constante devido à libertação ininterrupta de fármacos para o ambiente e isto representa, um problema de exposição múltipla de longo prazo a baixas concentrações de compostos individuais, especialmente para espécies aquáticas (Daughton e Ternes 1999).

Efeitos nos organismos ambientais e avaliação de risco

Quanto aos efeitos ecotoxicológicos dos fármacos em organismos não visados, um vasto número de estudos concentrou-se nos antibióticos com a finalidade da possível formação de microrganismos patogénicos exógenos e naturalmente resistentes aos antibióticos, possíveis riscos associados para o ser humano e problemas relativos a estações de tratamento, devido à inibição e desaparecimento de microrganismos de degradação. Outros estudos lidaram com esteroides e hormonas sexuais, devido às alterações metabólicas e estruturais observadas nas espécies aquáticas.

O que dificulta a avaliação dos efeitos de outros tipos de fármacos nos organismos, que são diferentes e podem ser filogeneticamente muito afastados, por exemplo, do ser humano, é o facto dos alvos metabólicos, enzimáticos, clínicos e comportamentais não serem facilmente identificáveis.

Para além disso, também os testes toxicológicos agudos e crónicos clássicos apresentam dificuldades práticas e teóricas, já que as concentrações de fármacos individuais no ambiente aquático são muito inferiores do que as doses efetivas e, como tal, não aparentam ser capazes de produzir efeitos agudos.

Inclusivamente, testes padrões realizados em moluscos, algas, etc., podem não ser suficientemente sensíveis para destacar os efeitos de certas moléculas, em termos de quantidade e estrutura, não sendo classificadas como "xenobióticas". Por este motivo, estão a ser desenvolvidos testes alternativos em organismos e grupos de organismos possivelmente mais sensíveis. Finalmente, deve ser dito que os estudos comuns se concentram frequentemente na análise de compostos individuais, enquanto a monitorização de dados relativa a cursos hídricos superficiais sugere uma investigação dos efeitos de misturas de fármacos.

Na literatura científica de livre acesso, os dados disponíveis sobre a toxicidade aguda remetem para poucas moléculas e dados sobre toxicidade crónica são ainda mais escassos. Os valores da concentração efetiva 50 (EC50) e concentração letal 50 (LC50) relativos a alguns fármacos para seres humanos e que abrangem valores cerca de 6 vezes superiores foram observados em diferentes espécies aquáticas. Entre tais fármacos, pelo menos 10 são muito tóxicos ou extremamente tóxicos (parâmetros de toxicidade aguda de 0,1–1 mg/L e $<$ 0,1 mg/L, respetivamente):

- Alendronato, amitriptilina, carvedilol, etinilestradiol, fluticasona, fluoxetina, fluvoxamina, midazolam, paclitaxel, tioridazina (CSTEE,2001).

Encontra-se em progresso a avaliação dos riscos ambientais (ARA) para espécies aquáticas. Este tipo de estudo é normalmente baseado na computação do coeficiente de risco, que é definido, para cada substância individual, como a razão entre a concentração prevista ou medida na água (PEC, MEC) e a concentração sem efeitos (PNEC), sendo esta última extraída de dados de toxicidade a médio e longo prazo para organismos aquáticos. Tais procedimentos referem-se a regras gerais estabelecidas pela Comissão Europeia para fazerem avaliações de risco para o ambiente e para o ser humano nos *Technical Guidance Documents* da UE (TGD) (*European Chemical Bureau* 2003) após exposição substâncias químicas novas e já existentes e a biocidas. Estas mesmas regras gerais adaptam-se às diretrizes para a avaliação de risco ambiental dos produtos farmacêuticos para seres humanos, que foram recentemente entregues pela Agência Europeia dos Medicamentos (EMEA) no contexto de autorização de marketing (EMEA – CHMP 2006). Deve ser mencionado que, neste contexto, qualquer risco potencial para o ambiente, e particularmente no ambiente aquático, não implica uma recusa ou remoção de uma autorização de marketing, mas a possibilidade de adotar medidas de precaução e de segurança para mitigar a poluição das águas, como rótulos de aviso com as datas de validade dos produtos e a eliminação adequada de produtos não utilizados e expirados (EMEA – CHMP 2006).

Apesar da pequena quantidade de informações ecotoxicológicas, alguns investigadores conseguiram defenir que produtos farmacêuticos para seres humanos tais como:

. ibuprofeno,
. ácido acetilsalicílico,
. ácido mefenâmico,
. amitriptilina,
. amoxicilina,
. dextropropoxifeno,
. fluoxetina,
. oxitetraciclina,
. paracetamol/acetaminofeno,
. propanolol,
. tioridazina

podem estar presentes na água superficial em níveis de risco que não são negligenciáveis para organismos aquáticos (Christensen 1998; Stuer-Lauridsen et al. 2000; Jones, Voulvoulis, e Lester 2002).

Mais recentemente, um estudo de avaliação ambiental com 11 produtos farmacêuticos prioritários que foram relevantes para os recursos hídricos da Noruega (cefuroxima, ciclofosfamida, ciprofloxacina, diclofenac, etinilestradiol, ibuprofeno, metoprolol, paracetamol, sulfametoxazol, tetraciclina. trimetoprim) foi realizado por investigadores dos *Norwegian Institutes for Water Research and of Public Health* (Grung et al. 2008) com base nos protocolos da EMEA (EMEA – CHMP 2006). Também deste estudo, resultaram coeficientes de risco tendo com base os efeitos de toxicidade agudos nas algas, invertebrados aquáticos e peixes, sendo que 5 substâncias mostraram resultados alarmantes (PEC/PNEC$\succ$1):

. ciprofloxacina,
. diclofenac,
. etinilestradiol,
. sulfametoxazol,
. tetraciclina.

Uma tentativa de comparação com a CME medida nos efluentes de uma estação de tratamento de efluentes urbanos (na área de Oslo) confirmou um coeficiente de risco desfavorável pelo menos para a ciprofloxacina, enquanto uma monitorização mais extensa para o etinilestradiol foi sugerida pelos autores.

Quanto ao risco de exposição indireta de humanos a fármacos através da água potável, um estudo com 64 produtos farmacêuticos (Webb, Ternes, e Gibert 2003) deve ser referido, o qual indica as concentrações investigadas de fármacos detetados na água (tanto em níveis máximos ou, no caso de pequenos vestígios, níveis definidos através de limites de quantificação (LOQ)). Estas concentrações, uma vez transformadas em doses diárias, foram comparadas com as doses terapêuticas mínimas diárias. Dez compostos (clofibrato, ibuprofeno, diclofenac, ácido fenofíbrico, bezafibrato, fenazona, carbamazepina, iopamidol, iopromida e diatrizoato) apresentaram concentrações superiores a LOQ (1–50 ng L^{-1}), variando entre 3 a 86 ng L^{-1}. Para todos os compostos analisados, as doses diárias previstas, com valores variando entre $\leq$ 1 ng dia^{-1} até 172 ng dia^{-1}, demonstraram que pelo menos três ordens de magnitude inferior às doses terapêuticas diárias, no intervalo 0,010–20000 mg dia^{-1}, e para 90% deles, a razão encontrada foi de 1/150,000. De acordo com os dados de monitorização e com a metodologia aplicada, o risco de exposição humana através da água potável foi provado como sendo negligenciável mesmo estendendo a avaliação de risco para casos de uma exposição a longo prazo (70 anos). Uma abordagem interessante sobre a avaliação de risco para a saúde humana (HRA) devido à exposição direta/indireta (por exemplo, água potável/consumo de peixe) a fármacos e metabolitos também foi aplicada a 26 compostos frequentemente detetados nos recursos hídricos dos EUA (Schwab et al. 2005). Resumidamente, o estudo implica o cálculo da ingestão diária aceitável (IDA) começando principalmente a partir dos menores efeitos observados (MEO) para os parâmetros terapêuticos (pontos de partida ou POD's) corrigidos com um conjunto apropriado de fatores de incerteza (Ufs). Os POD's variam entre um mínimo de 0,0007 (digoxina e digoxigenina) até um máximo de 100 mg kg^{-1} dia^{-1} (desidronifedipina) e Ufs combinados de 1 até 1000. Em segundo lugar, PNEC's apenas para a água potável, água potável/peixes, e apenas peixes foram calculadas tanto para adultos como para crianças e comparadas com concentrações medidas ou estimadas para a água potável. Por fim, os coeficientes de risco calculados resultaram ser consideravelmente menores do que 1 para todos os compostos para os três cenários de exposição para crianças (piores casos),

o que indica a ausência de riscos apreciáveis nas concentrações de água reportadas/estimadas. Contudo, esta abordagem não foi aplicada a hormonas, estrogénios ou agentes citotóxicos.

Todavia, deve ser dito que os métodos acima mencionados não podem ser aplicados a moléculas genotóxicas ou geralmente cancerígenas, visto que nenhum valor limite pode ser definido em tais casos. Além disso, a presença de fármacos na água em níveis sub-terapêuticos, especialmente quando a longo prazo, podem causar efeitos imprevisíveis que podem ainda não ter sido estudados (Webb, Ternes, e Gibert 2003).

Aspetos legislativos sobre a proteção do ambiente aquático.

A legislação europeia relativa à proteção dos ambientes aquáticos e organismos relacionados é maioritariamente representada pela Diretiva 2000/60/CE (WFD) do Quadro de Ação da Água., pela Diretiva filha 2006/118/CE (GWD) para a proteção da água subterrânea e pela Diretiva filha 2008/105/CE (PSD) que refere a Lista de Substâncias prioritárias da UE (também conhecida como Anexo X à WFD) para as águas superficiais e Normas de Qualidade Ambiental (NQA) relacionadas. De acordo com a WFD, GWD e PSD, todos os cursos hídricos europeus devem atingir um "bom" estatuto ecológico e químico até 2015, através da adoção de medidas destinadas a reduzir, limitar e prevenir a poluição, e a reverter as crescentes tendências de contaminação para todos os contaminantes que, até essa data, estão/estarão em risco de não cumprirem as suas NQA para a água superficial (PSD/WFD), Qualidade Padrão da Água Subterrânea (GWD), Lista de poluentes mínimos e indicadores para a água subterrânea (GWD), valores Limite para os poluentes das águas subterrâneas (GWD), etc.

Neste contexto, os produtos farmacêuticos cuja pressão nos ecossistemas aquáticos e nos organismos aquáticos tenha sido documentada desde há mais de 20 anos em vários países da UE devem ser consideradas como novos candidatos prioritários na atual revisão da Lista de Substâncias Prioritárias da UE. A revisão da lista da UE e a subsequente definição de novas e pertinentes NQA são baseadas nos riscos significativos para o, ou pelo ambiente aquático de acordo com o Art.16 do Quadro de Ação da Água. Uma metodologia simplificada e pragmática foi desenvolvida no âmbito da Estratégia de Implementação Comum (CIS) do WFD, tendo em consideração tanto os dados de monitorização e os dados de modelação. Entre os possíveis fármacos prioritários, deve-se notar que algumas substâncias citotóxicas / genotóxicas / reprotóxicas (tamoxifeno, ciclofosfamida, etc.), estrogénios sintéticos e hormonas podem já ser consideradas como relevantes para o Ponto 4 Anexo VIII do WFD (Lista Indicativa dos Principais Poluentes: "*Substâncias e preparações, ou produtos de degradação das mesmas, que comprovadamente possuam propriedades cancerígenas ou mutagénicas ou propriedades que possam afetar as funções esteroidogénicas, a tiroide, a reprodução ou outras funções endócrinas no, ou através ambiente aquático*"). Por outro lado, a inclusão de fármacos chave na Lista de Substâncias Prioritárias da UE deve resultar numa extensa monitorização do ambiente aquático, sedimentos e biota nos países da UE, apoiada pela última Diretiva filha 2009/90/CE que define os critérios de desempenho mínimos para os métodos de análise química nas atividades de monitorização relevantes para o WFD e a GWD.

Conclusões

O problema relativo à presença de fármacos no ambiente aquático parece ser extremamente significativo, visto que os resultados de vários estudos sobre os cursos hídricos superficiais e subterrâneos em muitos países em anos recentes, em junção com alguns

dados provenientes de estudos ecotoxicológicos em espécies não-alvo, identificam esses compostos como novos contaminantes ambientais, que podem alterar o equilíbrio dos ecossistemas aquáticos. De facto, a utilização cada vez maior de fármacos para seres humanos e medicamentos veterinários (criação de gado e aquacultura) nos países desenvolvidos é suscetível de produzir um aumento de libertação de fármacos para a água e, portanto, da sua presença como contaminantes, tendo em consideração os limites das tecnologias atualmente usadas nas estações de tratamento para a remoção e redução de fármacos e dos seus metabolitos. Aliás, as principais leis ambientais atualmente vigentes na Europa, juntamente com as que visam a proteção e produção da água para consumo humano, não providenciam parâmetros ou recomendações para direcionar a atenção das autoridades de saúde para os fármacos como agentes de contaminação, e igualmente porque o papel destas autoridades é inevitavelmente e primariamente associado com a proteção, bem-estar e desenvolvimento da população humana. Contudo, uma inclusão dos fármacos prioritários (por exemplo, substâncias citotóxicas, genotóxicas, estrogénios e hormonas, fármacos persistentes na água e sedimentos, etc.), devido ao seu potencial risco ambiental deve ser incluída na atual e futuras revisões da Lista de Substâncias Prioritárias, no âmbito do WFD. Consequentemente, tendo em consideração os potenciais riscos devido à presença de fármacos na água, são necessários mais esforços para expandir o conhecimento sobre este tipo de contaminação, especialmente nas áreas de monitorização do comportamento ambiental de estudos ecotoxicológicos na biota aquática e sedimentos e das tecnologias de tratamento destinadas a limitar a liberação de fármacos para o ambiente aquático.

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Anexo 3 – Artigo "*Pharmaceuticals as emerging contaminants and their removal from water. A review*" e Tradução

Chemosphere 93 (2013) 1268–1287

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www. elsevier.com/locate/chemosphere

Review

Pharmaceuticals as emerging contaminants and their removal from water. A review

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highlights

- Water pollution by pharmaceuticals has been acknowledged as an environmental problem.
- Many of pharmaceuticals are not effectively removed by conventional treatments.
- Activated carbons generally demonstrated a high capacity to adsorb pharmaceuticals.
- Research interest has been shown in the application of O_3 to remove pharmaceuticals.
- Pharmaceuticals are degraded by UV radiation/photosensibilizer and gamma radiation.

articleinfo

Article history:
Received 19 February 2013
Received in revised form 29 May 2013
Accepted 26 July 2013
Available online 8 September 2013

Keywords:
Pharmaceuticals
Removal
Adsorption
Ozonation
Photodegradation
Radiolysis

abstract

The main objective of this study was to conduct an exhaustive review of the literature on the presence of pharmaceutical-derived compounds in water and on their removal. The most representative pharmaceutical families found in water were described and related water pollution issues were analyzed. The performances of different water treatment systems in the removal of pharmaceuticals were also summarized. The water treatment technologies were those based on conventional systems (chlorine, chlorine dioxide, wastewater treatment plants), adsorption/bioadsorption on activated carbon (from lotus stalks, olive-waste cake, coal, wood, plastic waste, cork powder waste, peach stones, coconut shell, rice husk), and advanced oxidation processes by means of ozonation (O_3, O_3/H_2O_2, O_3/activated carbon, O_3/biological treatment), photooxidation (UV, UV/H_2O_2, UV/$K_2S_2O_8$, UV/TiO_2, UV/H_2O_2/TiO_2, UV/TiO_2/activated carbon, photo-Fenton), radiolysis (e-Beam, ^{60}Co, ^{137}Cs. Additives used: H_2O_2, SO^{2-}_3, HCO^-_3, CH_3. OH, CO^{2-}_3, or NO^-_3), and electrochemical processes (Electrooxidation without and with active chlorine generation). The effect of these treatments on pharmaceutical compounds and the advantages and disadvantages of different methodologies used were described. The most important parameters of the above water treatment systems (experimental conditions, removal yield, pharmaceutical compound mineralization, TOC removal, toxicity evolution) were indicated. The key publications on pharmaceutical removal from water were summarized.

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http://dx.doi.org/10.1016/j.chemosphere.2013.07.059

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1. Introduction

Over the last fifteen years, pharmaceuticals have been receiving increasing attention as potential bioactive chemicals in the environment (Kümmerer, 2009). They are considered as emerging pollutants in waterbodies because they still remain unregulated or are currently undergoing a regularization process, although the directives and legal frameworks are not set-up yet. Pharmaceuticals are continuously introduced into the environment and are prevalent at small concentrations (Kolpin et al., 2002), which can affect water quality and potentially impact drinking water supplies, ecosystem and human health (Yuan et al., 2009; Sirés and Brillas, 2012).

Although pharmaceuticals have been present in water for decades, their levels in the environment have only recently begun to be quantified and acknowledged as potentially hazardous to ecosystems (Kolpin et al., 2002; Fent et al., 2006; Jjemba, 2006). The development of new analytical techniques (e.g., liquid chromatography coupled to mass spectrometry [LC-MS], tandem MS [MS^2], or LC-MS^2) has allowed the detection of extremely low concentrations (1g ng L^{-1}) of these compounds in very complex matrixes in liquid and solid states (Petrovic´ et al., 2005; Díaz-Cruz and Barceló, 2006; Ternes and Joss, 2006), in wastewater (Kanda et al., 2003; Hernández et al., 2007), and in surface and ground waters (Boyd et al., 2003; Drewes et al., 2003). These techniques have been used to detect and quantify around 3000 biologically active chemical compounds in the environment (Richardson, 2006), prompting numerous analytical chemistry studies aimed at optimizing and validating methods to prepare environmental samples for subsequent analysis.

The presence of pharmaceuticals in water is attributable to personal hygiene products, pharmaceutical industry waste, hospital waste and therapeutic drugs. The subsistence of trace pharmaceuticals and other xenobiotic compounds in finished drinking water is another public health concern, since little is known about potential chronic health effects associated with long term ingestion of mixtures of these compounds through drinking water (Kümmerer, 2001; Stackelberg et al., 2004). Thus, it is an emerging issue in environmental science and engineering to achieve effective removal of pharmaceuticals, along with other priority pollutants, from wastewaters before their discharge. Thus, major efforts to investigate this problem and palliate its effects are prioritary (Daughton and Ternes, 1999; Kümmerer, 2004; Khetan and Collins, 2007; Kemper, 2008). With this background, the objective of this study was to conduct an exhaustive review of the literature on the presence of pharmaceutical-derived compounds in water and on their removal. The most representative pharmaceutical families found in waters are described and related water pollution issues are analyzed. We examine the performance of different water treatment systems in the elimination of pharmaceuticals, especially technologies that use adsorption on activated carbons and advanced oxidation processes (AOPs) that employ ozone, ultraviolet radiation, gamma radiation and electro oxidation.

2. Occurrence of pharmaceuticals in water

Therapeutic groups most commonly detected in water are: (i) anti-inflammatories and analgesics (paracetamol, acetylsalicylic acid, ibuprofen, and diclofenac); (ii) antidepressants (benzodiazepines); (iii) Antiepileptics (carbamazepine); (iv) lipid-lowering drugs (fibrates); (v) b-blockers (atenolol, propanolol, and metoprolol); (vi) antiulcer drugs and antihistamines (ranitidine and famotidine); (vii) antibiotics (tetracyclines, macrolides, b-lactams, penicillins, quinolones, sulfonamides, fluoroquinolones, chloramphenicol and imidazole derivatives); (viii) other substances (cocaine, barbiturates, methadone, amphetamines, opiates, heroin, and other narcotics) (Bush, 1997).

The pollution produced by pharmaceutical products in surface and ground waters has been acknowledged by many countries as an environmental problem and has led to the establishment of a research field known as Pharmaceuticals in the Environment. The pharmaceutical industry uses the designation Active Pharmaceutical Ingredients to describe products that are pharmacologically active, resistant to degradation, highly persistent in aqueous medium, and potentially able to produce adverse events in water organisms and have a negative impact on human health.

The following characteristics of pharmaceuticals, most of which have a molecular mass <500 Da (Lipinski et al., 1997), differentiate them from conventional industrial chemical contaminants: (a) they can be formed by large and chemically complex molecules that vary widely in molecular weight, structure, functionality, and shape; (b) they are polar molecules with more than one ionizable group, and the degree of ionization and its properties depend on the pH of the medium; they are lipophilic and some of them are moderately soluble in water; (c) pharmaceuticals such as erythromycin, cyclophosphamide, naproxen, and sulfamethoxazole can persist in the environment for more than a year, and others, e.g., clofibric acid, can persist for various years and become biologically active through accumulation, and (d) after their administration, the molecules are absorbed, distributed, and subject to metabolic reactions that can modify their chemical structure.

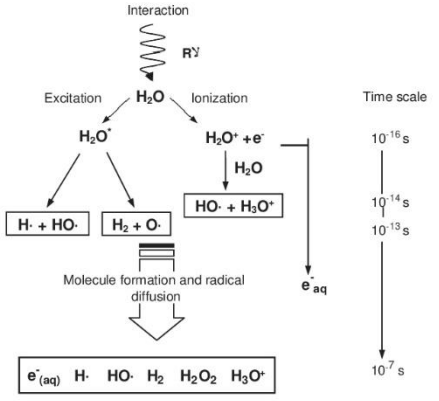

Fig. 1. Species generated in pure water radiolysis at neutral pH (adapted from Choppin et al. (2002)).

After their administration, pharmaceuticals can be excreted without being transformed or they can be metabolized by biochemical reactions in two routines: a first routines in which oxidation, reduction, hydrolysis, and alkylation reactions take place; and a second routines in which glucuronide or sulfate conjugates are formed and excreted by urine or bile in the form of more polar and hydrophilic derivatives, as a metabolite or as a mixture of multiple metabolites (Silverman and Hoffman, 1984; Heberer, 2002a; Jones et al., 2005a; Cunningham et al., 2006).

These compounds enter the environment in two ways: by their inclusion in normal rubbish tips, which is avoidable; and via feces or urine after their consumption by humans and animals, which is evidently more difficult to prevent.

Fig. 1 in Supplementary Material depicts the different possible pathways by which pharmaceutical compounds and other personal health products enter water. After their release into the sewage system, they pass through wastewater treatment plants (WWTPs) and enter water systems, where a large variety of these compounds and their metabolites have been detected (Drewes et al., 2001; Miao et al., 2002; Soulet et al., 2002; Jones et al., 2005b), producing a complex mixture of compounds that may have synergetic effects. Some of these compounds are more bioactive than their metabolic precursor.

Pharmaceuticals used in veterinary medicine are excreted onto the ground or directly into surface waters without passing through a WWTP, making their control and follow-up much more challenging.The ground can act as a major source of water contamination (Alder et al., 2001), since most of these compounds and their metabolites are soluble in water, and they are excreted by urine and feces (Halling-Sørensen, 2001). In intensive livestock farming, pharmaceuticals may indirectly enter the environment through the application of manure and purines as fertilizers and can pass to humans through the food chain. Pharmaceuticals used in fish-farms are directly released into surface water (Halling-Sørensen et al., 1998).

Unfortunately, as depicted in Supplementary Material (SM) (Figure SM-1), some of these pharmaceuticals are not completely removed by WWTPs (Halling-Sørensen et al., 1998; Ternes, 1998; Ternes et al., 1999; Heberer, 2002b; Boyd et al., 2003). Recent studies demonstrated that conventional treatment plants, mainly based on the use of microorganisms, are inadequate to effectively destroy this type of organic compounds, due to their complex molecular structure and low concentrations in the water, and that the percentage of compound removed can be lower than 10% (Ternes et al., 2002; Stackelberg et al., 2004; Jones et al., 2005a).

The pharmaceuticals most frequently found in water treatment effluents are: antibiotics, antacids, steroids, antidepressants, analgesics, anti-inflammatories, antipyretics, beta-blockers, lipid-lowering drugs, tranquilizers, and stimulants. These pharmaceuticals have been detected in the surface and ground waters of Germany (Ternes, 1998; Hirsch et al., 1999; Putschew et al., 2000; Ternes and Hirsch, 2000), Holland (Belfroid et al., 1999), Switzerland (Soulet et al., 2002), Italy (Castiglioni et al., 2004), Spain (Rodríguez et al., 2003; Carballa et al., 2005), United States (Drewes et al., 2001; Kolpin et al., 2002), Canada (Ternes et al., 1999; Miao et al., 2004), China (Sui et al., 2010; Chen et al., 2011; Yuan et al., 2013) and Brazil (Ternes et al., 1999), among others. In a study of the River Ebro in Spain, around 20 pharmaceuticals were identified at 18 sampling points, at concentrations similar to mean European findings (Petrovic´ et al., 2005). Table SM-1depicts the maximum pharmaceutical concentrations detected in surface water by different authors between 1999 and 2004 (Daughton and Ternes, 1999; Kolpin et al., 2002; Boxall et al., 2004).

Various studies have reported the presence of these compounds in river water (Ternes et al., 2002, Lin and Reinhard, 2005; Ellis, 2006). The range of contaminants detected is striking, with researchers finding up to 60 different compounds in the drinking water of Berlin (Stan and Heberer, 1997; Heberer et al., 1997; Heberer, 2002b). A wide study of 28 sampling stations conducted by Associated Press in the United States (Donn et al., 2008) demonstrated the presence of pharmaceutical traces in the drinking water of 24 major cities, including Philadelphia, Washington, New York, and San Francisco.

3. Pharmaceutical removal in water treatment systems

3.1. Conventional systems

There are currently no legally regulated maximum permitted concentrations of pharmaceuticals in the environment, despite their unknown impact on the environment and human health. Based on the precaution principle, the European Union Water Framework Directive produces an updated list of priority substances every four years (2000/60/EC) and has identified compounds from pharmaceuticals as potential pollutants.

The use of chlorine is still the most widespread conventional treatment for disinfecting drinking waters. Various studies on the chlorination of aromatic compounds demonstrated that the chlorine reaction rate can be strongly affected by the presence of different functional groups in the benzene ring. The reaction is usually rapid in pharmaceutical products containing amines, giving rise to chlorinated compounds (Pinkston and Sedlak, 2004). Thus, metropolol and sulfamethoxazole give rise to chloramines as an oxidation product. Studies on the removal of acetaminophen, the active compound of paracetamol, showed that it reacts with chlorine to form numerous subproducts, two of which have been identified as toxic compounds (Glassmeyer and Shoemaker, 2005; Bedner and MacCrehan, 2006a). At least five subproducts are formed in diclofenac chlorination, although none of them are chloramines (Bedner and MacCrehan, 2006b), and the degree of mineralization achieved is not acceptable.

Chlorine dioxide is a more potent oxidant than chlorine and can degrade numerous organic compounds by oxidation. However, it does not combine with ammonium or chlorinate organic substances, which is an advantage with respect to taste, smell, and the formation of organochlorinated toxic species. Research into the use of ClO_2 to oxidize persistent pharmaceutical products in the environment found that it is only effective for certain antibiotics, including 17â-ethinylestradiol, sulfamethoxazole, roxithromycin, and diclofenac (Huber et al., 2005). ClO_2 reacts selectively with functional groups with high electron density, such as tertiary amines and phenoxides. In comparison to ozone, ClO_2 reacts slower and with fewer compounds; in comparison to chlorine, it reacts faster with sulfonamides, macrolides, and estrogens, but, unlike chlorine, it does not react with bezafibrate, carbamazepine, diazepam, or ibuprofen (Huber et al., 2005).

In general, WWTPs comprise a primary system of physicochemical treatments and a secondary system that consists of a biological reactor formed by actived sludge. These conventional plants have a limited capacity to remove pharmaceutical products from urban wastewaters, since most of the compounds cannot be metabolized by microorganisms as source of carbon and may even inhibit the activity of the microorganisms or produce their bioaccumulation in the food chain. Although further research is required on this issue, it is known that conventional WWTPs do not remove all pharmaceuticals from wastewaters. Table 1 shows the amounts of various pharmaceuticals detected in inlet and outlet waters of various WWTPs, confirming that many of these substances are not effectively removed by the treatments.

In primary treatments, some pharmaceuticals can be removed by adsorption, whereas others remain in the water, e.g., ibuprofen,

Table 1
Pharmaceutical concentrations detected in wastewaters of various WWTPs before and after treatment.

Type of pharmaceutical	Substance detected	WWTP inlet (ng L^{-1})	WWTP outlet (ng L^{-1})	References
Analgesics and anti-inflammatories	Ketoprofen	451	318	Petrovic´ et al. (2005)
	Naproxen	99	108	
	Ibuprofen	516	266	
	Diclofenac	250	215	
	Acetaminophen	10194	2102	
Lipid-lowering drugs	Bezafibrate	23	10	
	Clofibrate	72	28	
	Gemfibrozil	155	120	
Antiepileptics	Carbamazepine	420	410	
Antacids	Ranitidine	188	135	
Antibiotics	Azithromycin	152	96	
	Metronidazole	80	43	
	Sulfamethoxazole	590	390	
	Trimethoprim	1172	290	
b-Blockers	Atenolol	400	395	
	Sotalol	185	167	
	Propanolol	290	168	

naproxen, sulfamethoxazole, and iopromide (Carballa et al., 2004). Subsequent biological treatments remove 30–75% of anti-inflammatories and antibiotics (Carballa et al., 2004). There have been various reports that carbamazepine is not appreciably removed by WWTPs (Ternes, 1998; Heberer, 2002a; Strenn et al., 2004; Clara et al., 2005).

According to Heberer (2002a), out of the most commonly used analgesics, WWTPs can eliminate paracetamol, acetylsalicylic acid, and ibuprofen but are not effective to remove diclofenac. With regard to antibiotics, penicillins readily hydrolyze in water and tetracyclines precipitate with cations such as Ca^{2+}, accumulating in treatment plant sludge (Daughton and Ternes, 1999). Hence, in general, most of these emerging micropollutants are not completely eradicated in WWTPs, and therefore remain in effluents and contaminate surface and ground waters, which are the main source of drinking water (Halling-Sørensen, 2001).

In short, conventional treatment systems are unable to com- pletely remove a large amount of the organic micropollutants pres- ent in urban wastewaters. More effective and specific treatments are required to reduce the environmental and potential impact of effluents and comply with increasingly strict legislation. Tertiary water treatments include: biological systems to remove nitrogen; ionic exchange to remove ions; chemical precipitation to remove phosphorus; distillation to remove volatile organic compounds; liquid–liquid extraction; adsorption on activated carbon to remove organic and inorganic pollutants; and AOPs to remove toxic biorefractory organic compounds, based on the generation of radicals, mainly the $HO^{\bullet}$ radical, with high oxidizing power. Many of these systems are under research and have yet to be applied on an industrial scale, since there is a lack of good quality data on the mechanisms involved, the influence of operational variables, the reaction kinetics, and reactor design issues.

Different water treatments and their effect on pharmaceutical compounds are described below, centering on: adsorption/bioadsorption on activated carbon, ozonation, photooxidation, radiolysis and electrooxidation without and with active chlorine generation.

3.2. Adsorption on activated carbon

There have been numerous studies on the adsorption of aromatic compounds in aqueous solution, but the underlying mechanisms must be established to enhance the effectiveness of this process to remove these contaminants. This remains controversial, and the following different mechanisms have been proposed: (1) Dispersive interactions between p electrons of the aromatic ring and p electrons of the graphene planes of the activated carbon surface (2) Formation of a donor–acceptor complex involving carbonyl type surface groups, which act as donors, and the aromatic ring of the organic compound, acting as acceptor and (3) Electrostatic/dispersion interactions and formation of hydrogen bridge bonds (Coughlin and Ezra, 1968; Moreno-Castilla et al., 1995; Tessmer et al., 1997; Radovic et al., 1997; Leng and Pinto, 1997; Karanfil and Kilduff, 1999; Franz et al., 2000; Stoeckli and Hugi-Cleary, 2001; Moreno-Castilla, 2004; Rivera-Utrilla et al., 2005).

Given the uncertainty about the interactions involved in these adsorption processes, it is not possible to establish a general adsorption mechanism. However, an exhaustive review published by Radovic et al. (2001) on the adsorption of aromatic compounds on activated carbon drew the following conclusions: (a) The mechanism is complex, with electrostatic and adsorbent-adsorbate dispersion interactions. (b) The efficacy of the process is determined by the adsorbate solubility, the adsorbate and adsorbent hydrophobicity, and the strength of p-p interactions. (c) The strength of p-p interactions can be modified by adsorbate or activated carbon aromatic ring functionalities. (d) Medium pH plays a very important role in the adsorption process.

The main advantage of using activated carbon to remove pharmaceuticals is that it does not generate toxic or pharmacologically active products. According to the literature, activated carbons generally demonstrate a high capacity to adsorb pharmaceuticals (Dutta et al., 1999; Fuerhacker et al., 2001; Adams et al., 2002; Snyder et al., 2007; Simazaki et al., 2008; Choi et al., 2008a,b; Yu et al., 2008b). Rivera-Utrilla et al. (2009) conducted an extensive study on the adsorption of antibiotics (nitroimidazoles) on different types of activated carbons, finding an increase in the adsorption rate with a decrease in the percentage of oxygen and an increase in the hydrophobicity of the carbon. Hence, in general, hydropho- bic interactions appear to govern the adsorption kinetics. Nitroimidazole adsorption was largely determined by the chemical properties of the carbon. Application of the Langmuir equation to the adsorption isotherms showed an elevated adsorption capacity (X_m = 1.04–2.04 mmol g^{-1}) for all contaminants studied. Table 2 lists some details of these adsorption processes.

One of the most important aspects of the adsorption processes from the point of view of treatment plant design is the adsorption kinetics. However, in general, few studies about the adsorption of pharmaceuticals on activated carbon have been focused both on the overall adsorption rate and the mass transport mechanisms controlling this process. Ocampo-Pérez et al. (2012) investigated the global adsorption rate of tetracycline on adsorbents obtained from treatment sludges. Experimental data of tetracycline concen- tration decay curves were interpreted with kinetic models

Table 2
Key publications on pharmaceutical adsorption on activated carbons.

Reference	Adsorbent	Pharmaceutical	Experimental conditions	Observations	Removal or adsorption capacity
Liu et al. (2012)	GAC – LS (from lotus stalks)	Trimethoprim, bacteriostatic antibiotic	$[C]_o$ = 29–87 mg L^{-1} V = 50 mL Carbon dose: 10 mg pH = 6 Time contact: 3 d T = 25 °C	Four kinds of phosphorus oxyacids ($H_3P_3O_9$), i.e. H_3PO_4, $H_4P_2O_7$, HPO_3 and H_3PO_3, were used to activate LS	$q_{m,H3PO4}$ = 332 mg g^{-1} $q_{m,H4P2O7}$ = 345 mg g^{-1} $q_{m,HPO3}$ = 119 mg g^{-1} $q_{m,H3PO3}$ = 118 mg g^{-1}
Baccar et al. (2012)	GAC (from exhausted olive-waste cake)	Ibuprofen, analgesic Ketoprofen, anti-inflammatory Naproxen, anti-inflammatory Diclofenac, anti-inflammatory	$[C]_o$ = 10.04, 19.28, 14.80, 19.78 mg L^{-1}, respectively V = 15 mL Carbon dose: 10–450 mg pH = 4.1 Time contact: 26 h T = 25 °C	Activated carbon was produced via chemical activation using phosphoric acid Increasing pH gradually reduced the uptake of the four drugs. The increase of temperature in the range 4–40 °C does not have a perceptible effect on the adsorption processes	$q_{m,IB}$ = 12.6 mg g^{-1} $q_{m,KE}$ = 24.7 mg g^{-1} $q_{m,NA}$ = 39.5 mg g^{-1} $q_{m,DI}$ = 56.2 mg g^{-1}
Cabrita et al. (2010)	GAC – B (from coal) – NS (from wood) – PP (from plastic waste) – CC (cork powder waste) – CP (from peach stones)	Paracetamol	$[C]_o$ = 120 mg L^{-1} V = 15 mL Carbon dose: 10 mg pH = 5.8 Time contact: 24 h T = 30 °C	Samples prepared bychemical activation of biomass residues showed reasonably high removal efficiencies and fast rate of adsorption	$q_{m,B}$ = 255 mg g^{-1} $q_{m,NS}$ = 267 mg g^{-1} $q_{m,PP}$ = 200 mg g^{-1} $q_{m,CC}$ = 204 mg g^{-1} $q_{m,CP}$ = 113 mg g^{-1}
Quesada-Peñate et al. (2009)	GAL27 (from wood) – S23 (from coconut shell) – C1 (from casuarine)	Levodopa	$[C]_o$ = 0.031–1.281 g L^{-1} Carbon dose: 0.1 g for L27 and 0.05 g for S23 and C1 Time contact: 24 h T = 25 °C V = 100 mL	The activated carbons are characterized using low temperature nitrogen adsorption, thermogravimetry analysis and Boehm titration. Five models (Langmuir, Jovanovic, Freundlich, Redlich–Peterson and Khan) are evaluated to fit the experimental data	$q_{m,L27}$ = 195 mg g^{-1} $q_{m,S23}$ = 205 mg g^{-1} $q_{m,C1}$ = 320 mg g^{-1}
Carabineiro et al. (2011)	GAC (Norit Rox 0.8)	Ciprofloxacin, synthetic antibiotic	$[C]_o$ = 20 mg L^{-1} V = 20 mL Carbon dose: 20 mg pH = 7 Contact time: 3 d T = 30 °C	GAC was oxidized with nitric acid (5M). Furthermore, GAC sample was thermally activated at 350 and 900 °C	q_m = 250 mg g^{-1} $q_{m,HNO3}$ = 195 mg g^{-1} $q_{m,350\ °C}$ = 205 mg g^{-1} $q_{m,900\ °C}$ = 320 mg g^{-1}
Ahmed and Theydan (2012)	GAC (*Albizia lebbeck* Seed pods)	Cephalexin, antibiotic	Initial concentrations (20, 40, 60, 80, and 100 mg L^{-1}) V = 20 mL Carbon dose: 10 mg pH = 7 Contact time: 120 min T = 30 °C	Microwave technique has been adopted for preparation of two activated carbons by using KOH and K_2CO_3 activation	$q_{m,KOH}$ = 127 mg g^{-1} $q_{m,K2CO3}$ = 118 mg g^{-1}
Kim et al. (2010)	PAC CAG (Both from James Cumming & Sons Pty Ltd.)	Trimethoprim, synthetic antibiotic	Carbon dose: variable pH = 4, 6 and 10 T = 25 °C Contact time: 5 d $[C]_o$ = 50 mg L^{-1}	Toth isotherm model was better for describing the adsorption equilibrium than Freundlich and Langmuir models in both carbons pH 4 was the optimum to remove Trimethoprim from aqueous solution	PAC_{qm} = 257.9 mg g^{-1} GAC q_m = 257.9 mg g^{-1}
Mestre et al. (2011)	GAC (Sisal waste) – VP (BakerCorp's) – NSAES (Norit sae super)	Paracetamol, analgesic Ibuprofen, anti inflammatory	GAC dose: 10 mg pH = 4–6 T = 30 °C Time contact: 6 h $[C]_o$ = 120 mg L^{-1}	An activated carbon sample with a surface area of 1038 m^2 g^{-1} and pore volume of 0.49 cm^3 g^{-1} was obtained	Paracetamol q_{SW} = 124.5 mg g^{-1} q_{VP} = 119.1 mg g^{-1} q_{NSAES} = 151.9 mg g^{-1} Ibuprofen

						q_{SH} = 139.8 mg g^{-1}	
						q_{VP} = 121.2 mg g^{-1}	
						q_{NSAIS} = 166.3 mg g^{-1}	
Choi et al. (2008b)	GAC400 (Calgon carbon)	Oxytetracycline–HCl	Tetracyclines, antibiotics	GAC column 5 × 200 cm	Synthetic and natural water (pH 8.1; DOC: 3.12 mg L^{-1}); alkalinity: 65 mg L^{-1})	90%	F400
	– Samchully (coconut shell)	Minocycline–HCl		Flow: 200 mL min^{-1}		70%	
		Doxycycline		[C]$_0$ = 10 μg L^{-1}		80%	
		Meclocycline sulfosalicylate			Effectiveness comparison between coagulation and adsorption:	65%	
		Chlortetracycline				85%	
		Demeclocycline–HCl			Superior outcome for adsorption	90%	
		Tetracycline			Superior outcome with carbon F400	95%	
Snyder et al. (2007)	PACAC800 (Acticarb)	Ibuprofen, anti-inflammatory		Pilot scale and laboratory	Four natural waters characterized	16–30%	5 mg L^{-1}
	– WPM (Calgon carbon)	Iopromide, X-ray contrast		PAC dose: 1, 5, and 50 mg L^{-1}	Effectiveness decreases in the presence of natural organic matter	30–50%	PAC
		Sulfamethoxazole, antibiotic		contact: 4 h		36–56%	WPM
		Gemfibrozil, lipid regulator		[C]$_0$ = 100 ng L^{-1}; V = 1.5 L		37–55%	
		Diclofenac, anti-inflammatory				38–46%	
		Naproxen, anti-inflammatory				52–58%	
	GACHydrodarco (Norit)	Diazepam, anxiolytic		Carbon column		65–85%	
	– Superdarco (Norit)	Acetaminophen, antipyretic		PAC dose: 1, 5, and 50 mg L^{-1}		73–84%	
		Carbamazepine, antiepileptic		Contact in column: 7.6 min		74–86%	
		Trimethoprim, antibiotic		[C]$_0$ = 100–200 ng L^{-1}		76–96%	
		Triclosan, antibacterial				90–96%	
		Fluoxetine, antidepressant				91–92%	

(first-order, second-order, Langmuir, and intraparticle diffusion) and diffusional models (pore volume diffusion model and surface diffusion model). It was reported that the tetracycline adsorption rate is controlled by intraparticle diffusion and that diffusion in the pore volume represents >80% of total intraparticle diffusion. This indicates that surface diffusion does not play a major role in tetracycline diffusion on the different adsorbents used.

In the case of partial or coupled treatments, e.g.: oxidation-adsorption, a specific oxidation treatment to remove persistent pharmaceuticals is followed by the adsorption of intermediate products on the activated carbon, diminishing their toxicity and pharmacological activity.

Micropollutants that resist conventional processes can be removed by membrane filtration (nanofiltration and reverse osmosis) or adsorption on activated carbon. However, the retention capacity of both methods can be reduced through blockage by natural organic matter in water (Summers et al., 1989; Newcombe et al., 1997; Karanfil et al., 1999; Heijman et al., 2007; Saravia and Frimmel, 2008).

3.3. Technologies based on AOPs

As commented above, polluted water can generally be treated effectively by biological treatment plants, using adsorbents or conventional chemical treatments (chlorination, ozonation, or permanganate oxidation). However, these procedures are occasionally not capable of degrading pollutants to the levels required by law or essential for the subsequent use of the effluent. AOPs are very effective in the oxidation of numerous organic and inorganic compounds. These processes are all based on the generation of free radicals ($HO^{\bullet}$, $O_2^{-\bullet}$, $HO_2^{\bullet}$), notably the hydroxyl radical ($HO^{\bullet}$), highly reactive species that can successfully attack most organic molecules, with elevated reaction rate constants that range from 10^6 to 10^9 M^{-1} s^{-1}. These radicals can generate numerous systems, making AOPs highly versatile (Brillas et al., 1998; Andreozzi et al., 1999; Huber et al., 2003; Esplugas et al., 2007; Baumgarten et al., 2007; Von Sonntag, 2008). Their potential to remove pharmaceutical-derived pollutants from water is examined below.

3.3.1. AOPs based on ozone

Considerable research interest has recently been shown in the application of O_3, O_3/OH^-, O_3/H_2O_2, and O_3/activated carbon systems for the removal of pharmaceuticals from water. Table 3 lists some key studies, with a summary of the experimental conditions and results.

In a wide-ranging study, Ikehata et al. (2006) recorded the kinetic parameters of O_3 and O_3/H_2O_2 systems in the removal of pharmaceuticals from water. When the O_3/H_2O_2 system was applied with 5 mg L^{-1} O_3 and 1.8 mg L^{-1} H_2O_2, it showed high efficacy in the removal of clofibric acid, ibuprofen, and diclofenac, obtaining 98% mineralization (Zwiener and Frimmel, 2000). O_3 alone was not completely effective to degrade diclofenac, with only 32% mineralization.

Various research groups are exploring the potential of the ozone/activated carbon system to remove organic pollutants from water, but there has been little investigation of its use against pharmaceuticals. Sánchez-Polo et al. (2008) studied its use to remove nitroimidazole in static and continuous regime and reported that the simultaneous use of ozone and activated carbon considerably increases the effectiveness in comparison to direct ozonation or application of the O_3/H_2O_2 system and reduces the total organic carbon and toxicity. Beltrán et al. (2009) applied this system to remove diclofenac from water and confirmed that simple ozonation cannot remove the compounds formed during the first minutes of treatment, since most are refractory to ozone (40% TOC removed in 120 min). They also found that ozonation in the presence of

Table 3
Key publications on pharmaceutical removal from water by O_3-based AOPs.

Pharmaceutical	Group/type/use	Conc. in water[a] (μg L^{-1})	Experimental conditions	Observations	Removal %	References
Levofloxacin	Antibiotic	0.087–0.52[b]	$[O_3]_0$ = 2500 ppm $[L]_0$ = 16.4 mg L^{-1} T = 27.5 °C pH 3–7 (Buffer) [t-BuOH] = 30 mM $[H_2O_2]$ = 2–100 μM	Degradation was about 2 times faster at pH 10 compared to pH 3 and 7 Degradation at the quinolone moiety resulted in the formation of isatin and anthranilic acid	99.9	De Witte et al. (2009a)
Sulfadiazine, Sulfamethizole, Sulfamethoxazole, Sulfathiazole	Sulfonamides, synthetic antimicrobials	330–1160	O_3 flow rate of 1.2 L min^{-1} $[O_3]_0$ = 1–3.2 mg L^{-1} $[S]_0$ = 1000 μg L^{-1} $[HCO_3^-]$ = 2–20 mM T = 22 °C pH = 2–10	Sulfonamides exhibited moderate reactivity towards aqueous ozone, k_{O3} > 2 × 10^4 M^{-1} s^{-1} at pH of 2. The mol of ozone absorbed by the solution per mol of sulfonamides removed varied in the range of 5.5–12.0	99.9	Garoma et al. (2010)
Ciprofloxacin	Antibiotic	0.313–124	O_3 flow rate of 120 mL min^{-1} $[Cip]_0$ = 7.5–45 mg L^{-1} pH 3–10 (buffer) T = 6–62 °C [t-BuOH] = 30 mM	Desethylene ciprofloxacin was identified, based on HPLC–MS analysis, as one of the degradation products Formation of desethylene ciprofloxacin was highly dependent on pH, with the highest concentration measured at pH 10	95	De Witte et al. (2009b)
Sulfamethoxazole (SMX)	Antibiotics	1.9	$[SMX]_0$ = $[CTCN]_0$ = 30 mg L^{-1}	CTCN was more quickly oxidized than SMX	99.9	Kim et al. (2012)
Chlortetracycline (CTCN)		0.69	pH_{SMX} = 4.63 pH_{CTCN} = 4.33 T = 22 °C	Ozone primarily reacts with SMX by attacking the aniline (p-sulfonylaniline) moiety	99.9	
Triclosan	Antimicrobial	0.5–4.5	$[Tric]_0$ = 10 mg L^{-1} pH = 7 T = 25 °C $[O_3]_0$ = 2 mg L^{-1}	Samples were prepared by mixing O_3 stock solutions into triclosan stock solutions in different volume ratios to reach the molar rations of triclosan: O_3 1:1, 1:3 and 1:5	1:1 = 94 1:3 = 97 1:5 = 99.9	Chen et al. (2012)
Mefenamic acid	Non-steroidal anti inflammatories	0.44–0.43	$[MEF]_0$ = 0.54 mg L^{-1} pH = 4–9 (buffer) T = 25 °C $[O_3]_0$ = 0.7 mg L^{-1}	Degradation occurred during the first 5 min of treatment The degree of mineralization was relatively limited: only 25% of Mefenamic acid was mineralized at pH 9	pH 4 = 37.5 pH 7 = 42.5 pH 9 = 45.8	Chang et al. (2012)
Amoxicillin	Antibiotic, b-lactam	0.12	$[C]_0$ = 5.0 × 10^{-4} M pH = 5.5 (buffer), $[O_3]_e$ = 1.6 × 10^{-4} M, 4 min; 2-methyl-2-propanol (radical scavenger)	Low mineralization degree even with long treatment times; phenolic ring hydroxylation k_{O3} = 4 × 10^5 M^{-1} s^{-1} (pH = 2.5); k_{O3} = 6 × 10^6 M^{-1} s^{-1} (pH = 7); k_{O3} = 3.93 × 10^9 M^{-1} s^{-1} (pH = 5.5)	90 5 (TOC)	Cortacans Torre et al. (2006)
Bezafibrate	Lipid-lowering drugs, lipid regulator	–	Laboratory scale $[C]_0$ = 0.5 μM $[O_3]$ = 0.1–2 mg L^{-1} [t-BuOH] = 10–50 mM pH = 7–8 (phosphate buffer 5–50 mM); T = 10–20 °C; 10 min	Four natural waters with different DOC (1.2–3.7 mg L^{-1}) and alkalinity (0.7–4.1 mM) k_{O3} = 590 ± 50 M^{-1} s^{-1} k_{OH} = 3.3–9.8 × 10^9 M^{-1} s^{-1}	>95	Huber et al. (2003)
		0.08	Laboratory scale $[C]_0$ = 1 μg L^{-1} $[O_3]$ = 1.5 mg L^{-1} Laboratory scale $[C]_0$ = 1 μg L^{-1} $[O_3]$ = 3.0 mg L^{-1}	k_{O3} = 10^2–10^3 M^{-1} s^{-1} Simulation in a real treatment plant: sedimentation, flocculation ($FeCl_3$/$Ca(OH)_2$), filtration with GAC, decantation, and slow filtration in sand bed	50 80	Ternes et al. (2002)
		0.14	Laboratory scale $[O_3]$ = 0.23 mM; pH 7.8–8.7	Characterized and filtered and wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	≈94 ≈15 (TOC)	Rosal et al. (2008)

Table 3 (*continued*)

Pharmaceutical	Group/type/use	Conc. in water[a] (μg L^{-1})	Experimental conditions	Observations	Removal %	References
			$[C]_0$ = 126 ng L^{-1}			
Clarithromycin	Antibiotic, macrolides	0.06–0.33	$[C]_0$ = 1 × 10^{-6} M $[O_3]$ = 10^{-5} M pH (phosphate buffer)	Ultrapure water k_{O3} = 7 × 10^4 M^{-1} s^{-1} (pH 7) Subproduct determination Toxicity test (*P. putida*)	100	Lange et al. (2006)
Ciprofloxacin	Antibiotic, fluoroquinolones	0.5–0.7	Laboratory scale $[O_3]$ = 0.23 mM; pH = 7.8–8.7 $[C]_0$ = 572 ng L^{-1} Laboratory scale $[O_3]$ = 0.23 mM $[C]_0$ = 741 ng L^{-1} $[H_2O_2]$ = 20 mM, 0.15 mL (30% w/v) every 5 min in 5 L	Characterized and filtered wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	98 ≈15 (TOC) >93 >90 (TOC)	Rosal et al. (2008)
Clofibric acid	Lipid regulator metabolite	0.09	Laboratory scale $[C]_0$ = 1 μg L^{-1} $[O_3]$ = 0.5 mg L^{-1} Laboratory scale $[C]_0$ = 1 μg L^{-1}	Simulation in a real treatment plant: Sedimentation, flocculation ($FeCl_3$/$Ca(OH)_2$), filtration with GAC, decantation, and slow filtration in sand bed	10–15 ≈40	Ternes et al. (2002)
		1	$[O_3]$ = 2.5–3.0 mg L^{-1} $[C]_0$ = 1.0–1.5 mM; $[O_3]$ = 1.0 × 10^{-3} M; pH = 2.0–6.0; 60 min $[C]_0$ = 11.2 mg L^{-1}	k_{O3} = 2550 M^{-1}s^{-1} (pH 6.5) k_{O3} = 29.8 M^{-1} s^{-1} (pH 2.0) $[TOC]_0$ = 180 mg L^{-1} Synthetic water	100 50 (TOC) 100	Andreozzi et al. (2003a) Andreozzi
		–	$[O_3]$ = 0.42 mM pH = 7.6; T = 298 K; 1, 2, and 5 min	Toxicity measurement (Rotoxkit) with algae and rotifera. No toxic product generation	(in 2 min)	et al. (2004)
Diclofenac	Anti-inflammatory	10 (28.4)	Laboratory scale $[C]_0$ = 26 μM (8 mg L^{-1}) Molar ratio: (O_3: diclofenac) 10:1. With and without t-BuOH; $[O_3]_e$ minimum for 10 μg L^{-1} of diclofenac = 0.016 mg L^{-1}	k_{O3} = 6.8 × 10^5 M^{-1} s^{-1} (by competitive reaction with buten-3-ol); Proposal of O_3 and HO$^{\cdot}$ reaction mechanisms Subproducts: diclofenac-2,5-iminoquinone (32%), 5-hydroxydiclofenac (7%), 2,6-dichloroaniline (19%)	100 (complete degradation of potentially toxic primary products)	Sein et al. (2008)
Gemfibrozil	Lipid-lowering drug, lipid regulator	0.6	Laboratory scale $[O_3]$ = 0.23 mM; pH 7.8–8.7 $[C]_0$ = 618 ng L^{-1} Laboratory scale $[O_3]$ = 0.23 mM $[C]_0$ = 608 ng L^{-1} $[H_2O_2]$ = 20 mM, 0.15 mL (30% w/v) every 5 min in 5 L	Characterized and filtered wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	>99 ≈15 (TOC) >99 >90 (TOC)	Rosal et al. (2008)
Ibuprofen	Anti-inflammatory	-	Laboratory scale $[C]_0$ = 0.5 μM $[O_3]$ = 0.1–2 mg L^{-1} [t-BuOH] = 10–50 mM pH = 7–8 (phosphate buffer 5–50 mM); T = 10–20 °C; 10 min	4 Natural waters with different DOC (1.2–3.7 mg L^{-1}) and alkalinity (0.7–4.1 mM) k_{O3} = 1.6 ± 1.0 M^{-1} s^{-1} k_{OH} = 3.3–9.8 × 10^9 M^{-1} s^{-1}	40–77	Huber et al. (2003)

(*continued on next page*)

Table 8 (*continued*)

Pharmaceutical	Group/type/use	Conc. in water[a] ($\mu g\ L^{-1}$)	Experimental conditions	Observations	Removal %	References
		0.13 ± 0.03	Pilot plant (2 $m^3\ h^{-1}$) $[C]_o$ = 0.13 $\mu g\ L^{-1}$ $[O_3]$ = 5–15 $mg\ L^{-1}$ pH = 7.2; 18 min	[DOC] = 23.0 $mg\ L^{-1}$; DQO = 30.0 $mg\ L^{-1}$; DBO_5 = 2.8 $mg\ L^{-1}$; Microorganism disinfection (*clostridium*, *streptococci*, *E. Coli*). Economic assessment	>62	Ternes et al. (2003)
		–	$[C]_o$ = 2 $\mu g\ L^{-1}$ $[O_3]$ = 1.0–5.0 $mg\ L^{-1}$ Molar ratio: $(O_3:H_2O_2)$ = 2:1 10 min	Surface and ultrapure water	99.4	Zwiener and Frimmel (2000)
Ketoprofen	Anti-inflammatory	0.3	Laboratory scale $[O_3]$ = 0.23 mM; pH = 7.8–8.7 $[C]_o$ = 335 $ng\ L^{-1}$	Characterized and filtered wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	69 =15 (TOC)	Rosal et al. (2008)
			Laboratory scale $[O_3]$ = 0.23 mM $[C]_o$ = 346 $ng\ L^{-1}$ $[H_2O_2]$ = 20 mM, 0.15 mL (30% w/v) every 5 min in 5L		70 >90 (TOC)	
Lincomycin	Antibiotic, macrolides	-	$[C]_o$ = 0.5 mM $[O_3]_o$ = 0.4 mM pH = 5.5–7.5 [*t*-BuOH] = 10 mM	k_{O3} = 1.53 × $10^5\ M^{-1}\ s^{-1}$ (pH 3) k_{O3} = 4.93 × $10^5\ M^{-1}\ s^{-1}$ (pH6.7) k_{OH} = 4.37 × $10^9\ M^{-1}\ s^{-1}$ (pH 5.5) k_{OH} = 4.59 × $10^9\ M^{-1}\ s^{-1}$ (pH 7.5) without toxicity in 1 h and regardless of pH	100 (in 2 min) <10 (TOC in 180 min)	Andreozzi et al. (2006)
Metronidazole	Antibiotic, antibacterial	0.2	Laboratory scale $[O_3]$ = 0.23 mM; pH = 7.8–8.7 $[C]_o$ = 188 $ng\ L^{-1}$	Characterized and filtered wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	91 =15 (TOC)	Rosal et al. (2008)
			Laboratory scale $[O_3]$ = 0.23 mM $[C]_o$ = 212 $ng\ L^{-1}$ $[H_2O_2]$ = 20 mM, 0.15 mL (30% w/v) every 5 min in 5 L		92 >90 (TOC)	
Naproxen	Anti-inflammatory	0.10 ± 0.01	Pilot plant (2 $m^3\ h^{-1}$) $[C]_o$ = 0.1 $\mu g\ L^{-1}$ $[O_3]$ = 5–15 $mg\ L^{-1}$ pH = 7.2; 18 min	[DOC] = 23.0 $mg\ L^{-1}$; DQO = 30.0 $mg\ L^{-1}$; DBO_5 = 2.8 $mg\ L^{-1}$; Microorganism disinfection (*clostridium*, *streptococci*, *E. Coli*). Economic assessment	>50	Ternes et al. (2003)
		0.33–0.39	Laboratory scale $[O_3]$ = 0.23 mM; pH = 7.8–8.7 $[C]_o$ = 334 $ng\ L^{-1}$	Characterized and filtered wastewaters: 10 domestic and 8 urban Subproducts: low molecular weight oxalates and carboxylates	>93 =15 (TOC)	Rosal et al. (2008)
			Laboratory scale $[O_3]$ = 0.23 mM $[C]_o$ = 389 $ng\ L^{-1}$ $[H_2O_2]$ = 20 mM, 0.15 mL (30% w/v) every 5 min in 5 L		>94 >90 (TOC)	

[a] Usual concentrations detected in water according to authors.
[b] Yasojima et al. (2006) and Kim et al. (2009).

activated carbon considerably enhances diclofenac mineralization (-95% of the TOC removed in 120 min) and completely eliminates the toxicity.

Gómez-Pacheco et al., 2011 investigated the effectiveness of ozone and technologies based on the simultaneous use of ozone–hydrogen peroxide, ozone-activated carbon, and ozone-biological treatment in the removal of tetracyclines (TCs) from water. The results obtained showed, regardless of the TC under study, TC degradation was completed after 10 min of ozonation. A slight decrease in total organic carbon and toxicity was observed with longer TC ozonation treatment time. The presence of H_2O_2 during TC ozonation considerably increased the TC removal rate. Moreover, the O_3/H_2O_2 system mineralized a high fraction of the total organic carbon. The presence of activated carbon during ozonation increased the TC removal rate and also produced a decrease in the concentration of TOC and a reduction in toxicity.

3.3.2. AOPs based on UV radiation

The excellent capacity of hydroxyl radicals to oxidize organic compounds has led researchers to explore their photochemical generation. In nature, it is common to find compounds that can decompose by photochemical reactions from solar light application. This degradation depends on the radiation wavelength (k), compound molar absorption capacity (e), and quantum yield (U) (Kari et al., 1995), which are related by the following equation:

$$U_k = \frac{k_k}{2{:}303 E_k e_k} \quad (1)$$

k_k, degradation kinetic constant at a given k (s^{-1}); E_k: energy emitted by the source (Einstein s^{-1} m^{-2}); e_k: absorption coefficient of the compound at the k in question (m^2 mol^{-1}); U_k: quantum yield at the k in question (mol $Einstein^{-1}$).

The most widely used radiation for photolysis has a k of 200–400 nm, i.e. in the ultraviolet spectrum region. The structure of the molecule will determine whether it is capable of absorbing a given type of radiation and increasing its energy to reach an ex- cited state, possibly reaching bond rupture and hence degradation. If compounds are not degraded by direct photolysis, they may be indirectly degraded by radical generation. This type of AOP offers multiple advantages over non-photochemical technologies, as follows: (i) some contaminants undergo direct photolysis; (ii) the addition of chemical reagents is not required; (iii) it reduces the amount of certain oxidants needed in combined systems; (iv) it is less affected by drastic pH changes.

Most pharmaceuticals are photoactive, i.e., they absorb luminous radiation. Various studies have demonstrated that numerous pharmacologically active compounds can be photodegraded, since they generally contain aromatic rings, heteroatoms, and other functional groups that allow absorption of solar radiation or produce reactions with photosensitizing species that induce their photodegradation in natural water (Boreen et al., 2003; Lin and Reinhard, 2005).

The effectiveness of direct photooxidation is governed by the contaminant absorption spectrum and the quantum performance of the process. However, when H_2O_2 is added during photooxidation, the predominant mechanism derives from the high reactivity of hydroxyl radicals, which permits lower doses of UV radiation to be used in comparison to direct photooxidation (Rosenfeldt and Linden, 2004).

Irradiation with UV light is a well-established method for water disinfection (Hijnen et al., 2006) and is increasingly used to treat pharmaceutical-polluted wastewater (Kang et al., 2004; Lazarova and Savoye, 2004). Hence, photolysis and photochemical processes play important roles in the removal of pharmaceutical compounds from water (Boreen et al., 2003; Lin and Reinhard, 2005).

Ibuprofen, one of the antiinflammatories most frequently found in water, does not effectively absorb by solar light, ruling out the use of direct photooxidation (Tixier et al., 2003; Packer et al., 2003). Naproxen, another common antiinflammatory, can be photodegraded (Lin and Reinhard, 2005), but the products of naproxen photooxidation are more toxic than the original pharmaceutical (Boscá et al., 1990, 2001; Jiménez et al., 1997; Packer et al., 2003; Brigante et al., 2004; Isidori et al., 2005). The photodegradation of triclosan and triclocarban also produces subproducts (chlorodioxins and chloroanilines, respectively) that are highly toxic and persistent in water (Aranami and Readman, 2007).

Diclofenac rapidly decomposes by direct photooxidation, indicating that this pathway is one of its main degradation mechanisms (Buser et al., 1998; Boscá et al., 2001; Poiger et al., 2001; Andreozzi et al., 2003b). However, the UV/H_2O_2 system was found to degrade this drug with 39% mineralization after 90 min of treatment (Vogna et al., 2004), and the Photo-Fenton system completely oxidized diclofenac after 60 min and achieved total mineralization after 100 min of solar irradiation (Ravina et al., 2002; Pérez-Estrada et al., 2005).

Studies on clofibric acid photodegradation showed that the presence of nitrates and humic acids in water increases pharmaceutical degradation rate due to radical generation (Andreozzi et al., 2003b). The presence of TiO_2 in photocatalytic treatments also facilitates the degradation of clofibric acid into numerous aro- matic and aliphatic subproducts (Doll and Frimmel, 2004, 2005).

The photochemical behavior of carbamazepine has been studied by various research groups (Andreozzi et al., 2002, 2003b; Vogna et al., 2004; Doll and Frimmel, 2004, 2005; Lam and Mabury, 2005), who reported that epoxycarbamazepine is the main degradation subproduct, among other compounds that are yet to be identified. Direct carbamazepine photolysis in ultrapure water gives rise to numerous intermediates during photodegradation, including acridine, which has a marked mutagenic and carcinogenic character (Chiron et al., 2006).

Alternatively, it is also possible to use another type of radical species to photodegrade pharmaceutical, i.e., $SO_4^{\bullet-}$ radical, which has proven to be more effective than the $HO^{\bullet}$ radical to eliminate the cytarabine antineoplastic (Ocampo-Pérez et al., 2010).

Buxton et al. (1988) demonstrated that the photogeneration of highly reactive species, such as $HO^{\bullet}$ radicals, limits the persistence in aqueous medium of some of the subproducts generated by the direct photolysis of pharmaceutic compounds, finding specific degradation rate constants ranging from 10^7 to 10^{10} M^{-1} s^{-1}. Consequently, there is considerable interest in processes based on the generation of $HO^{\bullet}$ radicals for pharmaceutical removal from waters. Table 4 summarizes key studies on the use of AOPs based on UV radiation to remove pharmaceuticals from water.

3.3.3. AOPs based on gamma radiation

Radiolysis is based on the generation of radicals, highly reactive electrons, ions, and neutral molecules through the exposure of water to high energy electromagnetic radiations (Ferradini, 1961; Burns and Sims, 1981; Getoff, 1996), using X-rays, gamma radiation emitted by radioactive sources of ^{60}Co ($t_{1/2}$ = 5 271 yr, E_c = 1 173, and 1 332 MeV) and ^{137}Cs ($t_{1/2}$ = 30 170 yr, E_c = 0-661 MeV), or electron linear accelerators.

Ionizing radiations gradually lose their energy through inelastic collisions with water molecules, which they ionize or excite. Highly active radicals are formed by a complex mechanism, including e^-_{aq}, $H^{\bullet}$, and $HO^{\bullet}$, ions (e.g., H_3O^+), and stable molecules (e.g., O_2, H_2, and H_2O_2) (Eq. (2) and Fig. 1). All of these chemical species are primary radiolytic products that subsequently modify and degrade the pollutant molecules (Woods and Pikaev, 1994). The degradation or mineralization process of micropollutants in water takes place in the following stages: (a) formation of active free radicals

Table 4
Key publications on pharmaceutical removal from water by AOPs based on UV radiation.

Pharmaceutical	Group/type/use	Treatment	Experimental conditions	Observations	Removal %	References
Oxytetracycline Doxycycline Ciprofloxacin	Antibiotics	UV UV/H_2O_2	LP-Hg lamp $[C]_0$ = 5 LM Toxicity assay with *vibrio fischeri* bacteria Types of water: ultrapure, treated water, surface and wastewater	The fastest degradation was observed in treated water The toxicity increased in UV photolysis, while in UV/H_2O_2 process, toxicity increased first, and then decreased	UV <30% UV/H_2O_2: 100% after 11448 mJ cm^{-2}	Yuan et al. (2011)
Metronidazole Dimetridazole Tinidazole Ronidazole	Antibiotics	UV	LP-Hg lamp T = 25 °C Toxicity assay with *vibrio fischeri* bacteria Types of water: ultrapure, groundwater, surface and wastewater	Very low quantum yields obtained for the four nitroimidazoles Degradation by-products are more toxic than the initial products Similar reaction rate constants were obtained in different types of water	83% 82% 76% 73%	Prados-Joya et al. (2011)
Carbamazepin (CBZ)	Antiepileptic	UV	LP and MP lamp	Removal of SMX and DCF was largely attributed to direct photodegradation	<5%	Lekkerkerker-Teunissen et al. (2012)
Diclofenac (DCF)	Anti-inflammatory	UV/H_2O_2	UV doses ranged from 300–700 mJ cm^{-2}	CBZ was not appreciably removed by UV or UV/H_2O_2 treatment	>80%	
Sulfamethoxazole (SMX)	Antibiotic		[H_2O_2] = 0–10 mg L^{-1}		>90%	
Amoxicillin	Antibiotic	UV UV/H_2O_2	Low pressure Hgarc-UV lamp $I = 8 \times 10^{-7}$ Einstein L^{-1} s^{-1} T = 20 °C [H_2O_2] = 0.4–10 mM Antibacterial activity was measured using *Escherichia coli* bacteria	Pseudo-first order kinetics Low mineralization was achieved in both processes UV/H_2O_2 process effectively eliminated antibacterial activity	UV <20% (60 min) UV/H_2O_2 99% (20 min)	Jurg et al. (2012)
Tetracycline	Antibiotics	UV	$[C]_0$ = 10–100 mg L^{-1}	The degradation rate constants were pH-dependent and favored at pH 10	100% (in 120 min)	Gomez-Pacheco et al. (2012)
Oxytetracycline		(254–320 nm)	[Humic acid] = 6–80 mg L^{-1}	The TCs photooxidation rate was higher in natural water than in ultrapure water		
Chlortetracycline		800 W	Natural waters: Surface, groundwater, wastewater Toxicity assay with *vibrio fischeri* bacteria	The toxicity was lower than in the original solution after 60 min of treatment		
Amoxicillin Ampicillin Cloxacillin	Antibiotics	UV/TiO_2 UV/H_2O_2/TiO_2	$[C]_0$ = 104, 105, and 103 mg L^{-1} respectively pH = 5 DOC = 8.4 mg L^{-1} TiO_2 (Anatase > 99%) UV(365 nm)	Pseudo-first order kinetics k = 0.007, 0.003 and 0.029 min^{-1}, respectively The highest degradation was achieved at pH 11	UV/TiO_2 20%, 10%, 60% UV/TiO_2/H_2O_2 ≈100%	Elmolla and Chaudhuri (2010)
Propranolol metronidazole	b-Adrenergic Antibiotic	UV-A (254 nm) UV-C (365)	$[C]_0$ = 50–10 mg L^{-1} Irradiation time: 0.5–24 h	Synthetic water Toxicity measurement by using Allium test 12% of the organic matter content was photodegraded Degradation byproducts showed a less toxicity than the original pollutants	≈50% (8 h)	Dantas et al. (2010)
Carbamazepine	Antiepileptic	UV/H_2O_2	$[C]_0$ = 7.1 mg L^{-1} LP-Hg lamp (2.51 × 10^{-6} E s^{-1}) [H_2O_2] = 5 and 10 mM; pH = 7.6; T = 298 K; 1, 2, and 5 min	Synthetic water Toxicity measurement (Rotoxkit) with algae and with rotifera No toxic byproduct generation	100 (in 2 min)	Andreozzi et al. (2004)
Clofibric acid	Lipid regulator metabolite	UV/H_2O_2	LP-Hg lamp (17 W); (2.7 × 10^{-6} Eins s^{-1}); $[C]_0$ = 1.0 × 10^{-3} M; $[H_2O_2]_0$ = 1, 10, 20, and 30 mM; T = 298 K; 60 min	k_{OH} = 2.38 × 10^9 M^{-1} s^{-1} Φ = 1.08 × 10^{-2} mol E^{-1} (pH = 5.5) $[TOC]_0$ = 120 mg L^{-1}	100 90 (TOC)	Andreozzi et al. (2003a)
		UV/H_2O_2	$[C]_0$ = 11.2 mg L^{-1} LP-Hg lamp (2.51 × 10^{-6} E s^{-1}) [H_2O_2] = 5 and 10 mM; pH = 7.6; T = 298 K; 1, 2, and 5 min	Synthetic water Toxicity measurement (Rotoxkit) with algae and with rotifera No toxic product generation	100 (in 2 min)	Andreozzi et al. (2004)

Table 4 (*continued*)

Pharmaceutical	Group/type/use	Treatment	Experimental conditions	Observations	Removal %	References
Diclofenac	Anti-inflammatory	UV/H_2O_2	$[C]_0$ = 2.8 mg L^{-1} LP-Hg lamp (2.51 × 10^{-6} E s^{-1}) $[H_2O_2]$ = 5 and 10 mM; pH = 7.6; T = 298 K; 1, 2, and 5 min	Synthetic water Toxicity measurement (Rotoxkit) with algae and with rotifera No toxic product generation	100 (in 2 min)	Andreozzi et al. (2004)
Lincomycin	Antibiotic, macrolides	UV/H_2O_2	$[C]_0$ = 0.03 mM LP lamp (254 nm) [t-BuOH] = 10 mM	k_{OH} = 4.37 × 10^9 M^{-1} s^{-1} (pH 5.5) k_{OH} = 4.59 × 10^9 M^{-1} s^{-1} (pH 7.5) No toxic product generation	= 80 (in 5 min)	Andreozzi et al. (2006)
Metronidazole	Antibacterial antibiotic	UV UV/H_2O_2 Fenton Photo-Fenton	LP lamp 254 nm (1.5 mW cm^{-2}); MP[a] lamp 200–400 nm (1.9 mW cm^{-2}); $[C]_0$ = 6.0 [M; pH 6.0; $[H_2O_2]$ = 25 and 50 mg L^{-1} $[Fe^{2+}]$ = 3, 6, and 12 [M (pH 3.5)	U = 0.0033 mol E^{-1} LP U = 0.0080 mol E^{-1} MP Pseudo 1st order kinetics for UV and UV/H_2O_2 2nd order kinetics for Fenton and Photo-Fenton	6–12 58–67 53–76 74–94	Shemer et al. (2006)
Ofloxacin	Antibiotic, fluoroquinolones	UV/H_2O_2	$[C]_0$ = 560 [g L^{-1} LP-Hg lamp (2.51 × 10^{-6} E s^{-1}) $[H_2O_2]$ = 5 and 10 mM; pH = 7.6; T = 298 K; 1, 2, and 5 min	Synthetic water Toxicity measurement (Rotoxkit) with algae and with rotifera No toxic product generation	100 (in 2 min)	Andreozzi et al. (2004)
Penicillin G (procaine benzylpenicillin)	b-Lactam antibiotic	Photo-Fenton	pH = 3; 30 min; $[Fe^{3+}]$ = 1.5 mM; $[H_2O_2]$ = 25	COD_0 = 600 mg L^{-1} TOC_0 = 450 mg L^{-1} [a] BOD_5 = 53 mg L^{-1}	56 (COD) 42 (TOC)	Arslan-Alaton and Gurses (2004)

(in times in the order of 10^{-10} s); (b) diffusion of radicals (in times in the order of 10^{-5} s), and c) induction of reactions between primary radiolytic products and pollutant molecules.

$$H_2O \rightarrow [2.8]HO^{\bullet} + [2.7]e^-_{aq} + [0.6]H^{\bullet} + [0.72]H_2O_2 + [2.7]H_3O^+ + [0.45]H_2 \quad (2)$$

The values in square brackets in Eq. (2) are the number of molecules formed with the absorption of 100 eV of energy in an air-free medium at pH 7.0 (Spinks and Wood, 1990).

Processes based on high-energy electromagnetic radiations are more economic and effective on a large scale than other techniques used to remove persistent micro pollutants from waters (Kurucz et al., 1995; Bolton et al., 1998). In contrast to UV radiation, where a proportion of photons are absorbed by the pollutant, there is a high probability that gamma radiation energy is absorbed by water molecules, producing their radiolysis and generating the abovementioned species (Fig. 1).

Among the primary species produced by the interaction of gamma radiation and water molecules, e^-_{aq}, $H^{\bullet}$ act as strong reducing agents and $HO^{\bullet}$ as a strong oxidant, leading some authors to describe these processes as Advanced Oxidation/Reduction Processes (AO/RPs) (Cooper et al., 2008). The proven efficacy of this technology to remove persistent pollutants from water has prompted research interest in its usefulness for the removal of pharmaceutical products (Ikehata et al., 2006; Cooper et al., 2008; Song et al., 2008; Yu et al., 2008a). It is applied in some treatment plants in various countries but is not in widespread use due to inadequate knowledge of its performance and the necessary safety conditions (Huber et al., 2003; Cooper et al., 2008; Song et al., 2008).

Little research has been published on the use of gamma radiation to remove pharmaceuticals from water. In 2008, it was reported that b-lactams, which are not removed by conventional wastewater treatments, are destroyed by this novel technology (Song et al., 2008); after irradiation with a electron linear accelerator and a radioactive source of ^{137}Cs, the combination of oxidizing ($HO^{\bullet}$) and reducing ($H^{\bullet}$, e^-_{aq}) species achieved 81%, 92%, and 95% effectiveness in the removal of penicillin V, penicillin G, and amoxicillin, respectively. Table 5 summarizes the most important publications on pharmaceutical removal by gamma radiation.

Cooper et al. (2008) studied the effects of gamma radiation on three types of contaminants that pose major challenges to treatment plants: (i) disinfection subproducts (trihalomethanes [THMs]), (ii) pharmaceutical products, representative of emerging contaminants, and (iii) the most common natural radical scavenger, natural organic matter. The pharmaceuticals selected for this research were sulfonamides, a family of antibiotics that prevails in aqueous medium in concentrations up to 1.9 [g L^{-1} (Hirsch et al., 1999; Halling-Sørensen, 2001; Boyd et al., 2003; Ternes et al., 2004). The values of specific reaction rate constants obtained for four sulfonamides were of the order of 8 × 10^9 M^{-1} s^{-1} for the $HO^{\bullet}$ radical, and around 2 × 10^{10} M^{-1} s^{-1} for the hydrated electron (e^-_{aq}). The effectiveness of the $HO^{\bullet}$ radical to remove the four sulfonamides reached 53%, whereas e^-_{aq} obtained percentage removal of 70% in some cases. Results showed that the activity of both radicals AO/RPs may offer a major advantage over systems that only generate $HO^{\bullet}$ radicals.

Sánchez-Polo et al. (2009) investigated the decomposition and mineralization of nitroimidazoles in waste and drinking water using gamma irradiation. They found that the decomposition yield was higher under acidic conditions than in neutral and alkaline media. Results obtained showed that, at appropriate concentrations, H_2O_2 accelerates nitroimidazole degradation by generating additional $HO^{\bullet}$; however, when the dosage of H_2O_2 exceeds the optimal concentration, the efficacy was reduced. The presence of t-BuOH ($HO^{\bullet}$ radical scavenger) and thiourea ($HO^{\bullet}$, $H^{\bullet}$ and e^-_{aq} scavenger) reduced

Table 5
Key publications on pharmaceutical removal from water by gamma radiation.

Drug	Group/type/use	Experimental conditions	Observations	Removal	References
Iopromide	X-ray contrast media	e-Beam (ELV-8, 2.5 MeV, 100 kW) Dose: 500–50000 Gy $[C]_o$ = 10–100 μM Additives: H_2O_2, SO_3^{2-}, HCO_3^-	Degradation of Iopromide was carried out via oxidation and reduction mechanism e_{aq}^- mainly attacks the iodo-group, whereas HO˙ non-selectively reacts with the side chains of the benzene ring rather than the iodo-group	100% Dose 25000 Gy	Kwon et al. (2012)
Chloramphenicol (CPL)	Antibiotic	e-Beam and source of ^{60}Co $[C]_o$ = 0.1–1 M pH 4–8 Dose rate 91 Gy min^{-1} Solutions were saturated with: N_2O, N_2(*t*-BuOH), N_2, air	HO˙ radical can add onto the CPL aromatic ring or can abstract H-atom from the side chain The toxicity increased as a function of dose up to 1.0 kGy	100% Dose (2500 Gy)	Csay et al. (2012)
Ketoprofen	Anti inflammatory	^{60}Co c-rays source Dose rate: 80 Gy min^{-1} $[C]_o$ = 10 mM pH = 2.6–11.2 *T* = 22 °C Additives: H_2O_2, CH_3OH, CO_3^{2-}, NO_3^- thiourea, humic acid	Chemical oxygen demand and total organic carbon content measurements on irradiated aerated solutions showed that using irradiation technology ketoprofen can be mineralized. The initial toxicity of the solution monitored by the *Daphnia magna* test steadily decreased with irradiation	100% Dose (5000 Gy)	Illes et al. (2012)
Diclofenac	Anti inflammatory	^{60}Co c-rays source Dose: 300–1000 Gy $[C]_o$ = 20–50 mg L^{-1} pH = 2.6–11.2 *T* = 22 °C Additives: H_2O_2, CH_3OH, CO_3^{2-}, NO_3^- thiourea, humic acid	The degradation of diclofenac took place via oxidation by HO˙ radicals and reduction by e_{aq}^- and H˙ The presence of humic acid and NO_3^-, did not affect the degradation efficiency	62.9% (pH 11.2) 75.6% (pH 6.31) 85.0% (pH 2.6) Dose (700 Gy)	Liu et al. (2011)
Diclofenac	Anti inflammatory	^{60}Co c-rays source Dose rate: 25 Gy min^{-1} $[C]_o$ = 0.1 mM Solutions were saturated with N_2O, *t*-BuOH or O_2.	The toxicity of the solutions decreased with absorbed dose and complete mineralization was achieved with prolonged irradiation	100% Dose: 1000 Gy	Homlok et al. (2011)
Ibuprofen (IBP)	Anti inflammatory	^{60}Co c-rays source Dose: 200–1100 Gy $[C]_o$ = 28.3 mg L^{-1} pH = 1.4–11 *T* = 22 °C Additives: H_2O_2, CH_3OH, CO_3^{2-}, NO_3^- thiourea, humic acid	Low concentrations of H_2O_2 and humic acid enhanced the IBP degradation, whereas the addition of CH_3OH, CO_3^{2-}, NO_3^- and thiourea restrained the IBP degradation	92% (pH 1.45) 90% (pH 4.23) 89% (pH 6.29) 85% (pH 8.94) 82% (pH 11.05)	Zheng et al. (2011)
Carbamazepine Ketoprofen	Anticonvulsant	^{60}Co c-rays source	All pharmaceuticals were persistent to biodegradation by sludge activated treatment	100%	Kimura et al. (2012)
Mefenamic acid	Anti inflammatory	Dose: 50–20000 Gy	k_{CPL} = 9.7 × 10^9, k_{OH} = 5.6 × 10^9, k_{OH} = 4.0 × 10^9, k_{OH} = 1.0 × 10^{10}, k_{OH} = 9.0 × 10^9 M^{-1} s^{-1}, respectively	Dose: 2000 Gy	
Clofibric acid	Anti inflammatory	$[C]_o$ = 5 μM			
Diclofenac	Lipid regulator	pH = 7.45			
	Anti inflammatory	Type of water: wastewater [TOC] = 50 mg L^{-1}			
Metropolol	b-Blocker	e-Beam and source of ^{60}Co $[C]_o$ = 1 mg L^{-1} Dose up to 50 kGy Saturation with N_2	Different effectiveness between e-Beam and ^{60}Co No pH influence (3–11). Excipient influence (ClNa, 1,2propanediol, and mannitol). Subproduct quantification Computational simulation k_{OH} = 5.2 × 10^9 M^{-1} s^{-1} ke$^-$ (aq) = 6.8 × 10^9 M^{-1} s^{-1}	100% Dose (e-Beam): 57 kGy 98.5% Dose (^{60}Co): 50 kGy	Slegers and Tikquin (2006)

Table 5 (*continued*)

Drug	Group/type/use	Experimental conditions	Observations	Removal	References
Cefaclor	Antibiotic, b-lactam	Source of ^{60}Co	Effectiveness calculation (G-value)	100% Dose: 1 kGy;	Yu et al. (2008a)
		$[C]_o$ = 30 mg L^{-1}	Kinetic study	TOC: 100% saturation with	
		Use of MeOH and thiourea	Influence of initial concentration	N_2O. Dose: 20 kGy	
		Saturation with O_2 and N_2O	Effect of radical scavengers		
Sulfamethoxazole	Antibiotic, sulfonamide	Source of ^{60}Co and e-Beam	k_{OH} = 8.5 ± 0.3 × 10^9 M^{-1} s^{-1}	53 ± 8%	Cooper et al. (2008)
		Dose up to 8.5 kGy	ke^-_{aq} = 1.00 ± 0.03 × 10^{10} M^{-1} s^{-1}	(due to HO)	
		Saturation with N_2O to isolate HO		71 ± 10%	
		High concentrations of *t*-BuOH to isolate e^-_{aq}		(due to e^-_{aq})	
		Low concentrations of *t*-BuOH at acidic pH to isolate H			
Amoxicillin	Antibiotic, b-lactam	e-Beam (E = 8 MeV); 3–5 Gy pulses every 2–3 ms; Source of ^{137}Cs;	k_{OH} = 6.94 ± 0.44 × 10^9 M^{-1} s^{-1}	95% (combination of HO and e^-_{aq})	Song et al. (2008)
		Irradiation rate (4.2-0.5) × 10^3 Gy h^{-1}		(Dose: 2.56 ± 0.06 kGy to	
		$[C]_o$ = 1 mM; Ultrapure water;	ke^-(aq) = 3.47 ± 0.07 × 10^9 M^{-1} s^{-1}	degrade 50%)	
		pH 7 (phosphate buffer 5 mM)			
Penicillin G (Procain benzylpenicillin)	Antibiotic b-lactam	Saturation with: N_2 or N_2O for e^-_{aq}or HO experiments	k_{OH} = 7.97 ± 0.11 × 10^9 M^{-1} s^{-1}	92% (combination of HO and e^-_{aq})	
		respectively	e^-_{aq} = 3.92 ± 0.10 × 10^9 M^{-1} s^{-1}	(Dose: 2.41 ± 0.11 kGy to	
		Presence of isopropanol 0.10 M (H and HO radical scavenger) in e^-_{aq} experiments		degrade 50%)	
Penicillin V (Phenoxymethyl penicillin)	Antibiotic b-lactam	Products: mixture of phenolic compounds	k_{OH} = 8.76 ± 0.28 × 10^9 M^{-1} s^{-1}	81% (combination of HO and e^-_{aq})	
			e^-_{aq} = 5.76 ± 0.24 × 10^9 M^{-1} s^{-1}	(Dose: 2.30 ± 0.02 kGy to degrade 50%)	

the nitroimidazole dagradation rate, indicating that degradation of this pollutant can take place *via* two pathways: oxidation by HO radicals and reduction by e^-_{aq} and H. The nitroimidazole removal rate was slightly lower in subterranean and surface waters than in ultrapure water and was markedly lower in wastewater.

Ocampo-Perez et al., 2011 determined the effectiveness of gamma radiation to degrade the antineoplastic cytarabine in aqueous solution. Cytarabine degradation in the presence of Cl^-, CO_3^{2-}; NO_3^-; NO_2^-, and humic acid showed a decrease in degradation rate with the increase in species concentration, largely due to competition of cytarabine with the above species for the reactive radicals generated, mainly HO radicals. Cytarabine degradation was slightly improved by the presence of small amounts of H_2O_2, which acted as promoter of HO radicals. Similar results were obtained by Velo-Gala et al. (2012) and Lòpez Peñalver et al., 2012 for the degradation of a contrast medium (diatrizoate) and tetracyclines (tetracycline, chlortetracycline, and oxytetracycline), respectively.

3.3.4. Electro-oxidation without and with active chlorine generation

The most popular electrochemical technique for wastewater remediation is the electrochemical oxidation, frequently called anodic oxidation (AO) when non-chloride solutions are treated (Sirés and Brillas, 2012). This procedure involves the oxidation of pollutants in an electrolytic cell by: (i) direct electron transfer to the anode, and (ii) indirect or mediated oxidation with heterogeneous radicals formed from water discharge at the anode, such as physisorbed OH or chemisorbed "active oxygen". The existence of these species allowed the proposal of two approaches (Comninellis, 1994; Marselli et al., 2003; Panizza and Cerisola, 2009): (i) the electrochemical conversion, where the refractory organics are selectively transformed into biodegradable compounds like carboxylic acids by chemisorbed "active oxygen", and (ii) the electrochemical combustion, where the organics are mineralized by physisorbed OH.

For wastewater treatment, high cell voltages are applied to achieve the simultaneous oxidation of pollutants and water, maintaining the anode activity, which has a strong influence on the selectivity and efficiency of the process yielding either electrochemical conversion or combustion depending on the anode material. Comninellis (1994) explained this different behavior by a model that assumes the existence of "active" and "non-active" anodes, respectively. Examples include Pt, IrO_2, and RuO_2 for the former and PbO_2, SnO_2, and boron-doped diamond (BDD) for the latter. In both kind of anodes, denoted as M, water is oxidized leading to the formation of physisorbed hydroxyl radical (M(OH)). In the case of "active" anodes, this radical interacts so strongly with their surface and it is transformed into the chemisorbed "active oxygen" or superoxide MO.

The MO/M pair is a mediator in the electrochemical conversion of organic compounds. Conversely, the surface of "non-active" anodes interact so weakly with M(OH) and this radical directly reacts with organics until total mineralization is achieved.

In AO, different reactive oxygen species (ROS) are produced, like heterogeneous OH, H_2O_2 from its dimerization and O_3 from water discharge at the anode surface, although the physisorbed OH is the strongest oxidant.

The BDD anode is the most potent "non-active" electrode known (Marselli et al., 2003 and Panizza and Cerisola, 2009) and it is considered the most suitable anode for treating organics by AO. When BDD is used, other weaker oxidizing species like peroxodisulfate, peroxodicarbonate, and peroxodiphosphate can be competitively formed with ROS from oxidation of the electrolyte ions like bisulfate, bicarbonate and phosphate, respectively (Panizza and Cerisola, 2009).

A very different behavior is found when the wastewater contains chloride ions since the generated active chlorine species such as Cl_2, $HClO/ClO^-$, and ClO_2^- can attack the organics in competition

Table 6
Percentage of TOC decay obtained for the electro-oxidation of synthetic pharmaceutical solutions with or without active chlorine species under selected conditions.

Pharmaceutical	Anode	Solution	Electrolytic system	% TOC removal	References
17α-ethinylestradiol	Ti/SnO_2	100 mL of 2.0 mg L^{-1} drug in 0.2 M Na_2SO_4, pH 6.2	Stirred tank reactor, 60 mA for 480 min	79	Feng et al. (2010)
17β-estradiol	BDD	250 mL of 0.5 mg L^{-1} drug in 0.1 M Na_2SO_4, pH 6.0	Stirred tank reactor, 350 mA for 270 min	94	Yoshihara and Murugananthan (2009)
Clofibric acid	Pt BDD	100 mL of 179 mg L^{-1} drug in 0.05 M Na_2SO_4, pH 3.0	Stirred tank reactor, 300 mA for 420 min	36 98	Sirés et al. (2006)
Diclofenac	BDD	100 mL of 30 mg L^{-1} drug in: —0.1 M Na_2SO_4 —0.1 M NaCl	Stirred tank reactor with three electrodes, 4 V vs. SCE[b] for 240 min	 83 72	Zhao et al. (2009)
	Pt BDD	100 mL of 175 mg L^{-1} drug in 0.05 M Na_2SO_4, phosphate buffer pH6.5	Stirred tank reactor, 300 mA for 360 min	46 97	Brillas et al. (2012)
Enrofloxacin	BDD	600 mL of 1.6 g L^{-1} drug in 0.05 M Na_2SO_4, pH 3.0	Undivided flow cell, liquid flow rate 2.5 L min^{-1}, 3.9 A for 15 h	83	Guinea et al. (2009)
Ibuprofen	BDD	200 mL of 1.75 mM drug in 0.035 M Na_2SO_4	Stirred tank reactor, 30 mA cm^{-2} for 360 min	75 92	Ciriaco et al. (2009)
Ketoprofen	BDD	250 mL of 5 mM drug in 0.1 M Na_2SO_4, pH 6.0	Stirred tank reactor, 49.5 mA for 1020 min	100	Murugananthan et al. (2010)
Oxytetracycline hydrochloride	Ti/RuO_2	50 mL of 950 mg L^{-1} drug in phosphate buffer, pH 5.45	Stirred tank reactor, 100 mA for 120 min	100[c]	Rossi et al. (2009)
Paracetamol	Pt BDD Ti/IrO_2 Ti/SnO_2 BDD	100 mL of 157 mg L^{-1} drug in 0.05 M Na_2SO_4, pH 3.0 50 mL of 1 mM drug in 0.025 M Na_2SO_4, pH 7.8	Stirred tank reactor, 300 mA for 360 min Divided plug flow reactor, liquid flow rate 1 mL min^{-1}, 200 mA for 210 min	17 98 1 40 73	Brillas et al. (2005) Waterston et al. (2006)
	Ti/RuO_2 BDD	100 mL of 1 mM drug in 0.1 M NaCl	Stirred tank reactor, 80 mA for 300 min	28 55	Boudreau et al. (2010a)
Sulfamethoxazole	BDD	45 mL of 1 mM drug in —0.1 M $NaClO_4$ —0.1 M NaCl	Stirred tank reactor, 20 mA for 300 min	78 69	Boudreau et al. (2010b)
	Ti/RuO_2-IrO_2	200 mL of 100 mg L^{-1} drug in 0.1 M Na_2SO_4, pH 3.9–10.0	Stirred tank reactor, 1500 mA for 60 min	90[c]	Zhang et al. (2009)

with radicals (Panizza and Cerisola, 2009). The additional generation of ClO_3^- and even the total transformation of the chlorinated ions into ClO_4^- have been suggested (Bergmann et al., 2009; Sánchez-Carretero et al., 2011). This procedure is usually called electro-oxidation with active chlorine and is based on the direct oxidation of Cl^- ion at the anode to yield soluble chlorine which diffuses away from the anode to be rapidly hydrolyzed and disproportionated to hypochlorous acid and chloride ion.

Table 6 collects the percentage of TOC removal for the AO and/or electro-oxidation with active chlorine of various pharmaceuticals under selected conditions. The BDD anode yields a much higher mineralization degree than other "non-active" anodes such as PbO_2 and SnO_2, as well as "active" anodes such as Pt and RuO_2, regardless of the presence/absence of chloride ion in the electrolytic system.

4. Conclusions

Although pharmaceuticals have been present in water for decades, their levels in the environment have only recently begun to be quantified and acknowledged as potentially hazardous to ecosystems. The pollution produced by pharmaceutical products in surface and ground waters has been acknowledged by many countries as an environmental problem. Nevertheless, there are currently no legally regulated maximum permitted concentrations of pharmaceuticals in the environment, despite their unknown impact on the environment and human health.

The amounts of various pharmaceuticals detected in inlet and outlet water of various WWTPs confirmed that many of these substances are not effectively removed by these treatments. Thus, conventional treatment systems are unable to completely remove a large amount of the pharmaceutical micropollutants present in urban wastewaters. More effective and specific treatments are required to reduce the environmental and potential impact of these pollutants. Among these treatments, both adsorption on activated carbons and advanced oxidation/reduction processes are under research and have yet to be applied on an industrial scale, since there is a lack of good quality data on the mechanisms involved, the influence of operational variables, the reaction kinetics, and reactor design issues.

The use of activated carbon to adsorb contaminants from pharmaceuticals (mainly aromatic compounds) has recently begun to be studied. The main advantage of using activated carbon to re- move pharmaceuticals is that it does not generate toxic or pharmacologically active products. According to the literature, activated carbons generally demonstrated a high capacity to adsorb pharmaceuticals which depended on the activated carbon type, pharmaceutical composition, and solution chemistry,

Research over the past few years has shown AOPs to be very effective in the degradation of numerous organic and inorganic compounds including pharmaceuticals. Considerable research interest has recently been shown in the application of O_3, O_3/OH^-, O_3/H_2O_2, and O_3/activated carbon systems for the removal of pharmaceuticals from water. In some cases, the removal yields obtained from direct ozonation were low (8–30%), and they

increased up to 100% when the ozonation was carried out in the presence of H_2O_2 or activated carbon.

Most pharmaceuticals are photoactive and, therefore, they absorb luminous radiation. Various studies have demonstrated that numerous pharmacologically active compounds can be photodegraded, since they generally contain aromatic rings, heteroatoms, and other functional groups that allow absorption of solar radiation or produce reactions with photosensitizing species that induce their photodegradation in natural water. In general, the removal percentages obtained by using UV radiation alone were quite low (lower than 30%), and they reached values around 100% when adding H_2O_2, TiO_2, or TiO_2/activated carbon.

Little research has been published on the use of gamma radiation to remove pharmaceuticals from water. The proven efficacy of this technology to remove persistent pollutants from water has prompted research interest in its usefulness for the removal of pharmaceutical products. The pharmaceuticals removal yield values reported by using this technology are higher than 50%, and, in most cases studied, these values run into 100%. These high removal yields are accompanied by a reduction in both TOC and solution toxicity.

In the last years, the decontamination and disinfection of waters by means of direct or integrated electrochemical processes are being considered as a very appealing alternative due to the significant improvement of the electrode materials and the coupling with low-cost renewable energy sources. Many electrochemical technologies are currently available for the remediation of waters contaminated by refractory organic pollutants such as pharmaceutical micropollutants, whose presence in the environment has become a matter of major concern.

5. Future outlook

Pharmaceutical products and their degradation byproducts are being increasingly detected in the environment. The rapid development of sensitive analytical techniques in recent years is enabling their analysis at trace levels and investigation of their fate and transformation pathways, which are still largely unknown. Information about the toxic effects of many of these compounds and their degradation byproducts on living organisms is also very limited. Scientific research on these subjects is increasing with the objective of providing a clearer picture of the behavior and toxicity of pharmaceutical compounds in the environment, as well as to assist the development of the means to safeguard living organisms from any adverse health effect originated from these widely used substances.

Monitoring the occurrence, transformation, and fate of pharmaceuticals in the environment poses two important challenges:

1. Development and optimization of analytical methods for different environmental samples. Approximately 150 pharmaceutical compounds have already been monitored in the environment, mainly in aqueous samples. The range of pharmaceuticals and metabolites encompassed by analytical methods must be enlarged, especially for environmental samples with the most complex matrices. The sensitivity of the methods must be optimized to enable easy, inexpensive, and environmentally friendly analysis of these compounds.
2. Environmental risk assessment studies must be performed for several pharmacologically active compounds and their metabolites and, especially, for mixtures of such compounds, because many pharmaceutical products are simultaneously present in the environment.

Sewage systems serving as the disposal path for most contaminants naturally excreted by humans constitute the main route of transfer of such compounds. Centralized municipal wastewater-treatment plants are, therefore, important point sources of micropollutants in the aquatic environment in the ''Urban Water Cycle''. Because the wastewater collection and treatment infrastructure enables only partial removal of pharmaceuticals, many processes have been integrated to attempt to control these pollutants. Questions related to the high cost of advanced treatment methods and options such as separation source and separate collection of urine are also extremely relevant with regard to energy use, cost, and removal, although high-volume wastewater collection is not an effective solution. Further studies are required to develop sustainable solutions for future generations.

Acknowledgements

The authors are grateful for the financial support provided by MEC-DGI and FEDER (CTQ2011-29035-C02-02), and the Junta de Andalucía (RNM3823 and RNM7522).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2013.07.059.

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