# Pharmaceuticals in the aquatic environment: sources, effects, treatment methods

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**Abstract**
Residues of daily usage products, including pharmaceuticals and personal care products (PPCPs) as well as pure organic compounds, particularly endocrine-disrupting chemicals (EDCs), can migrate to surface water ecosystems from point sources, e.g. wastewater treatment plants. Although the majority of these substances are present in water at very low concentrations, they started to be considered "new" hazardous environmental pollutants. Their presence in water became an important problem in the late twentieth century, when the production of organic chemicals increased. Certain low-molecular weight organic substances present in water ecosystems at low concentrations are likely to have adverse effects on animals and humans. Even short-term exposures of aquatic organisms to EDCs, especially at early developmental stages, can induce a variety of negative physiological effects. Even though direct negative effects caused by exposure have not been demonstrated, active substances of numerous drugs can accumulate in the tissues and reach higher trophic levels. Modern high-throughput separation and detection techniques, including gas/liquid chromatography coupled with mass spectrometry detectors (GC/LC-MS), allow detecting and quantifying trace amounts of micro-pollutants acting as EDCs in complex biosamples and technological processes, particularly during wastewater treatment. Moreover, limits of detection for many organic micro-pollutants have been determined. New measures to remove pharmaceuticals from sewage should be designed, as many treatment plants are not prepared to effectively eliminate such pollutants. The aim of the present study was to review the literature data regarding the presence of pharmaceuticals, PPCPs and EDCs in the environment (particularly aquatic) and to present the methods of sample determinations and sewage treatment. Additionally, low efficiency of traditional wastewater treatment processes was discussed.

**Keywords:** pharmaceuticals, endocrine disruptors, sewage treatment

## Introduction

### Pharmaceuticals in the environment

Active substances of pharmaceuticals are ubiquitous in the environment, yet only recently they started to be considered hazardous pollutants. Aquatic [1] and soil [2] ecosystems have been found to be particularly sensitive to such substances. The main sources of pollutants are municipal (generated by households) and hospital wastes as well as inadequately utilized, expired medicines, supplements and personal care products. Still another source is animal farms where steroid compounds (acting as growth promoters) and prophylactic antibiotics to prevent possible infections are commonly added to the feed [3].

During recent decades, studies on the effects of pollutants on the aquatic environment focused almost exclusively on priority pollutants, especially toxic and carcinogenic ones. The term "priority substances" was introduced by the Water Framework Directive, in Poland – by the water law. The list of these substances is included in the addendum X to the Water Framework Directive; detailed

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lists of substances and their limit values are determined at the level of legislation of individual member countries. According to the requirements of the Directive, priority substances should be determined cautiously taking into account scientific evaluation of potential risks. Moreover, priority substances include the group of hazardous priority substances, for which complete elimination of discharge and emission is required. While the „ecological policy" should generally restrict the introduction of any substances to natural ecosystems, particularly those impairing their functioning (e.g. biogenes accelerating eutrophization), in the case of priority substances, this policy should be stricter and gradually reduced (according to the principles of balanced development). Moreover, the introduction of hazardous priority substances to ecosystems should be completely eliminated, so their concentrations correspond to natural background concentrations (which is near zero in the case of synthetic substances).

Besides the priority substances listed in the addendum to the Directive, the legislation of member countries can also specify some other substances particularly harmful for the aquatic environment (in Poland, e.g. DDT), whose presence in water can lead to similar actual and legal consequences as the presence of priority substances. The list of priority substances is supplemented according to the current state of knowledge; since 2012, it also includes pharmaceutical active substances, i.e. 17 alpha-ethynylestradiol (EE2), 17 beta-estradiol (E2) and diclofenac. Table 1 presents the list of priority substances included in the addendum to the Water Framework Directive.

The priority substances constitute a small proportion of compounds, which can negatively affect the environment. There is a group of bioactive substances that have only recently been considered environmental pollutants [4,5]. This group includes drug ingredients (analgesics, antibiotics, anti-inflammatory drugs, synthetic hormones), active substances in personal care products, nutritive substances, sun protective agents, hormonal promoters of growth and many others. The above substances were chosen mainly due to their potential consequences, such as toxicity in the aquatic environment and mutations inducing the development of drug-resistant bacteria [6,7,8]. The compounds in question and their biologically active metabolites are being continuously introduced to the environment [9,10,11]. Amongst all the micropollutants that can occur in water and sewage, endocrine disrupting compounds (EDCs) have been of particular interest. They include natural and synthetic chemical compounds impairing the activity of hormones (mainly steroid ones) in humans and animals [12]. Hormones pose a high risk, as well. Ethynylestradiol (EE2) found in contraceptives induces the estrogenic effect already at low concentrations. Fish males exposed to EE2 in a concentration of 4.0 ng/dm$^3$ lose their secondary sex characteristics; moreover, their hormonal balance is impaired, which results in disappearance of gender differences (feminization of males), and ultimately impairs reproduction [13].

The majority of pharmaceuticals are not removed during water treatment, due to their physicochemical properties. Active substances from medicines can accumulate in the tissues and be transferred to higher trophic levels with the food chain, which makes them extremely hazardous to health or life of organisms, including humans. Estrone, estradiol, ethynylestradiol accumulate in the adipose tissue of aquatic organisms. The bioaccumulation factor (BAF) for fish ranges from 2.22 for estrone to 2.83 for ethynylestradiol [14].

The literature data indicate that a definite effect of toxicity for fish, alga and bacteria is observed at a water concentration of pharmaceuticals lower than 1 mg/dm$^3$ [15]. A review by Braush et al. contains thorough information on toxic effects of some selected groups of pharmaceuticals on aquatic organisms. One hundred and 50 substanc-

es from 35 pharmaceutical groups induced acute toxicity and 65 substances from 20 groups resulted in chronic toxicity. Moreover, the review presents standard and advanced ecotoxicological tests performed on aquatic organisms, demonstrating toxic effects at the molecular level (e.g. inhibition of cyclooxygenase) and at the population level ( changes in behaviour, impact on reproduction) [16]. To date, the studies regarding aquatic fauna (fish, crustaceans, molluscs) have focused on hormones, antibiotics, analgesics and antidepressants. The average water concentrations observed ranged from 0.1 to 100ng/g dry mass [17]. The most recent studies concentrate on consequences of exposure to a particular pharmaceutical substance rather than the presence of pharmaceuticals in the environment.

Brodin et al. have found that oxazepam changes the behaviour and feeding efficacy of wild perch (*Perca fluviatilis*), which is essential for a given population. The authors conclude that antidepressants in surface water can have ecological and evolutionary consequences [18]. Moreover, research regarded the distances to sewage treatment plants to determine the effects of exposure along a concentration gradient. Metcalfe et al. have demonstrated correlations between the introduction of antidepressants to water and accumulation of *Pimephales promelas* in organisms [19]. Fluoxetine is toxic for algae - $EC_{50}$ ranges from 24 to 4339 mg/dm$^3$ and for bentos - $LC_{50}$-15÷43 mg/kg sediment within 10 days ($LC_{50}$- medial lethal concentration). The toxicity of sertraline, another antidepressant, for green algae is at $EC_{50}$ 12 - 764 mg/dm$^3$ [20].

Diclofenac, an extremely popular drug, is characterized by the highest toxicity amongst non-steroidal anti-inflammatory drugs and shows chronic toxicity. Laboratory tests performed in rainbow trout (*O.mykiss*) have revealed acute hepatotoxicity of the drug as well as renal and branchial lesions (testing was carried out in acute toxicity, the exposure to the therapeutic substance was 28 days [21].

**Concentrations of the selected substances in the environment**

Not all active substances that get to treatment plants with sewage are completely removed during biological purification. The mean concentration of acetylsalicylic (ASA) acid in wastewater in Germany was 0.22 g/dm$^3$ [22]. In surface waters, concentrations were below the limit of detection. However, ASA readily transforms into its more active form – salicylic acid, ortho-hydroxyhippuric acid and gentianic acid metabolite. ASA metabolites were detected in samples of influent sewage in concentrations of 54 μg/dm$^3$, 6.8 μg/dm$^3$, 4.6 μg/dm$^3$, respectively [23]. Moreoevr, effective removal of the majority of active substances studied by purification of municipal wastewater was observed; only salicylic acid was detected in very low concentrations in sewage and rivers. On the other hand, substantially higher concentrations of salicylic acid were determined in sewage in Greece and Spain ( up to 13 μg /dm$^3$) [24,25], which could be caused by the use of ASA as a keratolytic agent in dermocosmetics and as natural food preservative [26]. A popular drug, paracetamol ( N-(4-hydroxyfenyl) acetamide) is also easily decomposed and removed by sewage treatment. In Germany, paracetamol was detected in less than 10% of sewage and was not detected in river water containing treated wastewater [22]. In the United Stated, in the study of 142 underflows sensitive to municipal sewage pollutants, paracetamol was detected in 17% of all samples of max. concentration of 10 μg/dm$^3$ [27]. During long-term study monitoring waste and surface water samples in Berlin, diclofenac was detected, the maximum concentration (3.02μg/ dm3) was found in influent water while the lowest level ( 2.51 μg/dm$^3$) in effluent water. The low index of removal, only 17%, shows inability of treatment plants to effectively remove this active substance, which was confirmed by [28,29]. Moreover, diclofenac is often detected in the amounts below μg/dm$^3$ in

sewage and surface waters in Austria, Brazil, Germany, Greece, Spain, Switzerland and the United States [30,31,22,28,32].

Ibuprofen is broken down in the human body to metabolites, which together with the basic form occur in water and sewage [33,34]. Although ibuprofen was found to be removed during sewage treatment, particularly carboxy-ibuprofen, the concentration of carboxy-ibuprofen remained at the similar level as that in the influent. The concentrations of ibuprofen in municipal sewage and rivers were lower, compared to concentrations of diclofenac [31]. In Spain, the concentrations of ibuprofen in samples of wastewaters were found to be 1.5 μg/dm$^3$, 0.87μg/dm$^3$ and 85.0 μg/dm$^3$. In the same study, its high concentration, up to 2.5μg/dm$^3$, was detected in surface waters.

Numerous studies were carried out, e.g. in Germany [35], Switzerland [36] and USA [37], to search for the presence of antibacterial drugs in surface waters and sewage. The levels of macrolide antibiotics, clarithromycin, dehydroerythromycin (erythromycin metabolite), roxithromycin, lincomycin, sulphonamides (sulfamethoxazole, sulfadimethoxine and sulfathiazole), fluoroquinolones (ciprofloxacin, norfloxacin and enrofloxacin), chloramphenicol, tylosin and trimethoprim, were low (μ/dm$^3$) in samples of sewage and surface waters. Moreover, penicillin was not detected in surface and underground waters, as it is readily hydrolysed [10].

Due to their hydrophilic properties, the majority of pharmaceuticals are retained very well in sewage systems. Polar groups (carboxyl, aldehyde and amine) of these compounds can interact with organic substances contained in sewage and cause increases in concentrations of pharmaceutical substances in sewage sludge [39]. Since no effective analytical methods have been available, the majority of studies concentrated on detection of pharmaceuticals in sewage [40]. Therefore, most of biological treatment plants show high efficiency in removal of drugs, resulting from sorption and sedimentation of these products from the sludge [15]. Drugs accumulated in sludge are likely will probably be carried to the terrestrial environment, causing serious environmental problems [41]. The studies have revealed that levels of drugs in sewage sludge ranged from several μg/kg to mg/kg, depending on collection sites and properties of the compound [42]. Due to possible bacterial mutations, the attention was mainly paid to antibiotics [44]. Study findings have demonstrated that tetracyclines, fluoroquinolones, sulphonamides and macrolides are the key groups of antibiotics detected in sludge samples in the United States [43] and Canada [42].

**Quantitative determinations (analytical methods)**

The majority of studies on drugs in sludge were confined to the development of analytical methods and devices in individual treatment plants [45]; therefore, the data regarding the presence of pharmaceuticals in sludge are scarce. Pharmaceutical in sludge should be studied more thoroughly due to their high concentrations and potentially negative effects on humans and animals [46]. The essential element of analyte quantification in complex matrices of environmental samples is the selection of an appropriate method of separation of chemically similar pharmaceuticals and the use of suitably sensitive and selective detectors (allowing determining even very low concentrations of pharmaceuticals in the presence of substances of similar physicochemical properties).

The use of technologically advanced devices for single- and multi-dimensional separation, in particular, gas chromatography and liquid chromatography coupled with various types of mass spectrometers ( i.e. MS-MS, APCI-MS, ESI-MS, CE-MS), enabled to detect various compounds, including drugs, in matrices of environmental samples. MS-MS detection is currently often

used due to increased analytical sensitivity and selectivity in complex matrices, such as sewage. GC-MS allows determination of such therapeutic substances as diclofenac, diazepam, ibuprofen, naproxen, and acetylsalicylic acid [47]. Thanks to LC-MS, antibiotics (penicillins, tetracyclines, sulphonamides, macrolides), ciprofloxacin, norfloxacin, naproxen, diclofenac, ibuprofen, diazepam can be determined [48]. Thin layer chromatography and immunochemical methods are applied less commonly [49].

**Treatment of pharmaceutical-contaminated sewage**

At present, the majority of municipal treatment plants are not appropriately prepared to remove drugs and their metabolites in mechanical and biological processes [50]. Conventional biological wastewater treatment plants use three-chamber biological reactors (denitrification, aerobic and anoxic chamber) or SBR reactors. During traditional biological treatment, thanks to changeable conditions in the chambers, microorganisms of active sludge remove contaminants by decomposing into simpler substances or using as building materials and reserves. SBR reactors are often applied for removal of drugs under laboratory conditions [51]. Moreover, membrane bioreactors are increasingly common. The membrane technology is considered to be the most effective in removing various contaminants flowing into treatment plants.

Furthermore, studies to evaluate the effectiveness of membrane methods have recently been carried out [52]. The membrane module is integrated with the device consisting of suitably coupled media streams of a classical bioreactor and the membrane separation centre.

In water treatment technologies, pressure techniques of membrane separation, e.g. microfiltration, ultrafiltration, and processes using electrical energy (e.g. electrodialysis) are most commonly used [52]. The essence of the process is to separate water or sewage (which are a solvent) from the substances analysed. The stream of water or sewage is passed through the semi-permeable membrane, where the solvent is separated from the contaminant. Membrane reactors are characterised by high effectiveness in removing bacteria and high quality of an eluate. Moreover, they enable to reduce the required area even by 50%, compared to biological reactors, and show a low consumption of energy. Sewage treatment can be improved by using modern method, such as UV exposure with chlorination or ozonation. Ozonation is an effective method for removal of micro-contaminants caused by diclofenac, carbamazepine and sulfamethoxazole [52].

The other effective methods of removal of toxic contaminants from sewage are photodegradation processes (photocatalytic oxidation) with the use of sunlight, UV radiation or photocatalysts) metal oxides, e.g..$TiO_2$, ZnO, $SnO_2$, and sulphates, e.g. ZnS, CdS). Photocatalysis is a free radical process, causing the formation of highly reactive hydroxyl radicals ($OH^{\cdot}$), which are poorly selective and capable of decomposition of a huge number of organic compounds. The products of degradation are intermediate substances, $CO_2$ and $H_2O$, and inorganic compounds [55]. $TiO_2$, characterised by high phytochemical stability, activity and resistance to changes in reaction environment, is most widely used [56]. Moreover, adsorption methods are commonly applied due to their high effectiveness in drug removal [57].

The study on removal of ibuprofen using active carbon obtained from cork waste, active carbon was activated chemically with water vapour and $K_2CO_3$ as well as with $K_2CO_3$ alone. Carbon activated with water vapour and $K_2CO_3$ was characterised by higher adsorption capacity due to more developed microporous structure. The assets of this method also include a wide range of operation, pH 2-11 and easy recovery ( even up

to 100%) [58]. A high effectiveness in reposing naproxen was observed while using the material made of apricot wastes, activated with $ZnCl_2$ [59]. The use of powdered activated carbon (PAC), 1 g/dm$^3$ in the membrane bio-activator to remove pharmaceuticals from sewage enabled to reduce ChZT by 95%, ammonium nitrogen by 70-80%, and phosphorus by about 80% [60]. He effectiveness depended on the kind of pharmaceutical removed. Moreover, granular active carbon )GAC) was applied. However, the process wad found to be less effective due to competition with other organic compounds present in sewage [61].

Another group of widely used absorbents is clays, i.e. montmorllonite, bentonites with quaternary ammonium cations - the micro-porous materials modified with $CO^{2+}$, $Cu^{2+}$ or $Ni^{2+}$[62]. The above additives increased the efficiency of removal of salicylic and clofibric acid, carbamabazepines and caffeine. Furthermore, aliphatic polyamides [63] were studied as effective adsorbents of ethynylestradiol (EE2); the findings are comparable to the use of commercial AMBERLTEXAD 4, despite of non-porous structure and a markedly smaller area. The use of 24.1L deposit containing 1.0g PA612 and contact with EE2 for 0.8-1.0 min, enabled the removal of 30 mg/dm$^3$ ethynylestradiol to the levels below the limit of HPLC detection. Still another group of absorbents is silica. Mesoporous MCM-41 silicates containing $Ni^{2+}$ demonstrated high effectiveness in removing naproxen from water [64].

**Summary**

Numerous studies focusing on consequences of occurrence of pharmaceuticals in the environment have been published. Their findings demonstrate many adverse effects of the presence of drugs and personal care products on different organisms. Environmental pharmaceuticals has been considered a global issue and not only concerning developed countries. The majority of people are not aware of dangers resulting from continuous and uncontrolled supply of drugs into aquatic ecosystems. Many widely available pharmaceuticals have been detected in treated sewage as well as surface and ground water in the concentration of up to mg/dm$^3$. Since standard methods of treatment cannot remove the pharmaceuticals, personal care products (PPCPs) or endocrine-disrupting compounds (EDCs) from sewage and surface waters, new and effective methods of water and sewage treatment should be searched for. At present, the studies focus on membrane, photocatalytic oxidation and adsorption methods. Unfortunately, the technologies used currently are effective only for removal of some groups of pharmaceuticals. It is essential to analyse thoroughly the occurrence of active pharmaceutical substances in sludge in order to eliminate the migration of these compounds to the soil. A multi-level approach to studies regarding consequences of occurrence of drugs in the environment and their effects on organism, especially in aquatic ecosystems, is needed.

**Table 1.** List of water policy priority substances with suggested amendments (Journal of Law of the European Union of 24.12 2008 [65]

| **Water policy priority substances** | **Substances that can be potentially considered as priority or hazardous priority substances** | **Suggested to be addend to the list of priority substances (since 31.01.2012)** |
|---|---|---|
| 1. Alachlorine | 1. AMPA | **A. Plant preservatives:** |
| 2. Anthracene | 2. Bentazone | 1. Aclonifen |
| 3. Atrazine | 3. Bisphenol-A | 2. Bifenox |
| 4. Benzene | 4. Dicofol | 3. Cypermethrin |
| 5. bromium diphenylether | 5. EDTA | 4. Dicofol |
| 6. cadmium and its compounds | 6. Free cyanide | 5. Heptachlor |
| 7. C10-13chloralcanes | 7. Glyphosate | 6. Quinoxyfen |
| 8. Chlorfenwinfos | 8. Mecoprop (MCPP) | **B. Biocidal substances:** |
| 9. Chlorpiryfos (ethyl chlorpiryfos) | 9..Musk xylene | 1. Cibutrin |
| 10. 1,2-dichloroetan | 10. Perflurooctanesulfonic acid | 2. Dichlorovos |
| 11. Dichloromethane | 11. Quinoxyfen | 3. Terbutryn |
| 12. DEHP | 12. Dioxins | **C. Industrial chemical compounds** |
| 13. Diuron | | 1. PFOS |
| 14. Endosulfan | | 2. HBCDD |
| 15. Fluoranten | | **D. Combustion by-products**: |
| 16. Hexachlorbenzene | | 1. Dioxins and digoxin-derivates |
| 17. Hexachlorbutadiene | | **E. Substances of pharmaceutical industry** |
| 18. Hexachlorcycloheaane | | 1. 17 alpha-ethynylestradiol (EE2) |
| 19. Isoproturon | | 2. 17 beta-estradiol (E2) |
| 20. Lead and its compounds | | 3. diclofenac |
| 21. Mercury and its compounds | | |
| 22. Naphthalene | | |
| 23. Nickel and its compounds | | |
| 24. Nonylphenol | | |
| 25. Octylphenol | | |
| 26. Pentachlorbenzene | | |
| 27. Pentachlorophenol | | |
| 28. Simazine | | |
| 29. Tributyltin compounds | | |
| 30. Trichlorbenzenes | | |
| 31. Trichloromethane (chloroform) | | |
| 32. Trifluralin | | |

**Table 2**. Concentrations and determination methods of active substances of the selected drugs in environmental samples

| Group | Active substance | Effects on humans or selected pathogens | Sample | Collection site | Method of determination | | | Concentration detected | Source |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Preparation | Chromatographic technique | Detector | | |
| Non-steroidal anti-inflammatory drugs | Diclofenac | Derivative of aminophenol acetic acid of strong anti-inflammatory, analgesic and antipyretic action. It acts mainly by inhibiting cyclooxygenases: constitutive COX-1, responsible for synthesis of prostaglandins of physiological functions rather than induced COX-2, responsible for synthesis of pro-inflammatory prostaglandins at the site of inflammation | Surface water | Germany | SPE | GC | MS MS/MS | 0.05 µg/dm$^3$ | [66] |
| | | | Surface water | USA | SPE | | MS | 10 µg/dm$^3$ | [67] |
| | | | Surface water | Switzerland | LLE | | MS | 12 ng/dm$^3$ | [69] |
| | | | Potable water | Germany | SPE | | MS | 0.4-0.9 µg/dm$^3$ | [68] |
| | | | Sewage | Canada | SPE | HPLC | ESI-MS | 10-20 ng/dm$^3$ | [48] |
| | Naproxen | Derivative of naphthaleneacetic acid showing anti-inflammatory and antipyretic effects. It acts mainly by inhibiting Cyclooxygenase COX-1 rather than COX-2, | Surface water | Germany | LLE SPE | HPLC | CE-MS MS | 0.5 µg/dm$^3$ | [70] |
| | | | Surface water | Germany | SPE | GC | MS MS/MS | 0.39 µg/dm$^3$ | [66] |
| | | | Surface water | USA | SPE | | MS | 10 µg/dm$^3$ | [71] |
| | | | Sewage | Canada | SPE | HPLC | ESI-MS | 5-20 ng/dm$^3$ | [48] |
| | Ibuprofen | Derivative of propionic acid of anti-inflammatory, analgesic and antipyretic effects. Action as above | Surface water | Switzerland | SPE | GC | MS | 0.1-1.0 µg/dm$^3$ | [69] |
| | | | Sewage | Canada | SPE | HPLC | ESI-MS | 5-20 ng/dm$^3$ | [48] |
| | | | Surface water | Germany | LLE SPE | HPLC | CE-MS MS | 0.6 µg/dm$^3$ | [70] |
| | | | Sea water | North Sea | LLE | GC | MS | 0.6 ng/dm$^3$ | [72] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Steroid hormones | Estrone | Ketone-hydroxyl derivative of estrane. A steroid estrogen- effects similar to estradiol. . | Surface water | USA | SPE | GC | MS | 0,01 µg/dm$^3$ | [71] |
| | | | Sludge | Germany | LLE SPE | HPLC GC | MS | 0.02 µg/dm$^3$ | [74] |
| | 17β- estradiol | The most potent form of estrogen in mammals. In humans, it is produced mainly by ovaries and placenta. It is also produced by the adipose tissue in men and women after menopause. | Sludge | Germany | LLE SPE | LLE SPE | MS | 0.02 µg/dm$^3$ | [73] |
| | | | Surface water | Poland | SPE | HPLC | DAD UV | 0,51 ng/dm$^3$ | [73] |
| | 17α- ethynylestradiol | Synthetic estrogen, a component of the majority of contraceptives currently used. It replaces physiological estrogens, whose production is inhibited during the use of such drugs | Surface water | Poland | SPE | | UV DAD | 0.47 ng/dm$^3$ | [73] |
| | | | Sludge | Germany | LLE SPE | LLE SPE | MS | 0.09 µg/dm$^3$ | [74] |
| Antibacterial drugs | Sulphonamides | Sulfanilic acid amides are analogues of PABA, competitively inhibit the action of the enzyme synthesising dihydrofolic acid. | Surface water | USA | SPE | HPLC | MS | 0.07-15 µg/dm$^3$ | [37] |
| | Trimethoprim | Chemotherapeutic agent inhibiting dihydrofolic acid reductase | Sea water | - | LLE SPE | | APCI-MS | 2.5 µg/dm$^3$ | [75] |
| | Sulfadiazines | *p*-amino-benzenesulfonic acid amide used as a bacteriostatic agent. | Sea water | - | LLE SPE | HPLC | APCI-MS | 2.5 µg/dm$^3$ | [75] |
| Drugs regulating lipid metabolism | Clofibric acid | Drug reducing the level of lipids used to fight high levels of triglycerides and cholesterol in blood. | Sea water | North Sea | LLE | GC | MS | 0.013 µg/dm$^3$ | [72] |
| | | | Surface water | Germany | SPE | | FID | 0.049 µg/dm$^3$ | [68] |

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