Issue of Pharmaceutical Compounds in Water and Wastewater: Sources, Impact and Elimination

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PHARMACEUTICALS are designed to have a physiological effect on humans and animals in trace concentrations. Persistence against biological degradation and their biological activity are key properties of these pollutants. Increasing consumption of pharmaceutical active compounds (PhACs) and their discharge to the municipal wastewater via excrete are a growing danger for water quality and thus for the health of citizens.

The entire discharge volume of medicines into the sewage net and the inefficiency of suitable wastewater treatment solutions to face such a problem, leads to high pharmaceuticals content in the drinking water. Due to its low degradability, 80% of these substances are raw discharged by excretion and flushed to the toilets and sewers to the sewage plants, where no rejection takes place, thus leading to growth of bacterial resistance. This leads to high pharmaceuticals content in the drinking water, people assimilate these substances, resulting in every time higher difficulties when treating common illnesses.

The aim of the present article is to review the issue of PhACs in the environment. The review focuses on the source, presence, fate, elimination, and treatment of PhACs in water and wastewater. This review includes: characteristics, occurrence and pathways of PhACs in water and wastewater, fate in the oriented sanitation, environmental and public health impacts. Furthermore, preventing pharmaceuticals in drinking-water, treatment technologies for their removal, knowledge gaps and future research for pharmaceuticals in drinking-water are also discussed. Advanced oxidation techniques, biological treatment systems, separation and treatment of urine for PhACs removal as effective tools are evaluated.

Keywords: Pharmaceuticals, Personal care products, Wastewater, Industrial wastes, Hospital wastewater, Urine and Feces.

Nowadays the increasing consumption of Pharmaceuticals and Personal Care Products (PPCPs) and its discharge to the municipal wastewater via excrete are a growing danger for water quality and thus for the health of citizens. The extended
use of antibiotics, hormones, endocrines, plasmids, analgesics, blood lipid regulators, non-steroidal anti-inflammatory drugs, beta blockers, and many other pharmaceutically active compounds (PhACs) is raising concern about its incidence in the environment and the spread of antibiotic resistance among bacterial populations against pharmaceuticals.

In the recent years, the environmental occurrence of PhACs, human and veterinary medication, has been a source of growing concern. Once these compounds are in aquatic systems, it has been shown that they can adversely affect both aquatic and non aquatic organisms and thus the ecosystem. Current water and wastewater treatment systems in most cases do not completely remove low concentrations of PhACs. Although the concentrations of these PhACs are well below the medical dose, there are concerns that the presence of mixtures of pharmaceuticals in drinking water may have long term consequences to human health especially to children, women of child bearing age, elderly and people with compromised immune systems.

Pharmaceuticals have been detected in ground and surface water, drinking water, tap water, ocean water, sediments and soil. Pharmaceuticals end up in soil, surface waters and eventually in ground and drinking water after their excretion (in un-metabolized form or as active metabolites). The sources are: humans or animals via urine or faeces, through the sewage system and into the influent of wastewater treatment plants. Veterinary pharmaceuticals; on the other hand contaminates directly in soil via manure and surface and ground waters by runoff from fields.

Pharmaceuticals are designed to have a physiological effect on humans and animals in trace concentrations. Persistence against biological degradation and their biological activity are key properties of these pollutants. They retain their chemical structure long enough to do their therapeutic work. Because of their continuous input, they could remain in the environment for a long time and their presence there is considered dangerous in both low and high concentrations. Their active ingredients are selected or designed because of their activity against organisms.

Thus, it is expected that they will be effective against bacteria, fungi and possibly non target higher organisms. For many compounds their potential effects on humans and aquatic ecosystems are not completely understood, especially if it is considered that they co-exist in mixtures with other chemicals forming the so-called chemical “cocktails”. The possible fates of pharmaceuticals, as all other xenobiotics; once they enter the aquatic environment are mainly three: (a) the compound is ultimately mineralized to carbon dioxide and water, (b) the compound does not degrade readily because it is lipophilic and is partially retained in the sedimentation sludge and (c) the compound metabolizes to a more hydrophilic molecule. The later passes through the wastewater treatment plant and ends up in the receiving waters (which are surface waters, mainly rivers). These compounds exhibit the highest persistence in the environment.

Pharmaceuticals released in the environment may impose toxicity (the extent of which depends on the specific compound in question) virtually on any level of the biological hierarchy, *i.e.* cells, organs, organisms, population, ecosystems, or the ecosphere. In addition to toxic effects, certain classes of pharmaceuticals like antibiotics may cause long-term and irreversible change to the micro-organisms genome, making them resistant in their presence, even at low concentrations. Meanwhile, the presence of the endocrine disrupting compounds (EDCs) in aquatic systems has caused considerable concern as these compounds are known to disrupt the human endocrine system (8).

*Characteristics of human pharmaceuticals*

**Introduction**

Human pharmaceuticals are consumed in high quantities worldwide. The consumption is in the range of tons per year per one pharmaceutical compound depending on the size of a country. The expectations are that these amounts will only keep increasing because of the improving in health care system and longer life expectations of people. The diversity of the human pharmaceuticals is large. In the Netherlands, for instance, there are 12000 human pharmaceuticals approved (authorized) (9).

Pharmaceuticals administered (it is a medical term, in other words consumed) by humans after required action in the body get excreted with urine and faeces as a parent (original) compound and usually as a number of metabolites. The toilet wastewater (consisting of urine and faeces flushed with clean water; often called black water) is mixed with other wastewater streams forming finally a sewage that enter the municipal sewer. In a sewage treatment plant (STP) effluents, many pharmaceuticals compounds do not get removed to a sufficient degree. This is because of the configurations of the current STPs that are not efficient enough to remove these micro pollutants. Consequently, they are present in the effluents of STPs, enter the surface water where they may pose effects onto aquatic life.

**Pharmaceutical metabolism and excretion**

Drug metabolism is the biochemical modification or degradation that takes place; usually, through specialized enzymatic systems. Drug metabolism often, converts lipophilic chemical compounds into more readily excreted polar products. Its rate is an important determinant of the duration and intensity of the pharmacological action of such drugs. Drug metabolism can result in toxification or detoxification / the activation or deactivation of the chemical. While both occur, the major metabolites of most drugs are detoxification products.

Drugs are almost all xenobiotics. Pharmaceuticals undergo a number of enzymatic transformations (metabolism) in human tissues including liver, intestine, kidney and lung. The main part of metabolism occurs in liver. Every drug is metabolised to different degree resulting in more polar metabolites with loss of some or all pharmacological activity of the parent substance (10). More polar character of transformed pharmaceuticals enables their excretion, although unmetabolized compounds leave also human body. Urine and faeces are two.
excretion routes of pharmaceuticals. Faeces contain usually unabsorbed drugs (oral administration) or drugs metabolites excreted in the bile (10). In Fig. 1 a distribution of excreted 35 pharmaceutical compounds between urine and faeces is shown (Moffat et al., 2004). It can be stated generally that 30% of the compounds are excreted in faeces and 70% in the urine. Commonly, glucuronide and sulphate conjugates of the parent drugs are the major excreted metabolites. It is supposed that glucuronide and sulphate conjugates may be at least partially hydrolyzed in sewage, thus effectively increasing the excreted contribution to sewage concentrations of the parent drugs (11).

![Diagram showing excretion of pharmaceuticals in urine and faeces](image-url)

Fig. 1. Fraction of excreted pharmaceuticals (parent compounds and metabolites) in urine and faeces for selected compounds.

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Pharmaceutical occurrence and pathways in water and wastewater

Introduction
Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. Pharmaceuticals contain active ingredients that have been designed to have pharmacological effects and confer significant benefits to society. The occurrence of pharmaceuticals in the environment and the water cycle at trace levels (in the range of nano-grams to low micrograms per litre) has been widely discussed and published in literature in the past decade. The increase in detection is largely attributable to the advances in analytical techniques and instrumentation. Many surveys and studies have confirmed the presence of pharmaceuticals in municipal waste water and effluents, and these have been identified as a major source of pharmaceuticals in drinking-water.

More systematic studies will help to further our understanding of the transport, occurrence and fate of pharmaceuticals in the environment, especially drinking-water sources. Standardization of protocols for sampling and analyzing pharmaceuticals would help to facilitate the comparison of data.

Wastewater
Pharmaceuticlas are primarily introduced into the environment via human excretion, sewage effluent, improper drug disposal, agricultural runoff, and livestock and veterinary waste. The ubiquitous use of pharmaceuticals in various settings has resulted in a continuous discharge of pharmaceuticals and metabolites into the environment, leading to their “pseudopersistence” in the environment. Significant advancements in the sensitivity of detection and analytical technologies and methods have made it possible to detect very low concentrations of pharmaceuticals in the range of nanograms to low micrograms per litre in the water cycle. The presence of several pharmaceuticals in the sewage treatment plant (STP) effluents has been confirmed in e.g. Germany, The Netherlands, Switzerland, United Kingdom, France, Greece, Sweden, Italy, Spain, United States, Canada, Brazil, Egypt and Australia.

Hospital wastewater
Hospital wastewater is a significant source of pharmaceuticals such as antibiotics, anti-cancer agents and iodinated contrast media. The share of specific antibiotics used in hospitals may vary between few percent up to 90% of total emission. Most hospitals are directly connected to sewer system and no pretreatment process takes place. Also, nursing homes are significant point sources of some specific pharmaceuticals.

Sewage sludge
Some antibiotics were detected in sewage sludge such as fluoroquinolones, ciprofloxacin, norfloxacin. Recently other antimicrobials, sulfapyridine, sulfamethoxazole, trimethoprim, azithromycin, clarithromycin and roxithromycin in sewage sludge were detected in activated sludge up to 0.20 mg kg\(^{-1}\) of dry matter. From neutral and acidic drugs only diclofenac was quantified above the limit of quantification (0.2 – 0.45 mg kg\(^{-1}\)).

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Surface water

To be able to describe negative effects of pharmaceuticals on the aquatic organisms a lot of monitoring studies are being performed to determine the concentration of different pharmaceutical compounds found in various aquatic compartments. Pharmaceuticals are present in surface water inmeasurable concentrations. Their concentrations depend on the type of pharmaceutical and its active ingredient and aquatic environment compartment and vary roughly from tens to hundreds of nano-grams per liter (surface water) to tens of micrograms per liter in raw influent. Compounds found most often in surface water are:

- almost all X-ray contrast media,
- few pain killers
- few beta-blockers
- antiepileptics (carbamazepine and primidon)
- antibiotics
- anaesthetics

Different pharmaceuticals were detected in surface water in monitoring studies \(^{18}\) are given in Table 1.

Ground water

Sacher (2001) analyzed 105 ground water wells and in one third of the tested ground water samples, 39 pharmaceuticals from groups beta-blockers, analgesics, antiepileptics, antirheumatics, antibiotics, iodinated X-ray contrast and media could be detected. Carbamazepine was detected in 21 ground water samples at a concentration up to 1.1 μg.L\(^{-1}\)\(^{19}\). In a German monitoring program of 32 bank filtration samples and 22 surface water samples sulfamethoxazole was found at concentrations up to 0.079 μg.L\(^{-1}\) and diatrizoate up to 1.4 μg.L\(^{-1}\)\(^{14}\). The highest concentrations for ground water samples were found for iodinated contrast media iopamidol, up to 2.4 μg.L\(^{-1}\)\(^{20}\). Among other pharmaceutical compounds, analgesics phenanzone, propyphenanzone, dimethylaminophenazone and lipid regulators gemfibrozil were detected in ng range \(^{21,22}\).

Drinking water

Routine monitoring programmes to test drinking-water for pharmaceuticals have not been implemented, as is the case for regulated chemical and microbial parameters. Generally, data on the occurrence of pharmaceuticals in drinking-water have resulted from surveys or targeted research projects and investigations. Available studies have reported that concentrations of pharmaceuticals in surface waters, groundwater and partially treated water are typically less than 0.1 μg.L\(^{-1}\) (or 100 ng.L\(^{-1}\)) and concentrations in treated water are generally below 0.05 μg.L\(^{-1}\) (or 50 ng.L\(^{-1}\)).

As pharmaceuticals contain active ingredients that are designed to achieve specific pharmacological effects based on their biological reactivity and biochemical properties, their presence at trace concentrations in the water cycle


**TABLE 1. Pharmaceuticals detected in surface water monitoring studies (18).**

<table>
<thead>
<tr>
<th>Pharmaceutical group</th>
<th>Substance</th>
<th>Max concentration (ng.L(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td>Chlorotetracycline</td>
<td>690</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>730</td>
</tr>
<tr>
<td></td>
<td>Norfloxacin</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Oxytetracycline</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>Roxithromycin</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>Sulphadimethoxine</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Sulphamethazine</td>
<td>220</td>
</tr>
<tr>
<td></td>
<td>Sulphamethizole</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Sulphamethoxazole</td>
<td>1,900</td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim</td>
<td>710</td>
</tr>
<tr>
<td></td>
<td>Tylosin</td>
<td>280</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Codeine</td>
<td>1,000</td>
</tr>
<tr>
<td></td>
<td>Acetylsalicylic acid</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>1,100</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>Aminopyrine</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>Indomethacine</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Naprofen</td>
<td>390</td>
</tr>
<tr>
<td></td>
<td>Phenazone</td>
<td>950</td>
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<tr>
<td><strong>Antianginal</strong></td>
<td>Dehydronifedipine</td>
<td>30</td>
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<tr>
<td><strong>Antihypertensive</strong></td>
<td>Diltaizem</td>
<td>49</td>
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<tr>
<td><strong>Antihyperlipidemic</strong></td>
<td>Gemfibrozil</td>
<td>790</td>
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<tr>
<td><strong>Antidiabetic</strong></td>
<td>Metformin</td>
<td>150</td>
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<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>Ibuprofen</td>
<td>3,400</td>
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<tr>
<td><strong>Beta blockers</strong></td>
<td>Betaxolol</td>
<td>28</td>
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<tr>
<td></td>
<td>Bisoprolol</td>
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<td></td>
<td>Carazolol</td>
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<tr>
<td></td>
<td>Metoprolol</td>
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</tr>
<tr>
<td></td>
<td>Propanolol</td>
<td>590</td>
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<tr>
<td></td>
<td>Timolol</td>
<td>10</td>
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<tr>
<td><strong>Bronchodilators</strong></td>
<td>Clenbuterol</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Fenoterol</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Salbutamol</td>
<td>35</td>
</tr>
<tr>
<td><strong>Contraceptive</strong></td>
<td>17a Ethinylestradiol</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Lipid regulators</strong></td>
<td>Bezafibrate</td>
<td>3,100</td>
</tr>
<tr>
<td></td>
<td>Clofibrate</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil</td>
<td>510</td>
</tr>
<tr>
<td><strong>X-ray contrast media</strong></td>
<td>Diatrizoate</td>
<td>100,000</td>
</tr>
</tbody>
</table>
has generated concerns among various stakeholders, including governments, regulators and the public, over potential risks to the environment and to human health through very low level exposure via drinking-water (17).

Due to a specific situation with water resources around the city of Berlin, some pharmaceutical compounds were detected in drinking water samples: clofibric acid (270 ng.l-1), diclofenac, propylphenazone, ibuprofen. Several compounds were detected in raw drinking water samples in SanDiego County, California, and were found to contain clofibric acid, ibuprofen, ibuprofenmethyl ester (23). Figure 2 illustrates the routes of pharmaceutical contamination of the aquatic environment and how they reach drinking water (11).

![Diagram of Pharmaceutical Contamination Routes](image)

**Fig. 2. Fate and transport of pharmaceuticals in the environment.**

**Human health risk assessment for pharmaceuticals in drinking-water:** Pharmaceuticals are normally governed by stringent regulatory processes and require rigorous preclinical and clinical studies to assess their efficacy and safety before Pharmaceuticals in Drinking-water commercialization. Therefore, pharmaceuticals are generally better characterized than other environmental contaminants.

The approaches of acceptable daily intake (ADI) or minimum therapeutic dose (MTD) were adopted as the point of departure in these studies to assess potential risks to human health through exposure to pharmaceuticals in drinking-water.

Margins of exposure (MOEs) were derived by comparing measured or modeled exposure levels in drinking-water with a reference exposure concentration, which was usually the ADI or MTD or sometimes a drinking-water equivalent level (DWEL). A judgment of safety could then be based on the magnitude of this MOE for the pharmaceutical under consideration. In other words, screening values to determine whether further action is warranted could be derived from the ADI or the MTD, with uncertainty factors applied as appropriate.

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Analysis of the results indicated that appreciable adverse health impacts to humans are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in drinking-water. Concentrations of pharmaceuticals in drinking-water are generally more than 1000-fold below the MTD, which is the lowest clinically active dosage. The findings from these three case-studies are in line with the evidence published over the past decade, which suggests that appreciable risks to health arising from exposure to trace levels of pharmaceuticals in drinking water are extremely unlikely.

**Fate of pharmaceuticals in the oriented sanitation**

**Source separation based sanitation concept**

A number of different wastewater streams are produced in households as a consequence of various human activities (Fig. 3). In the existing combined sanitation system, all the streams originating from the households are collected with the same piping system and end up to the conventional waste water treatment plants (WWTPs). Waste water streams can be separated based on their composition and concentrations (24). Black water originating from the toilets is one of the most concentrated streams and consists of faeces, urine and flush water. Grey water is the combination of the sub-streams originating from shower, bath, laundry and kitchen and is relatively diluted. Black water contains high organic contents as well as the major fraction of the nutrients in domestic wastewater. Besides, most of the pathogens and micro pollutants (pharmaceuticals, hormones …, etc.) are also present in this stream which has a small volume. Separating urine or black water stream from the others enables to concentrate the risks in a very small volume. This gives an opportunity to have a better control, enabling the recovery of nutrients and energy and limit the negative environmental effects (25).

![Fig. 3. Wastewater streams produced in households (6).](image-url)
Urine as fertilizer

Fate of pharmaceuticals in soil: Separate collection and processing of human urine is gaining interest.

First: This lies in the fact that human urine contains the largest fraction of nutrients: nitrogen (approximately 80%), phosphorus (approximately 50%) and potassium (approximately 70%) emitted from households. These nutrients could be used, after an appropriate treatment if required, as fertilizers in agriculture.  

Second: Human urine contains the largest fraction of human pharmaceuticals and their residues (metabolites, conjugates) excreted from human body. Separation, collection and treatment of urine may therefore reduce the amounts of residual pharmaceutical compounds that are currently discharged through sewer overflows and by WWTPs that are not designed to efficiently eliminate these compounds.

Third: Disconnection of the urine stream (or part of the stream) from the sewer would enable to save energy at WWTPs, that is spent for nitrification of ammonium mainly originating from urine. These are three important reasons why a separate, collection and treatment of urine is being considered. Routes of pharmaceuticals contamination of the aquatic environment is given in Fig. 4.

Fig. 4. Routes of pharmaceutical contamination of the aquatic environment.
Fate and behavior of pharmaceutical residues in plant tissues and soils:
Urine, also called yellow water, is discussed as an alternative fertilizer for agriculture as it contains relatively high concentrations of the macronutrients nitrogen, phosphorus, and potassium. But this usage of urine includes the risk of transfer of pharmaceutical residues to agricultural fields. Little is known on the fate of pharmaceuticals regarding their accumulation in soils, transfer to groundwater, and incorporation by plants. However, these effects cannot be excluded as fairly high concentrations of pharmaceuticals are expected in urine. The uptake of pharmaceuticals in plants and the effects they exaggerate on plant physiology and development were of major interest when crops are fertilized with urine. Literature states that the uptake of organic compounds by plants is correlated with the molecular weight of the organics.

It is assumed that a molecular weight of >1000 makes the absorption by plant cellular membranes impossible. Moreover, the octanol-water partition coefficient is looked at as a characteristic of the organics strongly affecting their uptake. Briggs et al. have detected that uptake into shoots was most efficient for chemicals with log $K_{ow} = 2$. In contrast, $K_{ow}$ is reported to be of lower importance. An ion-trap mechanism, i.e. a process with the chemical being neutral outside and dissociated inside the cell, is responsible for the incorporation of organics by plants. Additionally, literature shows that pharmaceuticals can affect plant growth when dosed insufficient concentrations and can be taken up by plants. The question is, whether pharmaceuticals are taken up by the investigated plants, and in which concentrations by which plant parts.

Biodegradability of PhACs from concentrated wastewater streams
The PhACs comprise a large group of chemical compounds (more than 3000 registered in EU) having different therapeutic mode of action in a human body, different chemical-physical properties and susceptibility to degradation in biological systems. After administered by humans they are metabolized and excreted partially as a parent compound (usually a small fraction) and a number of inactive or active metabolites.

In current STPs employing activated sludge process as a main treatment, PhACs are removed only partially. Discharged to surfacewater they form a threat to aquatic life and re-enter water cycle. Advanced post-treatment processes (e.g. oxidation techniques, tight membrane filtration, activated carbon adsorption) are reported to be promising techniques to further lower the concentrations of emitted PhACs. They are, however, very expensive since large waste water volumes need to be treated. A new sanitation approach, applying separation of waste water streams containing all (black water) or majority (urine) of PhACs could be adapted. The target is treatment that may enable to minimize the emission of human PhACs to the environment since it concerns a significantly smaller stream to be handled.
Environmental and public health impacts of pharmaceuticals

Certain environmental and public health risks can be anticipated from the exposure to the environmental pharmaceuticals. Besides, there are a few classes of pharmaceuticals that pose unambiguous impacts on the aquatic organisms, including microorganisms, phytoplankton, plants, crustaceans, fish and insects, as well as on soil microorganisms and possibly humans. These pharmaceutical classes include:

- Cytostatic agents, immunosuppressive drugs, and some genotoxic antibiotics because of their evident cytotoxic, carcinogenic, mutagenic and/or embryotoxic properties;
- Human and veterinary antibiotics because of their pronounced microbial toxicity and the development of antibiotics resistance in environmental bacteria including human pathogens;
- Natural and synthetic hormones because of their high efficiency, low effect thresholds and potential for endocrine disruption;
- Halogenated compounds such as iodinated X-ray contrast media because of their resistance toward biodegradation and their mobility and persistence in the environment and the food web;
- Heavy-metal containing drugs and non-therapeutic medical agents because of the toxicity of the metals in certain oxidation states.

In addition, the presence of other types of pharmaceuticals, such as analgesics and anticonvulsants, in drinking water is a potential public health issue. Although the concentrations found in finished water is generally very low, it is apparent that drinking water consumption is the major route of human exposure to the environmental pharmaceuticals (Fig. 3). Since the long-term health effects are still largely unknown for the exposure to the trace pharmaceuticals and their metabolites, especially as a mixture of biologically active compounds, the existence of these compounds in drinking water should be avoided on the basis of precautionary principle. Similarly, long-term exposure of aquatic organisms to trace pharmaceuticals in surface water may have some as-yet-known ecological impacts.

Preventing pharmaceuticals in drinking-water

Conventional drinking-water quality monitoring that focuses on end-product testing is resource intensive in terms of capital investment and human resources. Coupled with an expanding list of chemical contaminants in drinking-water and water sources that may be of insignificant health concern, an overemphasis on end-product monitoring and the upgrading of treatment infrastructure is not a sustainable, optimal use of limited resources. As outlined in the WHO Guidelines for Drinking-water Quality, the water safety plan approach is “the most effective means of consistently ensuring the safety of a drinking-water supply through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in the water supply from catchment to consumer”. Water safety plans highlight the importance of considering risk assessment and risk management comprehensively from source to tap and adopting preventive measures to address the source of risks.
Adapting the water safety plan approach to the context of pharmaceuticals in drinking-water means that: preventing pharmaceuticals from entering the water supply cycle during their production, consumption (i.e. excretion) and disposal is a pragmatic and effective means of risk management. Preventive measures need to be applied as close as possible to the source of the risk and hazard (40). Inappropriate disposal practices, such as flushing unwanted or excess drugs down toilets and sinks and discarding them into household waste, are common and may be the main contributors to pharmaceuticals in wastewater and other environmental media, such as surface waters and landfill leachate. Preventive measures, such as policies promoting or regulations governing disposal practices at concentrated point sources (e.g. health-care and veterinary facilities), can reduce the amount of pharmaceutical waste entering water bodies. In addition, take back programmes, guidance and enhanced consumer education will support efforts for the proper disposal of medicines and reduce the impact of pharmaceuticals entering our water sources (41).

Treatment technologies for removal of pharmaceuticals

Removal from drinking water

Having established that raw sewage and wastewater effluents are a major source of pharmaceuticals found in surface waters and drinking-water, it is important to consider and characterize the efficiency of processes for the removal of pharmaceuticals during wastewater and drinking-water treatment. Most of the research has been conducted at the laboratory scale or at full scale in developed countries, including the USA, Japan, the Republic of Korea and countries in Europe.

Even though wastewater and drinking-water treatment processes are not designed specifically to remove pharmaceuticals, they may do so to varying degrees. Pharmaceuticals are not “unusual” chemicals; their removal efficiencies during wastewater and drinking-water treatment are dependent on their physical and chemical properties. In cases where regulations require controls to mitigate risks from exposure to pesticides, treatment barriers may already be optimized to remove pharmaceuticals (42).

Conventional wastewater treatment facilities generally have activated sludge processes or other forms of biological treatment such as bio-filtration. These processes have demonstrated varying removal rates for pharmaceuticals, ranging from less than 20% to greater than 90%. The efficiency of these processes for the removal of pharmaceuticals varies within and between studies and is dependent on operational configuration of the wastewater treatment facility. Factors influencing removal include sludge age, activated sludge tank temperature and hydraulic retention time (43).

Removal from concentrated waste water streams

Black water: Black water (feces, urine, flush water), especially when collected with a minimum amount of flush water, constitutes a concentrated medium in terms of organic material, solids, nutrients and pharmaceuticals. Organic material can be removed and converted to biogas (energy carrier) by means of anaerobic digestion. As anaerobic digestion is not efficient towards removal of nutrients and micro-pollutants; an additional step has to follow. In simplified application the content of the digesters (sludge, effluent) could be used in agriculture. The caution has to be taken; however; as both media are not stabilized. The fate of pharmaceuticals; ‘on the fields’; and its effects on the crops is not completely clear yet. Most probably sorption and in the course of time degradation of many pharmaceuticals would take place. In order to polish the anaerobic effluent an aerobic step could be added in form of:

- suspended activated sludge;
- suspended activated sludge with membrane filtration (MBR);
- Fixed activated sludge–biofilm (trickling filter, rotating biological contactor (RBC), submerged filter, down-flow hanging sponge (DHS);
- Natural and semi-natural systems (facultative and maturation ponds, constructed wetland systems, aquatic plants).

In all of these systems removal of nutrients can be accomplished and further removal of organic material. Also, further degradation of pharmaceuticals will take place; the degree will depend on the system used and process conditions. The complete removal of all pharmaceutical compounds cannot be assured in aerobic treatment systems. If the objective is to eliminate the pharmaceuticals compounds to a low level, only advanced physical-chemical techniques can assure it. In order to optimize efficiency of these systems one has to make sure that the influent has a very good quality, especially in terms of organic material and suspended material (as low as possible)\(^{(44)}\).

Advanced physical techniques, which could be potentially applied and good results have been attained so far are:
- Oxidation techniques (ozone, advanced oxidation processes: combinations of \(\text{O}_3\), \(\text{UV}\), \(\text{H}_2\text{O}_2\), and \(\text{TiO}_2\));
- Sorption on activated carbon and
- Tight filtrations: Nano-filtration and reverse osmosis.

As much experience has been gained already with above mentioned techniques in production of drinking water, their application in wastewater treatment is quite limited. Very little experience, if any, has been gained with application of advanced physical-chemical techniques for the treatment of black water in order to remove pharmaceutical compounds. A general scheme for a recommended treatment of source separated black water has been presented schematically in Fig.5\(^{(45)}\).

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Removal from urine: Urine is produced in small quantities (1-1.5 L/person/day) and can be collected undiluted. Although considered as a relatively clean it still contains a significant load of organic material, nutrients, pathogens and pharmaceuticals. Regarding the small volume of the urine in certain situation, it could be treated separately using advanced physical-treatment at a relative high cost. Such a solution could be applied in situation when point sources emit elevated concentration of pharmaceuticals into the environment (hospitals and other health care centers, pharmaceutical industries). A train of processes applying aerobic biological degradation followed by advanced physical-chemical treatment could be applied as well. It has an advantage that a bulk of organic material is for a large part eliminated, allowing for optimization of a post-treatment in terms of lower doses of reagents, contact times, energy consumption … etc. When urine is used, after storing, as a fertilizer in agriculture, the pharmaceuticals will be removed, at least partially, as a consequence of the spectrum of (natural) processes in the course of time:

- Sorption on soil particles, roots,
- Filtration
- Biodegrading in soil;
- Exposure to sun – photolytic degradation.

The possible treatment configurations for separated collected urine are sketched in Fig. 6.

Recent Fenton and Fenton-like oxidation treatments have been researched to remove pharmaceutically active compounds from urine (47). In this study Fenton’s oxidation achieves high removal efficiency of pharmaceuticals from urine, particularly for the non-biodegradable portions, and it is highly dependent on the concentration of oxidant and catalyst. However, Fenton’s treatment is rated as uneconomical for treating large volumes of urine. For pre-treatment, lower dose of Fenton’s reagents can be used. For the elimination of the selected PhACs, the tested catalysts (Fe$^{2+}$ or Cu$^{1+}$) have been more efficient than activated carbon (47).

Fig. 5. A sequence of processes to apply for black water treatment in order to eliminate human pharmaceuticals emissions into the environment (48).
Conclusions, recommendations and knowledge gaps

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. They contain active ingredients that are designed to achieve pharmacological effects and confer significant benefits to society. Pharmaceuticals are primarily introduced into the environment via human excretion, sewage effluent, improper drug disposal, agricultural run off and livestock and veterinary waste. The ubiquitous use of pharmaceuticals in various settings has resulted in a continuous discharge of pharmaceuticals and metabolites into the environment, leading to their “pseudopersistence” in the environment. Significant advancements in the sensitivity of detection and analytical technologies and methods have made it possible to detect very low concentrations of pharmaceuticals in the range of nanograms to low micrograms per litre in the water cycle. As pharmaceuticals contain active ingredients that are designed to achieve specific pharmacological effects based on their biological reactivity and biochemical properties, their presence at trace concentrations in the water cycle has generated concerns among various stakeholders, including governments, regulators and the public, over...
potential risks to the environment and to human health through very low level exposure via drinking-water.

**Conclusion**

- Pharmaceuticals are consumed in high quantities worldwide and the expectations are that these amounts will continue increasing because of improving health care system and longer life expectations of people.
- Approximately 70% of pharmaceuticals are excreted with urine (metabolites, conjugates) from human body while 30% with faeces.
- Urine contains the largest fraction of nutrients: nitrogen (80%), phosphorus (50%) and potassium (70%) emitted from households. These could be used, after an appropriate treatment, as fertilizers in agriculture.
- As certain, PhACs remain persistent to biological degradation, extension of biological treatment (anaerobic-anoxic-aerobic) of source separated wastewater with physical or chemical process units will be unavoidable when the intention is to stop the emission of PhACs to the environment.
- Discharged to surface water, PhACs form a threat to aquatic life and re-enter water cycle. Advanced post-treatment processes (*e.g.* oxidation techniques, tight membrane filtration, activated carbon sorption) are reported to be promising techniques to lower further the concentrations of emitted PhACs. They are however very expensive since large wastewater volumes need to be treated.
- Future work on WWTP treatment optimization will show to what extent pharmaceuticals can be removed from wastewater and to what extent the implementation of an improved technology is feasible, taking into account other macro- and micro-pollutants as well as the broad variety of complex wastewater matrices.
- Disappearance of the present compound does not necessarily mean that the treatment was fully successful.

**Recommendation**

- A new sanitation approach, applying separation of waste water streams containing all (black water) or majority (urine) of PhACs and their target treatment, may enable to minimize the emission of human PhACs to the environment since it concerns a significantly smaller stream to be handled (sewage 200L/p/day; urine 1.5 L/p/d when collected undiluted, black water 7.5 L/p/d when vacuum toilet is applied). Little is known on the fate of PhACs when biologically treating very concentrated wastewater streams.
- In implementation of new sanitation approach (separation, sustainable and decentralized sanitation) should be considered. Much attention should be paid to the treatment of separated wastewater streams: urine, faeces, black water, grey water …etc for the elimination of harmful constituents and recovery of resources.
- There is a need to increase the knowledge about the fate of pharmaceuticals during sewage treatment for implementation of better removal techniques.
An important question that should be addressed is whether pharmaceutical residues are bio-available and, if so, what the environmental impact will be.

There is a lack of studies concerning the formation of transformation products in the environment following natural degradation or water treatment.

**Knowledge gaps and future research for pharmaceuticals in drinking-water**

Although current risk assessments indicate that very low concentrations of pharmaceuticals in drinking-water are very unlikely to pose any risks to human health, there are knowledge gaps in terms of assessing the risks associated with long-term, low-level exposures to pharmaceuticals and possible combined effects of chemical mixtures, including pharmaceuticals. Future research investigating the possible additive or synergistic effects of mixtures would be beneficial for an accurate exposure assessment to determine whether there are any potential risks to human health, taking into account sensitive subpopulations.

One of the key challenges in estimating exposures to pharmaceuticals in drinking water and assessing the potential risks to human health is the limited occurrence data for the diverse group of human and veterinary pharmaceuticals in use today. Implementing monitoring programmes is resource intensive in terms of costs, human resources and infrastructure, and there is also a lack of standardized sampling and analysis protocols to support monitoring studies. As such, future research looking into cost-effective methods to prioritize pharmaceuticals within the context of an overall risk assessment will benefit our appreciation of low levels of pharmaceuticals in drinking-water from a human health perspective.

**References**


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The increase in the use of pharmaceutical compounds in the current time, and their discharge into liquid waste and waterways is a growing concern due to its impact on water quality and health. Long-term use of antibiotics, hormones, and drugs, such as anti-inflammatory and beta blockers, poses a threat to the spread of these compounds in the environment and development of bacterial resistance to antibiotics.

Due to their poor biodegradability, about 80% of these compounds are discharged as primary waste and reach the liquid waste and plants that are irrigated with sewage water, where no rejection occurs, and thus, they lead to bacterial resistance in many places in Egypt, where there is no system to treat liquid waste, and thus, these substances are discharged directly into surface waters without prior treatment, which increases the risk of these substances entering the environment, affecting directly on the organs and entering the food chain.

The study aims to determine the effectiveness of simple and advanced techniques for treating various pharmaceutical and hormone contaminants in water and liquid waste. The study will focus on the technology of activated carbon for removing these contaminants and the combination of advanced and simple technologies will be based on the advantages and disadvantages, as well as the area and the cost. The results will be evaluated at the semi-industrial level. The study includes the fate of pharmaceutical substances during a complex advanced oxidation process using the generation of heat to break down the contaminants.

The study highlights the need for developing applicable and economically viable technology to control these pollutants. The study aims to develop an applicable technology that meets the needs of the liquid waste and wastewater treatment. The study will focus on the technology of activated carbon for removing these contaminants and the combination of advanced and simple technologies will be based on the advantages and disadvantages, as well as the area and the cost. The results will be evaluated at the semi-industrial level. The study includes the fate of pharmaceutical substances during a complex advanced oxidation process using the generation of heat to break down the contaminants.

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الكيميائية. كما تشمل تكنولوجيا الأغشية المسامية (مثال أغشية الترشيح الدقيق – تكنولوجيا أغشية النانو) للتخلص من المركبات الدوائية في المخلفات السائلة نطاق التجارب النصف صناعية.