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Medical Substances in Environmental Systems of the Central Asia Region

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Abstract

Nowadays pharmaceutical water contamination is a worldwide problem. Resulting from an absence of appropriate legislation, policies, and efficient treatment technologies, especially those developed to remove pharmaceuticals from wastewater, has led to the further contamination of soil and natural water bodies. The adverse impact this has on wildlife/human species reinforces the need to develop proper monitoring and detection techniques for pharmaceutical water contamination. This article focuses on the sources, fate, monitoring, and negative effects of pharmaceuticals globally and compares it with data from Kazakhstan and bordering Commonwealth of Independent States (CIS) countries. In general, Kazakhstan/CIS countries are demonstrating similar trends with other developed comparison countries in terms of types and concentrations of pharmaceuticals found. The major difference between Kazakhstan/CIS and developed countries is the absence of matured monitoring and legislation systems. On the other hand, removal of pharmaceuticals at wastewater treatment plants, which precede most sources of soil and natural water way pollution, is intensified by the development of the pharmaceutical industry and approval of novel drug types. This work shows that proper disposal, monitoring and legislation, efficient wastewater treatment, and development of accurate drug determination methods have significant potential in controlling pollution of the environment, including the water–soil nexus.

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1. Introduction

Wastewater carrying both organic and inorganic contaminants that can directly enter urban and natural water bodies or soil, which in turn could pollute environment, harm human health, and damage wildlife. The study on the presence and toxicological impacts of heavy metals, classified as conventional contaminants, have been intensively performed for many decades, whereas emerging contaminants (such as microplastics, pharmaceuticals, and personal care products) have been more recently identified and are less studied.[1-3] Among these emerging pollutants, the use of pharmaceutical drugs for human and animal health is expanding all over the world. The major categories of the medical drugs are analgesics and anti-inflammatory, narcotics, anesthetics, anticoagulants, antimicrobials, antipyretics, cardiac drugs, immunosuppressants, neurological and psychoactive drugs, chemotherapeutic drugs, diabetic and gastrointestinal medications, diuretics, hormones, and respiratory and tuberculosis combination drugs.[4,5] These substances form an enormous group of medications used mainly for therapeutic purposes in both human-beings and wildlife.[6] Due to their physico-chemical characteristics, they could skip wastewater treatment process and be persistent in an aquatic environment. Since the majority of pharmaceuticals have high polarity and low volatility[7] they could easily enter surface waters. According to Daughton *et al*.,[8] pharmaceutical products are uncontrolled chemical stressors that enter the environment.

Pharmaceutical compounds and their metabolites can enter the environment via different pathways such as direct discharge from drug manufacturing industries, immediate

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disposal of intact pharmaceuticals, various veterinary and agricultural practices, and excretion of human and animal wastes from the soil or sewage.[9,10] The widespread concerns on emerging pollutants come from their persistent nature and harmful impact on human health and wildlife including aquatic organisms.[11-13] In order to address these issues researchers have already started working on possible remediation and treatment processes, such as the development of functional adsorbents and membranes, implementation of advanced oxidation processes and electrochemical approaches that may either efficiently entrap or decompose them from water bodies.[14,15]

Pharmaceuticals are examples of emerging pollutants, amount of which is expected to increase in the future. Removal of pharmaceuticals is a challenging goal for low-income countries.[16] Furthermore, the demand for pharmaceutical use has been growing due to the increasing world population, widespread availability in the world market, investment in the healthcare field, and progress in medical research.[17] Nowadays, approximately 4,000 active pharmaceutical ingredients are in use and around 100,000 tons per year are consumed worldwide.[18] In comparison with other groups of chemicals, pharmaceuticals have less consideration, the consumption of drugs is continuous and the spread is global.[19] Over the past decades, the number of research articles related to pharmaceuticals monitoring in the environment has been increasing. The early association with the pharmaceuticals pollution stems back to 1940s pioneering literature; however, the use of pharmaceuticals in the environment as a discrete research subdivision has demonstrated a rapid growing trend at the end of 1990s.[20]

Developed countries of the EU and USA have a well-established monitoring systems and quantification approaches of pharmaceuticals in the environment.[12,21] However, developing countries are still lacking sufficient resources for monitoring and managing the presence of medical drugs in the environmental waters. The pollution of environment with pharmaceuticals in Central Asia and the Commonwealth of Independent States (CIS) countries is resulted by their uncontrolled utilization and disposal, inadequate sanitation policies, shortcomings in appropriate resources and technologies for wastewater treatment and absence of investigated data on adverse effects. In the CIS region, scientists from Kazakhstan[22-24] and Russia[25-27] were able to establish a baseline studies on monitoring, quantification and possible remediation approaches of pharmaceuticals. Despite these efforts, the gaps in the literature in Kazakhstan and the bordering CIS countries in terms of available resources and practices applied for data collection and monitoring of pharmaceuticals are still enormous. This literature review highlights the present situation of pharmaceuticals occurrence, their fate in the environment, environmental effects and monitoring approaches in Kazakhstan and the bordering CIS countries, and compares with the worldwide situation. The review is focusing on possible ways of minimization of adverse effects of pharmaceuticals on the environment and future perspectives based on best practices currently applied.

2. The sources of pharmaceuticals in the environment

The main sources of pharmaceuticals in the environment are illustrated in Fig. 1. Municipal wastewater is the main pathway of pharmaceutical ingredients to the environment. There can be a release of pharmaceutical ingredients which cannot be removed in the sewage treatment plants and it could lead to the pollution of water bodies.[28,29] In addition, in wastewater treatment plants pharmaceutical ingredients can be found in sludge. The polluted sludge may release pharmaceuticals into the soil, which later will enter groundwaters.[30,31]

When active pharmaceutical ingredients are present in municipal or industrial wastes, they also could leach from landfills.[32] Another source is coming from pharmaceuticals in veterinary use. Those drugs after excretion by animals could enter the soil and even reach groundwater. In addition, heavy rain could transfer some pharmaceutical compounds to surface water via runoff.[33] The pharmaceutical manufacturing process has been neglected as a source of drug release into the environment, since this release is controlled. In developing countries, however, the pharmaceutical manufacturing process is still a source of the contamination. For instance, ciprofloxacin was detected at 31 mg/L concentration in India, which is higher than the concentration level commonly could be found in municipal sewage effluents.[34,35] Hospital wastewater has its own role in the discharge of pharmaceuticals into the environment, as it is diluted by municipal wastewater by a factor of more than 100. Nevertheless, even though there is less the number of pharmaceuticals in use in hospitals than in common public discharge, hospital wastewater has a higher concentration of drugs than municipal sewage.[33] The alternative routes were introduced by Daughton and Ruhoy,[8] pharmaceuticals that are applied dermally can be released during showering or via sweat. In addition, pharmaceutical devices such as patches have a concentration of remainders and also can be a source of pollution into the environment.[8]

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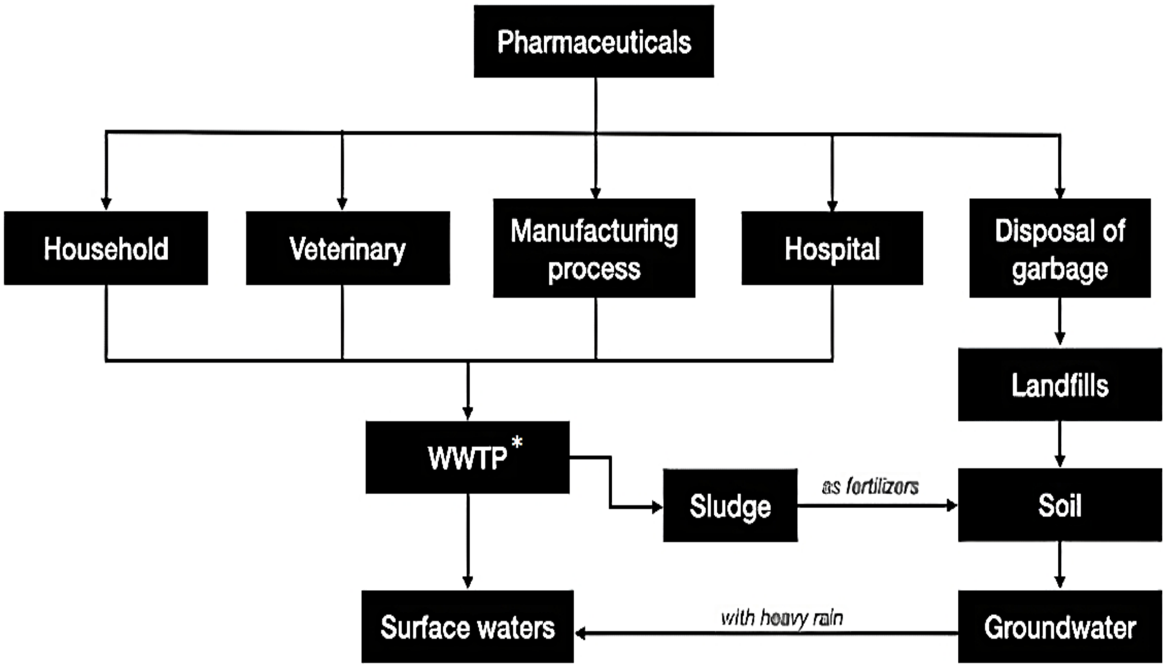

Fig. 1 Various ways of pharmaceutical release to the environment. *WWTP – wastewater treatment plant.

According to Kazakhstan legislation the medical waste classified as class A – non-hazardous waste, class B – epidemiologically hazardous waste, class C – extremely epidemiologically hazardous waste, class D – toxicologically hazardous waste, class E – radioactive waste. In 2017, the highest amount of the medical waste was produced in Akmola region.[36] In 2018 the following amount of waste has been observed country wide: class A 30,920 tons, class B 15,779 tons, class C 559 tons, class D 10,480 tons (as solids), 2,606 L (as liquids), 114,465 units (as devices), class E 57 tons.[37] One of the major problems of the country is non-controllable disposable of the medical waste. As result used syringes, masks, gloves and many more can be found in the city and wild nature.[38] Moreover, during COVID19 pandemic, increased and uncontrollable antibiotics consumption has been detected in Kazakhstan. There are two main reasons for that: antibiotics are available for purchase without a prescription and low public awareness related to such uncontrollable use.[39] Russian Federation does not monitor the impact of pharmaceutical waste.[40] Along with that according to the Federal Service for Surveillance in Healthcare for 9 months of 2019, the number of batches of medicines that entered civil circulation in Russia increased by 9% compared to the same period in 2018.[40] Now the treatment of pharmaceutical waste in Russia is carried out in accordance with the Russian Law – "Medical Waste". But certain provisions of legislative and regulatory documents contradict the data of modern research and require further development. Moreover, there are such pathways as clearance of unused and leftover drugs to landfills, aqua-culture treatment, watering with wastewater, the release of corpses of treated animals, incorrect consumption of containers and unopened drugs.[10,41] The pathways varies from region to region, since worldwide each country has its own management and regulation systems.[42]

3. Monitoring of pharmaceuticals in the environment

The occurrence of pharmaceuticals in water bodies was reported in the middle of the 1970s for the first time. Clofibric acid was found in the effluent of the Big Blue River sewage treatment plant in Kansas City, USA in 1976.[43] Then, some information about drugs present in the environment was recorded in England in 1985. However, more efficient studies started in the 1990s, as the occurrence of pharmaceuticals was noted in the local river and sewage treatment plants of Germany.[44] Furthermore, in the 1990s more advanced analytical equipment helped to find the presence of pharmaceuticals in rivers, ground and drinking water, and sewage treatment effluents.[43] In this way, in 1999–2000 in 30 states of USA 95 pharmaceuticals were found in 139 streams. In addition, the occurrence of 35 of pharmaceuticals were found in groundwater in 18 states.[18] Currently, worldwide 631 pharmaceutical compounds were detected. Antibiotics, analgesics, and estrogens were mostly analyzed in environmental waters.[17] Overall, if we consider therapeutic classes, 16% of non-steroidal anti-inflammatory pharmaceuticals, 15% of antibiotics, 12% of blood lipid-lowering agents, and 9% of sex hormones were found in the environment.[45] The occurrence of pharmaceuticals in over 71 countries was found, which brings pharmaceutical pollution to a global level.[17] In developed countries, these investigations were carried out and studies over the last decades. For the natural reservoirs, 178 types of drugs and their metabolites were found.[46] Table 1 provides data about the occurrence of pharmaceutical ingredients in surface waters and sewage

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Table 1. Occurrence of pharmaceuticals in surface waters and wastewater treatment plant effluents.

Country	Pharmaceuticals	Concentration, ng/L	Water body	References
Italy	Sulfamethoxazole	402	Surface water	
Sweden	Sulfamethoxazole	20–70		
Romania	Ibuprofen	30–115.20		
Germany	Carbamazepine	500–1,500		[47]
	Diclofenac	200–500		
Serbia	Carbamazepine	8–130		
France	Carbamazepine	52		
Kazakhstan	Aspirin	14–65	Wastewater effluent	[48]
Russia	Caffeine	3.8–446	Surface water	
	Ciprofloxacin	271		
	Diclofenac	270		[49]
	Drotaverine	36.1–41.1		
	Ketoprofen	260		
	Tetracycline	6.62		
Brazil	Acetaminophen	39.7–147	Surface water	
	Diclofenac	< 21–107		[50]
	Lidocaine	< 21		
	Sulfamethoxazole	< 27		
USA	Erythromycin	46.43	Wastewater	
	Sulfamethoxazole	1861.29	effluent	[51]
	Trimethoprim	121.86		
Kenya	Nafcillin	1.04±0.02	Surface water	
	Sulfamethoxazole	6.84±0.12		[52]
	Sulfanilamide	1.74±0.04		
	Trimethoprim	3.16±0.08		
Malaysia	Amoxicillin	1.39–7.45	Surface water	
	Caffeine	25.76–36.60		[53]
	Diclofenac	2.76–4.84		
United Kingdom	Ibuprofen	1105	Surface water	
	Diclofenac	154		[54]
	Sulfamethoxazole	< 50		
Italy	Carbamazepine	291.1	Wastewater	
	Sulfamethoxazole	127.20	effluent	[44]
	Amoxycillin	4.70		

treatment plant effluents worldwide.

It is obvious that the pharmaceuticals mentioned in the Table 1 are widely spread.[55-65] Along with that the different units of the sewage treatment plant in Spain surveyed a presence of pharmaceuticals, wherein the samples of effluents contained a high concentration widely used natural estrogens, anti-inflammatory and antibiotic pharmaceuticals as well as contrast media for radiography and active ingredients of cosmetic products such as galaxolide and tonalide[66] (not shown in Table 1).

A massive study was performed on 713 different active compounds that includes 142 metabolites in the United Nations (UN) region. The vast majority of studied pharmaceuticals (89%) including 127 metabolites were sensed in concentrations over the detection limit. Among these, 16 pharmaceuticals were found in levels of water bodies all over the region. Based on the results, the most common pharmaceutical compound was diclofenac (detected in 50 countries). At the same time, another commonly used medications such as naproxen, sulfamethoxazole, carbamazepine, and ibuprofen were identified in as many as 45 countries. It should be noted that relatively less studied pharmaceuticals, such as antiepileptics and antilipemic were similarly sensed in all UN regions.[17]

Unfortunately, at present, the determination of maximum concentrations of drugs that do not cause a negative effect to human health and ecosystems is limited, which makes it difficult to determine the maximum allowable concentrations of pharmaceuticals in water.[67] However, it can be argued with a high degree of probability that certain compounds and metabolites of the several classes of pharmaceuticals pose the greatest danger to the biosphere, which includes antibiotics,

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analgesics, endocrine drugs, antidepressants, hormones, and anticancer drugs.[68]

Even a selective analysis of published data shows that this problem is not well understood. There is practically no data on the entry of medicinal substances into lakes, swamps, or other water bodies. Due to the high consumption of analgesics and anti-inflammatory drugs, they are most commonly found in wastewater worldwide.[31]

4. Fate of pharmaceuticals in the environment

4.1 Sewage/Wastewater Treatment Plants (WWTPs)

In general, the existing treatment technological units eliminate organic components that comprise various types of the lipids, carbohydrates and proteins. However, they are not capable of eliminating the pharmaceuticals. Pharmaceuticals could be persistent in the environment and are not always absorbed or totally degraded down in the body. Currently, there are no treatment units, which are designed for removing pharmaceuticals and their metabolites.[69-76]

The pathway in the environment depends on physical and chemical characteristics of pharmaceuticals, environmental conditions, and microbial communities.[77] As pharmaceuticals have low volatility, in most cases they will move in the environment via aqueous systems. Pharmaceutical ingredients can be affected by biotic and abiotic processes in the environment. In aquatic biota biodegradation, photo-degradation and sorption could decrease the level of the pharmaceutical ingredients. In general, the study of the fate of pharmaceuticals is made via simulations in the labs. Therefore, we do not have enough data about the behavior of medical substances in the environment.[20,34]

According to national report on the state of the environment and the use of natural resources of the Republic of Kazakhstan and UN environmental performance reviews, pharmaceuticals may reach Kazakhstani nature due to the following: the malfunction/absence of treatment facilities, while urban wastewater is discharged through temporary settling tanks directly to the filtration fields.[78,79] At the same time, the management of polluted wastewaters is an important environmental problem for Kazakhstan, since there is no database on drugs pathways during their production/consumption processes. The excreted pharmaceuticals go through the sequence of the treatment processes in sewage treatment plants. During the screening and primary sedimentation stages pharmaceutical ingredients are not removed due to their low biological activity and individual pharmaceutical compounds are not adsorbed by solids.[80] On the stage of microbial degradation or sorption to solid some drugs can be eliminated. For example, activated sludge demonstrated 7% removal for diclofenac and 98% removal for ibuprofen and metformin by sorption process.[81] de Andrade *et al*., introduced low-cost sorbents, namely different types of clays, porous natural polymers, biochars, and industrial agricultural wastes.[81] In recent studies Campinas *et al*.[82] applied activated carbon, coagulation, flocculation, sedimentation and showed 65–79% elimination of pharmaceutical ingredients.

Due to the system of the WWTP designed to treat the pollutants of the bigger size and/or the comparatively decomposable contaminants in the mg/L range, the treatment efficiencies of medical drugs including acetylsalicylic acid, atenolol, carbamazepine, diclofenac, and propranolol generally are lower than 10%.[18] Some of the studies conducted assessment of the different WWTP on elimination of pharmaceuticals showed that acetaminophen (also known as paracetamol and panadol), estriol, sertraline, clarithromycin, ciprofloxacin, caffeine, and azithromycin have high elimination rates.[83,84] Physicochemical properties of the pharmaceuticals can contribute to their treatment efficiency; for example, adsorption to solids of diclofenac is increased due to its hydrophobicityand for sulfamethoxazole, adsorption occurred due to H-bonds formation when compound interacted with natural organic matter.[83]

According to Fent *et al*.,[29] biodegradation is one of the most efficient processes in wastewater treatment. The biodegradation of active pharmaceutical ingredients depends on hydraulic and sludge retention time.[29] For instance, in a recent study by Alobaidi *et al*.[85] with sludge retention time for 40 days, the removal of paracetamol was more than 95% and ranitidine showed a removal efficiency of 90%.In addition, biodegradation by bacteria in biofilters could be significant in the removal of pharmaceutical ingredients in the drinking water process.[86] For instance, Hasan *et al*.[86] explored the biodegradation of pharmaceutical ingredients by bacteria in the seasonally collected backwash water from a biofilter. As a result, in 225 h there was 90–92% of acetaminophen removal and 50% of ibuprofen was eliminated in 230 h. The study also demonstrated that the removal portion of drugs in biodegradation depends on the molecular structures of the substances, pH, temperature, and bacterial community.[86] Biodegradation rate of acetaminophen drops at some period due to decarboxylation of paracetamol which leads to further drug transformation: *p-aminophenol* intermediate is formed, amino groups of formed intermediate is consequently replaced by •OH radicals; intermediate is transformed into *hydroquinone*.[86] Then, oxidative ring of hydroquinone intermediate is opened accelerating the destruction of its chromophoric structure and damaged intermediate is effectively eliminated, so high removal of parent acetaminophen drug is achieved.[86] Ibuprofen, which is classified as polycyclic aromatic compound and is already very resistant to biodegradation, can be decelerated due to interference in the growth of bacterial community caused by blockage of entrance of bacterial enzymes with complex carbon chains of ibuprofen.[86] Most of the intermediates of ibuprofen are considered as highly toxic compounds; only 2-hydroxy ibuprofen intermediate was detected in the bioreactor suggesting that other intermediates are either fully eliminated by carbon mineralization or are formed only at more than 230 h of biodegradation.[86]

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The availability of twelve pharmaceuticals and personal care products at two sewage treatment plants in Beijing was studied monthly for one year.[87] Removal of personal care products by three biological treatment processes including conventional activated sludge, biological nutrient removal and membrane bioreactor were compared across different seasons. The removal efficiency of readily biodegradable personal care products was more consistent for membrane bioreactor in comparison with conventional activated sludge or biological nutrient removal (particularly during the cold seasons).[87] Moreover, membrane bioreactor demonstrated decent results on the removal of the pharmaceuticals under study including diclofenac, gemfibrozil, metoprolol, and trimethoprim, whereas conventional activated sludge and biological nutrient removal processes obtained negligible elimination efficiency for the same chemicals.[87] Hence, from all the above mentioned, it could be concluded that the sewage treatment plants cannot totally eliminate all released pharmaceuticals, however, they could reduce the concentration of drugs.

Another extensive study on remediation of pharmaceuticals with acidic forms investigated the treatment in an actual wastewater treatment plant by use of activated sludge and membrane biorector technologies. The researchers identified that a high surface area of the activated sludge in combination with membrane bioreactors contributed to adsorption of pharmaceuticals. However, the key mechanism of removal was recognized to be a biodegradation that was clearer in the case of diclofenac and negligible for refractory pharmaceutical – clofibric acid that demonstrated significantly slow dynamics of biodegradation.[88] Also, sorption onto the sludge occurred rapidly for ketoprofen and ibuprofen allowing gradual biodegradation of drugs.[88]

It should be mentioned that there also many pharmaceuticals compounds that are non-biodegradable. In Kazakhstan, non-biodegradable pharmaceutical waste is either burned or buried in landfills after neutralization at special facilities (incinerators).[89] In Russia, pharmaceutical waste is utilized with methods such as incineration, pyrolysis, plasma technology, and with a disinfectant solution.[90] However, non-biodegradable pharmaceutical compounds can still enter environment due to improper utilization of medicinal waste or via excretion of humans and animals, and conventional wastewater plants are capable of only partial pharmaceutical contaminant removal.

Pharmaceuticals with low biodegradation rate require additional treatment steps.[91] The persistent pharmaceuticals can be eliminated by secondary treatment with different conventional activated sludge and Advanced Oxidation Processes (AOPs).[92] The main mechanism of removal of pharmaceuticals is adsorption, which depends on adsorption capacity, surface area, and type of adsorbent along with physicochemical properties of target pharmaceuticals.[93,94] Degradation mechanism with AOPs is oxidation of the pharmaceuticals by highly reactive radicals that are activated with ozonation, persulfate-based AOPs, Fenton reaction or UV irradiation.[92] When treatment with AOP method is applied, ibuprofen, formula of which is $C_{13}H_{18}O_2$ or 2-(4-isobutylphenyl) propionic acid, in water can be degraded in several pathways. First, activated •OH radicals react with ibuprofen that consequently undergoes decarboxylation and loses 2-propanol and converting to 4-ethylbenxaldehyde.[95] Also, ibuprofen can deform into 1-(1-hydroxyenthyl)-4-isobutylbenzene as a result of the cleavage of its C-C bond to the carboxyl group. Another potential degradation mechanism for ibuprofen is conversion of pollutant into 4-isobutylacetophenone intermediate after series of oxidation steps.[95] All mentioned potential intermediated of ibuprofen can be completely terminated within an hour of degradation time.[95] Carbamazepine or 5H-dibenzo[b,f]azepine-5-carboxamide is fully eliminated by combination of AOPs, ozonation, and nanofiltration treatment methods. According to Yacouba *et al*., aromatic rings of carbamazepine experience hydroxylation during AOPs step consequently forming hydroxycarbamazepine and molecular reaction of ozone with carbamazepine results in formation of 1-(2-benzaldehyde)-4-hydro-(1H, 3H)-quinazoline-2-one.[96] The carbamazepine by-products are then efficiently removed with application of nanofiltration step in which pollutants are rejected due to small pore size of the membrane.[96] Application of powdered activated carbon along with ultrafiltration resulted in full elimination of the nortriptyline drug: positively charged drug was attracted to the negatively charged acidic groups located inside of the activated carbon pores.[93]

Furthermore, photodegradation demonstrates an influence on the elimination of drugs from sewage treatment plant.[97] For example, photocatalysis showed the removal of pharmaceutical ingredients by more than 70%.[98] For persistent pharmaceutical like carbamazepine, Up-flow Anaerobic Sludge Blanket in combination with a membrane bioreactor showed the removal efficiency from 49.8% to 70% which is achieved by partial accumulation of the drug onto sludge followed by physical removal with microfiltration membrane.[99]

Another example of non-biodegradable compound is acetaminophen. Approximately 58–68% of ingested panadol is excreted through the kidneys with urine and enters the city sewage system.[100]. In Europe, according to researchers, the concentration of paracetamol in treated wastewater can reach up to 6 μg/L, while in the US it might reach as high as 10 μg/L. For the photocatalytic decomposition of acetaminophen in an aqueous medium, a series of catalysts have been developed.[100] According to authors, a visible light was employed as a photocatalytic degradation source of acetaminophen using a catalyst made of core-shell structured microspheres of the composite Ag_2S-ZnO as a core and a layer of reduced graphene oxide as a shell. Acetaminophen is decomposed via the direct oxidation of compound with negatively charged $•O_2$ radicals.[100] The results revealed a complete decomposition of acetaminophen in aqueous medium within 1-hour of irradiation,[100] which shows that the synthesis of novel

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catalysts might be one of the solutions to tackle the pollution issues of water with drugs.

Wastewater treatment plants have been identified as hot spots for pharmaceutical waste, such as antidepressants, antimicrobials, and active ingredients in non-prescription medicines. At the present time, the level of pharmaceutical residues allowed to enter the environment is not controlled or regulated by law, regardless of ecotoxicological impact of mentioned micro-contaminants on living organisms in aquatic systems. The disposal of pharmaceutical waste is highly variable depending on the degree of treatment applied by the wastewater treatment plant.[83] For instance, a large study was conducted on over 60 pharmaceuticals, illegal medications, and their metabolites in wastewater (seven treatment plants using diverse technical solutions of treatment) and rivers in Great Britain over the course of a year. This extensive study included the efficiency evaluation of the treatment processe.[101] According to the results, a strong correlation is present between the type of operated treatment technology and removal efficiency of pharmaceuticals. For instance, the efficiency was moderate (less than 50%) when applied the trickling filters, while it was as high as 60% and above with activated sludge treatment. The authors highlight that the kinetics of remediation rate varied depending on pharmaceutical compounds.

4.2 Surface water

Pharmaceuticals that regularly enter and accumulate in water affect not only the ecology of rivers and lakes but also aquatic organisms. For example, antibiotics that have entered a water body make microorganisms resistant to drugs,[102] and cause genetic changes in some species.[103]

There are several processes that can occur with pharmaceuticals in surface waters: sedimentation, adsorption, bioaccumulation, degradation, hydrolysis, and photolysis.[60,104] For example, gemfibrozil and ibuprofen could be bioaccumulated in zebrafish and high concentration of accumulated drugs, 11 mg/L and 25 mg/L respectively, results in development of fish anomalies, while significantly less of accumulated diclofenac – 1 μg/L causes cytopathological damage in rainbow trout.[104] Hydrolysis has a minor impact on the degradation of drugs in surface waters.[20] However, pharmaceuticals could degrade by photolysis. Photodegradation is influenced by latitude, organic compounds, eutrophication state, and solar radiation intensity.[104] Also, dissolved organic matter present in the surface water can accelerate photodegradation by generating the reactive species including hydrated electron and •OH radicals that react with pharmaceuticals and alter their chemical structure.[105] According to Wang *et al.*, photodegradation is controlling mechanism of diclofenac elimination in surface water and drug is degraded into 2,6-dichloroaniline, 2-chloroaniline, and 2,6- dichlorophenol compounds under 1 h of photolysis.[104] Buser *et al.*[106] conducted a study on the behavior of diclofenac in surface waters and also found that it is not persistent and can be eliminated by photodegradation. The photolysis process along with the reactive species has been important in the degradation of danofloxacin, fluvastatin, and paroxetine in the Suwannee River.[105] In the study by Baena-Nogueras *et al*.[107] that was focusing on photolysis (at pH 7), most of the antibiotics showed full degradation, for analgesics and antiinflammatories degradation ranged from 44% to 100%. Nevertheless, the photolysis process could not remove some persistent pharmaceutical ingredients such as carbamazepine, amitriptyline, and gemfibrozil, it requires a change of pH, which will lead to 75% retention.[107] During photolysis, sulfadiazine can be transformed via desulfonation or oxidation mechanisms and sulfamethoxazole is hydroxylated after rearrangement of its isoxazole ring.[107] For enrofloxacin and ciprofloxacin drugs, transformation mechanisms include hydroxylation of the heterocyclic ring, oxidation of C-C bond and piperazine moiety which further disintegrates chemical structure of mentioned fluoroquinolones.[107] Furthermore, antitumor pharmaceutical ingredients may spread in surface waters due to their high polarity and are persistent in the environment.[104] Several products of photodegradation could be more toxic than the original pharmaceuticals such as tetracycline, ibuprofen, and naproxen.[104] For example, ibuprofen degrades to 4-isobutylacetophenone under photolysis and this by-product is known to be more toxic to some aquatic biota than ibuprofen.[104]

Biodegradation is another process that may take place in surface waters. For example, triclosan and estrogen can be readily eliminated under aerobic conditions.[108,109] However, ibuprofen, diclofenac, ofloxacin, and nortriptyline are very resistant to biodegradation under aerobic conditions.[110-113] Furthermore, biodegradation efficiency could be altered due to binding of dissolved pharmaceuticals to sediments.[104]

For example, a mixture of ten pharmaceutical products turned out to be several times more toxic than the sum of the toxicities of these products separately. As a result, the toxic effect of a group of dissolved medicinal substances can be observed even when the concentration of pharmaceuticals is low. In addition to the effects of individual drugs and their degradation products, a significant problem in the accumulation of pharmaceuticals in water bodies is their synergistic effect.[114]

4.3 Soil

Pharmaceuticals that are released into the soil could degrade in different rates, where the half-lives may range from days to years. For example, half-lives of ibuprofen, triclosan, and estriol is 1706, 400, 26 days (in saturated soil), respectively.[115] The pharmaceuticals in soil could be eliminated with several mechanisms as degradation, accumulation by crops, and soil sorption.[115] The degradation rate is influenced by soil properties such as organic carbon content, pH, moisture, and soil bioactivity. Low degradation of carbamazepine in soil was reported by Yu, Liu, and Wu,[68] it is a result of insufficient sorption and persistency, while under aerobic conditions, drug can be eliminated with contribution of microbial degradation.[115] Wu *et al*. confirmed that the degradation rate of chloramphenicol, caffeine, tinidazole, and metronidazole in soil is influenced by organic matter content and microbial activity. Enrofloxacin could be eliminated by bioaccumulation into white fungal roots present in the soil medium.[115]

Furthermore, the veterinary pharmaceuticals after excretion will go to the manure and based on the mobility of pharmaceutical ingredients, they could reach the soil.[116] For instance, veterinary medicines such as abamectin and ivermectin have low mobility in soil.[117] Nevertheless, their degradation can be influenced by climatic conditions, as in the summer ivermectin has six times less half-life than in the winter season. Pharmaceuticals can be accumulated in plants from soil. Plants cultivation onto polluted soils demonstrated minor effect on the pharmaceutical compounds degradation.[118] On the other hand, the addition of the biochar into the soil elevates the adsorption of the pharmaceuticals on soil surface and limits its bioavailability.[119] Moreover, the degradation rate of the substance in sandy soil is higher than in loam soil.[120] The study by Wu *et al*.[121] showed that irrigation of the soil with reclaimed water leads to the growth of pharmaceuticals such as sulfamethoxazole, triclosan, and trimethoprim on the ground. In addition, it led to the transformation of the microbial community in the soil.[121] It can be noted that some pharmaceuticals will not degrade in soil, and as result of it reach groundwaters or leaching fields in this way affecting terrestrial and aquatic biota.[116]

5. Environmental and public health effects of pharmaceuticals

Nowadays more than 1500 pharmaceutical ingredients are in use. Hence, studying the ecotoxicological consequences of all compounds on living organisms is a great challenge.[122] It is suggested to concentrate on pharmaceutical substances that may cause threats,[123] to narrow down the list of substances and concentrate on the effect of drugs on living organisms.[44] Currently, a group of pharmaceutical ingredients with threats has been identified based on various prioritization approaches.[44,122-126]

The influence of drugs on aquatic biota and people has not been fully studied. The main reason is that pharmaceutical concentration in the environment is low, therefore biological impact on an organism cannot be found in acute exposure.[44] As a result, there is chronic exposure to drugs in low concentration for living organisms. In addition, in the environment pharmaceuticals do not occur individually, they met in a mixture with other chemical substances. As a result, it could lead to synergic effects.[44,127] According to Zuccato *et al*.,[44] there is a risk of water-tolerated pharmaceuticals to aquatic organisms, which could lead to mutations and produce genetic modifications.

The effect of pharmaceutical pollution on humans is very complex assessment process. It is due to unknown concentrations and toxicity of pharmaceuticals, which might have long-term implications on public health.[128,129] According to Qiu, the assessment of the potential risks from antibiotics to public health (based on the maximum trigger quotient) demonstrated that even with relatively high removal of the pollutants, notable risks for public health persists in the wastewater.[130] Malchi *et al*. studied the uptake of the pharmaceuticals via polluted vegetables with threshold of toxicological concern (TTC) method and results showed that a child may absorb the lamotrigine TTC concentration through a daily consumption of a vegetable.[131] The potential side effects of the lamotrigine poisoning includes cardiac dysrhythmias, headaches, and seizures.[132]

The most well-known case of pharmaceutical exposure to living organisms was from diclofenac which led to a decrease in the vulture population. The effect of diclofenac was investigated in several papers.[133-135] The early studies of the diclofenac effect mainly focused on vulture decline in South Asian regions.[134,135] The decrease of the population of three species of vultures as *Gyps bengalensis*, *Gyps indicus,* and *Gyps tenuirostris* reached above 95% across the Indian subcontinent. The results of studies showed that most mortality of vultures is associated with visceral gout and huge accumulation of uric acid on and within internal organs. Diclofenac was discovered in the kidneys of vultures. The species were exposed to diclofenac when they consumed carcasses of livestock that had been treated by this substance.[134,135] Furthermore, diclofenac was detected in the liver and plasma.[133] The study conducted by Swan *et al*.[135] confirmed that vultures are sensitive to diclofenac treatment. The investigation showed the mortality of *Gyps africanus* and *Gyps fulvus* within 2 days after exposure.[135] In recent decades, concern about the diclofenac effect on vultures arose in other regions such as the African continent and Spain.[136,137]

The effect of diclofenac was also investigated on the aquatic organism as rainbow trout *Oncorhynchus mykiss.*[138,139] Schwaiger *et al*.[138] indicated the potential risk of diclofenac to the fish organisms. Histopathological organ failure was at 5 μg/L concentration and 28 days exposure.[138] The study by Triebskorn *et al*.[139] showed the failure of kidneys and gills, and the severe effect on the liver of rainbow trout *Oncorhynchus mykiss*.

Another extensive study on diclofenac was conducted by Acuna *et al*..[140] It was found that the global annual consumption of diclofenac by humans is approximately 1443±58 tons. In different freshwater ecosystems, the compound was detected in the concentration range from 21 to 722 ng/L in 38 countries. The substance was included into the EU ‘watch list’ which established a maximum allowable concentration of 100 ng/L. However, diclofenac was not considered a substance with high priority risk for aquatic organisms.[140]

Intersex fish in England is another example of the effect of the pharmaceutical compound on a living organism. Feminized fish was found on 86% of surface waters in the UK.

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The feminization of fish was associated with the presence of female vitellogenin protein in intersex fish. The feminized male fish was exposed to estrogen compounds in water that comes from sewage effluent.[127] The high level of estrone and 17ß-estradiol, and low level of 17α-ethinylestradiol were found in investigated domestic effluents. Correlations between hormones in the effluents and the presence of vitellogenin were shown.[141-143] Panter *et al*.[143] investigated the threat of 17α-ethinylestradiol on male fathead minnows. The result showed an increase in vitellogenin concentration in plasma during acute exposure to substances in the range of 30–120 mg/L.[143] Balch and Metcalfe[144] explored the effect of 17ß-estradiolon female leukophore-free strains of fish (Japanese medaka). All tested male fish were feminized to the female gonadal phenotype. Earlier study by Martin-Robichaud *et al*.[145] also showed the feminization of lumpfish after consumption of *Artemia* that was treated with 17ß-estradiol. It is important to note that the occurrence of intersex fish could lead to the reproduction issues of fish.[142]

Several studies about the adverse effect of pharmaceutical compounds on aquatic organisms were conducted.[122,127,146-148] For example, it was found that clotrimazole could cause a threat to microalgal communities, and lead to growth inhibition.[148] Cleuvers[127] investigated the ecotoxicological risk of naproxen, diclofenac, carbamazepine, clofibric acid, ibuprofen, captopril, metformin, metoprolol, and propranolol on marine organisms as crustacean *Daphnia magna*, green algae *Desmodesmus subspicatus* and macrophytes *Lemna minor*. *Desmodesmus subspicatus* and *Daphnia magna* were sensitive to propranolol with median effective concentration (EC50) of 5.8 mg/L and 7.5 mg/L, respectively. Macrophyte *Lemna minor* was susceptible to diclofenac with EC50 7.5 mg/L. Overall, most drugs had an effect on the growth inhibition of *Lemna minor*. The mixture of drugs had a stronger effect on exposed organisms rather than single compounds.[127] Another exposure of *Daphnia magna* to fluoxetine and clofibric acid showed an effect on the reproduction system of the organism, while a mixture of compounds led to the mortality of zooplankton.[146] Studies conducted by Cleuvers, Flaherty and Dodson, demonstrated that the effect of a mixture of pharmaceutical substances on algae is uncertain and needs more investigations.[127,146]

Guo *et al*.[122] investigated the sensitivity of a group of algae species tolincomycin, tylosin, and trimethoprim. The results showed that cyanobacteria were sensitive to lincomycin exposure with EC50 in the range of 0.095–0.13 μmol/L. The vulnerability of diatom to trimethoprim was detected at EC50 = 7.36–74.61 μmol/L. Both cyanobacteria and diatom were sensitive to tylosin.[91]

Another group of authors[149] conducted a study on the effects of the combined (six) antimicrobial sulfonamides and their compounds of degradation (as sulfonic acid and sulfanilamides) on green algae *Scenedesmus vacuolatus* and duckweed *Lemna minor*. The results illustrated the threat of sulfanilamides to the organisms, while sulfonic acid exposure did not show the negative effect. The mixtures of sulfonamides and sulfanilamides, however, exhibited a high threat, *i.e*. EC50 < 1 mg/L for *Lemna minor and* 1–1.5 mg/L for *Scenedesmus vacuolatus*.[149]

Melvin, Cameron, and Lanctôt studied the reactions of amphibians to pharmaceutical mixtures.[150] The authors identified a devastating effect of cumulative toxicity on striped marsh frog (Limnodynastes peronii) exposed to a mixture of several pharmaceuticals in comparison to the separate compounds of sulfamethoxazole, carbamazepine and naproxen. The results showed that mixtures of non-steroidal pharmaceuticals, commonly found in wastewater, can affect the development of amphibians.

6. The priority pharmaceuticals in Kazakhstan

The pharmaceutical market in Kazakhstan has increased in 2020 to 21.3% in comparison with 2019 and the highest growth rate was observed in the summer (with a peak in July): sales increased 2 times in monetary terms, which coincided with a significant increase in cases of COVID-19 infection in the country.[151] There are 7,455 pharmaceuticals are registered in Kazakhstan.[152] According to statistics of 2020, there are 89 enterprises in the pharmacological sector of Kazakhstan that deals with manufacturing of medications and medicinal devices, wherein 33 are manufacturing medications, 41 medical devices, and 15 equipment for healthcare centers. It should be noted that only 10% share of the pharmaceuticals industry by local companies, while the majority of pharmaceuticals products manufactured and imported from abroad. In the structure of registered medicines, original drugs make up 1,863 or 25%, generics – 5,410 or 73%, and biotechnological – 182 or 2%. At the same time, domestic manufacturers of medical devices significantly increased production capacity during the pandemic, and the production of demanded drugs for the treatment of COVID-19 like azithromycin, levofloxacin, antiviral pharmaceuticals, *etc*. was increased. The amount of manufacturers of medicinal masks and protecting uniforms enlarged from 6 to 15, and it is also planned to release more than 50 additional types of drugs.[152] Table 2 shows the rating data for the sale of medicines in Kazakhstan in 2020.

Table 2. Sales of medicines in Kazakhstan in 2020.[151]

Rating	Type of medicines	Sales in billion KZT
1	Antiviral drugs for systemic use	35.3
2	Anti-inflammatory and antirheumatic agents	15.9
3	Drugs affecting the renin-angiotensin system	11.4
4	Sex hormones and modulators of the reproductive system	8
5	Drugs for the treatment of eye diseases	7.5

In Kazakhstan the pharmaceutical market observed the highest growth rate in summer 2020 (with a peak in July), and sales volume doubled in monetary terms, which coincided with a significant increase in cases of COVID-19 infection in the country.[151] It should be mentioned that according to latter the leading drugs were paracetamol and ceftriaxone. In the key months of 2021 (March, June, and July), the most active demand for these drugs was observed. In addition, the release of new drugs, as well as drugs intended for the treatment of COVID-19, supplied from the country in a pandemic mode, had an impact.[151] Table 3 provides information on top-priority pharmaceuticals that were identified according to ecotoxicological risk-based prioritization study in surface waters and WWTP of different countries.[125]

As can be seen from the table, in many countries as, for example, Kazakhstan, the UK, France, Iran, Korea, Italy, a large number of different groups of medicinal substances are used and the study of their distribution in the environment requires a systematic scientific approach. It has been established that in Kazakhstan, as well as in the world, there are no regulatory documents for the determination of the content of medicinal substances in surface and wastewater, which does not allow them to be regulated. The main environmental problem for the Republic of Kazakhstan is the lack of a regulatory framework for maximum permissible concentrations of medicinal substances entering wastewater or surface water during their production or consumption. For Astana, as well as for the whole of Kazakhstan, the urgency of the issue of contamination of surface, drinking, and wastewaters with medicinal substances are associated with a little study, the lack of certified analytical methods for their determination, and normatively established maximum permissible concentration values.

Practical challenges associated with implementing pharmaceutical monitoring programs in Kazakhstanis due to the absence of consistent sampling and examination procedures, high cost, and restricted availability of analytical techniques needed to quantity the possible presence of various pharmaceutical substances. Local circumstances must be taken into account and consideration should be given to existing water and wastewater treatment processes and pharmaceuticals commonly prescribed, used, or produced in a given catchment area.[158,159]

In October 2020, the Government of Kazakhstan implemented a comprehensive plan to develop the pharmaceutical sector up to 50% (fraction) by 2025.[152] In order to create new and develop existing pharmaceutical production, consequently reducing import dependence, a number of measures of state support for domestic producers have been developed and are being implemented through the conclusion of long-term contracts for the supply of drugs for up to 10 years. The Law of the Republic of Kazakhstan "On Public Health and Health Care System" contains regulations onto the contract for the manufacturing of pharmaceuticals and medical products, which ensure a full agreement with the requirements of good manufacturing practice (GMP) for medications according to the international standard for quality assurance systems for medical devices.[160] It has been forecasted that proper control and utilization will improve environmental situation in Kazakhstan, however, no special inspections have been made since 2020 in the country.[161]

Table 3. Top priority pharmaceuticals in different countries.[125]

Kazakhstan [125,151,152]	Amoxicillin, Clarithromycin, Azithromycin, Diclofenac, Carbamazepine, Acetylsalicylic acid, Sulfamethoxazole, Sulfanilamides, Ibuprofen
United Kingdom [122]	Amitriptyline, Amoxicillin, Azithromycin, Carbamazepine, Ciprofloxacin, Clarithromycin, Diclofenac, Estradiol, Metformin, Mezalazine, Omeprazole, Orlistat
France [153]	Amoxicillin, Aspirin, Ofloxacin, Propranolol, Carbamazepine, Furosemide, Clarithromycin, Diclofenac, Sertraline, Fluoxetine, Fenofibrate
United States [154]	Erythromycin, Oxytetracycline, Sulfamethoxazole, Fluoxetine, Nitroglycerin, Clofibrate, Ibuprofen, Acetominophen, Estradiol, Diclofenac, Caffeine, Carvedilol, Metronidazole, Trimethoprim, Tetracycline
Switzerland [155]	Ethyinylestradiol, Atovaquone, Sertraline, Estradiol, Mycopphenolate mofetil, Propranolol, Acetylsalicylic acid, Naproxen, Felodipine, Ketoconazole, Paracetamol, Amitriptyline, Fluoxetine, Dipyridamole
Iran [156]	Amoxicillin, Cephalexin, Clavulanic acid, Penicillin, Trimethoprim, Sulfamethoxazole, Azithromycin, Erythromycin
Korea [157]	Amoxicillin, Apramycin, Bromhexine, Ciprofloxacin, Diclazuril, Dihydrostreptomycin sulfate, Doxycycline, Enramycin, Erythromycin, Fenbendazole, Flofenicol, Fluvalinate, Ivermectin, Monensin sodium, Norfloxacin, Oxytetracycline
Italy [44]	Amoxicillin, Atenolol, Hydrochlorothiazide, Rantidine, Clarithromycin, Ceftriaxone, Furosemide, Bezafibrate, Ciprofloxacin, Enalapril, Spiramycin, Omeprazole
Russia [49]	Amoxicillin, Ampicillin, Azithromycin Ciprofloxacin, Clarithromycin Norfloxacin, Tetracycline, Trimethoprim Erythromycin, Codeine, Ranitidine, Bezafibrate, Carbamazepine Caffeine, Ketoprofen, Diclofenac, Enalapril, Enalaprilat, Drotaverine, Ethinylestradiol

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The Comprehensive Plan for the Development of the Pharmaceutical and Medical Industry for 2020–2022, approved on October 6, 2020, provides the main directions for supporting and developing the pharmacological and medicinal industry: laws and regulations governing pharmaceutical-related activities, circulation of medications, and medical devices within Eurasian Economic Union, state support measures, research, and development work, attracting investments, staffing the industry, labeling, traceability of medicines and increasing the capacities of domestic manufacturers of medications and medicinal devices.[152]

The National Report of the Ministry of Ecology, Geology and Bioresources for 2018 presents the results of the project "Problems of the environmental situation of the Shchuchinsko-Borovoye resort area and the development of veterinary and sanitary measures." Within the framework of the project, complex studies of surface waters were carried out, however, no studies of medicinal drugs were carried out.[78] It is also indicated there that the quality of the water of the Yesil River and the water reservoir Vyacheslavskoye is rated as “moderately polluted” water, and there is also no data on the analysis of medicinal drugs.

Recent studies showed that research on the analysis of water quality of the transboundary Ural River (between Russia and Kazakhstan) and the Kazakh sector of the Caspian Sea, are severely polluted by chlorinated aromatic compounds, heavy metals, oil pollutants, and pesticides, resulted from manufacturing companies and agricultural sectors nearby. According to findings, the mentioned toxic pollutants exist not only in the water bodies, but also accumulated in the tissues of marine animals. Another reasons of strong contamination of the Caspian Sea is hydrocarbons of petroleum industry caused by offshore oil production.[162] However, the authors did not investigate the contamination of these water areas with medicinal substances.

According to the available literature data, the monitoring and quantification of pharmaceuticals is not carried out at the territory of Kazakhstan. This study is of high importance in the field of assessing water quality for public health, as well as in adapting new approaches and methods to identifying pharmaceuticals in water and, as a result, interpreting the results in relation to human health. The results of the study of the means used to show that Kazakhstan does not conduct a study of the entry and distribution of both priority antibiotics.[125] and drugs of other groups (analgesics, anti-inflammatory, *etc*.) into the environment.[126] Pharmaceutical substances that are not biodegradable, such as carbamazepine, must also be considered.

Based on the literature data it is assumed that different groups of pharmaceutical substances and their metabolites, residues of personal care products, steroids, and others are present in the domestic wastewater of Astana. In further studies, it is planned to pay attention to the detection and determination of such drugs as tetracycline, ceftriaxone, sulfamethoxazole, acetylsalicylic acid, paracetamol, metronidazole, ibuprofen, diclofenac, mildronate, and caffeine. These substances are widely distributed and are in high demand in many countries of the world, including Kazakhstan (Table 4).

Tetracycline, the world's second largest produced and consumed antibiotic, and its analogues, are the most detected antibiotics (80% of wastewater samples) at the inlet and outlet of wastewater treatment plants.[175,176] Similarly, sulfanilamide is found everywhere in reservoirs and wastewater concentrations up to 600 ng/L.[168] Aspirin and paracetamol a class of analgesics and anti-inflammatory drugs, is included in the list of important medications of the World Health Organization, as well as in the list of vital and essential medicines of Kazakhstan.[177,178]
The widespread use of these drugs determines their relatively high share in the total volume of drugs supplied to treatment facilities, which, in turn, necessitates monitoring of their concentrations and studying methods of wastewater treatment from pharmaceuticals using them as model pollutant.[179] The treatment and neutralization of sewage requires the use of particularly effective methods. One such solution was implemented in Denmark, where, with the participation of Grundfos, a wastewater treatment plant was commissioned to turn hospital wastewater into clean water. The results showed that drug residues from treated water were removed by 99.9%.[180]

A WHO report[158] recommends regular monitoring of pharmaceuticals in water resources and drinking water at the national level, in the absence of regulatory mandates, to assess possible levels of prevalence and exposure, in combination with an evaluation of possible risks of exposure to the health of human beings via potable water.

The concentration levels of the large fractionof pharmaceutical substances in the aquatic environment could be decreased by natural processes (such as adsorption to sludge, solar or photodegradation, and biodegradation) or by succeeding drinking water and wastewater treatment processes. In spite of having some distinct pharmacological properties, pharmaceuticals could also be removed using similar approaches with some modifications since the fundamental remediation rules and processing conditions still depend on physical and chemical properties of target pollutant (that is similar to organic compounds) and technological solutions applied.

Careful discharge and usage of pharmaceuticals, which helps to substantially minimize the existence of these compounds in water bodies, soil and plants, will reduce their adverse effects to humans (for instance, antibiotic-resistant infection).[181] This in turn could be accomplished by implementing several of precautionary measures, which includes the cultivating public awareness about probable harmful effects of pharmaceuticals to the environment, highlighting a necessity towards rational drug design, and disposal of pharmaceuticals. One essential practice towards reduction of pharmaceuticals in the environment could be the

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Table 4. The most common pharmaceuticals and their application fields.

Pharmaceutical	Formula	Mode of action	Use	References
Aspirin	$C_9H_8O_4$	analgesic	Used as an analgesic, antipyretic and anti-inflammatory agent	[163-165]
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	anti-inflammatory	Treatment of inflammation state	
Tetracycline	$C_{22}H_{24}N_2O_8$	antibiotic	Disturbs the formation of a complex between the transfer RNA and the ribosome, which leads to the suppression of protein synthesis. Active against gram-positive microorganisms	[166,167]
Sulfanilamide	$C_6H_8N_2O_2S$	antibiotic	Treatment of bacterial infections	[168]
Ceftriaxone	$C_{18}H_{18}N_8O_7S_3$	antibiotic	The bactericidal activity of ceftriaxone is due to the suppression of cell wall synthesis. In vitro, ceftriaxone has a broad spectrum of activity against gram-negative and gram-positive microorganisms	[169]
Sulfomethaxazole	$C_{10}H_{11}N_3O_3S$	antibiotic	Destruction of bacteria that cause infections. Prescribed for the prevention of pneumonia during a course of chemotherapy	[81,121]
Paracetamol	$C_8H_9NO_2$	analgesic	Used as an analgesic, antipyretic and anti-inflammatory agent	[170,171]
Metronidazole	$C_6H_9N_3O_3$	antimicrobial	Used against protozoa, intestinal and other infections	[172,173]
Ibuprofen	$C_{13}H_{18}O_2$	anti-inflammatory	Has analgesic and antipyretic effect	[147,174]

education on appropriate disposal ways and employing more systematic programs to return any unused drugs through centralized points. In accordance with the principle underlying the water safety plan of controlling pollutants at the initial point itself, it would be worthwhile to study currently available treatment technologies in wastewater treatment plants and apply new scientific advancements into practice to more efficiently eliminate toxic pharmaceuticals and emerging pollutants in general from the core pathway of entrance to the water bodies.

7. Current situation in CIS countries

The pollution of the environment with pharmaceuticals is a current issue in many countries, including the CIS countries that border with Kazakhstan. Therefore, it is vital to consider this matter by taking into account the situation with neighbouring states.

Uzbekistan is one of the Central Asian countries that has a prolonged borders with Kazakhstan. According to statistics, more than 60% of the citizens of this country are densely populated in countryside areas. In Uzbekistan, the quality of wastewater discharge by enterprises into the network is regulated. In accordance with the Decree of the Cabinet of Ministers of the Republic of Uzbekistan "On additional measures to improve environmental activities in the field of public utilities" (No. 11 of March 26, 2019), resorcinol is currently included in the list of especially toxic pollutants. In the Republic of Uzbekistan, the following is of concern: sewage from households that are not connected to a centralized sewerage network is discharged into waterproofed cesspools. Wastewater from cesspools is collected by washing machines for further disposal at nearby treatment facilities. There are currently no rules for managing septic tanks in Uzbekistan.[105] The situation with the disposal of the medical waste in Uzbekistan is similar to Kazakhstan. In Republic of Uzbekistan, SanPiN 0317-15 is regulating the storage, deactivation, transportation, processing, and utilization of the medical waste officially. In real life, however, this regulation is neglected leading to the release of the medical waste to the environment.[182]

The Kyrgyz Republic, which is bordering the south part of Kazakhstan, allows the use of treated sewage for irrigation of all crops, but strict control must be exercised by the State Inspectorate for Environmental and Technical Safety and the State Sanitary and Epidemiological Station. The places where wastewater is used must be checked in accordance with the Rules for the Protection of Surface Water.[183,184] The legal framework of Kyrgyzstan determines the generation of pollutants per capita, such as carbon and suspended solids, that can enter wastewater (according to SNiP 2.04.03-85). A serious threat to the health of residents is the unsafe water supply caused by the lack of water pipes or the existence of

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water supply systems that are in poor technical condition and do not follow the requirements of sanitary norms and rules. For example, according to the development program of Kyrgyzstan for 2018–2022, only a third of the country's villages are provided with clean drinking water 24 hours a day. Many rural communities have no running water at all, and residents rely on small streams called ditches for irrigation water. In addition, more than a third (34.4%) of all 1134 water pipes in the Kyrgyzstan does not comply with sanitary standards and rules for maintaining sanitary protection zones, due to the lack of disinfection and treatment facilities. This, in turn, causes a contamination of tap water with various pollutants.[183,184] Another source of contamination of the nature by the pharmaceuticals is unproper disposal of the medical waste, like in Kazakhstan and Uzbekistan.[185]

The Asian part of Russia is also characterized by water resources and wastewater pollution by contaminants including drugs. A steady decline in the intensity of water pollution is observed. There is a decrease in the industrial activity of woodworking processes (including pulp and paper), chemical and petrochemical industries, electric power, and metallurgy. The volume of polluted wastewater in the Asian part of Russia (Perm, Tomsk) is going down over time, presumably due to less water use in these sectors. Studies of drugs and their metabolites in waste and surface water bodies in the Russian Federation are insufficient and focused primarily on the Central and North-West territories. Average concentrations of pharmaceuticals detected in surface, raw and treated wastewater samples were 136, 360 and 181 ng/L, respectively.[49]

Pharmaceutical surveys of aquatic ecosystems and bottom sediments in the North-West territories identified a number of over-the-counter drugs, including the psychostimulants caffeine, the anti-inflammatory ketoprofen and diclofenac, and the antispasmodic drotaverine hydrochloride. More recently in Russia studies were conducted on detection of pharmaceuticals in water bodies as part of the Baltic Sea Action Plan (BASE). According to the results, 20 pharmaceuticals were identified in Saint Petersburg wastewaters, although the original targets were only diclofenac and ethinyl estradiol (as the most common and prioritized type of pharmaceutical pollutants).[49] In summer the concertation of diclofenac in wastewaters reached 355 ng/L, while in winter it went up to 550 ng/L. The scientists estimated a possible environmental concentration of diclofenac in the Neva River to be about 5 ng/L. Nonetheless, the detected diclofenac accumulation in the effluent was significantly higher than in the influent of wastewater. This phenomenon is elucidated by the formation and discharge of conjugated diclofenac metabolites during the secondary wastewater treatment. Similar results were found for another studied pharmaceutical compound – ethinylestradiol - that showed a concentration of 0.4 ng/L.[49] Another work focusing on the North-West region of Russia reported Novikova *et al*. studied the pollution of six surface waters in Russian Federation with different pharmaceuticals the results showed the caffeine was present in all of the studied surface waters within concentrations of 3.8–446 ng/dm^3, and concentrations of ketoprofen, diclofenac, and ciprofloxacin were up to 123, 60, and 31 ng/dm^3, respectively.[47] In 2021 Chernova *et al*., studied occurrence of drugs in the Eastern Gulf of Finland (Russia) and found the following major pharmaceuticals: caffeine, carbamazepine and ketoprofen at 97.9, 2.8 and 14.4 ng/L concentration, respectively. According to the authors, these three pharmaceuticals reached the Gulf via effluents of WWTPs.[186]

In the Republic of Tajikistan the sanitary situation is characterized by the depreciation of the sewerage network, sections of collectors with insufficient capacity or inoperative condition, inefficient wastewater treatment due to the emergency state of the infrastructure. Investment in the rehabilitation and expansion of the sewer network was very limited over the past 25 years. Surface runoff is mainly diverted to open channels and pipes along the streets. The drains are maintained and updated along with the streets and are in better condition than the sewer network. Therefore, it cannot provide proper wastewater treatment for the entire city. Such inadequate wastewater treatment poses a risk to the environment and human health.

8. Concluding remarks and future perspectives

Pollution of the environment by pharmaceuticals necessitated the development of relevant standards. Article 16 of the EU Water Framework Directive (2000/60/EC) defines a strategy to deal with water chemical pollution and is initiating the formation of systematic measures to combat drug contamination. For example, in the Russian Federation the hygienic standards were developed and approved for the content of a certain list of medicines in the air of the working area and atmospheric air, drinking water, and water reservoirs for drinking, cultural, household, and fisheries purposes.[187] In connection with the development of the pharmaceutical industry, the increase in the production and consumption of medicines, and the development of hygienic standards for already-used and newly developed drugs becomes relevant.

To minimize the public health risk from penetration of pharmaceuticals into the environment, primarily via wastewaters, with further contamination of waters and soil, we propose to focus our efforts on three main areas:

1. Improvement of the regulatory and methodological framework aimed at establishing control and monitoring over the ingress of various amounts of drugs into the environment from different sources of production, use, and consumption.
2. Propose efficient treatment/collection/disposal methods that take into account characteristics and behaviour of drugs; and identify marker pharmaceutical pollutants that allow assessing the levels of drug concentrations in different environmental systems.
3. Development of methods for performing measurements of high-accuracy for the determination of various drugs,

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including HPLC-MS or tandem mass spectrometry. This will allow determining the main sources of pharmaceutical waste entering natural systems, their migration routes, assess the degree of environmental pollution, and prevent negative consequences.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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