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Monitoring and Evaluation of Pharmaceutical Eco-Pollutants in Wastewater in Kazakhstan Cities

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ABSTRACT

Currently, the pharmaceutical industry is one of the most developing and dynamic sectors of the global economy. Existing methods of wastewater treatment do not always allow the complete removal of pharmacological preparations, which leads to the fact that these substances enter water resources and can have a negative impact on ecosystems and human health. Due to the increase in water pollution with pharmacological preparations, there is a need for more in-depth research in this area. Assessment of the level of contamination with pharmacological substances in the wastewater of megacities is an important aspect of environmental protection and public health. The purpose of this research work is to evaluate pharmacological pollutants in the wastewater of megacities. This study is aimed at identifying APIs (active pharmaceutical ingredients) that are most likely to have a negative impact on the environment in Kazakhstan. To analyze the content of Amoxicillin, Clarithromycin, Ofloxacin, Ciprofloxacin, Atenolol, Metoprolol, Propranolol, Paracetamol, Ibuprofen, Diclofenac, Cabramazepine and other medicinal substances, standards of these substances were added to the wastewater sample and analyzed by the HPLC-MS method. As a result of this research work, information was obtained on the current level of contamination with pharmacological substances in the wastewater of megacities and their impact on ecosystems and human health. The results of the study can be used to develop measures to reduce pollution and conserve water resources for future generations.

Keywords: pharmaceuticals, waste water, pollution, environment, eco-pollutants, purification.

INTODUCTION

There are several large cities in Kazakhstan, including the capital Astana, as well as Almaty and Shymkent - two cities of republican significance. All these cities are megacities, have a large population, high density of buildings and developed infrastructure. All this entails the need for efficient use of resources, including water resources, which are a key component of human life and its environment. In this paper, the characteristics of water resources of Kazakhstan's megacities, including Astana, Almaty and Shymkent, will be considered.

Cities are an important source of pollution, where many people take medications every day. Pharmaceuticals can enter the environment through the sewer system if they are not completely removed during wastewater treatment in the appropriate treatment facilities. In addition, pharmaceuticals can enter rivers and lakes through waste from the food and pharmaceutical industry. One of the main sources is emissions from the production facilities of pharmaceutical

companies. Most pharmaceutical enterprises are located on the banks of rivers and lakes, which leads to contamination of surface waters with drugs used in the production process.

In addition to these sources of pollution of water systems, pharmaceuticals can also enter the environment from other sources, such as agriculture and aquaculture. In agriculture, the use of veterinary drugs can lead to the appearance of pharmaceuticals in the environment through pets and birds. In turn, pharmaceuticals can enter rivers and lakes through animal husbandry waste, as well as through soil leaching as a result of irrigation. In addition, the use of fertilizers and pesticides in agriculture can also lead to contamination of water resources with pharmaceuticals [Deblonde et al., 2013]. Thus, comprehensive measures to improve the water supply and wastewater treatment system, control water pollution and raise public awareness of problems in this area are necessary to ensure the sustainable development of Kazakhstan's megacities and preserve the environment for future generations. Pharmaceutical compounds can enter the environment from various sources. Some of the main sources include the production of pharmaceuticals, the use of these drugs, as well as their emissions from medical institutions and industrial enterprises. The production of pharmaceuticals is one of the most significant sources of pollution of the water systems of the pharmaceutical compounds [Beisenova et al., 2020]. Contamination can occur both during the manufacturing process and during storage and disposal of unused pharmaceutical compounds residues. Such pollution can occur as a result of industrial waste emissions, which may contain high concentrations of various pharmaceutical compounds. The purpose of this study was to rank pharmaceuticals in data-poor regions on examplre Kazakhstan and Russia. This approach was based on previous studies, but since national use data were not available, information on the occurrence of active ingredients in pharmaceutical products was used as the basis for characterizing exposure. It was expected that APIs present in many products would be used more widely than APIs present in only a few products.

Due to the fact that currently in Kazakhstan the process of urbanization is intensive, especially in large metropolitan areas of the country, pollution from pharmaceuticals is also increasing. The presence and quantity of pharmaceutical contaminants in the natural environment, especially through urban wastewater pollution, has not been sufficiently studied. Therefore, the research object is to identify the amount of pharmaceutical pollutants of the highest priority for the surface waters of Kazakhstan in the wastewater of large cities (Almaty, Astana, Shymkent). Research task is identify the amount of pollutants before and after wastewater treatment for further recomendation of monitoring and assessment of pharmaceuticals in surface waters in developing countries' cities on the Kazakhstan example.

MATERIALS AND METHODS

As part of the study, 3 megacities of the country were selected: Astana, Shymkent and Almaty. These cities were chosen because of their high population density and intensive activity, which can lead to large releases of pharmaceutical substances into the environment (Table 1).

This study is aimed at identifying APIs (active pharmaceutical ingredients) that are likely to have a negative impact on the environment in Kazakhstan. For this purpose, APIs were selected that had a potential danger to the aquatic environment in the Republic of Kazakhstan. Previously, studies were conducted by Aubakirova B.N. and Beisenova R.R. to determine priority pharmaceuticals for surface waters of Kazakhstan. The approach was developed to consider potential impacts on apical endpoints (mortality, growth and reproduction of aquatic biota) in aquatic ecosystems of Kazakhstan and Russia, as well as impacts on possible non-apical endpoints consistent with the therapeutic mechanism

Table 1. Study area for assessment of pharmaceutical pollutants in Kazakhstan

Megapolisies	Area, km^2	Population	Location
Astana	797,33	1,430,467	The banks of the Ishim River in North part of Kazakhstan
Almaty	683,5	2,211,198	The extreme southeast of Kazakhstan, at the foot of the Trans-Ili Alatau mountains
Shymkent	1170	1,222,055	The south part of Kazakhstan

of action of API. 20 APIs were selected based on the amount of product containing the ingredient for pharmaceutical products in Kazakhstan and pharmaceutical products used in veterinary practice in Russia. The number of pharmaceutical products that contain active pharmaceutical ingredients was also taken into account, the most widely used compound being paracetamol (a pain reliever), followed by hydrochlorothiazide (a diuretic used to treat high blood pressure, swelling and fluid retention) and metronidazole (an antibiotic) for Kazakhstan pharmaceutical market, clarithromycin, ciprofloxacin, amoxocillin, ibuprofen, carbamazepine, propronalol and others [Aubakirova B.N., 2017]. The relative exposure of those APIs used in 3 or more products was characterized by estimating the exposure index for surface waters. EI was calculated by multiplying the number of API-containing products available on the market, the average daily dose and the proportion of the drug not metabolized by the patient, as well as the proportion not removed by wastewater treatment plants (WWTP) [Halling-sorensen et al., 2008]. The share of non-metabolized APIs was obtained from peer-reviewed articles and available online databases. Compounds without data were considered completely eliminated from the body. The proportion not removed by wastewater treatment plants was estimated using the equation proposed by the guidelines for environmental risk assessment of medicines for human use (EC 2003) [ECA, 2016], with minor changes (Equation 1):

$$F_{wwpt} = 1 - \frac{Sludge_{inhab} \times K_{oc} \times foc_{sludge}}{WasteW_{inhab} + Sludge_{inhab} \times K_{oc} \times foc_{sludge}} \quad (1)$$

where: F_{wwtp} is the proportion of pharmaceuticals released from wastewater treatment plants. The wastewater parameters were derived from the EU technical guidelines on chemical risk assessment (EC 2003), as they are widely recognized for use in risk assessment. WasteWinhab is the amount of wastewater per person per day, which was taken to be 200 liters/day. Sludgeinhab is the mass of sludge waste per person per day (inh/d), which was assumed to be 0.074 kg/inh/day (EC 2003) [Sampter, 2010]. Focsludge (the proportion of organic carbon in the sediment) was assumed to be 0.326. The OU-soil distribution coefficient (K_{oc}) was estimated using a model established for ionizing organic chemical compounds proposed by Franco and Trapp.

Assessment of apical effects

Predicted no-effect concentrations (PNECs) were calculated for each API using Equation 2. To estimate PNECs, we collected all available experimental ecotoxicological data on the toxicity of APIs to apical endpoints of aquatic organisms from peer-reviewed articles using Google scholar, Web of Knowledge, and Scopus, and also online datasets [FASS, 2011]. Data contained acute and chronic ecotoxicity endpoints as lethal half-maximal concentration/effect concentration (LC/EC_{50}) values. For substances for which no experimental ecotoxicity data were available, quantitative structure-activity relationship (QSAR) tools were used to fill any gaps [OECD, 2009]. This software helped identify potential analogues and build a data matrix based on them. We initially selected a protein binding profile. We then selected ecotoxicological information in the endpoints section, which included growth, immobilization, and mortality. We then used the ECOSAR aquatic toxicity classification system in the categorization module. Finally, the toolkit processed the data with a common structure (70–90%). In cases where the tool determined that predictions were not accurate, those predictions were not included in the priotyping analysis. The following Equation 2 was used:

$$PNEC = \frac{EcoTox}{AF} \quad (2)$$

where: *PNEC* is the predicted no-effect concentration, *EcoTox* is the most sensitive ecotoxicological data for the aquatic sector, and *AF* is the safety factor. The *AF* factor was selected based on the Technical Guidelines for Risk Assessment [ECA, 2016].

Non-apical endpoints. To account for nonapical effects associated with the therapeutic regimen of each API, we used an approach similar to that proposed by Huggett et al. (2003), and collected information on therapeutic plasma concentrations (HtPC) of each API in humans. Information on HtPC was obtained from online databases [Medsafe, 2015, Drugs.com, 2016, Kim S et al., 2016].

API ranking

The last stage of the study was the prioritization of API. Risk scores were used to rank compounds. Basically, the assessment was made by dividing the exposure indices for water and fish by PNEC or TCP (therapeutic plasma concentration).

APIs with the highest ratings were classified as substances that should be included in the list of concerns. Wastewater sampling was carried out in accordance with the methods established by the State Standard and international standards for the selection and analysis of water samples, as well as taking into account the specific features of each sewage treatment plant [Roos et al., 2012].

Experimental ecotoxicity data for aquatic fish and/or algae were available for 154 of the 237 APIs, and HtPC data were available for 201 of them. Therefore, experimentally based PNECs were used for prioritization for 70% of connections, and for 66 connections, PNECs defined using QSAR were used. The highest ranked substances based on apical ecotoxicological endpoints are amoxicillin, clarithromycin, azithromycin, ketoconazole and benzylpenicillin, while the highest ranked compounds based on non-apical evaluation are lisinopril, orlistan, estradiol valerate, drotaverine and estradiol [Dong et al., 2013].

In the course of the study, a comprehensive analysis of wastewater samples for the presence of pharmacological substances was carried out. Wastewater samples were collected at several points at each sewage treatment plant, including those located immediately before and after the treatment stages. To preserve the quality of wastewater samples, sterile glass vials previously washed with distilled water were used. Each sample was marked accordingly with the date and place of sampling. The samples were transported to the laboratory in a refrigerator with a temperature no higher than +4 °C to prevent distortion of the analysis results.

RESULTS

The Figure 1 shows pharmaceuticals that were prioritized as water pollutants by volume of consumption in Kazakhstan. The first 20 APIs were selected, which are common and make up more than 3 pharmaceutical products that are included in the national register of pharmaceuticals used in Kazakhstan (Figure 1). The same APIs are given in Figure 2 for pharmaceuticals that were included in the national register of the Russian Federation, drugs used in veterinary practice (Figure 2). For Russia, mainly antibiotics and antiparasitic products such as Oxytetracycline, Fipronil, Amoxicillin, and Praziquantel were widely used in veterinary pharmaceutical products. When APIs used in fewer than three products in the pharmaceutical market of Kazakhstan were excluded, a list of 237 APIs was obtained for further prioritization. For Russia in veterinary practice, these were 98 APIs. Experimental data on the ecotoxicity of aquatic species such as daphnia, fish and algae were available for

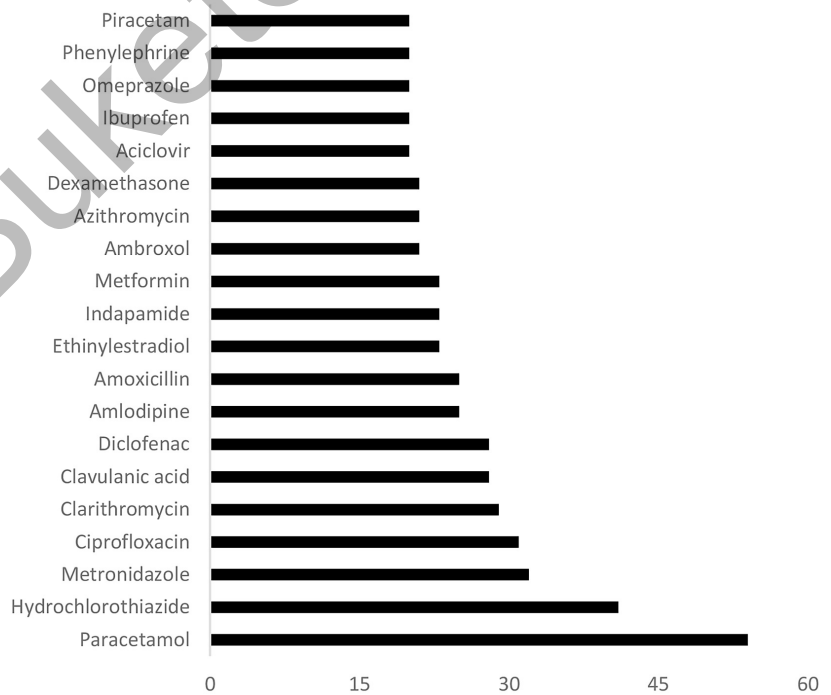

Figure 1. Top 20 active ingredients used in Kazakhstan, by number of products

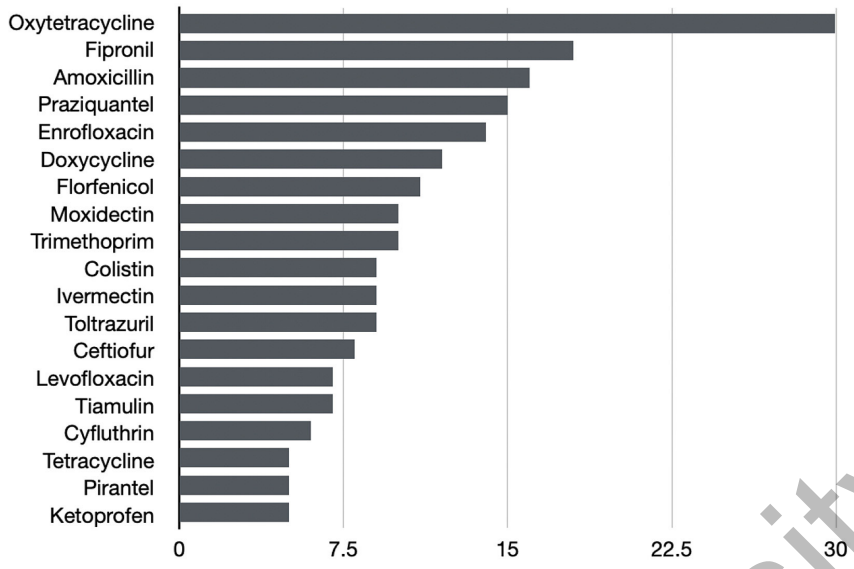

Figure 2. Top 20 active substances used in veterinary practice in Russia, by number of products

154 of 237 APIs in Kazakhstan, and for Russia 88 of 98 APIs. Therapeutic concentration data in human plasma were available for 201 of 237 in Kazakhstan pharmaceutical products, and in Russian -77 of 98. For prioritization, predicted no-effect concentration (PNEC) based on experimental data was used for 70% of compounds, and PNEC based on QSAR for 66 connections of Kazakhstan APIs, and 22 Russian APIs. The highest-ranking compounds for apical ecotoxicology scores were amoxicillin, clarithromycin, azithromycin, ketoconazole, and benzylpenicillin, while the highest-ranking compounds for non-apical scores were lisinopril, orlistat, estradiol valerate, drotaverine, and estradiol. Table 4 shows the top five compounds by disease classification. The classification of diseases is based on classes of disease cases registered in healthcare institutions in Kazakhstan in 2021 [MHSD, 2014] and veterinary drugs in Russia in 2023 (Table 2–3). The study found that the main drugs that may cause concern in Kazakhstan are amoxicillin, clarithromycin, azithromycin, ketoconazole, benzylpenicillin, terbinafine, drotaverine, diclofenac, benzathine benzylpenicillin and telmisartan, which were identified as environmentally high-risk drugs because they had highest risk estimates. Most of the pharmaceuticals that rank high in our research data in Kazakhstan and Russia relate to the treatment of infectious and parasitic diseases, so most of them are antibiotics and anthelmintics (Table 4). Currently, antibiotics are one of the most well-studied pharmaceutical classes in terms of acute toxicity to aquatic organisms [Brausch, et al., 2011]. However, we still have limited data on the chronic effects of many antibiotics in aquatic ecosystems. Most ecotoxicological studies have focused on the acute toxicity of antibiotics to algal species, and EC50 values range from 0.002 mg/L to 1283 mg/L [Guo et al., 2015].

Most substances on the rating list are reported to have toxic effects on aquatic organisms. For example, Shi et al. in 2012 showed that clotrimazole can affect the larval development stage of X. tropiclalis and lead to the death of X. tropiclalis even at low concentrations (0.1 μg/L) [Shi, 2012]. In 2008, Porsbring et al. assessed the toxicity of clotrimazole to natural microalgae communities in 2009. Research results have shown that this compound inhibits the growth of algal communities and can change their pigment profile and physiology [Porsbring, 2009]. Hegelund et al. in 2004 studied the response of fish to ketoconazole. Their results showed that this compound had an effect on rainbow trout and killifish at doses of 12 and 100 mg/kg, as it inhibited the activity of fish cytochrome enzymes [Hegelund et al., 2004]. The Holling-Sorensen study showed that benzylpenicillin was toxic to M. aeruginasa, with an EC_{50} of 0.005 mg/L [Halling-Sorensen, 2000]. There are a large number of published studies describing the environmental risks of clarithromycin. For example, Oguz and Mihçokur in 2014 studied the environmental risks of drugs in Turkey and concluded that

Table 2. Summary information on the classification of API in Kazakhstan according to cases of morbidity in the population

#	Classification of diseases	API interfaces with the highest rating (EI_{river}:PNEC)	API interfaces with the highest rating (HtPC:EI_{fish})
1	Respiratory diseases	Xylometazoline Beclomethasone Chloropyramine Pheniramine Clemastine	Loratadine Clemastine Montelukast Dextromethorphan Fexofenadine
2	Diseases of the circulatory system	*Telmisartan* Atorvastatin Rutoside Losartan Captopril	Lisinopril Telmisartan Amiodarone Rosuvastatin Amlodipine
3	Digestive system diseases	Drotaverine Ursodeoxycholic acid Thioctic acid Bisacodyl Pioglitazone	Orlistat Drotaverine Repaglinide Loperamide Hyoscine butyl bromide
4	Diseases of the genitourinary system	Ketoconazole Levonorgestrel Nystatin Miconazole drospirenone	Estradiol valerate Estradiol Miconazole Ethinyl estradiol Ketoconazole
5	Diseases of the eye and its appendages	Neomycin Betaxolol Tropicamide	Betaxolol Neomycin Tropicamide
6	Diseases of the hematopoietic organs	Clopidogrel	Clopidogrel
7	Nervous system diseases	Cinnarizine Paracetamol Betagistine Carbamazepine Gabapentin	Cinnarizine Fentanyl Acetylsalicylic acid Tramadol Valproic acid
8	Diseases of the musculoskeletal system and connective tissue	Diclofenac Etofenamate Ketoprofen Clodronic acid Naproxen	Methyl salicylate Diclofenac Indomethacin Benzydamine Ketoprofen
9	Infectious and parasitic diseases	*Amoxicillin* Clarithromycin *Azithromycin* Benzylpenicillin *Terbinafine*	Clotrimazole Isotretinoin Disulfiram *Terbinafine* *Azithromycin*
10	Tumors	Oxaliplatin Cisplatin Mycophenolic acid Capecitabine Paclitaxel	Paclitaxel Mycophenolic acid Imatinib Anastrozole Topotecan
11	Mental and behavioral disorders	Citicoline Piracetam Fluoxetine Clozapine Sertraline	Sertraline Fluoxetine Chlorpromazine Risperidone Clozapine

Note: Pharmaceuticals in bold indicate that they typically rank at the top of the drug rankings for both risk ratios. Pharmaceuticals in italics indicate that they are found in the top 5 APIs for both Russia and Kazakhstan. API – active pharmaceutical ingredients; EIw – exposure index of surface waters; PNEC – predicted non-effect concentration; HtPC- therapeutic plasma concentrations; EIfish – exposure index in fish plasma.

may be invaluable in determining the broader impact of APIs around the world.

As a result of the calculation, the highest priority veterinary ingredients in Russian surface waters were the following: Megestrol, Colistin, Amoxicillin, Streptomycin, Milbemycin oxime, Telmisartan, Ketoconazole.

After prioritizing API for Kazakhstan and Russia the concentration of API in Kazakhstan's megapolicies were selected for studiing of quality

Table 3. Summary information on the classification of APIs in Russia by groups of veterinary pharmaceuticals

#	Classification of using	API interfaces with the highest rating (EI_{river}:PNEC)	API interfaces with the highest rating (HtPC:EI_{fish})
1	Antiparasitic drugs	Milbemycin oxime Salinomycin Etofenprox Fenbendazole Ivermectin	Salinomycin Thymol Diethyltoluamide Formic acid Aversectin
2	Antibacterial drugs	Colistin *Amoxicillin* Streptomycin Azithromycin *Ampicillin*	Nifuroxazide Nosiheptide Enramycin Ceftiofur Florfenicol
3	Painkillers and anti-inflammatory drugs	Benazepril Tramadol Pyriproxyfen Cloprostenol Propranolol	Benazepril Cloprostenol Prednisolone Flunixin Pimobendan
4	Antifungals, antiseptics, gastrointestinal drugs	Megestrol Telmisartan Trazodone succinate Terbinafine Ketamine	Chlorhexidine Bismuth subnitrate Terbinafine Ketamine Trazodone succinate

Note: Pharmaceuticals in bold indicate that they typically rank at the top of the drug rankings for both risk ratios. Pharmaceuticals in italics indicate that they are found in the top 5 APIs for both Russia and Kazakhstan. API – active pharmaceutical ingredients; EIw – exposure index of surface waters; PNEC – predicted non-effect concentration; HtPC – therapeutic concentration in human and animal plasma; EIfish – exposure index in fish plasma.

Table 4. The highest priority APIs have been identified in the surface waters of Kazakhstan and Russia

Kazakhstan	Russia	United Kingdom [63]	France [32]	United States [6]	Switzerland [64]	Iran [85]	Korea [86]	Spain [87]
Amoxicillin Clarithromycin Azithromycin Ketoconazole Benzylpenicillin Terbinafine Drotaverine Diclofenac Benzathine benzylpenicillin Telmisartan Disulfiram Oxytetracycline Ofloxacin Atenolol Carbamazepine	Megestrol Colistin Amoxicillin Streptomycin Milbemycin oxime Telmisartan Ketoconazole Benazepril Azithromycin Tramadol Pyriproxyfen Salinomycin Ampicillin Etofenprox	Amitriptyline Amoxicillin Atorvastatin Azithromycin Carbamazepine Ciprofloxacin Clarithromycin Diclofenac Estradiol Metformin Mezalazine Omeprazole Orlistat	Amoxicillin Aspirin Ofloxacin Propranolol Carbamazepine Furosemide Clarithromycin Diclofenac Sertraline Fluoxetine Fenofibrate Paroxetine Fluvoxamine	Erythromycin Oxytetracycline Sulfamethoxazole Fluoxetine Nitroglycerin Clofibrate Ibuprofen Acetominophen Estradiol Diclofenac Caffeine Carvedilol Metronidazole Trimethoprim Tetracycline	Ethyinylestradiol Atovaquone Sertraline Estradiol Mycopphenolate mofetil Propranolol Acetylsalicylic acid Naproxen Felodipine Ketoconazole Paracetamol Amitriptyline Fluoxetine Dipyridamole	Amoxicillin Cephalexin Clavulanic acid Penicillin Trimethoprim Sulfamethoxazole Azithromycin Erythromycin	Amoxicillin Apramycin Bromhexine Ciprofloxacin Diclazuril Dihydrostreptomycin sulfate Dpxycycline Enramycin Erythromycin Fenbendazole Flofenicol Fluvalinate Ivermectin Monensin sodium Norfloxacin Oxytetracycline	Amoxicillin Atenolol Hydrochlorothiazide Rantidine Clarithromycin Ceftriaxone Furosemide Bezafibrate Ciprofloxacin Enalapril Spiramycin Omeprazole

clarithromycin may pose a potential hazard to living organisms due to its high bioconcentration factor [Oguz et al., 2014]. In addition, the substance was found in surface waters with the highest concentration of clarithromycin in rivers in Italy – 0.02 μg/L [Calamari et al., 2003]. Over the past decades, a significant amount of literature has been published on the toxicity and prevalence of diclofenac. A recent study by Acuna et al. reported that the emergence of diclofenac was mentioned in 142 articles covering 38 countries. Moreover, there were 156 reports of ecotoxicological effects of this substance [Acuna t al., 2015].

Overall, this assessment gives priority to prescription APIs that are most likely to be present in Kazakhstan's surface waters and may pose the greatest risk to living organisms. We recommend that these compounds be taken into account in future studies to monitor API concentrations in the environment of Kazakhstan and establish the level of risk for the country's ecosystems. It would be interesting to consider the effect of a mixture of pharmaceuticals on surface waters. Although the paper focuses on prioritizing pharmaceuticals used in Kazakhstan, the design of the approach means that it can be applied to other countries with limited data on API use. Thus, this approach

API in minicipality waste waters. The results of the studies are listed in Table 5, which indicates the class of the drug, the international nonproprietary name (INN), as well as the concentrations of these substances in three megacities. The table 1 shows that in the three megacities of Kazakhstan: Almaty, Astana and Shymkent the number of APIs is different, this is due, first of all, to the difference of population in these three large cities in Kazakhstan. As of October 1, 2023, the population of Astana city was 1,430,467 people, Almaty is the largest city in Kazakhstan by population: as of October 2023, the city had a population of 2,211,198 [Office of National Statistics of Kazakhstan, 2023]. Shymkent in 2024 has 1,222,055 inhabitants [Office of National Statistics of Kazakhstan, 2024]. This explains the high content of some APIs in Almaty such as amoxicillin, ibuprofen, diclofenac. The most part of APIs are highly concentrated in Shymkent, which is explained by the fact that the city has a pharmaceutical plant Pharmchem, which has been operating since the times of the Soviet Union, and this further aggravates the state of surface water pollution with pharmaceutical contaminants. In Astana, the two studied APIs were in higher concentrations than in other cities, this may be due to the fact that the high content of pollutants is influenced by the climatic conditions of the Northern region and the stability of the drugs. The results of studies to determine the concentrations of drugs after purification in the megacities of the country are listed in Table 6, which indicates the class of the drug, the international nonproprietary name (INN), as well as the concentrations of these substances in three megacities. The difference between the contents before and after treatment in the studied three cities may indicate that the condition of treatment facilities in Almaty and Shymkent is not in good condition compared to Astana. In Astana, due to the fact that it has recently been using innovative methods of wastewater treatment due to the capital factor, the API content decreases to a greater extent after treatment. From the conducted research, it was found that in the treated wastewater of the Astana sewage treatment plant, the concentration of amoxicillin is 40 ng/l, clarithromycin is 32 ng/l, ofloxacin – 3 ng/l, ciprofloxacin – 30 ng/l, atenolol – 10 ng/l, metoprolol – 160 ng/l, propranolol – 90 ng/l, paracetamol – from 60 ng/l, ibuprofen – 102 ng/l, diclofenac – from 98 ng/l, cabramazepine 40 ng/l.

The following concentrations were found in the treated wastewater of the sewage treatment plant in Almaty: amoxicillin 60 ng/l, clarithromycin – 58 ng/l, ofloxacin – 5 ng/l, ciprofloxacin – 50 ng/l, atenolol – 15 ng/l, metoprolol – 223 ng/l, propranolol – 95 ng/l, paracetamol – 71 ng/l, ibuprofen – 145 ng/l, diclofenac – 165 ng/l, cabramazepine 57 ng/l. The following concentrations were found in the treated wastewater of the Shymkent sewage treatment plant: amoxicillin 54 ng/l, clarithromycin – 61 ng/l, ofloxacin - 4 ng/l, ciprofloxacin – from 55 ng/l, atenolol – 9 ng/l, metoprolol - 260 ng/l, propranolol – 98 ng/l, paracetamol – 69 ng/l, ibuprofen – 134 ng/l, diclofenac – 180 ng/l, cabramazepine 65 ng/l. These results show that pharmaceutical substances that can have potencial of a negative impact on the environment and human health because they have been found in the wastewater of sewage treatment plants in various cities. Concentrations of these substances in treated wastewater are also high, which indicates

Table 5. Concentrations of API detected in wastewater before treatment

No.	Drug class	API	Concentration, ng/l		
			Astana	Almaty	Shymkent
1	Antibiotics	Amoxicillin	190	270	260
2		Clarithromycin	850	760	650
3		Ofloxacin	45	50	70
4		Ciprofloxacin	120	100	120
5	Beta blockers	Atenolol	38	45	55
6		Metoprolol	890	800	910
7		Propranolol	150	170	185
8	Nonsteroidal anti-inflammatory drugs	Paracetamol	1200	1350	1600
9		Ibuprofen	550	720	650
10		Diclofenac	480	600	550
11	Antiepileptic drugs	Carbamazepine	1200	1020	940

Table 6. Concentrations of drugs detected in wastewater before treatment

No.	Drug class	Mnn	Concentration, ng/l					
			Astana		Almaty		Shymkent	
			Before	After	Before	After	Before	After
1	Antibiotics	Amoxicillin	190	40	270	60	260	54
2		Clarithromycin	850	32	760	58	650	61
3		Ofloxacin	45	3	50	5	70	4
4		Ciprofloxacin	120	30	100	50	120	55
5	Beta blockers	Atenolol	38	10	45	15	55	9
6		Metoprolol	890	160	800	223	910	260
7		Propranolol	150	90	170	95	185	98
8	Nonsteroidal anti-inflammatory drugs	Paracetamol	1200	60	1350	71	1600	69
9		Ibuprofen	550	102	720	145	650	134
10		Diclofenac	480	98	600	165	550	180
11	Antiepileptic drugs	Carbamazepine	1200	40	1020	57	940	65

the inefficiency of existing methods of water purification from pharmacological pollutants. In particular, the largest amount of pharmaceutical substances was found in the wastewater of sewage treatment plants in Almaty and Shymkent, which may be due to a higher level of environmental pollution in these regions.

DISCUSSIONS

Most of the drugs in our rating were discovered during monitoring studies around the world. This provides a level of confidence in the approach. For example, amoxicillin was detected at concentrations of 28 μg/L and 82.7 μg/L in German hospital wastewater during the daytime [Kummerer, 2001]. Yasojima et al. in 2006 showed clarithromycin and azithromycin at concentrations of 647 ng/L and 260 ng/L in Japanese wastewater [Yasojima, 2006]. Some APIs have been studied in great detail in the world and have ecotoxicological data for aquatic organisms, for example, Amoxicillin has the following data, which are given in Table 7. The concentrations of amoxicillin we found are much lower than the above-mentioned doses for aquatic biota, but antibiotics can affect not only aquatic biota, but also the residual concentration through drinking water can reduce human sensitivity to the antibiotic and therefore increase the effective dose. We also previously conducted computational studies for Russia to determine the potential hazards of veterinary pharmaceutical products that are widely used in Russia. These turned out to be mainly antibiotics and antiparasitic products such as Oxytetracycline, Fipronil, Amoxicillin, Praziquantel. In a comparative study, when APIs used in less than three products in the pharmaceutical market of Kazakhstan were excluded, a list of 237 APIs was obtained for further prioritization. For Russia in veterinary practice there were 98 APIs. According to preliminary calculations of the Risk Assessment of Pharmaceutical Ingredients for Kazakhstan, the highest exposure rates in surface waters were observed for benzylpenicillin, metronidazole, sulbactam, ceftriaxone and sulfamethoxazole, while the highest exposure rates in fish plasma were observed for lisinopril, orlistat, telmisartan, drotaverine and terbinafine [Tulugenova, 2022]. For Russia, the highest exposure rates in surface waters were observed for megastrol, colistin, amoxicillin, streptomycin, molbemycin-oxime, and the highest exposure rates in fish plasma were for salinomycin, thymol, nosiheptide, nifuroxoside and chlorhexidine [Wilkinson, et al., 2022, Tulegenova et al., 2021]. Experimental data on the ecotoxicity of aquatic species such as daphnia, fish and algae were available for 154 of 237 APIs in Kazakhstan, and for Russia 88 of 98 APIs. The highest-ranking compounds for apical ecotoxicology scores were amoxicillin, clarithromycin, azithromycin, ketoconazole, and benzylpenicillin, while the highest-ranking compounds for non-apical scores were lisinopril, orlistat, estradiol valerate, drotaverine, and estradiol. Although the ranking approach used a different approach than previous studies, the results show that some of the top-ranked compounds in this study were also highly ranked in earlier prioritization

Table 7. Ecotoxicological information on amoxicillin

Aquatic species	Toxic doses	Time	Concentration, mg/l	Reference
Daphnia magna	EC_{50}	24 hour	1000	[Mutiyar et al., 2013]
Anabaena CPB4337	EC_{50}	72 hour	56.3	[FASS, 2011]
Oryzias latipes	LC_{50}	96 hour	1000	[FASS, 2011]
Pseudokirchneriella subcapitata	EC_{50}	72 hour	1500	[FASS, 2011]
Synechococcus leopoliensis	EC_{50}	72 hour	0.00222	[Santos, 2010]
Synechococcus leopoliensis	NOEC	chronic	0.00078	[Santos, 2010]
Lemna minor	EC_{50}	7 days	21.8	[Aubakirova et al., 2017]
Chlorella species	EC_{50}	96 hour	853.54	[Aubakirova et al., 2017]

Note: EC_{50} – half-maximal effective concentration; LC_{50} – median lethal dose; NOEC is the concentration that has no observable effect.

studies. For example, amoxicillin, clarithromycin, diclofenac, and azithromycin with the highest risk scores were identified as high priority in the UK ecotoxicology risk prioritization study by Guo et al. [Guo et al., 2016]. Moreover, amoxicillin was found to be the chemical of greatest concern to aquatic life in the UK, France, Italy, Iran, Korea and Spain. Cooper et al. concluded that sulfamethoxazole, diclofenac and clarithromycin were high-risk drugs in a study conducted in the USA [Cooper et al., 2008]. Ketoconazole was identified as one of the priority substances in the study by Roos et al. in aquatic ecosystems in Switzerland [Roos, 2012]. Lisinopril, orlistat, estradiol valerate, cinnarizine, drotaverine, estradiol and clotrimazole have been found to have minor effects on fish. Estradiol was identified by Guo et al. as having the potential to have subtle effects on fish [Guo et al., 2016].

CONCLUSIONS

Determining the concentration of these substances in wastewater is important in order to assess the level of environmental pollution and take measures to reduce emissions and improve the efficiency of wastewater treatment methods. In addition, some of these substances can be potentially dangerous to human and animal health, so their concentration in wastewater should be controlled and reduced to a safe level. To successfully remove many pollutants, including priority pharmaceuticals, additional purification methods using oxygen oxidation, catalytic oxidation with hydrogen peroxide, and ozone can be introduced. Researchers show the possibility of purifying various drugs using this technological method [Gurinovich et al., 2012]. Data on the concentration of pharmacological substances in the treated wastewater of the KOS cities of Astana, Almaty and Shymkent can be useful for developing strategies to improve water quality and reduce the impact of pharmacological pollutants on the environment and human health. In addition, the results of this study can serve as a basis for taking measures to reduce emissions of pharmacological substances into the environment and establish strict requirements for permissible concentrations of these substances in wastewater. It is also necessary to take into account the possible consequences of water purification measures that may lead to the transfer of pharmacological pollutants to other ecosystems, for example, to soil or groundwater. Therefore, it is also necessary to conduct monitoring and research to identify possible transfers of pollutants and take appropriate measures to prevent negative consequences. In order to verify the correct complete purification during monitoring, the maximum permissible concentrations of the highest priority pharmaceuticals for Kazakhstan in relation to aquatic biota should be taken into account. During monitoring, ongoing monitoring of qualitative and quantitative analyzes of priority pharmaceuticals would help manage environmental toxicity issues of these pollutants. In general, solving the problem of surface water pollution with pharmacological pollutants is an important task for society. Carrying out measures to improve the quality of water resources, together with scientific research and public activity, can contribute to the conservation of biological diversity, improve the quality of life of people and ensure environmentally sustainable development.

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