**REPORTS OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN**
ISSN 2224-5227 **https://doi.org/10.32014/2019.2518-1483.1**
Volume 1, Number 323 (2019), 5 – 10

UDC 57.042
IRSTI 87.15.21

N.A. Ibragimova[1], M.B. Lyu[1], D. Snow[2], A.N. Sabitov[1]

[1] JSC «Scientific Center for Anti-infectious Drugs», Almaty, Kazakhstan;
[2] Water Sciences Laboratory University of Nebraska, Nebraska, USA
nailya.73@mail.ru, mlyu@mail.ru, dsnow1@unl.edu, aitugans@mail.ru

ON THE QUESTION OF THE NECESSITY OF NORMATING BIO-TRANSFORMED SUBSTANCES MEDICINAL PREPARATIONS IN OBJECTS OF THE ENVIRONMENT (SHORT MESSAGE)

Abstract. After entering the body, medications are subjected to a cascade of interrelated biochemical reactions, which result in not only is the pharmacological effect achieved, but also the formation of the biotransformation products. Theses chemicals ultimately wind up in waste water, where they are also exposed a whole complex of abiotic and biotic processes. As a result, chemical compounds with new properties can be formed, able to change physiological, biochemical, genetic and other parameters living organisms and to enter the food chain into the human body. Therefore, it can be argued about the urgent problem on the necessity of predicting and understanding biotransformed products of medicinal products in environmental objects, and including wastewater, which will determine the impact of the risks health risks, expand (supplement) the standards of environmental pollution and define a strategy for finding and developing new drugs.

Key words: drugs, biotransformation, rationing, waste water, water resources.

Pharmaceutical preparations are used in medicine all over the world and are defined as substances used for the prevention, diagnosis, treatment of the disease, include more than 4000 kinds of chemicals with different physico-chemical, biological properties and different biochemical effects. Once introduced into the body, they can be metabolized or remain unchanged. As a result, a mixture of pharmaceutical preparations and their metabolites enters the waste water, and depending on the polarity, water solubility and stability, some of these compounds may not be completely removed or transformed during the purification process [1]. The products of drug transformation can be preserved in environmental objects, which affect the processes of circulation of substances and energy in natural ecosystems and may even affect human health [2].

The main source of products of biotransformation of medicinal products to environmental objects are man and animals [3]. Also, medicinal products can flow through the sewage system, passing through a sewage treatment plant and then entering open water sources or with household waste to a landfill [4]. Medicinal products may not be used by patients due to discontinuation due to side effects, recovery of the patient or the achievement of their shelf life. [5]. Thus, for example, paracetamol with a concentration of 117 μg/l, ciprofloxacin 269 ng/l, and even cocaine 57 ng/l were determined in the landfill leachate [6].

Seven antibiotics and one antibiotic-metabolite with a detection rate of 3.1 to 62.5% were found in the delta of the Snake River (Idaho, USA). At the same time, five of the detected 21 antibiotics are both veterinary and used for human treatment [7].

In European countries, analgesics and anti-inflammatory drugs such as acetylsalicylic acid and non-steroidal anti-inflammatory drugs (for example, ibuprofen) are in great demand, followed by antibiotics

[8]. A significant amount of medicinal substances is not easily biodegradable in the purification system and likely to occur in unchanged form or in the form of metabolites enters surface and groundwater. It is this source of pharmaceutical pollution of the environment that practically cannot be controlled and regulated by existing standards [9]. In 2011, WHO published a report on "Drugs in drinking water" on the contamination of water with pharmaceutical products, which is becoming a serious global environmental problem. Traces of medicines are found in various aquatic systems [10].

In European countries has effectively established a policy return to the pharmacy unused medications, which are then sent for destruction by high-temperature combustion [11]. The conducted sociological researches have shown, that the highest proportion among European countries belongs to Sweden, where about 43 % of respondents return unused medicines to the pharmacy. In the UK, there are 22 high-temperature furnaces for incineration of waste products of pharmaceutical enterprises, which leads to economic costs of delivery, and delivering vehicles must comply with safety principles [12].

It is known that medicinal preparations cannot be removed in the process of wastewater treatment, their components are found in water and bottom sediments. After using dissolved air and ozone oxidation, pharmaceutical wastewater meets the water quality standards for wastewater. For example, when ozone is used, ibuprofen is removed from the waste water to 95 %, while the removal rate of bezafibrate is in the ranges 50-90 % [13].

Pharmaceuticals can pollute the soil mainly through the use of sewage sludge as fertilizer or irrigation of crops with treated wastewater [14]. In addition, the deposited pharmaceutical compounds may be leached from the soil into the surface waters after the rains [15].

After administration entering the body, pharmaceutical preparations are generally absorbed and metabolized. This process is influenced by the chemical-physical characteristics of drugs: molecular size, the degree of ionization and the relative solubility of lipids. After absorption, the drug enters the bloodstream, and after performing its action, the drug can be metabolized to a more hydrophilic substance for isolation. If the drug remains lipophilic, it will again be reabsorbed and remain in the body for a longer period. Metabolism of pharmaceutical preparations can be accompanied by the formation of polar metabolites with a lower activity, which are easily excreted from the body in the form of biologically active or toxic metabolites [16].

All the chemicals undergo transformation with the metabolizing enzymes mainly of the intestine and liver. As is known, in mammals the clearance of xenobiotics includes several phases, and in the first two phases these substances undergo structural modifications. In the first phase, the chemical is activated through the introduction of a polar (reactive) functional group. For example, in the first phase, the key enzyme is cytochrome P450 (CYP), which oxidizes the substrate, thereby increasing the cytotoxicity of the chemical. The second phase is accompanied by an increase in molecular weight, a decrease in reactivity and an increase in transportability. And, finally, the third phase contributes to the elimination of this chemical from the cell into the intercellular environment. The enzymes catalyzing these reactions are highly specific and capable of generating various metabolic products. Therefore, after administration and absorption, pharmaceutical preparations can be withdrawn from the body without changes, in the form of conjugates, in the form of basic metabolites or mixtures thereof. Data show that tetracyclines, penicillins, fluoroquinolones (excluding propranolol) and betaxolol are released unchanged, while analgesics and anti-inflammatory drugs are intensely metabolized, although the percentage of excretion for most metabolites is unknown [17].

The most important environmental problem in Kazakhstan is the scarcity of water resources, so the use of treated wastewater can be considered as an important alternative [18]. Because wastewater is continuous introduced into the environment of Kazakhstan, these pharmaceutical chemicals are especially important to monitor and understand. The main objectives of the wastewater treatment process is the elimination of coarse solid particles, the reduction of readily assimilable organic wastewater fractions, e.g., nitrogen and phosphorus, removal of slowly biodegradable organic substances and pathogenic microorganisms by active silt [19]. It is now known that microbial communities are key components of the organic substance in the biogeochemical cycling maintaining the balance of natural ecosystems [20]. The microbiological consortium is provided with influence a variety of abiotic and biotic factors, which directly affects the quality of wastewater. For example, a decrease in bacteria also can be due to spontaneous cell death [21].

Water after mechanical cleaning goes for biological treatment in an aerotank - a structure with constantly circulating in the aeration tank waste water, in the entire thickness of which in active silt, aerobic microorganisms develop. For a normal process biochemical oxidation in aerotanks it is necessary to continuously supply air, which is achieved by means of pneumatic, mechanical or pneumomechanical aeration. Methods of biological purification are based on the ability of microorganisms use organic compounds, contained in sewage, as a nutrient substrate: the more active silt and substrate, the faster the process of biochemical oxidation Active sludge has a 100-year history of use as a biological treatment of domestic and industrial wastewater [22].

Problems of ecological safety at wastewater treatment is associated with primary sediment and excess silt. As a result of cleaning, so-called "sewage sludge" or "solids of biological origin" which are an insoluble precipitate, obtained during purification or in subsequent sludge stabilization procedures [23]. On average, per ton of sewage sludge bout 80 kg of nitrogen, 200 kg of phosphate (P_2O_5), and 10 kg of potassium (K_2O) [24]. Thus, almost all chemical and microbiological pollution are concentrated in raw sludge – primary sludge and activated sludge - secondary sludge. The primary and secondary precipitates may be thickened up to 5 % by volume of dry matter on sludge compactors, to obtain a biosludge, which is transported further on the irrigation fields, as a rule, not far from the drives. Over time biosludge dried in natural conditions, however, there is transmission pollutants into the soil, groundwater, also into the air by transferring aerosols and microorganisms, and their products of vital activity. Such a method of recycling biosludge may be hazardous from an ecological and hygienic point of view.

Stabilized sewage sludge intended for agricultural land use needs to be subject to strict quality assessment for high metal content (cadmium, arsenic, copper, lead, mercury and zinc), persistent organic pollutants (aldrin chlorine compounds, dieldrin, heptachlor, DDT, lindane and others) and pathogenic microorganisms (bacteria, viruses, protozoa and helminths) to exclude their transmission through food chains [25].

Sewage sludge usually contains a large number of pathogenic bacteria of the genus *Salmonella spp.*, *Listeria spp.*, *Escherichia coli*, *Campylobacter spp.*, *Clostridium spp.* and *Yersinia spp.*, most of which are zoonotic [26-28].

The storage lake "Sorbulak" has more than 40-year history of operation and is one of the world's largest lakes-sedimentation tanks for sewage. The wastewater of the cities of Almaty, Talgar and Kaskelen that have passed mechanical and biological purification is dumped into the lake. The main task assigned to the Sorbulak basin is deep, long-term regulation of the sewage level and provision of natural self-purification of water with subsequent use for irrigation. Five tons of water every second comes in to "Sorbulak" provided that the total volume of the drive is 900 million cubic meters with the optimum mark of a normal retaining level of 620.5-622 meters. Therefore, to unload the Sorbulak, a channel was put into operation in the Ili River (right-bank Sorbulak Canal) and a reservoir with a capacity of up to 50 million cubic meters of water [29].

A significant number of drugs enters the environment through sewage systems. A significant number of medicinal substances is poorly biodegradable in the system of treatment facilities and in unchanged form or in the form of metabolites enters the surface and groundwater. It is this source of pharmaceutical environmental pollution that is practically not amenable to control and regulation by existing methods [30].

It is known that under the influence of abiotic and biotic factors, all substances entering the environment objects are subject to transformation, not exception - drug compounds often, from less harmful compounds by transformation more toxic substances are formed, which can be cumulated in objects of living nature and through the food chain to enter the human body, providing genotoxic, embryotoxic, teratogenic, mutagenic, carcinogenic and other actions. Transformation of medicinal substances in natural ecosystems practically has not been studied and their effect on various organisms is largely unknown.

Most drugs are eventually transported to the hydrosphere, where they undergo various transformations: phototransformation (both direct and indirect reactions through UV radiation); physical and chemical changes, degradation and mineralization; evaporation (mainly, some anesthetics, aromas); absorption by plants; animal accumulation [31]. Sources of fresh drinking water contribute to strategic resources. Main open water sources of the Republic of Kazakhstan have the status of cross-border facilities, therefore the state of water quality and including the residual finding of medicines in it is of great importance in ensuring the environmental safety of the country. In 2011, the WHO published a report "Drugs in drinking water" as the review of a large number of studies [32]. Water pollution of pharmaceutical products becomes a serious environmental problem worldwide. Traces of drugs found in different aqueous systems. However, at the present time residual products of pharmacological preparations are not included in the list of mandatory for the assessment of water quality [33].

The countries of Central Asia are characterized by rapidly developing pharmaceutical market with certain rules and culture of drug consumption. However, the problem of disposing of pharmaceuticals and the practice of discharging them into wastewater is of particular relevance.

The expected compounds likely to occur in regional wastewater effluent depend on use. Pavin M., Nurgozhin T. (2003), and others, using the standard methodology (WHO), the number and groups of drugs prescribed by doctors in the Primary Health Care Clinic in the Fergana region of Uzbekistan. It was found that the largest proportion of prescription drugs are antibiotics (57%): *Benzathine benzylpenicillin, Ampicillin, Sulphamethoxazole (Trimethoprim), Clodantoin, Streptomycin, Clindamycin, Nitrofurantoin.* Among non-steroidal anti-inflammatory drugs (NSAIDs) the most commonly prescribed *Acetylsalicylic acid*, *Indomethacin*, *Ibuprofen, Diclofenac*. The average number of prescribed drugs is 2.9 per person, which is higher than the national average of 2.2 drug [34].

At present, the main criterion for monitoring environmental pollution is the determination of excess MPC, but it will be advisable to introduce the degree of transformation of pollutants, including metabolites of drugs, in environmental objects. Rationing of environmental risks allow the development of a methodology reduction in environmental protection receipts residual products of pharmacological preparations and integrate it into the Program of development of Almaty city, in which one of the seven directions is ecology. Creation of a modern system management and recycling is interlinked with the main provisions concept on the transition of the Republic of Kazakhstan to a "green" economy and sustainable development. Perfection of the mechanism control the environment through the formation of a new model of management through environmentally oriented methods management provides solution of socio-ecological and economic problems.

Diclofenac is a derivative of phenylacetic acid, belonging to the class of nonsteroidal antiinflammatory drugs (NSAIDs), possessing anti-inflammatory, antipyretic, analgesic, antiplatelet and uricosuric action. As is known, the pharmacological activity of NSAIDs is associated with inhibition of the cyclooxygenase enzyme (COX, prostaglandin PGH2 synthase) catalyzing the conversion of arachidonic acid to prostaglandin PGH2. The pharmacokinetic characteristics of diclofenac: oral bioavailability 54 ± 2 %, time to reach maximum concentration (tmax) 2.5 hours, maximum concentration (Cmax) 0.42-2.0 μg/ml and volume distribution equal to 12 liters. The drug binds to plasma proteins by almost 99.7 %. Diclofenac is metabolized by oxidation and glucoronidation. And only about 1 % is excreted unchanged in the urine [35].

Metronidazole belongs to the group of nitroimidazoles, it shows efficacy against anaerobes, and in general in the treatment of bacterial infections and infections caused by protozoa, such as amoebiasis and including, caused by *Clostridium*. Metronidazole is included in the list of essential medicines of WHO as a basic medicinal product [36].

Cephalosporins have high therapeutic activity and widely used in medicine and veterinary medicine, however, their transformation is not known in the environment. The time of degradation of four cephalosporins (cefradins, cefuroxime, ceftriaxone and cefepime) in surface waters and only four cephalosporins were amorphously degraded with half-lives of 2.7-18.7 days [37].

Conclusions. Based on the above review of the literature it can be argued, that more attention of researchers of various specialties should be focused on the increasing supply of medicines and biotransformation products to the environment, including open water sources. Lake Sorbulak is also experiencing an increasing pressure on the receipt of medicines, since in the process of wastewater treatment medicinal preparations not removed and subjected to the process of transformation due to environmental factors and the activity of living organisms. As is known, water from this reservoir is used for fodder and crop irrigation and the components of biotransformation of drugs can come by the food chain into the human body. Ultimately the occurrence and environmental impact of these compounds must be understood for the sustainable protection of Kazakhstan water resources.

This brief report was prepared within the framework of grant financing of the CS MES RK of the project AP05132269 "Assessing the potential risk of drug transformation to the formation of microorganism resistance in the environmental objects of urbanized territories" for 2018-2020.

Н.А. Ибрагимова[1], М.Б. Лю[1], D. Snow[2], А.Н. Сабитов[1]

[1] АҚ « Инфекцияға қарсы препараттардың ғылыми орталығы», Алматы, Қазақстан;
[2] Су ғылымдары зертханасы Небраска университеті, Небраска, АҚШ

ҚОРШАҒАН ОРТА ОБЪЕКТІЛЕРІНДЕГІ ДӘРІЛІК ПРЕПАРАТТАР СУБСТАНЦИЯЛАРЫНЫҢ БИОТРАНСФОРМАЦИЯЛАНУЫН ЖҮЙЕЛЕУДІҢ ҚАЖЕТТІЛІГІНЕ ҚАТЫСТЫ МӘСЕЛЕЛЕР

Аннотация. Организмге енгеннен кейін дәрілер бірқанша биохимиялық әсерлерге ұшырай отырып, фармакологиялық нәтижеге жетумен бірге биотрансформациялық өнімдер де қалыптастырады. Десек, осы биотрансформациялық субстанциялар түптің түбінде қалдық суларға қосылып, сол жерде тағы бірқанша абиотикалық және биотикалық кешенді үрдістерге ұшырайды. Нәтижесінде жаңа түрпаттағы химиялық қосындылар пайда болып олар адам организміне физиологиялық, биохимиялық, генетикалық және өзге де жағдайларда әсер етуі кәдік. Сондықтанда қоршаған орта объектілеріндегі дәрілік препараттар субстанцияларының қалдық суларда биотрансформациялануының адам денсаулығына әсерін алдын ала болжаудың маңызы зор. Бұл сондайақ, қоршаған орта ластануының бүгінгі стандартан кеңейтіп, жаңа дәрі-дәрмек ойластыру стратегиясын жасақтауға негіз болмақ.

Түйін сөздер: дәрілік препараттар, биотрансформация, нормалау, су қорлары, су ресурстары.

Н.А. Ибрагимова[1], М.Б. Лю[1], D. Snow[2], А.Н. Сабитов[1]

[1] АО «Научный центр противоинфекционных препаратов, Алматы, Казахстан;
[2] Лаборатория водных наук Университет Небраски, Небраска, США

К ВОПРОСУ О НЕОБХОДИМОСТИ НОРМИРОВАНИЯ БИОТРАНСФОРМИРОВАННЫХ СУБСТАНЦИЙ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ В ОБЪЕКТАХ ОКРУЖАЮЩЕЙ СРЕДЫ (КРАТКОЕ СООБЩЕНИЕ)

Аннотация. После поступления в организм лекарства подвергаются целому ряду взаимосвязанных биохимических реакций, которые приводят не только к достижению фармакологического эффекта, но также к образованию продуктов биотрансформации. Эти биотрансормированные субстанции в конечном итоге обнаруживаются в сточных водах, где они также подвергаются целому комплексу абиотических и биотических процессов. В результате могут образовываться химические соединения с новыми свойствами, способными изменять физиологические, биохимические, генетические и другие параметры живых организмов и проникать по пищевой цепочке в организм человека. Поэтому можно утверждать об актуальной проблеме о необходимости прогнозирования и понимания биотрансформированных продуктов лекарственных средств в объектах окружающей среды и в том числе сточных водах, что позволит определить влияние рисков на здоровье, расширять (дополнять) стандарты загрязнения окружающей среды и разработать стратегию поиска и разработку новых лекарств.

Ключевые слова: лекарственные препараты, биотранформация, нормирование, сточная вода, водные ресурсы.

Information about authors:

Ibragimova N.A. - Leading Researcher of Pharmacology and Toxicology Laboratory;

JSC «Scientific Center for Anti-infectious Drugs», cand. biology. scien.; nailya.73@mail.ru; https://orcid.org/0000-0002-1618-900X;

Lyu M.B. – Deputy Head of the Laboratory of Pharmacology and Toxicology, JSC «Scientific Center for Anti-infectious Drugs», mlyu@mail.ru; https://orcid.org/0000-0002-7865-0017;

Dr. Snow Daniel D. – Water Sciences Laboratory University of Nebraska, Laboratory Director, Ph.D., 1840 N. 37th St | Lincoln, NE 68583-0844; dsnow1@unl.edu | p:1 402.472.7539 | f: 1 402.472.9599| c: 1 402.304.3748; ttps://orcid.org/0000-0003-0885-0504;

Sabitov A.N. – Managing test base management JSC «Scientific Center for Anti-infectious Drugs», cand. chemical scien.; aitugans@mail.ru; ttps://orcid.org/0000-0003-3677-8685.

REFERENCES

[1] Daughton C, Ternes T. (**1999**) Pharmaceuticals and personal care products in the environment: agents of subtle change?, Environ Health Perspect, 107:907-938. DOI: 10.2307/3434573 (in Eng).

[2] Musson S, Townsend T et al. (**2007**) A continuous collection system pharmaceutical wastes: a pilot for household project, J Air Waste Manag, 57(7):828-835. DOI: 10.3155/1047-3289.57.7.828 (in Eng).

[3] Ort C, Lawrence M, Reungoat J et al. (**2009**) Determining the fraction of pharmaceutical residues in wastewater originating from a hospital, Water Res, 44(2):605-615. DOI: 10.1016/j.watres.2009.08.002 (in Eng)

[4] Vellinga A, Cormican S, Driscoll J et al. (**2014**) Public practice regarding disposal of unused medicines in Ireland, Sci Total Environ, 478:98-102. DOI: 10.1016/j.scitotenv.2014.01.085 (in Eng).

[5] Boxall A, Sinclair C, Fenner K et al. (**2004**) When synthetic chemicals degrade in the environment, Environ Sci Technol, 38(19):368A-375A (in Eng).

[6] Musson S, Townsend T. (**2009**) Pharmaceutical compound content of municipal solid waste, J Hazard Mater, 162:730-735. DOI: 10.1016/j.jhazmat.2008.05.089 (in Eng).

[7] Dungan R, Snow D, Bjorneberg D. (**2017**) Occurrence of Antibiotics in an Agricultural Watershed in South-Central Idaho, J Environ Qual. DOI: 10.2134/jeq2017.06.0229 (in Eng).

[8] Stackelberg P, Furlong E, Meyer M et al. (**2004**) Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant, Sci Total Environ, 329:99-113. DOI: 10.1016/j.scitotenv.2004.03.015 (in Eng).

[9] P Deo Randhir, U Halden Rolf (**2013**) Pharmaceuticals in the Built and Natural Water Environment of the United States, Water, 5 (3):1346-1365. DOI.org/10.3390/w5031346 (in Eng).

[10] Pharmaceuticals in drinking-water/ WHO/ HSE/WSH/11.05/ World Health Organization (**2011**) USEPA. Summary of the Clean Water Act. Available online: https://www.epa.gov/lawsregulations/summary-clean-water-act (in Eng).

[11] Seehusen D, Edwards J. (**2006**) Patient practices and beliefs concerning disposal of medications, J Am Board Fam Med, 19(6):542-547. DOI: 10.3122/jabfm.19.6.542 (in Eng).

[12] Tong A, Peake B, Braund R. (**2011**) Disposal practices for unused medications around the world, Inviron Int, 37(1):292-298. DOI: 10.1016/j.envint.2010.10.002 (in Eng).

[13] Choi M, Choi D, Lee J et al. (**2012**) Removal of pharmaceutical residue in municipal wastewater by DAF (dissolved air flotation)-MBR (membrane bioreactor) and ozone oxidation, Water Sci Technol, 12:2546-2555. DOI: 10.2166/wst.2012.429 (in Eng).

[14] Ternes T, Joss A, Siegrist H. (**2004**) Scrutinizing pharmaceuticals and personal care products in wastewater treatment, Environ Sci Technol, 38:393A-398A. (in Eng).

[15] Pedersen J, Soliman M et al. (**2005**) Human pharmaceuticals, hormones and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater, J Agric Food Chem, 53:1625-1632. DOI:10.1021/jf049228m (in Eng).

[16] Galbraith A, Bullock S, Manias S et al. (**2004**) Pharmacokinetics: absorption and distribution, In: Fundamentals of Pharmacology: A Text for Nurses and Health Professionals, 4th Ed. Pearson Education Limited, Essex, England. P. 109-114.

[17] Guengerich F. (**2001**) Common and Uncommon Cytochrome P450 Reactions Related to Metabolism and Chemical Toxicity, Chem Res Toxicol, 14(6):611-650. DOI: 10.1021/tx0002583 (in Eng).

[18] Концепция по переходу Республики Казахстан к «зеленой» экономике. http://www.led-ca.net/assets/files/Concept_Rus-GreenEcon-Kaz.pdf

[19] Muela A, Orruño M, Alonso M et al. (**2011**) Microbiological parameters as an additional tool to improve wastewater treatment plant monitoring, Ecol Indic, 11:431-437. DOI.org/10.1016/j.ecolind.2010.06.014 (in Eng).

[20] Kent A, Yannarell A, Rusak J et al. (**2007**) Synchrony in aquatic microbial community dynamics, ISME, J1:38-47. DOI: 10.1038/ismej.2007.6 (in Eng).

[21] Wanjugi P, Harwood V. (**2013**) The influence of predation and competition on the survival of commensal and pathogenic fecal bacteria in aquatic habitats, Environ Microbiol, 15:517-526. DOI: 10.1111/j.1462-2920.2012.02877.x(in Eng).

[22] Sheik AR, Muller EL, Wilmes P. (**2014**) A hundred years of activated sludge: time for a rethink, Front Microbiol., 5: 47. DOI: 10.3389/fmicb.2014.00047 (in Eng).

[23] Arcak S, A. Karaca E et al. (**2000**) A study on potential agricultural use of sewage sludge of Ankara wastewater treatment plant, In Proceedings of the International Symposium on Desertification, Konya, Turkey. P. 345-349.

[24] Eberle WM, Whitney DA and Powell GM. (**1994**) Sewage sludge use on agricultural land. Cooperative Extension Service, Kansas State University, Manhattan.

[25] Saleem M, Al-Malack M et al. (**2001**) Seasonal variations in the microbial population density present in biological sludge, Environ Technol. 22:255-259. DOI: 10.1080/09593332208618285 (in Eng).

[26] Straub T, Pepper I, Gerba C. (**1993**) Hazards from pathogenic microorganisms in land-disposed sewage sludge, Rev Environ Contam Toxicol, 132:55-91. (in Eng).

[27] Strauch D. (**1998**) Pathogenic microorganisms in sludge Anaerobic digestion and disinfection methods to make sludge usable as a fertilizer, Eur Water Manage, 1:12-26. DOI: 10.1111/j.1462-2920.2012.02877.x (in Eng).

[28] Rao V, Metcalf T, Melnick J. (**1986**) Human viruses in sediments, sludges, and soils, Bull World Health Organ, 64:1-13. DOI: 10.1111/j.1462-2920.2012.02877.x (in Eng).

[29] http://www.centrasia.ru/newsA.php?st=1418960640.

[30] Randhir P. Deo, U. Halden Rolf (**2013**) Pharmaceuticals in the Built and Natural Water Environment of the United States, Water, 5 (3):1346-1365. DOI: 10.3390/w5031346.

[31] Duca G. (**2009**) Pharmaceuticals and Personal Care Products in the Environment Chapter in NATO Security through Science Series, Environmental Security March. DOI: 10.1007/978-90-481-2903-4_3.

[32] Pharmaceuticals in drinking-water/ WHO/ HSE/WSH/11.05/ World Health Organization 2011.

[33] USEPA. Summary of the Clean Water Act. Available online: https://www.epa.gov/lawsregulations/summary-clean-water-act.

[34] Pavin M, Nurgozhin T, Hafner G, Yusufy F and Laing R. (**2003**) Prescribing practices of rural primary health care physicians in Uzbekistan, Tropical Medicine and International Health, 8:182-190. DOI: https://doi.org/10.1046/j.1365-3156.2003.00992.x (in Eng).

[35] Smith FG, Wade AW, Lewis ML, Qi W. (**2012**) Cyclooxygenase (COX) inhibitors and the newborn kidney, Pharmaceuticals (Basel), 5:1160-1176. DOI: 10.3390/ph5111160 (in Eng).

[36] Freeman CD, Klutman NE, Lamp KC. Metronidazole. (**1997**) A therapeutic review and update, Drugs, 54(5):679-708. DOI: 10.2165/00003495-199754050-00003 (in Eng).

[37] Jiang M, Wang L, Ji R. (**2010**) Biotic and abiotic degradation of four cephalosporin antibiotics in a lake surface water and sediment, Chemosphere, 80(11):1399-1405. DOI: 10.1016/j.chemosphere.2010.05.048.