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# Risk analysis of Sofia city drinking water for pharmaceutical residues

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Directive 2020/2184 focuses on the quality of water intended for human consumption. It sets rules to protect human health by ensuring safety and quality through the whole system to the end user. The Directive covers risk assessments, water safety plans, and setting new substances for monitoring. Water supply companies play a crucial role in managing risks from the watershed to the tap. Since 2019 "Sofiyska voda" JSC is analyzing and evaluating all the risks for water safety and started monitoring the main water source for pharmaceutical residues due to the lack of official information on the topic using a proven methodology. In this study six critical control points (CCP) for sampling from the main water source to the drinking water supply were identified as important for investigation of the possible pollution with the most common pharmaceuticals. The aim of the study is to analyze different groups of pharmaceuticals in the six CCP and to estimate the risk to the drinking water of Sofia. It was found that currently the risk of contamination of the main water source - Iskar Dam and drinking water with pharmaceutical products is minimal.

**Keywords:** pharmaceuticals in surface water, Iskar Dam, drinking water treatment plants

## INTRODUCTION

With the development of analytical methods over the last decade and their increased sensitivity to detect minute concentrations of chemicals, the chance of detecting residues of chemicals of different origins in surface waters is increasing [1-5]. With the industrialization of society, increase in life expectancy and improvements in human health, the use of pharmaceuticals is proportionately increasing [3]. Through excretion, various chemicals, some of which are pharmaceuticals or their metabolites, enter wastewater, and in very low concentrations have a major impact on the ecosystems associated with the water bodies concerned. The evidence on the impact of pharmaceutical residues in surface waters and their long-term impact on human health is not yet sufficiently convincing to be included as hazardous monitoring indicators in the EU legislative framework. Single large-scale studies bring together the data accumulated in recent years on the occurrence of drug residues in surface and drinking waters worldwide [2, 4, 5]. Risk Assessment and Risk Treatment are the basic elements of Risk Management standards (ISO31000:2018) including risks for drinking water quality. The three obligatory steps of the Risk Assessment are: Risk identification, Risk analysis and Risk evaluation. The Risk identification includes finding, recognizing and describing the hazards. The Risk analysis includes determination of risk consequences and risk likelihood. The Risk evaluation includes comparison of data with legal restrictions, quantitative evaluation of the power of environmental impact and level of likelihood. The aim of the present study is to analyze different groups of pharmaceuticals in six CCP and to analyze the risk to the drinking water of Sofia.

### *Action of pharmaceuticals and medicines*

Drugs are chemically or biologically active compounds that affect the mechanisms of metabolism in organisms with the intended purpose of improving physical condition and healing by humans, animals and plant protection. An established effect of their widespread use is, on the one hand, the targeted effect on the organism and on the other hand, the non-targeted (indirect) effect on aquatic organisms [6]. It has been observed that fish continuously exposed to a water stream (treated and untreated domestic fecal water) containing residues of pharmaceuticals, have a tendency to sex shift towards a higher proportion of females [7, 8]. When the concentrations of pharmaceuticals in surface and drinking water are significantly below levels that

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would have a pharmacological effect on human health, exposure to low levels (typically on the order of nanograms per liter) of pharmaceuticals is generally considered to pose no risk to human health [9, 10]. The WHO guidelines for drinking water in the presence of pharmaceuticals are given in [11]. When no guidance values are provided to designate a substance in water as hazardous to human health, it goes through a lengthy evaluation procedure. When a negative effect is proven, these substances fall under the Watch List (WL). The first WL or substances in surface water was established in 2015 and in its fourth revision from 2022, the report proposes seven categories of additional substances [12]. The seven groups include two biocides (azoxystrobin, fipronil), two antibiotics (clindamycin, ofloxacin), one pharmaceutical product (metformin and its metabolic product guanylurea), synthetic hormones (levonorgestrel, levonorgestrel, norethisterone) and sunscreen agents (avobenzone, octocrylene, oxybenzone). The Water Frame Directive is under revision and soon new requirements (about 70 priority pollutants with new Environmental quality standard values) together with a new Watch List will be published.

*Pathways of hazardous intrusion into surface water as a result of drug use*

In summary, the pathway that pharmaceuticals pass through is presented in Fig. 1: *Production* - residues of medicines in production effluents; *Domestic wastewater* - after the use of the pharmaceutical product, excretion or washing away of unmetabolized pharmaceuticals and their metabolites that enter the sewerage network from hospitals, households and the discharge of unsuitable medicines into the sewerage system. In large cities, domestic wastewater is treated in biological wastewater treatment plants (WWTP). In this case, pharmaceuticals that have not been degraded are most often accumulated in the activated sludge, which after treatment is in some cases used to fertilize agricultural land.

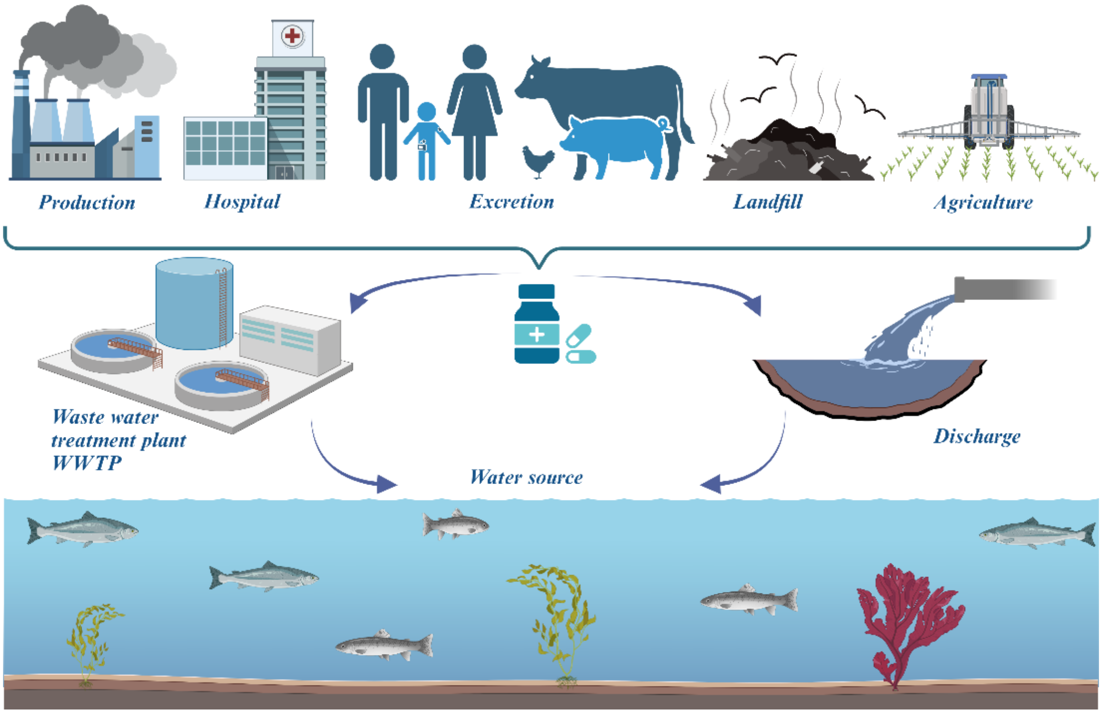


**Fig. 1.** Pathways of release of pharmaceuticals into the environment

*Diffuse contamination from agriculture and farming* - the use of veterinary pharmaceuticals is one of the pathways of diffuse contamination, as is the fertilization of stabilized sludge with accumulated contaminants. Humans, farm animals excrete some of the ingested doses of drugs that reach surface waters from the spreading of manure by treated animals. A direct pathway for large amounts of antibiotics to enter surface waters is due to fish farms where antibiotics are given to fish in a dosed feed form [6].

*Direct discharges and leachate from landfills* - the introduction of unusable pharmaceuticals into the general municipal waste stream results in the formation of leachate, which is a potential source of pharmaceuticals. Another scenario for the distribution of pharmaceuticals and their degradation products (bio, photo) and metabolism *throughout the food chain* is their *bioaccumulation* in aquatic organisms and sediments.

Table 1 presents information from 71 United Nations (UN) countries on more than 600 pharmaceutical representatives. The countries are grouped by region and the pharmaceuticals are reduced to 16 that are commonly found. In all UN regions, diclofenac ranks among the top 5 most frequently detected pharmaceuticals in the environment, the four other pharmaceutical substances being carbamazepine (antiepileptic), sulfamethoxazole (antibiotic), ibuprofen and naproxen (both analgesics).

**Table 1.** Number of countries in each United Nations group in which positive detection of pharmaceutical substances in surface waters, groundwater, and/or tap or drinking water has been reported [2].

| *Pharmaceutical substance* | Africa | Asia-Pacific | EEG* | GRULAC* | WEOG* | Global |
|---|---|---|---|---|---|---|
| *Diclofenac*[1] | 3 | 8 | 13 | 3 | 23 | 50 |
| *Carbamazepine*[2] | 3 | 6 | 13 | 2 | 24 | 48 |
| *Ibuprofen*[1] | 3 | 8 | 10 | 2 | 24 | 47 |
| *Sulfamethoxazole*[3] | 5 | 9 | 10 | 2 | 21 | 47 |
| *Naproxen*[1] | 2 | 8 | 10 | 2 | 23 | 45 |
| *Estrone*[4] | 1 | 10 | 6 | 2 | 16 | 35 |
| *Estradiol*[4] | 2 | 9 | 4 | 2 | 17 | 34 |
| *Ethinylestradiol*[4] | 1 | 8 | 3 | 2 | 17 | 31 |
| *Trimethoprim*[3] | 2 | 9 | 3 | 2 | 13 | 29 |
| *Paracetamol*[1] | 1 | 6 | 4 | 3 | 15 | 29 |
| *Clofibric acid*[5] | 1 | 3 | 5 | 2 | 12 | 23 |
| *Ciprofloxacin*[3] | 1 | 5 | 1 | 2 | 11 | 20 |
| *Ofloxacin*[3] | 1 | 4 | 1 | 1 | 9 | 16 |
| *Estriol*[4] | 1 | 1 | 2 | 1 | 10 | 15 |
| *Norfloxacin*[3] | 1 | 4 | 1 | 2 | 7 | 15 |
| *Acetylsalicylic acid*[1] | 1 | 4 | 1 | 2 | 7 | 15 |

These 16 substances are the only ones that have been found in each region.
Therapeutic groups: 1- analgesics; 2- antiepileptics; 3- antibiotics; 4- estrogens; 5- lipid-lowering drugs.
*EEG-eastern Europe; GRULAC-Latin America and Caribbean; WEOG-western Europe and others

According to literature data [2], the global distribution of pharmaceutical residues shows that Bulgaria falls into the group of countries with between 11 and 30 identified pharmaceutical residues. The classification done by the authors divided surveyed countries in groups depending on the number of the pharmaceuticals detected in surface, ground and tap /drinking water (1-3; 4-10; 11-30; 31-100; 101-200; No data). Currently, no survey has been carried out on pharmaceutical residues in the watershed of the Iskar Dam and of the drinking water of Sofia.

## MATERIALS AND METHODS

### *Experimental design*

No pharmaceutical company discharging wastewater into the Iskar dam watershed was identified from the survey. The largest settlement that generates wastewater is Samokov with a permanent population of over 25 000. The settlement has an urban WWTP and a regional landfill for the municipalities of Samokov, Dolna Banya, Kostenets and Ihtiman, serving a population of approximately 60 000 people. The leachate from the depot is discharged into the environment without biological treatment. According to the BDDR register [13], there are about 42 sewerage systems of domestic and fecal nature that discharge their treated and untreated water into the main tributaries of the Iskar Dam, rivers Iskar and Palakaria. The selection of CCPs is in accordance with the anthropogenic pressure.

Fig. 2 shows the identified potential emitters of pharmaceuticals [14]. Filters "Discharge points surface water bodies" (pink dot), "settlements without constructed sewerage" (yellow dot) on visualization are applied.

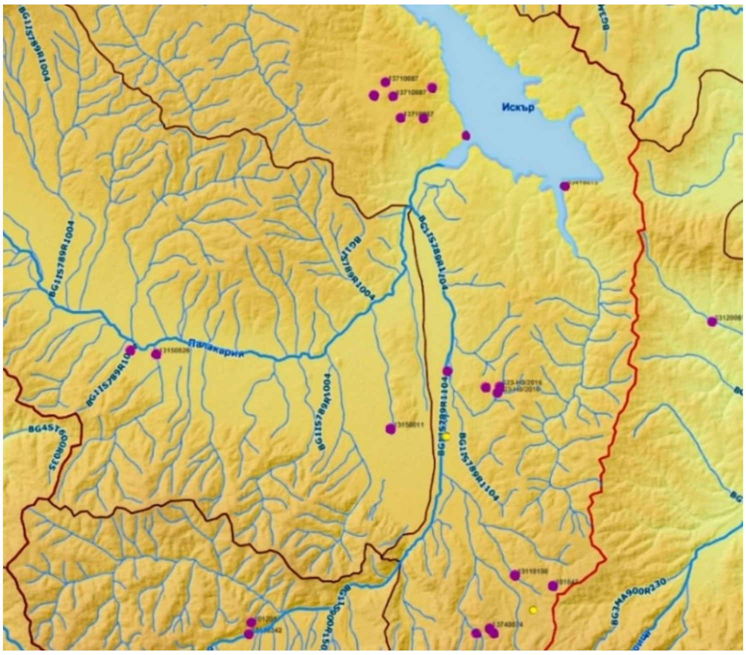


**Fig. 2.** Scheme of potential sources of pharmaceutical residues in the watershed of the Iskar Dam [14].


**Fig. 3.** CCPs for sampling.

The sampling points from Iskar Dam are presented in Fig. 3 - CCP1 Stork nest, 0m; CCP2 Stork nest -15m; CCP3 Intake tower 0m; CCP4 Intake tower -25m; CCP5 Drinking water treatment plant (DWTP) Pancharevo, filtered (drinking) water; CCP6 DWTP Bistritsa filtered (drinking) water. CCP1 and CCP2 are representative for surface water with anthropogenic pressure, close to Iskar Dam inlet; CCP3 and CCP4 are representative for Iskar Dam outlet (Intake tower). CCP5 and CCP6 are representative for drinking water.

In the present study, *21 indicator* drugs and *bisphenol A*, which is an endocrine disruptor and can be considered from the group of estrogens, were selected, as no drugs from this group were studied in general monitoring. *Twenty-two monitored indicators* were selected based on their representativeness in terms of the presence of specificity - residues of pharmaceuticals, which are not yet included for mandatory monitoring both by EU member states and Bulgaria on the one hand and representativeness in terms of *major groups* of medicines on the other.

An exception is bisphenol A, which is present as a new monitoring parameter in Directive 2184/2020 [15]. The common groups of medicines and the individual representatives are: *1/ Antibiotics* – led to resistance to bacterial pathogens. One of the most common antibiotics - *Sulfamethoxazole* is frequently found in water matrices due to its extensive use in human and animal healthcare; *2/ Analgesics: Naproxen, Diclofenac, Ibuprofen, Paracetamol, Ketoprofen* pose risks to human health and organisms due to their poor degradability and widespread presence in aquatic systems; *3/ Anticonvulsants: Carbamazepine, 10,11-Epoxycarbamazepine, Gabapentine* and *Levetiracetam*, are used for treating epilepsy, neuropathic pain, and psychiatric disorders; *4/ β-blockers:* widely used for cardiovascular diseases, β-blockers like *Atenolol, Bisoprolol, Irbesartan, Metoprolol, Sotalol, Valsartan* are present in water due to their extensive use and limited biodegradation even in wastewater treatment plants (WWTPs); 5/ *Antidepressants*: commonly prescribed for anxiety, depression, and chronic pain, antidepressants such as *Venlafaxine, o-Desmethylvenlafaxine, Oxazepam, Primidone, Tramadol* are found in water bodies; 6/ *Endocrine-Disrupting Compounds (EDCs):* estrogens and phenolic compounds disrupt normal endocrine functions in humans and wildlife. Common EDCs include natural and synthetic estrogens *Estrone* and phenols - *bisphenol A*. These substances, found in various products, can decrease reproductive fitness and increase cancer risk in humans, especially through contaminated drinking water; 7/ *Lipid-Lowering Drugs:* used to manage cholesterol and triglyceride levels in patients. Examples for them are: *Bezafibrate, Gemfibrozil*. Other representatives from different groups such as *8/ Bronchodilators* are *Theophylline;* and *glucose-lowering drug Metformin.*

Water was sampled in 2022 and 2023 for determination of bisphenol A and 2023 for residual concentrations of pharmaceuticals. Samples were collected according to the requirements of ISO 5667-4:2016 and analyzed by Ultra-performance liquid chromatography-mass spectrometer (UPLC/MS) in the laboratory of SGS Bulgaria. The raw (CCP1, CCP2, CCP3 and CCP4) and drinking (CCP5 and CCP6) water samples for pharmaceutical residues from 2023 were taken according to the requirements of ISO 5667-4:2016. The analysis was performed at the Vivaqua laboratory, Brussel by liquid chromatography with electrospray ionization mass spectrometry (LC/MS-ESI) and liquid chromatography tandem mass spectrometry (LC/MS-MS) [16]. Both of the laboratories are accredited under ISO 17025 Testing and calibration laboratories.

## RESULTS AND DISCUSSION

There are a number of studies that discuss the prevalence and impact of various pharmaceutical compounds in aquatic environments. These compounds, found in European water matrices [4, 5, 9, 10], are categorized into antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, β-blockers, antidepressants, endocrine-disrupting estrogens and phenols, and lipid-lowering drugs. The results of our 2023 survey are presented in Table 2.

Table 2 shows that out of twenty-one indicators tested, only 2 samples showed the presence of traces of Theophylline. All other indicators in the 6 CCP per site indicated that drug residues are below the method detection limit. The points where Theophylline was reported are representative of surface water from CCP1, 2 (Stork nest) a recreation area subject to moderate anthropogenic pressure. As can be seen from Fig. 2a, there are urbanized areas near CCP1 and CCP2, that do not have a sewage system and discharge their wastewater into cesspools or directly into the dam, which is a prerequisite for the introduction of drug residues from untreated wastewater.

The results of the study done in 2007 [17, 18] by the JRC, are presented selectively in Table 3 only for the point directly related to the upper reaches of the river Iskar with a potential contribution to the pollution of the Iskar Dam. Diclofenac, a commonly used analgesic for humans and animals, is the most frequently detected pharmaceutical globally. It has been found in 50 countries [2]. Studies in European countries [17, 18] show Sulfamethoxazole concentrations in surface waters. Naproxen (analgesic), was detected in 69% of over 100 monitored European rivers, with concentrations up to 2.027 μg/L [17, 18]. The likely cause is the discharge of wastewater from municipal wastewater treatment plants. According to the data of [2] for the EEG region, the mean and maximum concentrations of Diclofenac ranged between 0.111 - 4.2 μg/L, Carbamazepine was between 0.131 - 7.6 μg/L and Sulfamethoxazole was between 0.033 - 0.3 μg/L. Compared to the European average and maximum values, the concentrations of drug residues, detected in 2007 in the Iskar River [17] before flowing into the dam, were significantly lower.

**Table 2.** Results for 21 popular pharmaceuticals detected wordlife screened in water of Iskar Dam and drinking water in DWTP Bistritsa and Pancharevo

| *Parameter* | *Unit* | *CCP1* | *CCP2* | *CCP3* | *CCP4* | *CCP5* | *CCP6* | *LOQ** |
|---|---|---|---|---|---|---|---|---|
| *10,11-Epoxycarbamazepine*[1] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 |
| *Atenolol*[2] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 |
| *Bisoprolol*[2] | μg/L | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 |
| *Carbamazepine*[1] | μg/L | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 |
| *Gabapentine*[1] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 |
| *Ibuprofene*[3] | μg/L | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 |
| *Irbesartan*[2] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | 0.01 |
| *Levetiracetam*[1] | μg/L | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 |
| *Metformine*[4] | μg/L | <0.250 | <0.250 | <0.250 | <0.250 | <0.250 | <0.250 | <0.250 |
| *Metoprolol*[2] | μg/L | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 |
| *Naproxene*[3] | μg/L | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.0250 |
| *o-Desmethyl-venlafaxine*[5] | μg/L | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 |
| *Oxazepam*[5] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 |
| *Paracetamol (Acetaminophen)*[3] | μg/L | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 | <0.020 |
| *Primidone*[5] | μg/L | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 | <0.025 |
| *Sotalol*[2] | μg/L | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 | <0.010 |
| *Sulfamethoxazole*[6] | μg/L | <0.040 | <0.040 | <0.040 | <0.040 | <0.040 | <0.040 | <0.040 |
| *Theophylline*[7] | μg/L | 0.079 | 0.042 | <0.040 | <0.040 | <0.040 | <0.040 | <0.040 |
| *Tramadol*[5] | μg/L | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 |
| *Valsartan*[2] | μg/L | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 |
| *Venlafaxine*[5] | μg/L | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 | <0.015 |

*LOQ - Limit of quantification

Therapeutic groups: 1- anti-convulsants; 2- β-blockers; 3- analgesics; 4- glucose-lowering drugs; 5- anti-depressants; 6- antibiotics; 7- bronchodilators

**Table 3.** Pharmaceuticals in Iskar River [17], upper the Iskar Dam *vs* proposed values for Environmental quality standards (EQS) [19]

| *Parameter* | *Unit* | *MEC * 2007 [17]* | *AA EQS** Inland surface waters [19]* | *MAC EQS*** Inland surface waters [19]* |
|---|---|---|---|---|
| *Carbamazepine*[1] | μg/L | 0.026 | 2.5 | 1600 |
| *Diclofenac*[2] | μg/L | 0.001 | 0.04 | 250 |
| *Sulfamethoxazole*[3] | μg/L | 0.032 | N/A | N/A |

Therapeutic groups: 1- antiepileptic drugs; 2 – analgesics; 3 – antibiotics; *MEC is minimum equivalent concentration; ** AA EQS is annual average environmental quality standards; *** MAC EQS is maximum allowable concentration environmental quality standards

**Table 4.** Results for bisphenol A in drinking water in DWTP Bistritsa and Pancharevo 2022 – 2023 *vs* parameter threshold in Directive 2184/2020 [15]

| *Sampling year* | *Parameter* | *Unit* | *CCP5* | *CCP6* | *LOQ** | *Parametric value [15]* |
|---|---|---|---|---|---|---|
| 2022 | *Bisphenol A,* | μg/L | <0.003 | <0.003 | <0.003 | 2.5 |
| 2023 | *Bisphenol A,* | μg/L | 0.006 | <0.003 | <0.003 | 2.5 |

*LOQ - Limit of quantification

The data [17] are compared to the values in the Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive [19] in Table 3. Most common pharmaceuticals have been detected in 2007, but the levels are quite low.

Table 4 presents information on the concentration of bisphenol A as an endocrine disruptor in CCP5 and CCP6 (drinking water that is directed to the water supply network). Concerning both sampling dates on 2022 and 2023, the bisphenol A concentration was <0.003 μg/L at DWTP Bistritsa which is the lowest concentration that can be reliably detected. In 2023, the bisphenol A concentration was 0.006 μg/L at DWTP Pancharevo. Compared with the limit in Directive 2184/2020 [15] of 2.5 μg/L for bisphenol A concentration in drinking water, these results indicate that the water treatment processes effectively maintain low bisphenol A levels, with concentrations below the LOQ in most cases.

## CONCLUSIONS

According to the public data for the economic development of the region, production, land use and wastewater treatment plants and discharges, currently there is no potential for pollution with pharmaceuticals in the watershed of Iskar Dam. Based on the analyses of the data on the presence of more than 20 pharmaceuticals in the surface and drinking water from the Iskar Dam, the risk for pharmaceutical residues is low.

Future research will be focused on collecting a larger database of pharmaceutical concentrations. On their basis, a precise quantitative Risk assessment will be made and Risk management measures will be proposed. Despite the lack of a legislative framework, the authors recommend that a more in-depth survey, including sediment and fish components, should be carried out, complemented by chemical analyses for antibiotics and estrogens.

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As it is seen, the results from 2023 are not replicable due to the bigger volume of the Iskar Dam compared with Iskar River on the one hand, and due to upgrade (since 2007) of the waste water treatment of the 2 agglomerations (Dospey and Belchin) on the other.

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