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The Pharmaceutical Pollution of Water Resources Using the Example of the Kura River (Tbilisi, Georgia)

David Gurgenidze [1,*] and Valentin Romanovski [2,*]

[1] Department of Hydrotechnics and Civil Engineering, Georgian Technical University, M. Kostavav Str., 68, 0172 Tbilisi, Georgia
[2] Department of Materials Science and Engineering, University of Virginia, Charlottesville, VA 22904, USA
* Correspondence: gurgenidzedavid@gtu.ge (D.G.); rvd9ar@virginia.edu (V.R.)

Abstract: This article addresses the issues of pharmaceutical pollution of the Kura River. Existing published information on the pollution of the world's rivers and rivers in Georgia was analyzed. Based on laboratory studies of water samples within the city of Tbilisi, which were carried out to identify psychostimulating and analeptic drugs, antibiotics of the macrolide group, nicotine, and analgesic–antipyretics, the places with the highest levels of pollution were identified. Based on the analysis of the dynamics of growth in the sales of pharmaceuticals in the world and Georgia, empirical dependencies were obtained for predicting the growth in sales as an indirect factor that indicates an increase in the pollution of natural water sources. Particular attention is paid to improving the legislative framework for the disposal of products of industrial production sectors that are related to medicine, human health, and agriculture.

Keywords: environmental safety; water resources; raw sewage; anthropogenic impact; drug contamination; financial market of pharmaceuticals; global sales of prescription drugs

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1. Introduction

Monitoring the state of the environment makes it possible to predict and prevent the negative consequences associated with its change, such as mudflows [1], floods, and excess concentrations of pollutants in the components of the natural environment. According to the United States Geological Survey, emerging pollutants are defined as all synthetic or naturally occurring chemicals that are not included in the routine monitoring program but have the potential to enter the environment and cause known or suspected negative ecological, (eco)toxic, and/or human health effects. Pharmaceutical pollutants are recognized as one of six different classes of emerging pollutants [2]: personal care products (PCPs), endocrine-disrupting chemicals (EDCs), pharmaceutical pollutants (PPs), persistent organic pollutants (POPs), artificial sweeteners (ASs), and microplastics (MPs). Pharmaceutical pollutants are a type of emerging environmental contaminant that refers to the presence of pharmaceutical drugs or their metabolites in various environmental components, such as water bodies, soils, and even organisms. The following are some common classes of pharmaceutical pollutants: (i) Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs, such as ibuprofen, diclofenac, and naproxen, are widely used for their analgesic and anti-inflammatory properties. They are frequently detected in aquatic environments due to incomplete metabolism and excretion by humans and animals. (ii) Antibiotics: antibiotics, including penicillins, cephalosporins, tetracyclines, and fluoroquinolones, are commonly prescribed medications for treating bacterial infections. The discharge of antibiotic residues from wastewater treatment plants and agricultural activities can contribute to the presence of these compounds in the environment, potentially leading to the development of antibiotic-resistant bacteria. (iii) Hormones: hormones like estrogen, progesterone, and testosterone are used for various medical purposes, including contraception and hormone replacement therapy. These compounds can enter the environment through urine excretion, improper disposal of unused medications, and effluents from pharmaceutical manufacturing. (iv) Psychotropic medications: psychotropic medications, such as antidepressants (e.g., fluoxetine, sertraline, etc.), antipsychotics (e.g., risperidone, olanzapine, etc.), and anxiolytics (e.g., diazepam, alprazolam, etc.), are prescribed for mental health conditions. They can reach the environment through excretion, improper disposal, and wastewater discharge. (v) Beta-blockers: beta-blockers, such as propranolol and metoprolol, are commonly used for cardiovascular conditions like hypertension. These compounds have been detected in surface water and are known to have effects on aquatic organisms. (vi) Antiepileptic drugs: antiepileptic drugs, including carbamazepine and phenytoin, are prescribed to control seizures and epilepsy. Their presence in water bodies can be attributed to excretion and insufficient removal during wastewater treatment processes. (vii) Contrast agents: contrast agents, like iodinated compounds used in medical imaging procedures (e.g., X-rays, computed tomography scans, etc.), can enter the environment through improper disposal or release from hospitals and diagnostic centers. Recently, the issue of environmental safety of water resources that are exposed to drugs has become increasingly important [3,4]. Due to evidence that these pollutants affect how rivers and other bodies of water function ecologically, they are now being researched seriously. Until recently, these pollutants were not routinely monitored due to their low quantities. The regulation of industrial emissions from pharmaceutical industries and medical institutions, as well as the disposal of expired drugs, requires special attention, and the national legislation of Georgia should be brought in line with international environmental safety standards.

The development of methods for analyzing and assessing the environmental safety of the pharmaceutical industry and high-quality disposal when withdrawing medicines from circulation or when they expire remains relevant for the global community today. One of the main factors of anthropogenic impact on the hydrosphere is the increase in the use of pharmaceuticals by the population and agricultural production [5–7]. The purification of these substances dissolved in water is one of the most important and difficult problems to solve. The variety of compounds in terms of chemical composition and conditions of formation and existence requires individual studies for each specific case.

Studies show that already-released drugs inevitably end up in the environment and have adverse effects on it [8]. As a result, they return to the human body in the form of food, air, and water. As a result, there is an effect of "drug cycling" in the human environment.

The pace of the development of modern pharmaceutical production technologies and the production of new pharmaceutical forms, as well as the latest methods for diagnosing diseases and treating them, complicate the solution of environmental problems that are associated with reducing the risk of the penetration of drugs into the environment and, consequently, the manifestation of their negative impact on humans. A striking example of ecopharmaceutical pollution of the aquatic environment that affects humans is the inhabitants of the aquatic environment exposed to even relatively small concentrations of 0–1.0 μg/L of the nonsteroidal anti-inflammatory drug diclofenac. In trout fish that live in such a reservoir for 3–4 weeks, cytological changes appear in the kidneys, liver, and gills. Another unfavorable environmental factor is antibiotics in the aquatic environment. The reason for this is the widespread use of these drugs in veterinary medicine. This leads to the disruption of the self-purification process in water bodies and soil, and at lower concentrations in water bodies, bacteria resistant to antibiotics can appear, which can cause diseases in humans [2,9,10].

According to experts, from 35% to 50% of manufactured medicines turn out to be unnecessary and are thrown into landfill. The reasons for this are as follows:

- The excess volume of sold medicines;
- Their lack of demand;
- The expiration of storage and shelf life;
- Violations of norms and rules of production, warehousing, storage, and transportation.

Drug users also make a significant contribution to these processes. Notably, 15% of consumers flush unnecessary medicines down the drain, and about 75% of the population throws them into the general trash without realizing the danger. Various studies report traces of antidepressants, antibiotics, narcotic substances, contraceptives, hormonal drugs, and many others in nature (including in rivers, lakes, and ponds). So, for example, only on a US scale, according to the National Society of Pharmaceutical Associations, more than 220 thousand tons of medicines are poured into the sewer every year, and from those, up to 100 thousand tons of drugs are disposed of annually by the population alone. More than 120,000 tons of medicines are discarded or dumped into the sewers of US hospitals and healthcare facilities annually [11–14].

To date, the presence of more than 200 drugs and their metabolites have been confirmed in surface and ground waters [10]. The top list of detected pharmaceutical contaminants includes antibiotics, nonsteroidal anti-inflammatory drugs, analgesics, and hypoglycemic and hormonal drugs [15,16].

To reduce the anthropogenic load on water bodies, it is advisable, albeit not always possible, to use regenerative methods that allow compounds to be isolated from water without destroying their molecular structure, which allows substances to be returned to the production process as the main compound or processed into an alternative product. According to the latest technological advances, the priorities are filtration (media filtration and membrane systems), disinfection, ion exchange reactions, and carbon adsorption. A feasibility study of various technologies for deep water purification shows that adsorption methods are the most promising for technical water recovery [7]. The development of an optimal model for adsorption in the water purification process from organic pollutants requires the selection of an adsorbent, which contributes to both the technical implementation of the process and the economic feasibility of the proposed process [17–19]. Aluminosilicates, active carbon, and polymeric materials are recommended as adsorbents. Effective methods of deep purification are associated with high economic and resource costs, using scarce reagents with their subsequent regeneration, recycling, or waste disposal [7,20]. In general, conventional wastewater treatment methods are not very effective in removing emerging pollutants. Thus, wastewater containing emerging pollutants, if left untreated, could lead to serious outbreaks of communicable diseases, diarrhea, etc. [21]. It increases ecotoxicity [22] and bioaccumulation [23], damages DNA, and increases microbial resistance [24].

The task of quantifying the drug contamination of the hydrosphere is difficult, despite the emergence of new techniques and improvement in existing methods, due to the lack of a mechanism for the disposal of unnecessary or expired drugs. The most ordered system can be considered to be implementation, i.e., the financial component of the pharmaceutical market. In our opinion, implementation can most fully reflect the quantitative picture of drug pollution of the environment and its estimation, if we determine the nature and parameters of the functional relationship between years and sales volumes of prescription drugs, respectively.

Two main objectives of the paper were to analyze (*i*) the main pharmaceutical pollutants in the Kura River (Georgia) and (*ii*) the financial component of the global and Georgian pharmaceutical markets.

2. Materials and Methods

2.1. Object of Study

The object of the study was the Kura River. The Kura River is the largest river in Transcaucasia. It originates in the Armenian Highlands in Turkey. It flows into the Caspian Sea and flows through the territory of three states: Turkey, Georgia, and Azerbaijan, and for the last two, it is the main river. Part of the Kura basin (mainly its largest tributary, the Araks) is located on the territory of Armenia and Iran. The length of the Kura is 1364 km (185 km in Turkey, 390 km in Georgia, and 789 km in Azerbaijan). The river basin includes the entire territory of Armenia, the eastern part of Georgia, about 80% of the territory of Azerbaijan, and parts of the territories of Turkey and the Islamic Republic of Iran. The catchment area is 188 thousand km^2 (Figure 1). The territory of the Kura basin within

Georgia includes many tributaries of the first order, as well as, in whole or in part, several mountain river systems.

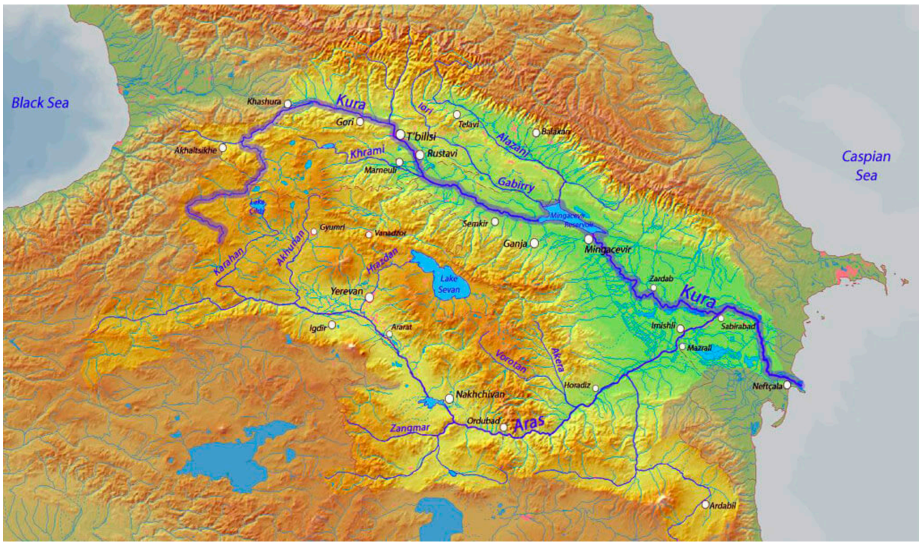

Figure 1. The river basin of Kura.

The density of the river network in the Kura River basin is 0.8 km/km^2. The formation of the main part of the underground component of the river runoff occurs in mountainous areas, with elevations of 1500–3000 m. Kura is formed by snow, rain, ground, and glacial waters.

The socioeconomic situation in the Kura basin (within Georgia) largely depends on natural factors. In the capital (Tbilisi), 60% of the population is concentrated. The rest of the basin is poorly urbanized, with about 32% of the population living in cities. The level of urbanization varies by region. The least urbanized is Kakheti (21%), and the most urbanized are ShidaKartli and KvemoKartli, with about 39% each, and in areas with agricultural development, the majority of water resources are used for agricultural production.

It follows from the above that the level of negative anthropogenic impact on the river basin is significant and should be considered as a combination of many factors, the magnitude of which depends on the size of the population and economic, household, or other activities. One of the main pollutants is pharmaceuticals used for both the needs of the population and veterinary medicine.

2.2. *Sampling*

Table 1 shows the GPS coordinates of polluted water sampling sites along the Kura River [19].

Table 1. The coordinates of polluted water sampling sites along the Kura River and marked with a red icon in Figure 2.

Site Number	GPS Coordinates	Site Description
2	41.822513, 44.760498	ZAHES—Tbilisi, Most Upstream Point
3	41.768066, 44.781505	Didube
6	41.641379, 44.934379	Between Tbilisi and Ponichala Reserve
9	41.596104, 44.956209	Before Algeti Tributary

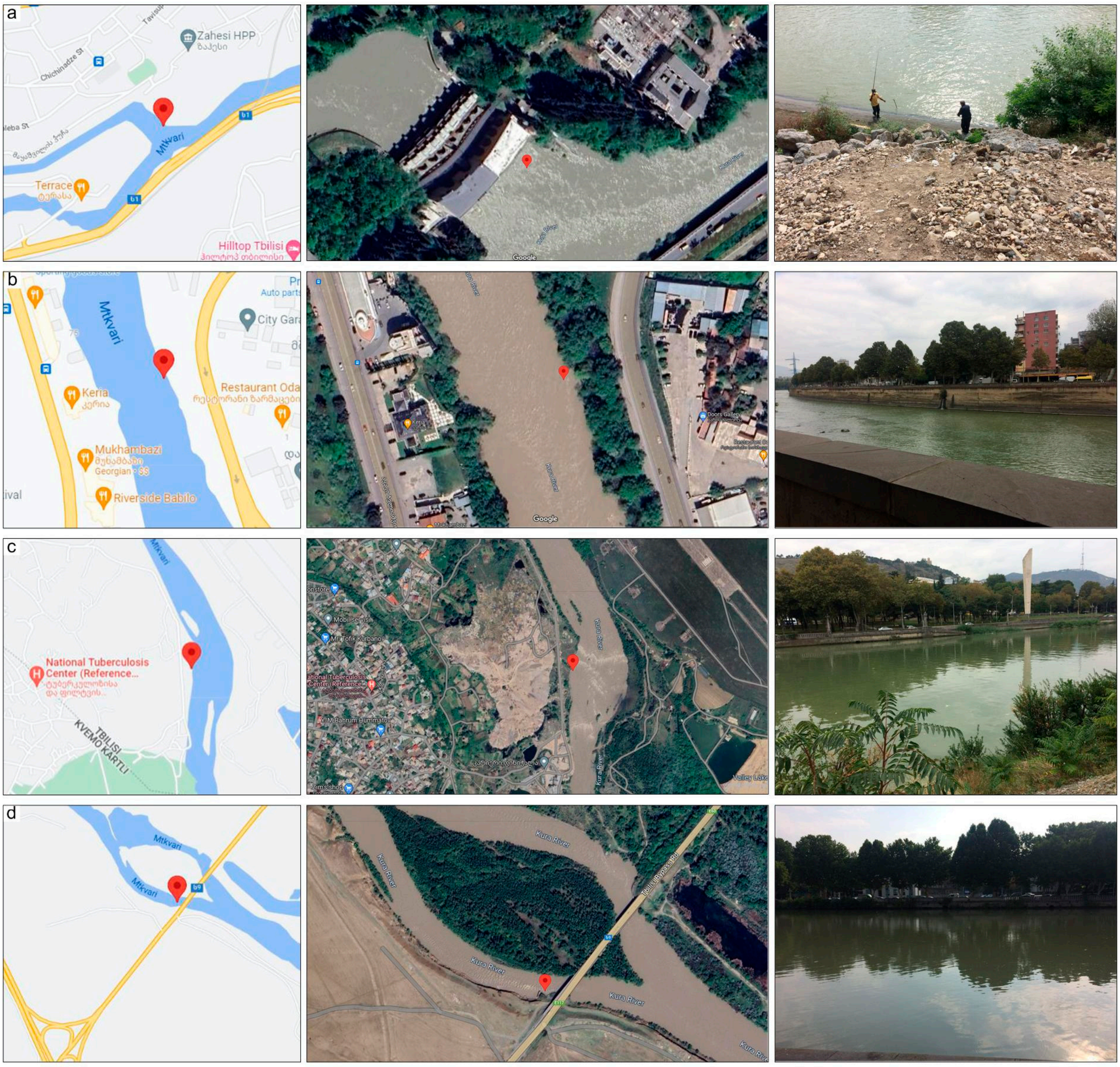

Figure 2. Map data: ZAHES—Tbilisi, most upstream point (**a**), Didube (**b**), between Tbilisi and Ponichala Reserve (**c**), and before Algeti Tributary (**d**).

Sampling sites provide the most complete picture of the location of facilities involved in pharmaceuticals, tourism, and catering. Figure 2 shows the cartographic data retrieved from Google Maps at the coordinates shown in Table 1.

For sampling water from the Kura River, four teams were designated, and all teams were equipped with the following set: three dark glass bottles with a volume of 5 mL, five plastic sterile disposable syringes, five syringe filters with a pore size of 0.45 µm, a bucket for samples with a volume of 200 mL and 10 m cord, and portable cooler with dry ice batteries. Sampling locations included sections of the river upstream, in the central part, and downstream within the city of Tbilisi (Table 1). Samples at each site were taken once and on the same day.

Water sampling was carried out at each site by throwing a prewashed bucket into the river water. Next, a filter was attached to the syringe, the bucket was filled, and 4 mL was poured into a dark glass vial. The samples were stored in a portable refrigerator.

Samples were kept frozen after collection until delivered to the laboratory. Samples were stored in the laboratory at −20 °C.

2.3. Determination of Water Composition

To analyze the quality of the water, we followed the "Sampling Protocols for Collecting Surface Water, Bed Sediment, Bivalves, and Fish for Priority Pollutant Analysis", established by the EPA [25]. The analysis was carried out using high-pressure liquid chromatography and tandem mass spectrometry (HPLC-MS/MS, Agilent LC 1260—AB Sciex MS 4500, Agilent Technologies, Santa Clara, California, USA). An Agilent Poroshell 120 column (4.6 × 50 mm, 2.7 µm) was used for the separation of the five target pharmaceuticals. The calibration curves of the targeted pharmaceuticals were plotted after the injection of mixed standard solutions for quantification. To guarantee the reliability and validity of the findings, lab safety protocols were followed. In the meanwhile, the internal standard method and the standard addition method were used to assess the qualitative and quantitative data of the target antibiotics. In accordance with the requirements for quantitative analysis, the correlation coefficients of the recoveries, relative standard deviations, and standard calibration curves varied from 0.9736 to 0.9997, 83.6% to 105.4%, and 1.4% to 5.7%, respectively. At signal-to-noise ratios of 3:1 and 10:1, the limits of detection and limits of quantification were, respectively, 0.009–0.063 ng/L and 0.031–0.168 ng/L.

The effects of the pollutants on aquatic organisms were analyzed based on the value of measured environmental concentration (MEC) and the predicted no-effect concentration (PNEC) [26]. The risk quotient was calculated using the maximum MEC and the PNEC of the pharmaceutical pollutants according to the following equation [26]:

$$RQ = MEC/PNEC \quad (1)$$

Based on the calculated RQ, risk measurement was classified into three categories [2]: $RQ < 0.1$ indicated less hazardous effects and thus low risk to the aquatic environment; $0.1 < RQ < 1$ indicated a moderate risk; and $RQ \geq 1$ indicated a high risk to aquatic organisms.

3. Results and Discussion

3.1. Pharmaceutical Pollution of the Kura River

The issue under study was the drug pollution of the river. Several studies [17,27–29], which have been carried out at the Georgian Technical University over the past few years, are devoted to Kura. The obtained results were compared with works in this field in other countries.

The results of the study of selected samples are shown in Table 2. The highest concentrations were observed in places where untreated sewage is discharged into the river (Didube and between Tbilisi and Ponichala), as well as in places adjacent to organized garbage dumps. The lowest concentrations were found in places with limited anthropogenic influence (before the Algeti Tributary) and with limited use of medicine (ZAGES—Tbilisi, the highest point).

Table 2. The concentration of pharmaceuticals found in the Kura River according to GTU, ng/L.

Name of Pharmaceuticals	Sampling Site Numbers			
	2	3	6	9
Caffeine (psychostimulant and analeptic)	4284	6500	786	2982
Clarithromycin (macrolide antibiotic)	120	179	–	–
Cotinine (nicotine)	120	231	152	74
Nicotine (nicotine)	864	1283	1493	480
Paracetamol (analgesic–antipyretic)	230	138	310	129
The total amount of pharmaceuticals by site	5618	8331	2741	3665

The total amount of pollutants in the analyzed sites, shown in Table 2, was as follows:

- ZAHES—Tbilisi, most upstream point: 5618 ng/L;

- Didube: 8331 ng/L;
- Between Tbilisi and Ponichala Reserve: 2741 ng/L;
- Before Algeti Tributary: 3665 ng/L.

The calculated risk quotient is shown in Table 3.

Table 3. Mean and maximum concentrations, as well as the calculated mean and maximum RQ values for the analyzed pharmaceuticals in Kura River.

Name of Pharmaceuticals	CAS	Mean Concentrations (ng/L)	Maximum Concentrations (ng/L)	PNECs (ng/L)	Mean RQ	Maximum RQ
Caffeine	58-08-2	3638	6500	320	11.36875	20.3125
Clarithromycin	81103-11-9	75	179	20	3.7375	8.95
Cotinine	486-56-6	144	231	1000	0.14425	0.231
Nicotine	54-11-5	1030	1493	400	2.575	3.7325
Paracetamol	103-90-2	202	310	500	0.4035	0.62

Caffeine, clarithromycin, and nicotine were found to have a high risk to aquatic organisms, and cotinine and paracetamol had a moderate risk in terms of both mean and maximum RQ.

Figure 3 shows the sampling locations with high (red), medium (orange and yellow), and low (green) pollution risk.

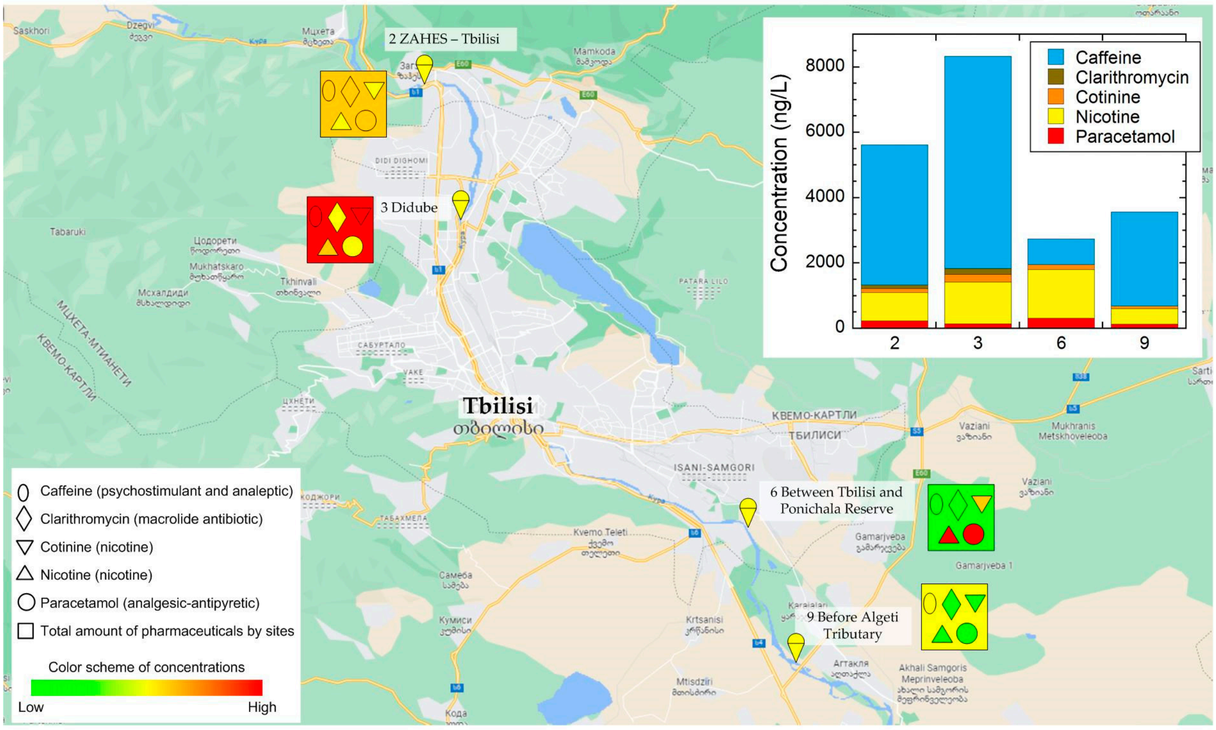

Figure 3. Sampling locations with high, medium, and low pollution risk.

The lack of systematization of implementation and forms of drug disposal did not allow for an accurate quantitative assessment of their turnover over time. When choosing this parameter, we adhered to the assumption that the change in the amount of drug pollutants in the environment, and hence in water, is proportional to the volume of drug sales.

The pharmaceutical pollution of the Kura River (Georgia) is a serious problem that can have a negative impact on the environment and human health. Pharmaceuticals can enter the Kura River through various routes: (i) Discharges from the pharmaceutical industry:

These include discharges of pharmaceutical substances in wastewater, dust emissions of medicines, and secondary pollution in the area of production waste disposal. The improper management and handling of waste from the pharmaceutical industries can lead to the release of medicines into the groundwater of the Kura River Basin. (ii) Misuse and improper disposal of medicines: The inappropriate use and mishandling of pharmaceuticals can result in their release into the environment. For example, throwing unused medicines down the toilet or in trash cans can end up in wastewater and eventually the Kura River. (iii) Effluents from sewage and wastewater treatment plants: Various pharmaceuticals enter wastewater from household drains, hospitals, laboratories, and pharmaceutical factories. Some of these drugs may be resistant to treatment at municipal wastewater treatment plants and end up in the Kura River with treated wastewater. The pharmaceutical pollution of the Kura River can have negative consequences for the river ecosystem and aquatic organisms. In addition, some of these drugs may have an impact on people's health, especially if they use the water from the Kura River for drinking or agriculture.

To combat the pharmaceutical pollution of the Kura River, measures and control actions are needed at various levels: (i) Regulation of emissions, discharges, and waste: Strict regulations and control in the first place on discharges of pharmaceuticals from the pharmaceutical industry and other sources (domestic consumption) will help reduce pollution in the Kura River. (ii) Education and awareness: Conducting educational campaigns on the use and disposal of pharmaceuticals helps to raise public awareness of these problems and to promote the handling of medicines. (iii) Improving the wastewater treatment system: The renovation and upgrading of municipal wastewater treatment facilities can help remove pharmaceuticals from wastewater more efficiently before they enter the Kura River. (iv) Monitoring and research: Regular monitoring of the content of pharmaceuticals in the Kura River will help to assess the level of pollution and take appropriate measures to prevent further damage. In general, a joint effort is needed between government agencies, the pharmaceutical industry, the population, and public organizations to reduce the pharmaceutical pollution of the Kura River and to ensure a clean and safe water environment.

3.2. Financial Component of the Global and Georgian Pharmaceutical Markets

When studying the problems of anthropogenic (drug) pollution of the environment, and, in particular, water resources, an analysis of the financial market of medicines was carried out. The economic component of the pharmaceutical market is one of the indirect factors that give a general idea of the volume and dynamics of growth in the number of drugs imported into the country.

According to the studies carried out by specialized organizations and independent researchers [10,15,16,19,29], which are related to pharmaceutical economics research, the size of the global pharmaceutical market is growing. While in 2008, drug sales amounted to USD 650 billion, in 2022, considering the population growth rate and the increase in life expectancy, the total sales amounted to more than USD 1210 billion (Table 4).

Based on the data in Table 3 and using the methods of mathematical statistics for processing small samples, an empirical dependence was obtained (2) as follows:

$$\text{WPDS} = 2.6533\text{Y2} - 10{,}661.6\text{Y} + 10{,}710{,}893 \text{ (USD billion)}, \quad (2)$$

where WPDS—worldwide prescription drug sales; Y—year.

The standard deviation from the original data was $R^2 = 0.9824$. In Figure 4, dependency graph (1) is shown in red, and a graph of worldwide prescription drug sales (WPDS) from 2008 to 2022 is presented in blue [20].

Table 4. Worldwide prescription drug sales (WPDS) from 2008 to 2022.

Years	World Sales of Prescription Drugs, USD Billion	Global Sales of Prescription Drugs by Addiction (1), USD Billion
2008	650	676
2009	663	672
2010	687	674
2011	729	682
2012	717	694
2013	724	712
2014	749	735
2015	742	764
2016	778	798
2017	822	837
2018	873	881
2019	931	931
2020	996	986
2021	1060	1047
2022	1121	1112
2023	-	1183
2024	-	1260
2025	-	1341

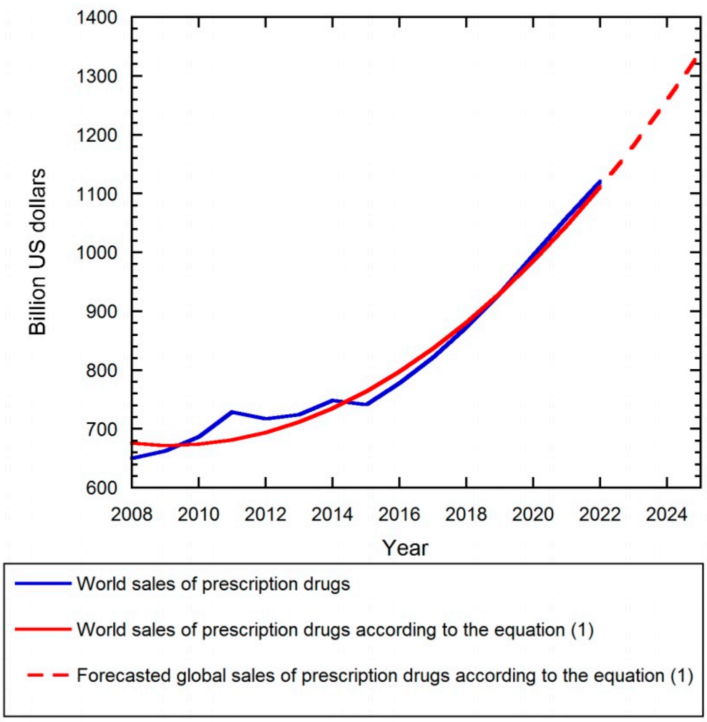

Figure 4. Worldwide prescription drug sales (WPDS) chart from 2008 to 2025.

The obtained results allowed us to extrapolate data for forecasting sales from 2022 to 2025 as a preliminary approximation (in Figure 4, the graph is shown with a red dotted line, with the data presented in Table 3).

The obtained results show that the trend of growth in the sales of receptor drugs will continue on a global scale and, compared with 2008, in 2025, sales volumes will increase by more than two times, reaching USD 691 billion. It should also be noted that, in many countries, internal regulations provide for the free sale of drugs (without prescription). A separate issue is the illegal trade of unregistered medicines, which makes it difficult to obtain reliable information but increases the total volume of sales, which means that the pollution of the environment, and hence water resources, is growing in direct proportion.

The largest consumers of drugs are the USA, Europe, and Japan [19,20,29]. At the same time, the level of drug consumption varies within different limits; for example, in the European Union, it ranges from 50 to 150 g per capita per year [19]. In recent decades, this figure has increased significantly. According to the available data, the level of consumption of antidepressants in 29 European countries increased by an average of 21% annually between 1995 and 2016. In addition, many countries in the region recorded a significant increase in the prescription of antibiotics, antiepileptics, antidiabetics, and some analgesics [2]. In general, anticancer drugs and antiviral agents are leaders in the global pharmaceutical market [19]. A similar situation is observed in Georgia.

It should be noted that the Georgian pharmaceutical market largely depends on imported drugs. As of 2021, 10,450 medicines are registered in the country. The dynamics of sales growth in USD from 2016 to 2020 is not significant and amounts to 7% (Table 5 and Figure 4), and in the national currency (GEL), it is 41%.

Table 5. Dynamics of sales growth in USD from 2016 to 2020.

Year	Sales Volume, mln. GEL	Sales Volume, mln. USD	Sales Volume according to Equation (2), mln. USD
2016	565	238	251
2017	676	270	253
2018	655	256	255
2019	716	254	256
2020	798	255	258
2021	-	-	260
2022	-	-	262
2023	-	-	264
2024	-	-	265
2025	-	-	267

This state is due to sharp fluctuations in the exchange rate of the national currency—lari (GEL). After processing the data using methods of mathematical statistics, an equation for empirical dependence (3) was formulated, and the results are presented in the red graph in Figure 3.

$$PDSG = 1.8Y - 3377.8. \quad (3)$$

where PDSG—sale of prescription drugs in Georgia in USD (Prescription Drug Sales in Georgia), Y—year.

The empirical dependence (3) gives a general idea of the state of the Georgian pharmaceutical market.

4. Conclusions

The pharmaceutical pollution of the hydrosphere is a problem that requires an integrated approach, both in the study of water resources and in the disposal of industrial products related to medicine, human health, and agriculture. Nonobservance or absence of legislation on the sale and disposal of pharmaceuticals did not allow us to quantify their turnover over time, and, consequently, the volume of pollutants released into the environment. Based on the work performed, the following conclusions can be drawn:

- A quantitative assessment of pharmaceuticals contaminants from the hydrosphere is difficult due to the lack of a regulated system of accounting and implementation and forms of dispensing pharmaceuticals to the population;
- One of the main indicators, in our opinion, which most fully reflects the quantitative data of the presence of pharmaceuticals as pollutants in the environment is the financial component of the pharmaceutical market;
- The empirical dependence Equations (2) and (3) give a general idea of the state of the world and Georgian pharmaceutical markets and allow for the forecasting of the growth in sales of pharmaceuticals by years;

- The change in the amount of pharmaceutical pollutants in the environment, and hence in water, is proportional to the volume of drug sales.

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