SAKARYA ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ DERGİSİ

Sakarya University Journal of Science
SAUJS

ISSN 1301-4048 e-ISSN 2147-835X Period Bimonthly Founded 1997 Publisher Sakarya University
http://www.saujs.sakarya.edu.tr/

Title: Investigation of Pharmaceuticals in Sakarya Sewage Wastewater

Authors: Berna KIRIL MERT, Cemil YILMAZ, Nihan ÖZENGİN

Recieved: 2022-01-19 00:00:00

Accepted: 2022-10-17 00:00:00

Article Type: Research Article

Volume: 26
Issue: 6
Month: December
Year: 2022
Pages: 1209-1223

How to cite
Berna KIRIL MERT, Cemil YILMAZ, Nihan ÖZENGİN; (2022), Investigation of Pharmaceuticals in Sakarya Sewage Wastewater. Sakarya University Journal of Science, 26(6), 1209-1223, DOI: 10.16984/saufenbilder.1060212
Access link
https://dergipark.org.tr/en/pub/saufenbilder/issue/74051/1060212

Sakarya University Journal of Science 26(6), 1209-1223, 2022

Investigation of Pharmaceuticals in Sakarya Sewage Wastewater

Berna KIRIL MERT *[1], Cemil YILMAZ[1], Nihan ÖZENGİN[2]

Abstract

Active substances of drugs can cause various adverse effects by accumulating in the ecosystem. Many medications are resistant to biodegradation, given the recipient media in conventional wastewater treatment plants, and are thus released into the environment after only partial purification or no purification at all. The study focuses on 13 different pharmaceutical compounds belonging to drug classes of anti-depressants, antiepileptic's, anti-inflammatories, beta-blockers, lidocaine, and stimulants. These compounds were selected with reference to the literature as the ones most commonly encountered in domestic wastewater, surface, and groundwater. The presence of these compounds in the wastewater samples from Sakarya sewage and wastewater treatment plant was investigated. For this purpose, composite samples were taken at various sampling points, and duly analyzed. The analysis revealed the presence of the pharmaceutical residues in the sewage waters from Sakarya Municipality. Some of them were still present in the effluent of the treatment plant. On the other hand, fluoxetine, propranolol, and metoprolol drug active ingredients were not detected at any sampling point. Among all the compounds examined, the highest percentage of residues were observed in the case of active caffeine and paracetamol**.** In the light of these findings, advanced treatment units such as high-pressure membrane systems (including ozonizing, ultrafiltration, and reverse osmosis) can help adsorption rates at the treatment plant, increasing removal efficiency regarding drug compounds.

Keywords: Pharmaceutical compounds, sewage wastewater, treatment, removal

1. INTRODUCTION

Given the widespread use of personal care products and pharmaceuticals, their ingredients have been seeping into aquatic environments in ever-increasing rates. The most critical factors leading to increased drug consumption include socioeconomic factors such as developments in science and technology as well as economic and cultural development, population growth, increased average life expectancy, urbanization, changes in income distribution, and the development of healthcare systems, not to mention the increase in the number of individuals who can benefit from these services [1].

* Corresponding author: bkiril@sakarya.edu.tr
[1] Sakarya University
E-mail: cemil_yilmaz@yahoo.com
ORCID: https://orcid.org/0000-0001-6993-7916, https://orcid.org/0000-0002-0283-6296
[2] Uludağ University
E-mail: nozengin@uludag.edu.tr
ORCID: https://orcid.org/0000-0002-7647-921X,

Water contamination may entail toxic effects on aquatic organisms, with consequences on the food chain, and cause direct effects on humans through consuming contaminated groundwater [2]. Usually, not all medication intake is retained by the human body; most is excreted in the form of urine and feces either in their original form or as active metabolites thereof [3]. The release of pharmaceuticals into the environment is quantified based on the dosage and the amount of drugs used, the frequency and intensity of excretion from the body, the tendency of the drug to be absorbed into solids, and the metabolic transformation capabilities of microorganisms in the wastewater treatment plant/storage area [4]. The amount of medical drugs used reach thousands of tons annually, and they eventually find their way into the sewage and treatment facilities. Although typical concentration levels detected are in the ng/L to low μg/L range, such micro-pollutants have still been observed to have toxic effects on aquatic organisms [5, 6].

These pollutants cannot be removed entirely during wastewater treatment. In addition, some pharmaceutical active substances are discharged from wastewater treatment plants to receiving environments almost unchanged. If they are not biodegradable or cannot be eliminated in treatment facilities, they can reach drinking water supply [7-9]. In this context, the problem is not limited to the drugs used in hospitals and homes. Drugs that are disposed of directly into the sewage system and garbage also contribute to the issue as primary sources of pollution [10]. Disposed drugs can mix with leachate water from landfills and cause pollution in aquatic systems [11]. Against this background, medicine ingredients that cannot be handily removed by wastewater treatment plants (WWTPs) cause pollution of groundwater and drinking water by being discharged into rivers, lakes, and estuaries [12, 13].

The conventional WWTPs' shortcomings in successfully removing PPCPs from wastewater pose major threats to aquatic ecosystems and local water supply systems. There is growing concern over the detection of PPCPs in freshwater resources, and increasing amounts of evidence indicate the potential adverse effects their presence could have on aquatic life and the quality of resources future generations of humans will need. Most of these pollutants are persistent, ecotoxic, and bio-accumulative by nature, thereby posing severe threats to the aquatic food chain and biological resources [14].

Monitoring studies have been gaining importance in recent years due to the increase in the production and use of chemicals in the form of pharmaceuticals and personal care products. These substances' resistance to biological treatment, the lack of strict regulations on discharges to surface water bodies, and the potential health risks of such compounds in aquatic environments make the matter even more urgent. Monitoring data on various pharmaceutical residues in wastewater treatment plants and treated wastewater has been documented over the past two decades. Most of these data have been compiled from Europe and North America, along with some countries in Northeast Asia, such as Japan, South Korea, and China. In recent years, some but comparatively sparse data pertaining to Southeast Asian countries have also found their ways into the literature [15, 16]. However, a growing amount of research has been taking place in recent years, studying these substances' potential effects on the health of the ecosystem [17-19]. Various studies found medicinal drugs and their metabolites at high rates in wastewater treatment plant effluents, surface waters, underground, and drinking water. Their ranges and concentration levels in aquatic environments vary depending on many factors such as location, the composition of sewage, design and operation of wastewater treatment facilities, proximity to wastewater facilities, and weather conditions (especially floods) [20,21]. The observation of micro-contaminants arising from the use of medicinal drugs, in aquatic environments, and

their potential effects on living creatures in this environment cause ever-increasing concerns.

Until recently, regulations did not mandate monitoring the presence of pharmaceuticals in freshwaters or wastewaters. However, changes were slowly breeding in the regulatory scene. For instance, 2013 saw the issuance of Directive 2013/39/EU in the EU, to expand on existing directives 2000/60/EC and 2008/105/EC. The new regulations especially focused on pharmaceuticals in the wider field of water policy, in a bid to control and reduce the contamination of aquatic environments by these compounds [22]. In response to the changes in the regulatory framework, new high-quality monitoring and prioritization measures were taken to meet the requirements as per article 16 of Directive 2000/60/EC. As part of the efforts, a watch list covering a number of contaminants was created. The list provided the basis of the requirements to monitor the presence of the contaminants named, to record data, and to assess the risk they may pose on the environment. The initial watch list introduced in the decision 2015/495/EU was subsequently revised in 2018/840/EU. Two years later, a further revision followed as the Decision 2020/1161/EU. The latest decision names the pharmaceuticals to be monitored so as to collect data for detailed assessment. Some of these compounds such as the antibiotics amoxicillin, ciprofloxacin, erythromycin, clarithromycin, azithromycin, sulfamethoxazole, and trimethoprim; the hormones 17-Alpha-ethinylestradiol, 17-Beta-estradiol, and estrone; the synthetic hormone norethisterone; the antidepressant venlafaxine; and three antifungal pharmaceuticals, clotrimazole, fluconazole, miconazole were already included in earlier versions of the watch list [23].

Pharmaceutical products monitored in this study were selected among the products with the highest sales in Turkey according to IMS Turkey Pharmaceutical Index and IMS Turkey Hospital Index. The compounds included in the study are Atenolol, Paracetamol, Caffeine, Lidocaine, Citalopram, Carbamazepine, Sertraline, Naproxen, Diclofenac, Etodolac, Metoprolol, and Propranolol. The presence of these compounds was investigated in samples taken from sewage and sewage treatment plants at certain points. Measures to be taken in the light of the data include curbing pharmaceutical use, prohibition or restriction of non-degradable substances. In parallel to these efforts waste control and reduction of discharge amounts, and appropriate storage will gain importance. The data will certainly inform efforts to make assessments regarding enhancing water treatment, and working with more advanced treatment systems.

2. MATERIAL AND METHOD

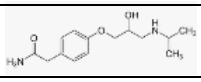
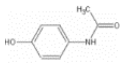
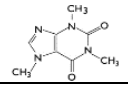
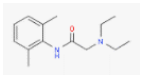
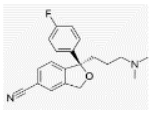
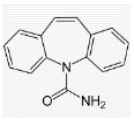
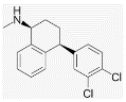
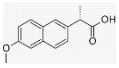
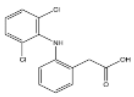
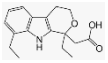
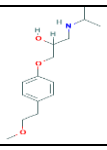
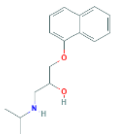
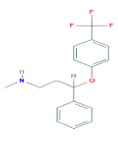
2.1. Monitored Pharmaceuticals

The pharmaceuticals monitored within the scope of the study are presented in Table 1.

2.2. Wastewater Sampling Points and Features

To determine the pharmaceutical concentrations in wastewater (both domestic and industrial) discharged into the sewage in Sakarya, sampling points were utilized in hospitals located on the sewerage network connecting to the Karaman Wastewater Treatment Facility serving the Sakarya region. In addition, samples were taken from the wastewater treatment plant influent and effluent. Located in the north of Sakarya Province, the Central Wastewater Treatment Facility affiliated with SASKI (Sakarya Water and Sewage Administration) treats wastewater from residences and industrial establishments. Wastewater from industrial establishments is pre-treated before being fed into the wastewater treatment facility. The facility is capable of treating 198,800 m^3/day in dry weather and 271,941 m^3/day in rainy weather. The facility's operations are based on two basic treatment methods: physical and biological.

Table 1 Properties of the pharmaceuticals analyzed [24].

Pharmaceutical products	Chemical Formula	CAS No	Molecular weight (g/mol)	Explanation
Atenolol		29122-68-7	266.3	Atenolol is a beta1-selective adrenergic antagonist.
Paracetamol		103-90-2	151.163	Paracetamol is an antipyretic and analgesic drug substance.
Caffeine		58-08-2	194.19	It is an alkaloid, also called guaranine or matein.
Lidocaine		137-58-6	234.34	Lidocaine is a medicine used to numb the tissue in a certain area.
Citalopram		59729-33-8	324.392	It is a selective serotonin reuptake inhibitor. Serotonin is the most selective molecule with the highest specificity.
Carbamazepine		298-46-4	236.269	Its primary use is in neuropathic pain relief and epilepsy medicine. It is not effective in absence seizures and myoclonus.
Sertraline		79617-96-2	306.229	Sertraline is an antidepressant that is a selective serotonin reuptake inhibitor.
Naproxen		22204-53-1	230.259	Naproxen is a non-steroidal anti-inflammatory drug.
Diclofenac		15307-86-5	296.14	Diclofenac is an effective medicine for pain relief on inflammatory conditions. It is a non-steroidal anti-inflammatory (NSAII) group drug.
Etodolac		41340-25-4	287.35	Etodolac is an non-steroidal and anti-inflammatory medicine derived from indole.
Metoprolol		51384-51-1	267.369	Metoprolol is a cardioselective beta-blocker commonly used in the treatment of hypertension and angina pectoris.
Propranolol		525−66-6	259.349	Propranolol is a non-selective beta-adrenergic receptor blocker (beta-blocker) widely used for the treatment of hypertension, heart rhythm, angina pectoris, and hyperthyroidism.
Fluoxetine		54910-89-3	309.332	Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) commonly used as an antidepressant.

With the support of SASKI, the current situation in Sakarya Province was assessed by taking samples from specific points for a period of six months. The sampling points are as follows:

- Four different hospital outlets (Adatıp Hospital, Altınova Hospital, Korucuk Training and Research Hospital, Sakarya Training and Research Hospital)
- Treatment plant intake and treatment plant outlet (at Karaman Wastewater Treatment Plant)
- One sewerage network

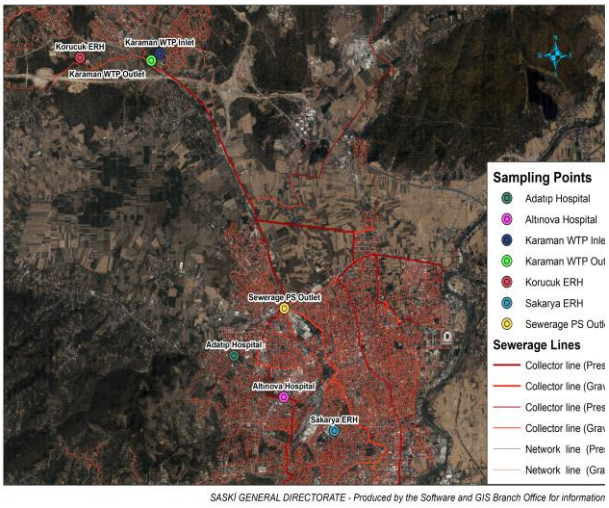


Figure 1 Map of sampling points

2.3. Pollutant Analysis Method

Prior to each round of analysis, mixed standard solution was prepared. The process involved diluting the stock solutions with ultrapure water produced by a Milli-Q unit. LC-MS-MS instrument was used for the analysis of microfoulers. The process took place on a liquid chromatography system (Agilent 6460 QQQ). An Agilent Poroshell C-18 (3x100mm, 2.7µm) column served as the medium of chromatographic separation, with 5 µl injection volume. A gradient elution program was used at 0.5 ml min^{-1} flow rate for both reservoirs with 5 mM ammonium formate + 0.1% formic acid in (A) water and (B) methanol. All samples were stored at 4°C in dark. Standards used are Sigma-Aldrich (Steinheim, Germany) and Dr., which were purchased from Ehrenstorfer (Augsburg, Germany).

MS/MS experiments were carried out on an ion mass spectrometer running in positive ion mode with multiple reaction monitoring (MRM). Instrument control and data collection functions were managed on MassHunter analyst software. The nebulizer was set to 35 psi, whereas the flow rate was 11 L/min. The temperature of the nebulizer was set to 300°C. The capillary voltage setting was 3,500 V while the source temperature was set to 400°C. The recoveries of samples extracted for quality assurance/quality control were calculated by comparing wastewater samples. With the calibration curve of 13 pharmaceuticals and good linearity, the R2 value for each micro-contaminant was found to be higher than 0.999.

TOC, COD, SS, and Ammonia parameters were set as per standard methods [25]. Analyses of pH, TDS, and conductivity parameters were performed with a multi-parameter measuring device (Hach HQ440d-Hach-Lange GmBH). The analyses for COD and TOC parameters, in turn, were based on 5310-B high-temperature catalytic oxidation method, using the 5220-D closed colorimetric reflux method for COD, and Teledyne Tekmar analyzer for TOC. The suspended solid (SSM) content of the samples was analyzed by drying at 103-105°C temperature range as stipulated by the 2540-D gravimetric method. Ammonia was produced through 4500 NH_3 B: Pre-Distillation Method.

3. RESULTS AND DISCUSSION

3.1.Sewage water characterization

The wastewater characteristics of the samples taken at the sampling points shown in Figure 1 are presented in Table 2.

Table 2 Sewage water samples analysis results.

Sampling Points	pH	Tds (mg/L)	EC (µS/cm)	TOC (mg/L)	COD (mg/L)	NH_3 (mg/L)	SS (mg/L)
Altınova Hospital	9.34	1601	827	98.60	508	24	115
Adatıp Hospital	8.02	674	327	23.64	180	4.3	25
Karaman WTP Inlet	8,15	953	476	21.27	256	4.2	220
Karaman WTP Outlet	8.08	791	382	10.03	22	2.3	20
Korucuk ERH	10.15	855	422	29.64	194	1.8	80
Sewage PS Outlet	8.13	753	368	18.79	96	4.2	35
Sakarya ERH	7.78	454	218,1	68.57	332	3.1	35

3.2. Pharmaceutical Values

Thirteen different pharmaceutical compounds including Paracetamol, Caffeine, Lidocaine, Citalopram, Carbamazepine, Sertraline, Naproxen, Diclofenac, Etodolac, Metoprolol, Propranolol, Fluoxetine (anti-depressants, antiepileptic's, anti-inflammatories, beta-blockers, lidocaine, and stimulant) were found in varying concentration levels. The results are presented below.

3.2.1. Anti-depressants

Anti-depressants find their way into M-WWTPs either in their original form, or in the form of their metabolized products present in human urine. For example, around 20 to 30 percent of fluoxetine taken is metabolized in human body, to form the active metabolites of the compound –i.e. fluoxetine glucuronide and norfluoxetine–, while the rest remains unprocessed, and eventually reaches sewage plants [26].

Golovko et al. (2014) kept track of citalopram and sertraline compounds in the inlet and outlet waters of a treatment plant for one year. At the inlet of the treatment plant, the concentration levels of these compounds were found to vary in the 0.027-0.18 µg/L and 0.007-0.027 µg/L ranges, respectively. At the outlet, the measured ranges for the two compounds were 0.03-0.12 µg/L and 0.003-0.006 µg/ L, respectively [27]. The treatment plant removal efficiencies for these compounds were found to be 18% and 81%, respectively. Another important study observed fluoxetine and sertraline compounds in fish [20].

As seen in Figure 2, in this study, fluoxetine was not observed in any sample taken from various points of the sewage system and at the wastewater treatment plant's inlet and outlet. Sertraline, in turn, was found only at the Korucuk Hospital sampling point, and at 0.2163 µg/L concentration level, while Citalopram was found only in the samples taken at Altınova Hospital (0.9399 µg/L concentration level) and at Korucuk Hospital (0.2312 µg/L concentration level).

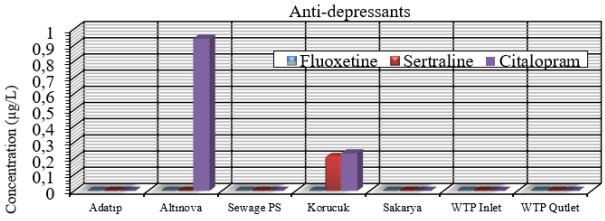


Figure 2 Antidepressant concentration levels at sampling points

3.2.2. Antiepileptics

Carbamazepine is a widely prescribed antiepileptic that is included in the EU's watch list of substances under the Water Framework Directive. The compound is observed often in groundwater, and at relatively high concentrations then. In the literature, the

maximum concentration levels noted for carbamazepine was 0.39 µg/L in 42% of samples collected from 164 locations in 23 European countries [28]. Nam et al. (2014), in turn, measured carbamazepine concentrations at wastewater treatment plants in the summer and winter months, to find 0.0031-0.0307 µg/L and 0.0052-0.0464 µg/L ranges, respectively [29]. In the present study, no carbamazepine was detected in the samples taken at the Altınova hospital (Figure 3). However, that observation proved to be an outlier, and concentrations in the 0.1462-0.4651 µg/L range were observed at other sampling locations. The concentration level at the wastewater treatment plant's intake was 0.2508 µg/L, compared to the 0.2438 µg/L figure measured at the plant's outlet. In a similar study, carbamazepine concentration levels in inlets and outlets of wastewater treatment plants in different countries were found to be in <0.04-3.78 µg/L and <0.005-4.60 µg/L ranges, respectively. Moreover, lifting efficiency was reported to be in the 0–62.3% range [30]. The results of the present study are consistent with these ranges noted in the literature.

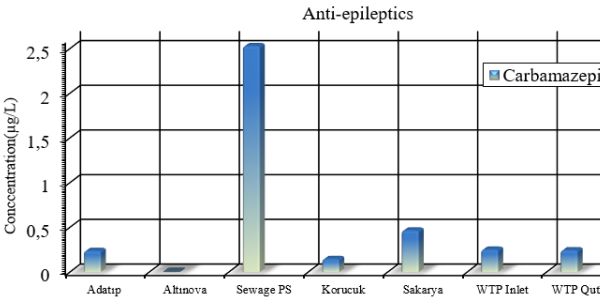


Figure 3 Antiepileptic concentration levels at sampling points

Previous studies show that some pharmaceutical compounds can be removed from the wastewater through adsorption taking place in physical purification processes. Other compounds, such as ibuprofen, naproxen, sulfamethoxazole, and iopromide compounds, in turn, can be eliminated through subsequent biological treatment stages, which achieve 30 to 75% removal rates for most anti-inflammatories and antibiotics. Carbamazepine is not one of them, however. Several reports show that wastewater treatment facilities are not effective in removing significant amounts of carbamazepine from wastewater [31-33].

3.2.3. Anti-inflammatories

Like antibiotics, NSAIDs such as naproxen and diclofenac can potentially be extremely toxic for various bacteria. Aquatic environments as well as human life are also subject to significant risks these substances may pose. In response, the European Union included diclofenac in the first version of the watch list (WL) issued under the Water Framework Directive (WFD) in 2015 (Decision 2915/495). More recently, however, the substance was removed from the WL under Decision 2020/1161, given the availability of adequate levels of high quality data produced through monitoring efforts [26].

Ibuprofen, diclofenac and paracetamol are the anti-inflammatories and analgesics which are most commonly detected in groundwater. The reason is their extensive consumption in response to the symptoms of a number of conditions. Mutiyar et al. (2018) noted that diclofenac is used commonly to treat pain and other symptoms suffered by human patients. However, a rather less expected use case of the substance is prevalent in livestock farming. Nonetheless, it is observed that the use of diclofenac on animal populations has been decreasing due to rapid urbanization [3]. In Delhi, India, the Yamuna River into which sewage waters are also discharged, ibuprofen and paracetamol compounds are detected, with average concentrations of 1.49 and 1.08 µg / L, respectively. Vystavna et al. (2017) detected 12 compounds in samples taken in 2012 and 2015 from the influent and effluent of the treatment plant [34]. It was also noteworthy that the measured concentrations of naproxen, triclosan, paracetamol, ibuprofen and carbamazepine detected in the influent of the plant had increased in that time frame. The most significant increases were observed in

the case of carbamazepine and naproxen, the concentration levels of which increased by 50 and 10 times, respectively. In contrast, the input concentrations of diclofenac and caffeine were reduced significantly.

The analysis of samples from Udy River exhibited decreasing concentration levels for diclofenac (-97%), triclosan (-88%), caffeine (-80%), and paracetamol (-5%), and increasing concentration levels for ibuprofen (+80%) and carbamazepine (+96%). Removal efficiencies observed in both years covered in the study were greater than 80% (high) for propranolol and naproxen, and between 50 and 80% (moderate) for other compounds included in the analysis.

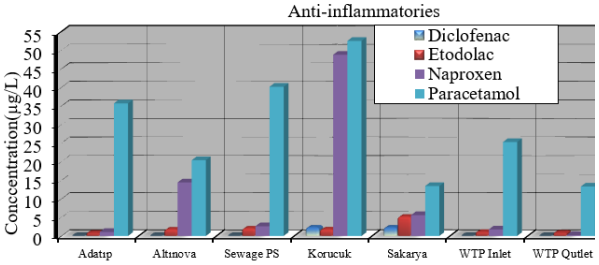


Figure 4 Anti-inflammatory concentration levels at sampling points

In this study, as seen in Figure 4, diclofenac was detected only in the samples taken at Korucuk and Sakarya Hospitals, with 2.3469 µg/L and 2.3234 µg/L concentration levels, respectively. Etodolac, Naproxen and Paracetamol compounds were detected in the 0.8683-5.2467 µg/L, 0.2362-48.8507 µg/L, and 13.3412-52.5798 µg/L ranges for all sampling locations, respectively. The results presented in another study for wastewater analyses conducted in different countries are close to the results reached here. The concentration level of diclofenac in wastewater was 3 µg/L, with a corresponding removal efficiency level of 17%. The comparable figures for naproxen were 1.8-40.7 µg/L and 40-100%, while the figures for paracetamol were 6.9 µg/L and 100% [35].

Paracetamol was detected in various European sewage wastewater treatment plants, with concentration levels ranging around 6 mg/L. Higher concentration figures were found elsewhere though, with values up to 10 mg/L being observed in some surface waters in the US, and up to 65 mg/L in the Tyne River in England. In addition, a study on organic wastewater pollutants in US waters found paracetamol in surface waters, at a maximum concentration of 10 µg/L with a frequency of 23.8 % [36].

Paracetamol is the most widely used analgesic/antipyretic globally and is a very common occurrence in hospital wastewaters (HWW), with concentration levels in 10^1 to 10^3 µg/L range. Paracetamol was also found in hospital sewage samples (at 7.5 µg/L concentration levels). Diclofenac is another typical analgesic, with concentrations in HWW ranging between 10^{-1} and 10^2 µg/L. Diclofenac concentrations in 0.83 to 3.59 µg/L range were detected in another set of HWW samples [37].

3.2.4. Beta Blockers

In a study on beta blocker concentrations in the city of Barcelona, Spain, Lopez-Serna et al. (2013) found various concentrations of propranolol (< 0.00938 µg/L) and metoprolol (at most 0.355 µg/L) in groundwater samples. In the case of wastewater, the picture varied from site to site, with the concentrations of atenolol observed in Cuernavaca, Mexico were around half of those detected in India [38].

The average concentration of atenolol reported in wastewater worldwide is 4.5 µg/L. At the inlet of the Acapantzingo treatment plant in Mexico, very high concentration levels were recorded for atenolol (0.2-3.1 µg/L) [39]. In another study, the atenolol compound was observed in relatively substantial concentrations as high as 21,610 µg/L in wastewater samples taken from municipal wastewater treatment plants after the final settling [40].

In this study, propanolol and metoprolol compounds were not detected at any point.

Atenolol concentration levels, in turn, were found to be 0-0.8949 µg/L. No atenolol was detected in the treatment plant's inlet and outlet (Figure 5).

In a similar study, Tran et al. (2018) found the following concentration levels at the influent and effluents of wastewater treatment plants for atenolol: 0-0.294.7 µg/L in Asia, 0.5-2.642 µg/L in North America, and 0-0.0331 µg/L in Europe. In the case of metoprolol, the concentration levels Tran et al. found were 0-0.0795 µg/L in Asia, 0.016-0.154 µg/L in North America, and 0-4.148 µg/L in Europe. Finally, their results for propranolol were 0-0.00956 µg/L in Asia, and 0-1.962 µg/L in Europe, which is quite low [16].

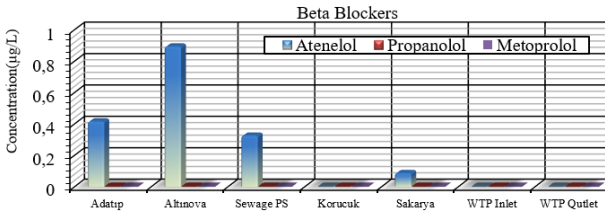


Figure 5 Beta Blockers' concentration levels at sampling points

3.2.5. Lidocaine

Local anaesthetic Lidocaine (LDC), also used as an antiarrhythmic agent, is another widely prescribed drug. Recent studies found LDC in wastewater samples from wastewater treatment plants, as well as samples taken from some rivers and lakes in Europe and North America. However, the data available on the removal rates achieved at wastewater treatment plants with respect to these compounds and their metabolites is limited.

While the amount of LDC at various points in Lake Constance, Switzerland was measured as 0.001 µg/L [41], levels as high as 0.01 µg/L were observed in surface waters in the Netherlands [42]. Oftentimes, studies on LDC presence in wastewater and its behavior in treatment plants found concentration levels in excess of 1 µg/L in untreated wastewater.

Rarely can wastewater treatment plants achieve complete removal of these compounds, often resulting in their discharge to receiving waters. The presence of these drugs –either in their original form or in the form of their metabolites– in surface waters is important because their infiltration into groundwater can pose a problem in terms of water quality. The average LDC concentration level noted in the literature is 0.107 µg/L, as observed in samples from wastewater treatment plants that only treat wastewater from homes and hospitals [42]. In this study, however, the Lidocaine levels in the samples ranged from 0.2207 µg/L to 4.8735 µg/L, with those taken at the intake of the treatment plant being on the lower end of the range (Figure 6). Furthermore, LDC was found to be completely removed at the outlet of the plant.

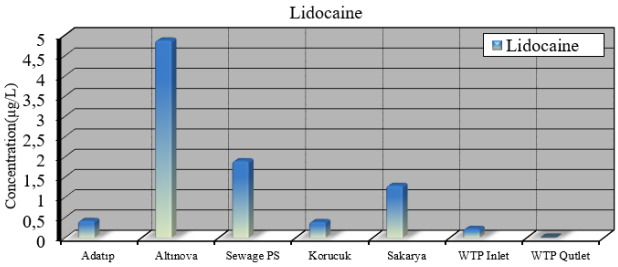


Figure 6 Lidocaine concentration levels at sampling points

3.2.6. Stimulant

Humans consume substantial amounts of coffee, tea and soft drinks containing caffeine, which is a most common stimulant. The average concentration of caffeine in these popular drinks is 360 mg/L. Upon discharge from human body in the form of urine, the substance reaches the sewage system. Studies have proven that caffeine can contaminate sewage wastewater, septic tanks, wastewater leachate and surface waters to which wastewater is discharged. Eventually, the substance finds its way to ground water.

Various studies have shown the presence of caffeine in sewage effluent, septic tanks, not to mention landfill leachates. Eventually, these sources lead to the contamination of surface water. From that point on, it is only a

matter of time for the substance to reach groundwater sources through contamination during the natural process of water recycling [28].

The substance is so widely consumed, and thus extremely high concentrations are not surprising to find in the environment. For instance, concentration levels reaching 146 µg/L have been reported in wastewater samples. Average caffeine concentrations measured at the inlets and outlets of various wastewater treatment plants in Seville, Spain, varied between 0.22–11.40 µg/L and 0.15-3.20 µg/L, respectively [43]. Yet another study reported caffeine concentration levels in the 12-499 µg/L range in a number of samples taken from wastewaters [44].

In the present study, the highest concentration of caffeine was detected in the samples taken at Korucuk Hospital, reaching 120 µg/L. The levels for the samples taken at other sites were also substantial. The intake of the treatment plant contained 33.8718 µg/L caffeine. However, it is noteworthy that the plant's removal rate for the substance was 100%. In Figure 7, the caffeine concentration values at the sampling points are given. Similar findings are reported in the literature, with removal efficiencies in the 49.9-99.6% range published for conventional wastewater treatment plants in China, Europe, Greece, Korea, Spain, and England [30].

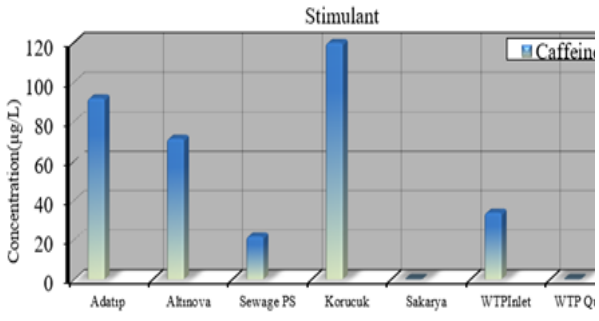


Figure 7 Stimulant concentration levels at sampling points

It is also noteworthy that Caffeine was also detected in Costa Rica's WWTPs with mean concentration in the influent being 69.9 g/L [45].

4. CONCLUSIONS

In the study, 13 different pharmaceutical compounds were investigated in sewage samples taken from 7 different measurement points, which are mainly from Sakarya sewerage and Karaman Wastewater Treatment Plant. The highest measured values are as follows: at Altınova sampling point, antidepressant citalopram with a concentration level of 0.9399 µg/L, beta blocker atenolol with a concentration level of 0.8949 µg/L and LDC with a concentration level of 4.8735 µg/L, at the Sewage PS sampling point, antiepileptic carbamazepine with a concentration level of 2.5281 µg/L, and at the Korucuk sampling point, anti-inflammatory paracetamol with a concentration level of 52.5798 µg/L, and stimulant caffeine with a concentration level of 120 µg/L. Fluoxetine, propranolol and metoprolol pharmaceutical compounds could not be detected at any sampling point.

The conventional treatment plant covered in the study was found to have efficiency levels in excess of 85% for caffeine, lidocoine and naproxen, whereas the plant's efficiency level was as low as 3% for carbamazepine. For pharmaceuticals that are difficult to remove, it is possible to achieve better removal efficiencies reaching 99.7% through advanced treatment. In this context, it is advisable to implement advanced treatment methods for conventional treatment units as well. These results highlight the alarming level of contamination of surface waters, and put the issue to the forefront of environment debate. On the other hand, the findings of this study show that, at current levels, there is no risk of acute toxicity of drug active ingredients. However, the threat of chronic effects cannot be ignored, given the fact that of multiple drugs find their way into water sources. Further monitoring of aquatic environments in

this area will make it easier to assess and evaluate aquatic organisms' and the environment's chronic or long-term exposure to these new types pollutants. Understanding the problem will be the first step for the efforts to improve water quality through better wastewater management.

Acknowledgments
We would like to thank Sakarya Water and Sewerage Administration for their support in sampling and contributing to our work.

Funding
This study was supported by the Science Master's Thesis Project named "Investigation of Drug Compounds in Sewage Water in Sakarya Province" within the scope of Sakarya University Scientific Research Projects numbered "2013-50-01-010".

The Declaration of Conflict of Interest/ Common Interest
No conflict of interest or common interest has been declared by the author.

Authors' Contribution
The authors contributed equally to the study.

The Declaration of Ethics Committee Approval
This study does not require ethics committee permission or any special permission.

The Declaration of Research and Publication Ethics
The authors of the paper declare that he complies with the scientific, ethical, and quotation rules of SAUJS in all processes of the paper and that he does not make any falsification on the data collected. In addition, he declares that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

REFERENCES

[1] R. R. Z. Tarpani, A. Azapagic "Life cycle environmental impacts of advanced wastewater treatment techniques for removal of pharmaceuticals and personal care products (PPCPs)," Journal of Environmental Management, vol. 215, pp. 258-272, June 2018.

[2] C. Morosini, E. Postè, M. Mostachetti, Vincenzo Torretta, "Pharmaceuticals in water cycle: a review on risk assessment and wastewater and sludge treatment," Environmental Engineering and Management Journal, Vol.19, No. 8, 1339-1378, August 2020.

[3] P. K. Mutiyar, S. K. Gupta, A. K. Mittal, "Fate of pharmaceutical active compounds (PhACs) from River Yamuna, India: An ecotoxicological risk assessment approach," Ecotoxicology and Environmental Safety, vol. 150, pp. 297-304, 15 April 2018.

[4] C. G. Daughton, T. A. Ternes, "Pharmaceuticals and personal care products in the environment: agents of subtle change," Environmental Health Perspectives, vol. 107, pp 907–938, 6 December 1999.

[5] G. Knopp, C. Prasse, T. A. Ternes, P. Corne, " Elimination of micropollutants and transformation products from wastewater treatment plant effluent through pilot scale ozonation followed by various activated carbon and biological filters," Water Research, vol. 100, pp. 580-592, 1 September 2016.

[6] C. Dai, S. Li, Y. Duan, K. H. Leong, Y. Tu, L. Zhou, "Human health risk assessment of selected pharmaceuticals in the five major river basins, China," Science of The Total Environment, 801, 149730, 2021.

[7] Q. Sui, J. Huang, S. Deng, G. Yu, Q. Fan, "Occurrence and removal of pharmaceuticals, caffeine and DEET in wastewater treatment plants of Beijing, China," Water Research, vol. 44, pp. 417–426, 2010.

[8] B. Subedi, N. Codru, D. M. Dziewulski, L. R. Wilson, J. Xue, S. Yun, K. Kannan, "A pilot study on the assessment of trace organic contaminants including pharmaceuticals and personal care products from on-site wastewater treatment systems along Skaneateles Lake in New York State, USA," Water Research, vol.72, pp.28-39, 2015.

[9] B. Subedi, K. Balakrishna, D. I. Joshua, K. Kannan, "Mass loading and removal of pharmaceuticals and personal care products including psychoactives, antihypertensives, and antibiotics in two sewage treatment plants in southern India," Chemosphere, vol. 167, pp. 429-437, January 2017.

[10] A. J. Ebele, M. A. E. Abdallah, S. Harrad," Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment," Emerging Contaminants, vol 3(1), p.p1-16., 2017.

[11] Holm, M. Bakken, O. Vangen, R. Rekaya, "Genetic analysis of age at first service, return rate, litter size, and weaning-to-first service interval of gilts and sows," Journal Animal Scence vol. Pp. 83:41-48, 2005.

[12] K. Fent, A. A. Weston, D. Caminada, "Ecotoxicology of human pharmaceuticals," Aquatic Toxicology, vol.76 (2), p.p 122-159, 2006.

[13] A, Kurt, B. K. Mert, N. Özengin, Ö. Sivrioğlu, T. Yonar, "Treatment of antibiotics in wastewater using advanced oxidation processes (AOPs)," Physico-Chemical Wastewater Treatment and Resource Recovery, Intech Open Science, Londrina, pp. 175-211, 2017.

[14] V. Singh, S. Suthar, "Occurrence, seasonal variations, and ecological risk of pharmaceuticals and personal care products in River Ganges at two holy cities of India," Chemosphere, 268, 129331, 2021.

[15] N. Han Tran, K. Y. Hoong Gin, "Occurrence and removal of pharmaceuticals, hormones, personal careproducts, and endocrine disrupters in a full-scale water reclamation plant," Science of the Total Environment, pp.1503–1516, 2017.

[16] N. Han Tran, M. Reinhard, K. Y. Hoong Gin, "Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions-a review," Water Research, vol. 133, pp. 182-207, 2018.

[17] S. Gaw, K. V. Thomas, T. H. Hutchinson, "Sources, impacts and trends of pharmaceuticals in the marine and coastal environment," Philos Trans R Soc. Lond. B Biol Sci., 369(1656), Nov 19 2014.

[18] P. K. Jjemba, "Excretion and ecotoxicity of pharmaceutical and personal care products in the environment," Ecotoxicology and Environmental Safety, vol. 63, no. 1, 2006, pp. 113-130, January 2006.

[19] D. W. Kolpin, E. T. Furlong, M. T. Meyer, E. M. Thurman, S. D. Zaugg, L. B. Barber, H. T. Buxton, "Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999−200: A National Reconnaissance," Environmental Science Technology, vol.36, no.6, pp. 1202–1211, 2002.

[20] Nikolaou, S. Meric, D. Fatta, "Occurrence patterns of pharmaceuticals in water and wastewater environments. Analytical and Bioanalytical Chemistry," vol. 387, no.4, pp. 1225-1234, 2007.

[21] J. Sui, H. Afzalimehr, A. K. Samani, M. Maherani, "Clear-water scour around semi-elliptical abutments with armored beds," International Journal of Sediment Research, vol.25, no.3, pp. 233-245, 2010.

[22] A. S. Ajibola, S. T. Fawole, F. O. Ajibola, G. O. Adewuyi, "Diclofenac and ibuprofen determination in sewage sludge using a QuEChERS approach: Occurrence and ecological risk assessment in three Nigerian wastewater treatment plants," Bulletin of Environmental Contamination and Toxicology, 106(4), 690-699, 2021.

[23] J. P. Fernandes, C. M. R. Almeida, M. A. Salgado, M. F. Carvalho, A. P. Mucha, "Pharmaceutical compounds in aquatic environments—Occurrence, fate and bioremediation prospective," Toxics, 9(10), 257, 2021.

[24] PubChem, National Institutes of Health. (2022). National Library of Medicine [Online] Available: https://pubchem.ncbi.nlm.nih.gov

[25] E. W. Rice, R. B. Baird, A. D. Eaton, L. S. Clesceri, APHA, Standard methods for the examination of water and wastewater, 21th Ed. American Public Health Association Publication, Washington, USA, 2012.

[26] O. F. S. Khasawneh, P. Palaniandy, "Occurrence and removal of pharmaceuticals in wastewater treatment plants," Process Safety and Environmental Protection, 150, 532-556, 2021.

[27] O. Golovko, V. Kumar, G. Fedorova, T. Randak, R. Grabic, "Seasonal changes in antibiotics, antidepressants/psychiatric drugs, antihistamines and lipid regulators in a wastewater treatment plant," Chemosphere, vol. 111, pp. 418–426, 2014.

[28] Q. Sui, X. Cao, S. Lu, W. Zhao, Z. Qiu, G. Yu, "Occurrence, sources and fate of pharmaceuticals and personal care products in the groundwater: A review" Emerging Contaminants, pp.14-24, 2015.

[29] S. W. Nam, B.-Il Jo, Y. Yoon, K. D. Zoh, "Occurrence and removal of selected micropollutants in a water treatment plant," Chemosphere, vol.95, pp.156–165, 2014.

[30] Y. Luo, W. Guo, H. H. Ngo, L. D. Nghiem, F. I. Hai, J. Zhang, S. Liang, X C. Wang, "A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment," Science of the Total Environment, vol. 473–474, pp. 619–641, 2014.

[31] Strenn, M. Clara, O. Gans, N. Kreuzinger, "Carbamazepine, diclofenac, ibuprofen and bezafibrate-investigations on the behaviour of selected pharmaceuticals during wastewater treatment," Water Science Technology., vol.50 (5), pp. 269–276, 2004.

[32] M. Clara, B. Strenn, O. Gans, E. Martinez, N. Kreuzinger, H. Kroiss, "Removal of selected pharmaceuticals, fragrances and endocrine disrupting compounds in a membrane bioreactor and conventional wastewater treatment plants, "Water Research. Vol.39 (19), pp. 4797-4807, 2005.

[33] J. Rivera-Utrilla, M. Sánchez-Polo, M. Á. Ferro-García, G. Prados-Joya, R. Ocampo-Pérez, "Pharmaceuticals as emerging contaminants and their removal from water. A review," Chemosphere, vol. 93(7), pp. 1268-1287, 2013.

[34] Y. Vystavnaa, Z. Frkovaa, L. Marchan, Y. Vergeles, F. Stolberg, "Removal efficiency of pharmaceuticals in a full scale constructed wetland in East Ukraine", Ecological Engineering, vol.108, , , pp.50-58, November 2017.

[35] Ş. Saygı, D. Battal, N. Ö. Şahin, "Çevre ve insan sağlığı yönünden ilaç atıklarının önemi," Marmara Pharmaceutical Journal,vol. 16, pp. 82-90, 2012.

[36] M. Khamis, R. Karaman, F. Ayyash, A. Qtait, O. Deeb, A. Manssra, "Efficiency of Advanced Membrane Wastewater Treatment Plant towards Removal of Aspirin, Salicylic Acid, Paracetamol and p-Aminophenol," Journal of Environmental Science and Engineering, vol. 5, pp. 121-137, 2011.

[37] E. A. Serna-Galvis, A. M.Botero-Coy, M. Rosero-Moreano, J. Lee, F. Hernández, R. A. Torres-Palma, "An initial approach to the presence of pharmaceuticals in wastewater from hospitals in Colombia and their environmental risk," Water, 14(6), 950, 2022.

[38] R. Lopez-Serna, A. Jurado, E. Vazquez-Sune, J. Carrera, M. Petrovic, D. Barcelo, "Occurrence of 95 pharmaceuticals and transformation products in urban groundwaters underlying the metropolis of Barcelona, Spain," Environmental Pollution, vol.174, pp.305-315, 2013.

[39] J. A. Rivera-Jaimes, C. Postigo, R. M. Melgoza-Alemán, J. Aceña, D. Barceló, M. López de Alda "Study of pharmaceuticals in surface and wastewater from Cuernavaca, Morelos, Mexico: Occurrence and environmental risk assessment," Science of the Total Environment, vol.613–614, pp.1263–1274, 2018.

[40] R. Salgado, V. J. Pereira, G. Carvalho, R. Soeiro, V. Gaffney, C. Almeida, V. Vale Cardoso, E. Ferreira, M.J. Benoliel, T.A. Ternes, A. Oehmen, M.A.M. Reis, J. P. Noronha, "Photodegradation kinetics and transformation products of ketoprofen, diclofenac and atenolol in pure water and treated wastewater," Journal of Hazardous Materials,vol. 244– 245, pp. 516– 527, 2013.

[41] P. C., Rua-Gomez, W. Püttmann, "Occurrence and removal of lidocaine, tramadol, venlafaxine, and their metabolites in German wastewater treatment plants," Environmental Science and Pollution Research, vol.19(3), pp.689-699, 2012a.

[42] P. C., Rua-Gomez, W. Püttmann, "Impact of wastewater treatment plant discharge of lidocaine, tramadol, venlafaxine and their metabolites on the quality of surface waters and groundwater," Journal of Environmental Monitoring, vol. 12, pp. 3047- 3310, 22 November 2012b.

[43] J. L. Santos, I. Aparicio, E. Alonso, "Occurrence and risk assessment of pharmaceutically active compounds in wastewater treatment plants. A case study: Seville city (Spain)," Environment International, vol. 33, pp. 596–601, 2007.

[44] J. M. Philip, U.K. Aravind, C. T. Aravindakumar, "Emerging contaminants in Indian environmental matrices - A review," Chemosphere, vol. 190, pp.307-326, 2018.

[45] D. Ramírez-Morales, M. Masís-Mora, J.R. Montiel-Mora, J. C. Cambronero-Heinrichs, S. Brice˜no-Guevara, C. E. Rojas-Sánchez, M. Méndez-Rivera, V. Arias-Mora, R. Tormo-Budowski, L. Brenes-Alfaro, C. E. Rodríguez-Rodríguez, "Occurrence of pharmaceuticals, hazard assessment and ecotoxicological evaluation of wastewater treatment plants in Costa Rica,"Science Total Environment,746, 141200, 2020.