Fate of selected pharmaceuticals in hospital and municipal wastewater effluent: occurrence, removal, and environmental risk assessment

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Abstract
The concentrations and distribution of β-blockers, lipid regulators, and psychiatric and cancer drugs in the influent and effluent of the municipal wastewater treatment plant (WWTP) and the effluent of 16 hospitals that discharge into the wastewater treatment plant mentioned in this study at two sampling dates in summer and winter were examined. The pharmaceutical contribution of hospitals to municipal wastewater was determined. The removal of target pharmaceuticals was evaluated in a WWTP consisting of conventional biological treatment using activated sludge. Additionally, the potential environmental risk for the aquatic receiving environments (salt lake) was assessed. Beta-blockers and psychiatric drugs were detected in high concentrations in the wastewater samples. Atenolol (919 ng/L) from β-blockers and carbamazepine (7008 ng/L) from psychiatric pharmaceuticals were detected at the highest concentrations in hospital wastewater. The total pharmaceutical concentration determined at the WWTP influent and effluent was between 335 and 737 ng/L in summer and between 174 and 226 ng/L in winter. The concentrations detected in hospital effluents are higher than the concentrations detected in WWTP. The total pharmaceutical contributions from hospitals to the WWTP in summer and winter were determined to be 2% and 4%, respectively. Total pharmaceutical removal in the WWTP ranged from 23 to 54%. According to the risk ratios, atenolol could pose a high risk (risk quotient > 10) for fish in summer and winter. There are different reasons for the increase in pharmaceutical consumption in recent years. One of these reasons is the COVID-19 pandemic, which has been going on for 2 years. In particular, hospitals were operated at full capacity during the pandemic, and the occurrence and concentration of pharmaceuticals used for the therapy of COVID-19 patients has increased in hospital effluent. Pandemic conditions have increased the tendency of people to use psychiatric drugs. It is thought that beta-blocker consumption has increased due to cardiovascular diseases caused by COVID-19. Therefore, the environmental risk of pharmaceuticals for aquatic organisms in hospital effluent should be monitored and evaluated.

Keywords Pharmaceuticals · Risk assessment · Hospital wastewater · Conventional treatment

Introduction
The growing population and the development of urbanization and industrialization have led to an increase in the concentration of some pollutants and introduced new pollutants in the environment (Belhaj et al. 2015). As a result of advances in medical treatment methods, the emergence of new diseases, the rising demand in the field of health care and economic advancements, and the production and consumption of pharmaceuticals have inevitably risen. Pharmaceuticals are complex molecules, and due to their extensive use, they have been determined to exist in different environmental matrices, such as wastewater, surface water, groundwater, drinking water, sewage sludge, and sediments. Pharmaceutical residues impose proven or predicted risks to microorganisms, fauna, and flora (Bartrons and Peñuelas 2017; Ashfaq et al. 2017). Pharmaceuticals are subdivided into different therapeutic groups, such as analgesics/anti-inflammatories, antibiotics, β-blockers, cardiac drugs, psychiatric drugs, lipid regulators,
and cancer drugs. These pharmaceuticals are among the commonly used drugs in hospitals and homes. Beta-blockers have been extensively taken for the treatment of abnormal heart rhythms, high blood pressure, angina pectoris, hypertension, and cardiac dysfunction (Yi et al. 2020). Atenolol, metoprolol, propranolol, and sotalol are the most widely used β-blockers (Khasawneh and Palaniandy 2021). Because β-blockers are becoming more widely used and are one of the most commonly found pharmaceuticals in the environment, it is possible to measure β-blockers and their metabolites in wastewater up to μg/L (Yi et al. 2020; Wilde et al. 2013). When studies on the occurrence of β-blockers in wastewater were examined, different concentrations were determined depending on drug use and wastewater treatment technologies in different countries (Yi et al. 2020). For example; β-blockers were detected in the range of 64–474 ng/L in Italy (Al Aukidya et al. 2012), in the range of 35–1600 ng/L in Finland (Vieno et al. 2007), in the range of 0.4–2110 ng/L in Spain (Biel-Maeso et al. 2018a), and in the range of 25–1530 ng/L in Switzerland (Alder et al. 2010) at the output of the wastewater treatment plant (WWTP).

In addition, β-blockers (atenolol, acebutolol, bisoprolol, celiprolol, metoprolol, nadolol, pindolol, propranolol, and sotalol) have a half-life of 3–8.7 days in water and are classified as “pseudopersistent” (Hernando et al. 2006; Ramil et al. 2010). Lipid regulators are widely used for the treatment of hyperlipidemia and are among the most common pharmaceuticals in wastewater. The current commonly used lipid regulators are gemfibrozil, bezafibrate, fenofibrate, and clofibric acid (Wang et al. 2019). More than 264 million people worldwide suffer from depression. The consumption of psychiatric drugs is higher than the consumption of other medical drugs (Melchor-Martínez et al. 2021). Thus, with the increasing consumption of psychiatric drugs, they have begun to be detected in wastewater, surface waters, and even drinking water around the world. For instance, the concentrations of psychiatric pharmaceuticals ranged from <dl to 3124 ng/L in WWTP influent and from <dl to 2956 ng/L in WWTP effluent (Kosma et al. 2019; Wu et al. 2015; Yuan et al. 2013; Lajeunesse et al. 2012; Oliveira et al. 2015). Psychiatric pharmaceuticals were also found in surface water (24.3 ng/L for diazepam, 0.4 ng/L for fluoxetine, 4 ng/L for lorazepam, 25.3 ng/L for carbamazepine in Chinese rivers) (Wu et al. 2015). Furthermore, psychiatric pharmaceuticals were detected at 1.9 ng/L (Wu et al. 2015) and 23.5 ng/L (Zuccato et al. 2000) for diazepam in drinking water. Psychiatric drugs can be grouped into antidepressants, anxiolytics, sedatives and hypnotics, antipsychotics, and mood stabilizers (Kosma et al. 2019). It is foreseen that there will be 21.4 million new cancer patients by 2032. Cancer medicines will be used more frequently as a result of this in forthcoming years. As cancer drugs are classified into cytotoxic and endocrine therapy drugs, they are a cause for concern (Oliveira Klein et al. 2021). Additionally, 33 emerging contaminants, including diclofenac, ibuprofen, carbamazepine, and clofibric acid, were identified in surface waters by the European Union (Hena et al. 2021).

Pharmaceuticals can enter environmental matrices in different ways, such as pharmaceutical production plants, hospitals, improper disposal, households and WWTPs, irrigation with treated or untreated wastewater, and atmospheric deposition (Ma et al. 2018; Ferrey et al. 2018; Martínez-Alcalá et al. 2021). After the COVID-19 pandemic, which emerged at the end of 2019, the consumption of pharmaceuticals has increased worldwide. The detection frequency and concentration of some pharmaceuticals post pandemic in Wuhuan surface water increased before the pandemic. Additionally, some antibiotics pose a medium/high risk for aquatic organisms (Chen et al. 2021). The concentrations of antiviral drugs and paracetamol in wastewater increased 170% and 198% compared to prepandemic concentrations in Greece, respectively (Galani et al. 2021). Kuroda et al. (2021) reported that the removal efficiency of antiviral drugs used to treat coronavirus disease with conventional wastewater processes is below 20%. These drugs pose a high risk for aquatic organisms in the receiving environment. In particular, due to the increase in the number of patients receiving therapy in hospitals during the COVID-19 pandemic, the pharmaceutical contribution of hospitals to urban wastewater has increased (Khan et al. 2021). Commonly used conventional WWTPs, which include primary and secondary treatment processes to remove pollutants such as organic matter and suspended matter, are not designed to eliminate these compounds; therefore, many pharmaceuticals go through conventional WWTP without adequate treatment. In addition, the main sources of pharmaceuticals in WWTPs are households and hospital wastewater. Hospital wastewater containing a large number of pharmaceuticals is generally discharged into sewer networks and treated together with domestic wastewater in WWTPs. Hospitals produce different amounts of wastewater containing different types and numbers of pharmaceuticals according to hospital characteristics. Determining the contribution of hospitals to the pharmaceutical load in WWTPs is important for the pretreatment of hospital wastewater (Tormo-Budowski et al. 2021; Semerjian et al. 2018; Santos et al. 2013). Pharmaceuticals have been detected worldwide at ng/L, ng/g, or μg/L levels and at μg/g levels in wastewater and the receiving environment, respectively (Maniakova et al. 2020). Pharmaceuticals have effects significantly reducing fertility in species such as cladoceran Daphnia magna and fish, endocrine disruption in receiving environments, and development of bacterial pathogen resistance (Semerjian et al. 2018).

In this context, a total of 18 commonly used pharmaceuticals of different therapeutic classes (β-blockers, lipid regulators, psychiatric and cancer drugs) were analyzed in sixteen
hospital effluents and the influent and effluent of municipal WWTP in Konya (Turkey) at two sampling dates in summer and winter Konya urban wastewater and examined 16 hospitals discharge to the Konya WWTP. For this reason, wastewater samples were taken from the Konya WWTP to determine the pharmaceutical load of the examined hospitals to the WWTP and to determine the treatment efficiency of pharmaceuticals. The plants have screening, grit removal, preliminary sedimentation, biological treatment with activated sludge process, and secondary sedimentation.

Pharmaceutical concentrations discharged into the sewer system of the examined hospitals were determined. Generally, hospital wastewater is an important source of pharmaceuticals in WWTPs. In this study, the pharmaceutical pollution load of the examined hospitals to the WWTP was revealed. The pharmaceutical removal of Konya WWTP was calculated with detected concentrations at influent and effluent of Konya WWTP. Konya WWTP effluent is discharged into the salt lake. Pharmaceuticals have some proven and predicted risks to the receiving environment. So, the potential ecotoxicological risk for pharmaceuticals was determined by using the risk quotient for aquatic organisms in the receiving environment.

Material and methods

Chemicals and equipment

Atenolol, sotalol, timolol, bezafibrate, pravastatin, tamoxifen, ifosfamide, and etoposide were obtained from Sigma (Switzerland), and metoprolol, propranolol, clofibric acid, fenofibrate, gemfibrozil, carbamazepine, diazepam, fluoxetine, lorazepam, and cyclophosphamide standards were obtained from Fluka (Switzerland). The physicochemical properties of the investigated pharmaceuticals are presented in the supplementary material (Table S1). HPLC-grade methanol, hydrochloric acid (37%), formic acid (98%), and ethylenediaminetetraacetic acid disodium salt solution (Na₂EDTA) were obtained from Merck (Darmstadt, Germany). While a glass fiber filter with a 1.2 μm pore diameter was acquired from Whatman (USA), a 0.45-μm nylon membrane filter was acquired from Whatman (USA). After dried under a rotary evaporator and gentle flow rate of approximately 1 mL/min. The extract obtained was redissolved in 400 μL methanol/water (50/50, v/v) after drying under a rotary evaporator and gentle stream of nitrogen gas.

Quantitative analyses of target compounds were carried out with LC-MS/MS systems. The mobile phase was eluent A (deionized water with 0.1% formic acid and 5 mM ammonium formate) and eluent B (methanol) for positive ion mode and eluent A (deionized water with 10 mM ammonium acetate) and eluent B (methanol) for negative ion mode. The most suitable carrier phase flow rate was determined to be 0.6 mL/min. The column temperature was 35 °C, and the injection volume was 2 μL. Analytical parameters determined for the pharmaceuticals are given in Table S2.

Physicochemical analyses such as pH, electrical conductivity (EC), total suspended solids (TSS), and chemical oxygen demand (COD) of wastewater taken from hospitals and the influent and effluent of municipal WWTP were carried out. The pH and EC measurements of the wastewater samples were performed with a Hach brand portable pH and EC measuring device. TSS measurements were carried out according to standard methods (APHA 1992). COD values were measured with a WTW brand spectrophotometer using ready kits. The pH, EC, TSS, and COD values of wastewater samples

Wastewater samples

Hospital effluents were collected from 5 state hospitals and 3 private hospitals in Meram District, and 1 private hospital in Karatay District and the influent and effluent of the municipal WWTP, which receives wastewater from the three districts in Konya. Effluent samples were taken from the discharge points of the hospitals into the sewage system. The bed capacities of the sampled hospitals vary between 27 and 1298 beds. The Konya sewerage system is a combined sewerage system in which wastewater and rainwater are collected in the same channel. There are physical treatments, biological treatments, and disinfection processes in the WWTP. Wastewater samples were gathered twice a year in summer and winter using a composite micro sampler (Durko, Turkey) and were stored at 4 °C until analysis.

Analytical procedures

Wastewater samples before extraction were passed through a glass fiber filter and a nylon membrane filter. The Oasis HLB SPE cartridge was conditioned with 5 mL of deionized water followed by 5 mL of methanol at a flow rate of approximately 2 mL/min. Samples were loaded into the cartridge at a flow rate of approximately 1 mL/min. After preconcentration of the sample, the cartridge was washed with 5 mL of deionized water at a flow rate of approximately 2 mL/min, and air was passed through the cartridge for 5 min to remove excess water from the cartridge. Elution of the compounds in the cartridge was carried out with 10 mL of methanol at a flow rate of approximately 1 mL/min. The extract obtained was redissolved in 400 μL methanol/water (50/50, v/v) after drying under a rotary evaporator and gentle stream of nitrogen gas.

Physicochemical analyses such as pH, electrical conductivity (EC), total suspended solids (TSS), and chemical oxygen demand (COD) of wastewater taken from hospitals and the influent and effluent of municipal WWTP were carried out. The pH and EC measurements of the wastewater samples were performed with a Hach brand portable pH and EC measuring device. TSS measurements were carried out according to standard methods (APHA 1992). COD values were measured with a WTW brand spectrophotometer using ready kits. The pH, EC, TSS, and COD values of wastewater samples
ranged from 6.58 to 8.63, from 525 to 7970 μS/cm, from 18 to 1218 mg/L, and from 183 to 819 mg/L in hospital wastewater and from 7.2 to 7.93, from 1706 to 2510 μS/cm, from 592 to 644 mg/L, and from 539 to 944 mg/L in municipal wastewater, respectively. The pH, EC, and TSS values were higher in hospital wastewater than in municipal wastewater.

**Environmental risk assessment**

An environmental risk assessment approach was used to assess the impact of pharmaceutical pollution on the aquatic environment. Risk quotient (RQ) values were calculated for three different trophic levels (algae, crustaceans, and fish) using Eq. (1):

\[
RQ = \frac{\text{MEC}_{\text{max}}}{\text{PNEC}}
\]

(1)

The meanings of the MEC_{max} and PNEC are as follows: maximum measured environmental concentration and predicted no-effect concentration, respectively. The PNEC values used for the calculations are presented in Table S3. The risk assessment criteria, where RQ < 0.1, suggest no adverse effect with insignificant risk. A value of 0.1 < RQ < 1.0 suggests a low risk, and there is a potential adverse effect. Values of RQ between 1 and 10 indicate a moderate risk, while a high ecological risk indicates values equal to or above 10 (Gomez et al. 2006; Deblonde and Hartemann 2013).

**Results and discussion**

**Pharmaceutical concentration in wastewater**

Table 1 demonstrates the minimum, average, and maximum concentrations of the pharmaceuticals detected in the wastewater samples. All compounds investigated were present in at least one influent, effluent, and hospital wastewater, with the exception of timolol and diazepam. This result indicates the widespread presence of pharmaceuticals in wastewater even after treatment. Pharmaceutical concentrations detected in previous studies are given in Tables 2, 3, 4, and 5. In this

| Pharmaceuticals          | Summer                  | Winter                  |
|--------------------------|-------------------------|-------------------------|
|                          | Hospital effluent | WWTP        | Hospital effluent | WWTP        |
|                          | Range | Mean | Median | Influent | Effluent | Range | Mean | Median | Influent | Effluent |
| Atenolol                  | <dl–163 | 35.3  | 13.3   | 424     | 163      | 47.2–919 | 156   | 67.8   | 154     | 139      |
| Metoprolol                | <dl–176 | 18.2  | 0.01   | 86.8    | 39.7     | <dl–48.7 | 6.69  | 2.43   | 7.43    | <dl      |
| Propranolol               | <dl–118 | 14.9  | <dl    | 3.31    | <dl      | 0.57–5.14 | 0.97  | 0.59   | 7.43    | 0.64     |
| Sotalol                   | <dl–6.60 | 0.41  | <dl    | 81.0    | 30.4     | <dl–78.5 | 7.54  | 0.22   | 7.43    | 0.03     |
| Timolol                   | <dl     | <dl   | <dl    | <dl     | <dl      | <dl     | <dl   | <dl    | <dl      | <dl      |
| Carbamazepine             | <dl–7008 | 509   | 20.8   | 136     | 101      | <dl–85.9 | 10.8  | <dl    | 11.9    | <dl      |
| Diazepam                  | <dl     | <dl   | <dl    | <dl     | <dl      | <dl     | <dl   | <dl    | <dl      | <dl      |
| Fluoxetine                | <dl     | <dl   | <dl    | <dl     | <dl      | 2.48–4.21 | 2.85  | 2.75   | 2.57    | 2.51     |
| Lorazepam                 | <dl–0.10 | <dl   | <dl    | <dl     | <dl      | 2.88–65.3 | 16.3  | 9.91   | 4.83    | 2.53     |
| Bezacistrate              | 0.04–0.63 | 0.18  | 0.14   | 0.41    | 0.15     | 4.44–8.79 | 6.40  | 6.08   | 8.24    | 18.18    |
| Clofibric acid            | 0.03–0.16 | 0.08  | 0.07   | 0.26    | 0.04     | <dl     | <dl   | <dl    | <dl      | <dl      |
| Fenofibrate               | 0.01–0.82 | 0.13  | 0.08   | 0.15    | 0.07     | 1.03–2.02 | 1.31  | 1.29   | 1.46    | 1.45      |
| Gemfibrozil               | 0.03–0.28 | 0.12  | 0.11   | 3.61    | 0.89     | 2.96–6.76 | 4.40  | 3.07   | 13.5    | 6.30      |
| Pravastatin              | 0.17–1.76 | 0.56  | 0.47   | 0.81    | 0.10     | 3.45–26.4 | 5.87  | 3.77   | 5.49    | 5.43      |
| Tamoxifen                 | 0.001–0.17 | 0.04  | 0.02   | 0.01    | <dl      | 1.74–3.93 | 2.48  | 1.77   | 3.37    | 3.31      |
| Cyclophosphamide          | 0.009–2.17 | 0.17  | 0.02   | 0.38    | 0.07     | 1.11–2.41 | 1.71  | 1.75   | 2.44    | 2.37      |
| Ifosfamide                | 0.01–0.31 | 0.06  | 0.03   | 0.38    | 0.11     | 1.80–2.87 | 2.26  | 1.88   | 2.83    | 2.80      |
| Etoposide                 | 0.04–5.69 | 0.61  | 0.25   | 0.30    | 0.07     | <dl     | <dl   | <dl    | <dl      | <dl      |
| Total β-blocker           | <dl–209 | 68.8  | 32.6   | 595     | 233      | 48.1–924 | 171   | 95.2   | 169     | 139      |
| Total psychiatric drugs   | <dl–7009 | 509   | 20.8   | 136     | 101      | 6.50–154 | 61.9  | 17.2   | 19.3    | 5.04      |
| Total lipid regulators    | 0.56–2.28 | 1.09  | 0.93   | 5.24    | 1.25     | 11.9–41.8 | 17.9  | 13.8   | 28.7    | 21.4      |
| Total cancer drugs        | 0.22–5.73 | 0.89  | 0.41   | 0.96    | 0.25     | 4.65–8.95 | 6.44  | 5.45   | 8.64    | 8.48      |
| Total pharmaceutical      | 0.83–7127 | 580   | 33.7   | 737     | 335      | 86.3–993 | 226   | 139    | 226     | 174      |

<dl means below the limit of detection
study, the maximum concentrations of β-blockers detected in hospital wastewater were 175 ng/L for metoprolol during the summer and 920 ng/L for atenolol during the winter. The concentrations of β-blockers in the influent and effluent of the municipal WWTP were <dl–424 ng/L in summer and <dl–153 ng/L in winter, and <dl–162 ng/L in summer and <dl–138 ng/L in winter, respectively. At the WWTP, atenolol was determined at maximum concentration in both summer and winter periods. Additionally, timolol compounds were not detected in hospital, influent, or effluent wastewater. When looking at the physicochemical properties of the β-blockers investigated, the atenolol compound has higher solubility than other β-blockers. In addition, the atenolol compound is excreted from the body at a rate of 40–50% in the main form and has a low log $K_{ow}$ value (0.16). Therefore, it has high mobility in aquatic environments. Due to these properties, it was detected in high concentrations in hospital and WWTP wastewaters. Even though the removal rates of the metoprolol, propranolol, and timolol compounds in the main form are low, the log $K_{ow}$ values are high. However, the sotalol compound is excreted in the main form at a rate higher than 75%, and the log $K_{ow}$ value is low. Atenolol was detected at high concentrations because there are many drugs containing atenolol as an active ingredient, and it is used in the treatment of more common diseases.

The minimum concentration of lipid regulators in hospital wastewater was 0.011 ng/L (fenofibrate) in summer and below the detection limit (clofibric acid) in winter. The maximum concentration in hospital wastewater was determined to be 1.76 ng/L (pravastatin) in the summer and 26.38 ng/L (pravastatin) in the winter. Lipid regulators were 0.15–3.61 ng/L in summer, <dl–13.51 ng/L in winter, 0.084–0.89 ng/L in summer, and below detection limit (clofibric acid) in winter. The removal rates of the lipid regulators in hospital wastewater were 53% for fenofibrate and 88% for pravastatin in summer, and 51% for fenofibrate and 90% for pravastatin in winter. The removal rates of the lipid regulators in WWTP wastewater were 75% for fenofibrate and 92% for pravastatin in summer, and 70% for fenofibrate and 96% for pravastatin in winter.

### Table 2: Beta-blockers detected in hospital effluent, WWTP influent, and effluent in the literature

| Country | Atenolol | Metoprolol | Propranolol | Sotalol | Timolol | Reference |
|---------|----------|------------|-------------|---------|---------|-----------|
| Hospital effluents | | | | | | |
| Denmark | 170–250 | 2900–3700 | 260–360 | 16–28 | – | Nielsen et al. (2013) |
| Portugal | 59–1069 | <dl–35.6 | 18.0–98.9 | <dl–89.1 | – | Santos et al. (2013) |
| Italy | 5100, 2400–5800 | 830, 740–1100 | 23, 43–85 | 4800, 48–5100 | <dl, <dl–33 | Verlicchi et al. (2012a) |
| USA | 1370–3790 | 750–3540 | 10–200 | 100–530 | nd–30 | Oliveira et al. (2015) |
| Spain | 1361, 3400 | 46 | 279, 1350b | 235a | – | Mendoza et al. (2015)a; Gomez et al. (2006)b |
| Taiwan | – | – | 54 | – | – | Lin and Tsai 2009 |
| Switzerland | 2315 | 1325 | – | – | – | Kovalova et al. (2012) |
| Finland | 2300 | 1700 | – | – | – | Ajo et al. (2018) |
| France | 796–2134 | – | 30–603 | – | – | Perrin et al. (2013) |
| Mexico | 200 | 2020 | – | – | – | Perez-Alvarez et al. (2018) |
| Turkey | <dl–919 | <dl–176 | <dl–118 | <dl–78.5 | <dl | In this study |
| WWTP influent | | | | | | |
| Portugal | 522a | <dla | 8.98a, 344b | 117a | – | Santos et al. (2013)a; Paiga et al. (2019)b |
| Italy | 2100 | 260 | 26 | 530 | 14 | Verlicchi et al. (2012b) |
| USA | 1340–6030 | 600–3020 | 20–70 | 120–510 | nd–20 | Oliveira et al. (2015) |
| Spain | 1620a, 1391b | 128b | 123a, 13b | – | 13a, 5b | Buel-Maeso et al. (2018a)a; Villar-Navarro et al. (2018)b |
| China | – | 114 | <dl | – | – | Dai et al. (2014) |
| UK | 12,913, 14,223 | 75, 94 | 557, 638 | – | – | Kasprzyk-Hordern et al. (2009) |
| Turkey | 154–424 | 7.43–86.8 | 3.31–7.43 | 7.43–81.0 | <dl | In this study |
| WWTP effluent | | | | | | |
| Portugal | 600a | 11.9a | 8.27a, ndb | 154a | – | Santos et al. (2013)a; Paiga et al. (2019)b |
| Italy | 73 | 180 | 18 | 320 | 10 | Verlicchi et al. (2012a) |
| USA | 130–650 | 500–2110 | nd–100 | 50–470 | nd–20 | Oliveira et al. (2015) |
| Spain | 1140a, 775b | 94b | 73a, 12b | – | 13a, 4b | Buel-Maeso et al. (2018a)a; Villar-Navarro et al. (2018)b |
| China | 157 | 6 | – | – | – | Dai et al. (2014) |
| UK | 2870, 2123 | 69, 41 | 265, 264 | – | – | Kasprzyk-Hordern et al. (2009) |
| Turkey | 138–163 | <dl–39.7 | <dl–0.64 | 0.03–30.4 | <dl | In this study |

En dash means not analyzed, and <dl means below the limit of detection

nd not detected
in summer, and <dl–8.18 ng/L in the influent and effluent of the WWTP, respectively. Gemfibrozil was detected at the highest concentrations in wastewaters taken from the influent and effluent of the WWTP in summer and winter. The lowest concentrations in the wastewater treatment plant were determined for fenofibrate compound in the influent, clofibric acid compound in the effluent in the summer, and clofibric acid compound in the influent and effluent in the winter.

Lipid regulators have high persistence (log $K_{ow}$: 2.5–5.2; half-life: 15–100 days). Bezafibrate and pravastatin compounds are excreted in the main form at high rates from the body. Lipid regulators have low water solubility, high log $K_{ow}$ values, and half-lives. Fenofibrate compounds are usually detected in wastewater at low concentrations due to their very small excretion from the body in the form of the parent compound. The oral doses of bezafibrate and pravastatin, which were predominantly detected in the samples, were excreted from the body at approximately 30% unchanged. Higher concentrations of lipid regulators were determined in all hospitals during the winter. This result can be explained by the tendency of the patients’ blood fat to increase during cold seasons (Ockene et al. 2004). Consumption of lighter foods during the summer months, depending on eating habits, reduces the consumption of cholesterol reducers.

In hospital wastewater, carbamazepine was detected at maximum concentrations of 7008 ng/L in summer and 85.9 ng/L in winter. In hospital wastewater, fluoxetine and diazepam were determined to be below the detection limit in all samples during the summer period. Lorazepam was determined to be below the detection limit in samples taken from hospitals, except for one hospital. Carbamazepine compounds were detected at 135 ng/L in the influent of the municipal WWTP and 100 ng/L in the effluent and in the winter period, while other compounds were determined to be below the detection limit. In the winter period, carbamazepine compound was determined as 11.9 ng/L, fluoxetine compound as 2.57 ng/L, lorazepam compound as 4.83 ng/L at the influent of the municipal WWTP, fluoxetine compound as 2.51 ng/L, and lorazepam compound as 2.53 ng/L at the effluent of the municipal WWTP. When the physicochemical

| Table 3 Lipid regulators detected in hospital effluent, WWTP influent, and effluent in the literature |
| Country | Bezafibrate | Clofibric acid | Fenofibrate | Gemfibrozil | Pravastatin | Reference |
|---------|-------------|---------------|-------------|-------------|-------------|-----------|
| Hospital effluent | | | | | | |
| Denmark | <10 | <10 | <12–28 | – | – | Nielsen et al. (2013) |
| Portugal | <dl–258 | – | – | nd–125 | <dl–306 | Santos et al. (2013) |
| Italy | 950, <dl–200 | 17, <dl–13 | 10, <dl | 19, <dl–33 | 620, 77–170 | Verlicchi et al. (2012b) |
| USA | nd | nd | – | 150–3250 | 30–480 | Oliveira et al. (2015) |
| Spain | 126 | – | 103 | – | – | Mendoza et al. (2015) |
| Taiwan | – | – | – | 760 | – | Lin and Tsai (2009) |
| Switzerland | 63a | – | – | – | 1600b | Kovalova et al. (2012)a; Escher et al. (2011)b |
| Turkey | 0.04–8.79 | <dl–0.16 | 0.01–2.02 | 0.03–6.76 | 0.17–26.4 | In this study |
| WWTP influent | | | | | | |
| Portugal | 490a | – | – | <qla, 59b | 218a | Santos et al. (2013)³; Paiga et al. (2019)b |
| Italy | 90 | 10 | 6 | 200 | 110 | Verlicchi et al. (2012a) |
| USA | nd | nd | – | 760–5380 | nd–350 | Oliveira et al. (2015) |
| Spain | 297a, 188b | 65b | 78b, 1b | 2870a, 3108b | 406b, ndb | Biel-Maesoa et al. (2018a)³; Villar-Navarro et al. (2018)b |
| China | 36 | – | – | 94 | – | Dai et al. (2014) |
| UK | 420, 600 | 19, 1 | – | – | <60 | Kasprzyk-Hordern et al. (2009) |
| Slovenia | – | – | – | – | – | Isidori et al. (2016) |
| Turkey | 0.41–8.24 | <dl–0.26 | 0.15–1.46 | 3.61–13.5 | 0.81–5.49 | In this study |
| WWTP effluent | | | | | | |
| Portugal | 4409a | – | – | <dla, 27b | 239a | Santos et al. (2013)³; Paiga et al. (2019)b |
| Italy | 36 | 20 | 3 | 110 | 540 | Verlicchi et al. (2012b) |
| USA | nd | nd | – | 230–540 | nd | Oliveira et al. (2015) |
| Spain | 73a, 24b | 2b | 24a, 1b | 1910a, 2578b | 138a, ndb | Biel-Maesoa et al. (2018a)³; Villar-Navarro et al. (2018)b |
| China | 15 | – | – | 117 | – | Dai et al. (2014) |
| UK | 231, 177 | 15, 6 | – | – | <60 | Kasprzyk-Hordern et al. (2009) |
| Turkey | 0.15–8.18 | <dl–0.04 | 0.07–1.45 | 0.89–6.30 | 0.10–5.43 | In this study |

En dash means not analyzed, and <dl means below the limit of detection
nd not detected
The properties of psychiatric drugs were examined, the water solubility of the fluoxetine compound was quite high compared to other compounds, and all of the investigated psychiatric compounds had high persistence (log $K_{ow}$: 2.45–4.08). Most carbamazepine appears to be excreted from the body without being metabolized. Summer term sampling was carried out at the end of August. During the change of seasons, the rate of people experiencing depression increases, which may raise the use of psychiatric drugs. In addition, one factor affecting the pharmaceutical concentrations in wastewater is dilution during the rainy seasons. The most commonly detected carbamazepine compound is the most commonly used psychiatric drug in psychiatric conditions such as epilepsy, mania, bipolar disorder, and anxiety, and it is eliminated from the body in its main form at a rate of approximately 28–72% of the dose taken. It remains in the water phase due to its low adsorptive rate in the sludge.

The detected maximum concentrations of the cancer drugs in hospital wastewater were 5.59 ng/L for etoposide in summer and 3.93 ng/L for tamoxifen in winter in the present study. In the summer, tamoxifen was detected at 0.17 ng/L, which was the minimum concentration. The maximum concentrations in influent wastewater were 0.38 ng/L for cyclophosphamide in summer and 3.37 ng/L for tamoxifen in winter. The maximum concentrations in effluent wastewater were 0.11 ng/L for ifosfamide in summer and 3.31 ng/L for tamoxifen in winter. Etoposide was found below the limit of quantification in all the samples analyzed in winter. Concentrations of etoposide and cyclophosphamide in WWTP were lower than their concentrations in hospital effluent. Other cancer drugs have been detected in close concentrations in hospital wastewater and WWTP samples. Etoposide is a medicine that is supplied to hospitalized patients rather than for domestic use, and it is excreted from the body in the form of the parent compound at a rate of 5–22%. The log $K_{ow}$ value is quite low and tends to remain in the water phase. Etoposide can react rapidly with chlorine and decompose (Santana-Viera et al. 2019). Tamoxifen, which was detected at high concentrations in the winter period,
has a longer half-life than other cancer drugs and was found at higher concentrations than other cancer drugs due to its persistence. Tamoxifen has a high consumption amount in breast cancer treatment. Additionally, it is used in reproductive control and hormone treatments for animals (Ferrando-Climent et al. 2014; Negreira et al. 2015). Cyclophosphamide is the most common drug and is a compound resistant to ozonation. Ifosfamide is prescribed less than the other investigated cancer drugs. Some studies have indicated that hospital wastewater and WWTPs contain low concentrations of cancer drugs (Santana-Viera et al. 2019; Ferrando-Climent et al. 2014; Ferre-Aracil et al. 2016). Santana-Viera et al. (2019) detected etoposide at concentrations of 376 ng/L and 620 ng/L in hospital wastewater in influent wastewater ranging from 620 to 5141 ng/L. Cyclophosphamide was detected in hospital wastewater at a concentration of 1218 ng/L and in effluent wastewater at a concentration of 91.3 ng/L. However, even at low concentrations, they can have a negative effect on aquatic biota, flora, and fauna. Additionally, continuous discharge, even at low concentrations, may cause their accumulation (Oliveira Klein et al. 2021).

In some studies, it has been determined that the pharmaceutical concentrations in wastewater show seasonal changes. For example, studies conducted in Switzerland and the USA have found that concentrations in winter were higher than those in summer (Valcarcel et al. 2013; Yu et al. 2013). Golovko et al. (2014) investigated 21 pharmaceuticals in WWTPs and reported that the total concentrations of target pharmaceuticals in WWTPs were higher during winter than during summer. Sui et al. (2011) and Yu et al. (2013) found higher pharmaceutical concentrations in wastewater in winter season. Seasonal conditions, regional factors, average age of the population, and processes of WWTPs can affect the presence of pharmaceuticals in wastewater (Golovko et al. 2014; Bueno et al. 2012). While the concentrations of pharmaceuticals in wastewater are generally higher in the winter season, the removals are higher in the summer season.
Pharmaceutical contribution from hospitals to municipal WWTP

The wastewater flow rate per bed was accepted as 1000 L/day for the purpose of determining the load brought by medicines used in hospitals in WWTPs (Metcalf and Eddy 2003), and the contributions from each hospital were calculated. The flow to the WWTP is 170,000 m³/day, with industrial flow accounting for 6%. Excluding industrial wastewater flow, the WWTP receives 159,800 m³/day. It is known that the foremost route of entry of pharmaceuticals into ecological systems is wastewater. Domestic usage, industry, and hospitals are thought to be the principal pharmaceutical sources in wastewater. According to some studies, hospitals are the most significant source of pharmaceutical load in municipal WWTPs, and it is recommended that their wastewater be discharged after pretreatment (Corre et al. 2012; Hawkshead 2008; Ternes et al. 2006). The pharmaceutical load and their contributions originating from each hospital are given in Table 6. In this study, the total pharmaceutical solids made from hospitals to the influent of WWTP were found to be 1.9% in the summer and 4.32% in the winter. Thomas et al. (2007) reported that the contribution from hospitals to municipal wastewater was less than 2% for other pharmaceuticals, excluding paracetamol compounds. Santos et al. (2013) determined the pharmaceutical contribution from hospitals to be between 0.03 and 8.9% for β-blockers, between 0.001 and 7.3% for lipid regulators, and between 0.009 and 11% for psychiatric drugs. Langford and Thomas (2009) discovered that hospitals contributed 11% of propranolol, 2% of atenolol, and less than 1% of carbamazepine and metoprolol. Azuma et al. (2016) detected 38 pharmaceutical compounds in the effluent of a hospital. The pharmaceutical contribution to the influent of the treatment plant at the effluent of the hospital ranged from <0.1 to 14.8%. Ort et al. (2010) determined the contribution from hospitals to be 1.8%, 0.4%, 4.1%, and 4.1% for atenolol, carbamazepine, gemfibrozil, and metoprolol compounds, respectively. The contribution of analgesics and anti-inflammatories made to the municipal WWTP from 16 hospitals was determined to be 0.01–3.23% in the summer period and 0–1.74% in the winter for each hospital. The total contribution from hospitals was determined to be 11.3% and 7.09% in the summer and winter, respectively (Aydin et al. 2019a). The contribution of antibiotic for each hospital was determined to be 0.01–3.57% in the summer and 0.003–11.4% in the winter. The total contribution from hospitals was determined to be 13.07% and 28.19% in the summer and winter, respectively (Aydin et al. 2019b). When the previous studies and the results of this study were taken into account, it was concluded that the main pharmaceutical source in WWTPs was not hospitals.

Table 6 The contribution of each hospital effluent to the load of pharmaceuticals in WWTP

| HE   | Number of beds | Type of hospital | Flow rate (m³/day) | Concentration of pharmaceuticals (ng/L) | Load of pharmaceuticals (mg/bed day) | Contribution (%) |
|------|----------------|------------------|--------------------|------------------------------------------|--------------------------------------|-----------------|
|      | Summer Winter | Summer Winter    | Summer Winter      | Summer Winter                            |                                      |                 |
| HE1  | 1298 UH       | 1298             | 315                | 507                                      | 0.31 0.51                            | 0.35 1.82       |
| HE2  | 1040 GH       | 1040             | 174                | 187                                      | 0.17 0.19                            | 0.15 0.54       |
| HE3  | 82 GH         | 82               | 721                | 90.4                                     | 0.72 0.09                            | 0.05 0.02       |
| HE4  | 194 UH        | 194              | 7127               | 91.7                                     | 7.13 0.09                            | 1.17 0.05       |
| HE5  | 376 PH        | 376              | 136                | 87.7                                     | 0.14 0.09                            | 0.04 0.09       |
| HE6  | 75 GH         | 75               | 0.83               | 140                                      | 0.0008 0.14                          | 0.0005 0.03     |
| HE7  | 27 GH         | 27               | 14.99              | 92.4                                     | 0.01 0.09                            | 0.001 0.01      |
| HE8  | 38 GH         | 38               | 14.15              | 86.3                                     | 0.01 0.08                            | 0.0005 0.009    |
| HE9  | 201 GH        | 201              | 236                | 993                                      | 0.24 0.99                            | 0.04 0.55       |
| HE10 | 47 GH         | 47               | 19.03              | 96.0                                     | 0.02 0.09                            | 0.001 0.02      |
| HE11 | 45 GH         | 45               | 272                | 112                                      | 0.27 0.11                            | 0.01 0.02       |
| HE12 | 103 GH        | 103              | 77.6               | 319                                      | 0.08 0.32                            | 0.007 0.09      |
| HE13 | 600 GH        | 600              | 27.7               | 222                                      | 0.03 0.22                            | 0.01 0.37       |
| HE14 | 420 GH        | 420              | 125                | 270                                      | 0.12 0.27                            | 0.04 0.31       |
| HE15 | 74 UH         | 74               | 11.1               | 181                                      | 0.01 0.18                            | 0.001 0.04      |
| HE16 | 903 UH        | 903              | 7.88               | 139                                      | 0.008 0.14                           | 0.006 0.35      |
| Total| HE5584        | 5584             | 9280               | 3615                                     | 0.40 0.28                            | 1.90 4.32       |

HE hospital effluent, UH university hospital, PH pediatric hospital, GH general hospital
Removal of pharmaceuticals in the WWTP

Pharmaceuticals are biologically active and resistant chemicals and are found in aquatic environments at levels of ng/L. The formation and concentration of pharmaceuticals in WWTP influents depend on socioeconomic status, consumption pattern, climatic conditions, and water consumption. However, the pharmaceutical concentrations in WWTP effluents depend on the properties of the pharmaceuticals and wastewater and the treatment processes applied (Khasawneh and Palaniandy 2021). The removal rates of pharmaceuticals in WWTPs are affected by the physicochemical properties of pharmaceuticals, such as polarity, volatility, persistence, adsorption, and lipophilicity (Majumder et al. 2019; Khasawneh and Palaniandy 2021). The removal performances of the four groups of pharmaceuticals in Konya WWTP are summarized in Fig. 1. It seems that pharmaceuticals had removal efficiencies between 0.68 and 100%. The Konya WWTP is designed to treat discharges from the equivalent of a population of 1,600,000. Its maximum treatment flow rate will be 300,000 m$^3$/day by 2030. Considering the results, it can be said that the treatment provided the high removal of metoprolol, sotalol, and carbamazepine from target compounds in winter and propranolol, clofibric acid, gemfibrozil, pravastatin, tamoxifen, cyclophosphamide, and etoposide in summer. Low removal efficiencies were observed in winter for compounds with high removal rates in summer.

Temperature is one of the foremost environmental factors inducing low removal efficiencies in cold seasons (Evgenidou et al. 2015). Biodegradation kinetic is slower than the one in summer on account of low temperatures in cold seasons on biological wastewater treatment processes (Ma et al. 2013). In distinct studies, it was reported that seasonal conditions have an influence on the elimination of pharmaceutical compounds found in wastewater treatment plants. For instance, it was reported that pharmaceutical compounds were removed in higher yields in summer in Greece (Kosma et al. 2014). Vieno et al. (2005) assigned a decrease in the removal efficiency of pharmaceutical compounds for the rate of biodegradation in winter. While Castiglioni et al. (2006) pointed out that the removal rates of pharmaceuticals are higher in summer than in winter, Yu et al. (2013) did not observe a substantial difference between the removal efficiencies obtained in both periods. Sun et al. (2014) determined that some pharmaceuticals were removed in the activated sludge biological treatment process at a higher rate in winter than in summer, and a positive correlation was found between hydraulic holding time and removal rates and it was stated that the treatment efficiency of some pharmaceuticals may decrease owing to the reduced hydraulic holding time in hot seasons. Similarly, in our study, most of the pharmaceuticals investigated were eliminated at higher rates during the summer period. Some pharmaceuticals showed higher removal rates in winter. Similar to the literature studies, these removals were observed in the biological treatment plant due to the temperature and hydraulic holding time.

The average removal efficiency was found to be 50–77% for atenolol and fluoxetine and < 50% for metoprolol, as
reported by Kumar et al. (2019). A WWTP from which the samples were taken had a primary treatment and a secondary treatment containing a five-stage Bardenpho process and a membrane bioreactor (MBR). Papageorgiou et al. (2016) reported negative removal rates and high removal rates for 55 pharmaceuticals in different therapeutic groups. They reported that the investigated WWTP is not able to efficiently remove complex mixtures of pharmaceuticals. In our study, it was reported that the removal efficiencies varied in a wide range (0.73–100%). Similar to the work of Papageorgiou et al. (2016), WWTPs are said to be insufficient in pharmaceutical treatment. Pharmaceuticals cannot be completely removed from wastewater in conventional treatment processes. Advanced treatment processes can be applied to remove pharmaceuticals from wastewater. Successful results have been acquired in the removal of pharmaceuticals by advanced oxidation methods (Bautitz and Nogueira, 2007; Wang and Wang 2016). For example, diazepam and bezafibrate removed 100% (Bautitz and Nogueira, 2010; Trovo et al. 2008), carbamazepine removed > 90% (Mohapatra et al. 2013), and gemfibrozil removed > 80% (Li et al. 2012) from wastewater by the Fenton oxidation process. Kim et al. (2009) investigated that 100% removal of bezafibrate, atenolol, metoprolol, propranolol, diazepam, and carbamazepine and more than 90% removal of clofibr acid were achieved with the UV/H2O2.

Environmental risk assessment

More than 200 pharmaceuticals have been detected in environmental matrices, such as different water sources and wastewater. The fate of pharmaceuticals and their effects on humans and the environment are uncertain (Couto et al. 2019). Most pharmaceutical compounds have high polarity and low volatility. Even at extremely low concentrations in the aquatic environment, they can have substantial ecotoxicological consequences, such as bioaccumulation, endocrine disruption, and drug resistance. Pharmaceutical concerns include an increase in the prevalence of cancer, antibiotic resistance, reproductive harm, and aberrant physiological processes (Wang et al. 2021). Table 7 comprises the pharmaceutical risk assessments for effluent wastewater in this study and literature studies. When “insignificant risk” is identified, the result is “acceptable” for the receiving environment; when “low risk” is identified, “more research” is necessary, and “detailed assessment” is required for the receiving environment in cases where “medium and high risk” is detected. Additionally, in this study, hospital wastewater and influent wastewater were evaluated in terms of risk. In the summer period, atenolol compounds showed a medium risk for fish in hospital wastewater and a high risk in the influent of WWTP. In hospital wastewater, propranolol and carbamazepine compounds showed a low risk for fish, *Daphnia magna*, and algae. During the winter, while atenolol compounds showed a high risk for fish in hospital wastewater and a moderate risk in the effluent municipal WWTP, the fluoxetine compound demonstrated a low risk for algae both in hospital wastewater and in the influent of the municipal WWTP. When Table 7 was examined, atenolol showed a moderate risk for fish in the summer and winter periods in this study. Fluoxetine showed a low risk for algae, and an insignificant risk was detected with other pharmaceuticals in this study. Mendoza et al. (2015) showed a high environmental risk for fish from propranolol and a medium risk for *Daphnia magna* from bezafibrate. Biel-Maeso et al. (2018b) identified a moderate risk for algae from propranolol.

Conclusions

This study addresses the analysis of four groups of pharmaceutical concentrations in hospital wastewaters and WWTP in summer and winter. The 18 target pharmaceuticals were detected at different concentrations (maximum, 7008 ng/L for carbamazepine). Beta-blockers and psychiatric pharmaceuticals were detected at higher concentrations in wastewater. The total concentrations of pharmaceutical groups in hospital wastewater were higher during winter than during summer, except psychiatric pharmaceuticals. In the WWTP, the total concentrations of lipid regulators and cancer pharmaceutical groups were higher in winter. It is still necessary to perform detailed studies on seasonal change. The contribution of the 16 hospitals to WWTP influent varied between 0.00005 and 1.818%. Flow rates of hospital wastewater remained at very low levels compared to WWTP influent. Therefore, pharmaceuticals detected in high concentrations in hospital wastewater are a small contribution. It has been concluded that pharmaceutical discharge from hospitals does not create a serious load on WWTPs. However, it is thought that the continuous discharge of pharmaceuticals from hospitals should be controlled. In this study, the environmental risk for *Daphnia*, fish, and algae was evaluated. The obtained results highlight that pharmaceuticals in WWTP effluent may pose a medium–high risk to aquatic life. However, more studies are still needed to identify the toxicities of pharmaceuticals for nontarget organisms. The observed removal efficiencies vary over a wide range for the investigated pharmaceuticals in WWTPs. Some compounds (metoprolol and carbamazepine in winter seasons and propranolol and tamoxifen in summer seasons) were completely eliminated during treatment. Our current research has shown that conventional treatment can be efficient for pharmaceutical removal. However, pharmaceutical removal depends on many factors, such as social and environmental conditions. Conventional systems under different operating conditions should be examined in detail.
| Pharmaceuticals | RQ | Species                | Result       | Reference                        |
|------------------|----|-----------------------|--------------|----------------------------------|
| **Beta-blockers**|     |                       |              |                                  |
| Atenolol         | $12 \times 10^{-2}$ | Fish                   | Low risk     | Mendoza et al. (2015)            |
|                  | $54 \times 10^{-4}$ | *Daphnia magna*        | Insignificant risk | Gros et al. (2010)               |
|                  | $7 \times 10^{-4}$  | Algae                  | Insignificant risk | Cleuvers (2005)                 |
|                  | $1 \times 10^{-2}$  | Algae                  | Insignificant risk | Biel-Maeso et al. (2018b)       |
|                  | $8.13$               | Fish                   | Moderate risk | In this study                    |
|                  | $5 \times 10^{-3}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $2 \times 10^{-4}$  | Algae                  | Insignificant risk |                                   |
| Metoprolol       | $14 \times 10^{-3}$ | *Daphnia magna*        | Insignificant risk | Mendoza et al. (2015)            |
|                  | $1 \times 10^{-5}$  | Fish                   | Insignificant risk | Gros et al. (2010)               |
|                  | $2 \times 10^{-4}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $1 \times 10^{-3}$  | Algae                  | Insignificant risk |                                   |
|                  | $286 \times 10^{-3}$| Algae                  | Low risk     | Cleuvers (2005)                 |
|                  | $4 \times 10^{-4}$  | Fish                   | Insignificant risk | In this study                    |
|                  | $45 \times 10^{-4}$ | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $2 \times 10^{-4}$  | Algae                  | Insignificant risk |                                   |
| Propranolol       | $115 \times 10^{-1}$| Fish                  | High risk    | Mendoza et al. (2015)            |
|                  | $81 \times 10^{-2}$ | Algae                  | Low risk     | Cleuvers (2005)                 |
|                  | $18 \times 10^{-1}$ | Algae                  | Moderate risk | Biel-Maeso et al. (2018b)       |
|                  | $3 \times 10^{-4}$  | Fish                   | Insignificant risk | In this study                    |
|                  | $8 \times 10^{-4}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $9 \times 10^{-4}$  | Algae                  | Insignificant risk |                                   |
| Sotalol           | $3 \times 10^{-2}$  | Algae                  | Insignificant risk | Mendoza et al. (2015)            |
|                  | $5 \times 10^{-5}$  | Fish                   | Insignificant risk | In this study                    |
|                  | $1 \times 10^{-5}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $11 \times 10^{-4}$ | Algae                  | Insignificant risk |                                   |
| Timolol           | $1 \times 10^{-2}$  | Algae                  | Insignificant risk | Biel-Maeso et al. (2018b)       |
|                  | nd                   | Fish                   | Insignificant risk | In this study                    |
|                  | nd                   | *Daphnia magna*        | Insignificant risk |                                   |
|                  | nd                   | Algae                  | Insignificant risk |                                   |
| Lipid regulators  |     |                       |              |                                  |
| Bezafibrate      | $12 \times 10^{-1}$ | *Daphnia magna*        | Moderate risk | Mendoza et al. (2015)            |
|                  | $75 \times 10^{-3}$ | Fish                   | Insignificant risk | Gros et al. 2010                |
|                  | $18 \times 10^{-3}$ | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $15 \times 10^{-4}$ | Fish                   | Insignificant risk | In this study                    |
|                  | $2 \times 10^{-4}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $4 \times 10^{-5}$  | Algae                  | Insignificant risk |                                   |
| Clofibric acid   | $27 \times 10^{-2}$ | *Daphnia magna*        | Low risk     | Gros et al. 2010                |
|                  | $15 \times 10^{-5}$ | Algae                  | Insignificant risk |                                   |
|                  | $4 \times 10^{-7}$  | Fish                   | Insignificant risk | In this study                    |
|                  | $5 \times 10^{-7}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $5 \times 10^{-7}$  | Algae                  | Insignificant risk |                                   |
| Fenofibrate      | $2 \times 10^{-1}$  | *Daphnia magna*        | Low risk     | Mendoza et al. (2015)            |
|                  | $18 \times 10^{-4}$ | Fish                   | Insignificant risk | In this study                    |
|                  | $4 \times 10^{-3}$  | *Daphnia magna*        | Insignificant risk |                                   |
|                  | $14 \times 10^{-3}$ | Algae                  |                      |                                   |
| Pharmaceuticals | RQ | Species | Result       | Reference                      |
|------------------|----|---------|--------------|--------------------------------|
| Gemfibrozil      | $57 \times 10^{-2}$ | Fish     | Low risk     | Gros et al. (2010)             |
|                  | $5 \times 10^{-2}$ | *Daphnia magna* | Insignificant risk |                                |
|                  | $13 \times 10^{-2}$ | Algae    | Low risk     |                                |
|                  | $7 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
|                  | $6 \times 10^{-4}$ | *Daphnia magna* | Insignificant risk |                                |
| Pravastatin      | $2 \times 10^{-4}$ | Algae    | Insignificant risk |                                |
|                  | $1 \times 10^{-4}$–$21 \times 10^{-3}$ | Algae    | Insignificant risk | Escher et al. (2011)           |
|                  | $22 \times 10^{-2}$ | Fish     | Low risk     | Gros et al. (2010)             |
|                  | $3 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
| Psychiatric drugs |      |          |              |                                |
| Carbamazepine    | $2 \times 10^{-1}$ | *Daphnia magna* | Low risk | Mendoza et al. (2015)          |
|                  | $4 \times 10^{-4}$–$283 \times 10^{-3}$ | Algae    | Insignificant risk | Escher et al. (2011)           |
|                  | $1 \times 10^{-4}$ | Fish     | Insignificant risk | Gros et al. (2010)             |
|                  | $47 \times 10^{-4}$ | *Daphnia magna* | Insignificant risk |                                |
|                  | $43 \times 10^{-4}$ | Algae    | Insignificant risk |                                |
|                  | $3 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
|                  | $7 \times 10^{-3}$ | *Daphnia magna* | Insignificant risk |                                |
| Diazepam         | $3 \times 10^{-3}$ | Algae    | Insignificant risk |                                |
|                  | $6 \times 10^{-4}$–$4 \times 10^{-2}$ | Algae    | Insignificant risk | Escher et al. (2011)           |
|                  | $22 \times 10^{-2}$ | Fish     | Insignificant risk | Gros et al. (2010)             |
|                  | $44 \times 10^{-4}$ | *Daphnia magna* | Insignificant risk |                                |
|                  | $38 \times 10^{-4}$ | Algae    | Insignificant risk |                                |
|                  | nd                | Algae    | Insignificant risk | In this study                  |
|                  | nd                | Fish     | Insignificant risk | In this study                  |
| Fluoxetine       | $1 \times 10^{-3}$–$78 \times 10^{-3}$ | Algae    | Insignificant risk | Escher et al. (2011)           |
|                  | $12 \times 10^{-3}$ | Fish     | Insignificant risk | Gros et al. (2010)             |
|                  | $41 \times 10^{-3}$ | *Daphnia magna* | Insignificant risk |                                |
|                  | $26 \times 10^{-3}$ | Algae    | Insignificant risk |                                |
|                  | $1.04 \times 10^{-1}$ | Algae    | Low risk     | In this study                  |
|                  | $3 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
|                  | $5 \times 10^{-3}$ | *Daphnia magna* | Insignificant risk |                                |
| Lorazepam        | $104 \times 10^{-3}$ | Algae    | Low risk     | Mendoza et al. (2015)          |
|                  | $5 \times 10^{-1}$ | Algae    | Low risk     |                                |
|                  | $104 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
|                  | $5 \times 10^{-3}$ | *Daphnia magna* | Insignificant risk |                                |
| Cancers drugs    | $1 \times 10^{-3}$ | Algae    | Low risk     |                                |
| Tamoxifen        | $24 \times 10^{-3}$ | Fish     | Insignificant risk | Ferrando-Climent et al. (2014) |
|                  | $1 \times 10^{-3}$ | Fish     | Insignificant risk | In this study                  |
|                  | $2 \times 10^{-3}$ | *Daphnia magna* | Insignificant risk |                                |
|                  | –                 | Algae    | Insignificant risk |                                |
Supplementary Information

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Data availability

Not applicable.

Author contribution

Senar Aydin: methodology, sampling and analyzing, and writing and reviewing
Arzu Ulvi: methodology, sampling and analyzing, and writing and reviewing
Mehmet Emin Aydin: methodology, sampling and analyzing, and writing including reviewing and editing

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Table 7 (continued)

| Pharmaceuticals | RQ       | Species                  | Result          | Reference                          |
|------------------|----------|--------------------------|-----------------|------------------------------------|
| Cyclophosphamide | 3 × 10⁻⁵ | *Daphnia magna*          | Insignificant risk | Negreira et al. (2014)            |
|                  | 25 × 10⁻⁶| *Daphnia magna*          | Insignificant risk | Ferrando-Climent et al. (2014)    |
|                  | 4 × 10⁻⁶ | *Daphnia magna*          | Insignificant risk | Gouvei et al. (2020)              |
|                  | 3 × 10⁻⁵ | Fish                     | Insignificant risk | In this study                      |
|                  | 1 × 10⁻⁶ | *Daphnia magna*          | Insignificant risk |                                    |
|                  | 2 × 10⁻⁴ | Algae                    | Insignificant risk |                                    |
| Ifosfamide       | 5 × 10⁻³ | Fish                     | Insignificant risk | Negreira et al. (2014)            |
|                  | 5 × 10⁻¹ | *Daphnia magna*          | Low risk         |                                    |
|                  | 1 × 10⁻⁴ | Algae                    | Insignificant risk |                                    |
|                  | 2.11 × 10⁻⁵| *Ceriodaphnia dubia*     | Insignificant risk | Gouvei et al. (2020)              |
|                  | 2 × 10⁻⁵ | Fish                     | Insignificant risk | In this study                      |
|                  | 1 × 10⁻⁶ | *Daphnia magna*          | Insignificant risk | In this study                      |
|                  | 2 × 10⁻⁴ | Algae                    | Insignificant risk |                                    |
| Etoposide        | nd       | Fish                     | Insignificant risk | In this study                      |
|                  | nd       | *Daphnia magna*          | Insignificant risk |                                    |
|                  | nd       | Algae                    | Insignificant risk |                                    |

nd means the concentration of compound in wastewater is below the limit of detection, and en dash means the PNEC value of tamoxifen on algae was not found.
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