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Environmental risk assessment of commonly used anti-cancer drugs

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Abstract

This study has been focused on the commonly used anti-cancer drugs (ACDs) in Turkey in terms of environmental toxicity, behaviors in sewage treatment plants (STPs), biodegradability and physicochemical properties. For this purpose, EPI Suite, estimation programme, has been used by employing BCFWIN, KOWWIN, KOCWIN, HENRYWIN, AEROWIN, ECOSAR, BIOWIN, STPWIN suites. Among 13 selected ACDs, Tamoxifen has been found as the most risky pharmaceutical due to its high Predicted Environmental Concentration (PEC) / Predicted No Effect Concentration (PNEC) value (2.96350). Even if the total removal efficiency of Tamoxifen is rather high (97.24%), the considerable portion (71.50%) has been retained on the treatment sludge leading to compose hazardous waste. Additionally, physicochemical parameters, log Kow (6.30), Kd (62230 L/g), log Koc (4.400) and BCF (6689 L/kg), calculated for Tamoxifen indicate that Tamoxifen has the highest sorption potential and tends to bioaccumulate in organisms, respectively.

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1. Introduction

Anti-cancer drugs (ACDs) are classified to two main groups as antineoplastic and immunomodulating agents (class L) by the Anatomical Therapeutic Classification (ATC) system based on their therapeutic purposes [1]. Antineoplastic agents are categorized into 5 sub-groups upon to their chemical structures and therapeutic properties such that; L01A: Alkylating agents; L01B: Antimetabolites; L01C: Plant alkaloids; and other natural products; L01D: Cytotoxic antibiotics and related substances; L01X: Other antineoplastic agents [1]. These antineoplastic drugs are discriminated from each other due to their different mode of actions [1]. Most chemotherapy drugs which are used to kill cancer cells and to inhibit the growth of these cells act as cytotoxic agents (L01D), so cytotoxic agents are considered to be in the most risky group from environmental point of view compared to the other antineoplastic agents [1]. On the other hand, cytostatic agents (L01X) used for treatment of cancer and other illnesses are differentiate from cytotoxic agents because of their specific action mechanism [1]. Cytostatic agents prevent cancer cells growing and spreading, without killing them in contrast to cytotoxic agents [2]. As well as antineoplastic agents, immunomodulating agents are also classified into sub-groups and these drugs are defined by their ATC codes like that; L02A: Hormone and related agents; L02B: Hormone antagonists and related agents; L03A: Immunostimulants, L04A: Immunosuppressants [3].

The amount of use for anti-cancer drugs is considerably high in many countries in the world [4]. Today, more than fifty different anti-cancer drugs have been used routinely in cancer care in United Kingdom [1]. According to the Pharmaceuticals and Medical Devices Institution report of Republic of Turkey Ministry of Health, the consumption of antineoplastic and immunomodulating drugs known as anti-cancer drugs were increased in 2007-2014 years associated with increasing cancer cases explained above. While 4.7 million boxes of anti-cancer drugs were consumed in 2007, this number was raised up to 9.3 million boxes in 2014. Also, box sales of anti-cancer drugs increased from 6.9 to 9.8 million boxes in the range of 2011-2016 years depending on the increment in cancer cases in respect to the Turkish Medicines and Medical Devices Agency report. Nowadays, the amount of use of anti-cancer drugs in hospitals and outpatients has been gradually increased due to the tendency in the increment of cancer cases and therapeutic and inhibitory effects of these drugs [5]. The main sources of anti-cancer drugs in aquatic environment are domestic and hospital wastewaters [6,7]. The penetration of these drugs to domestic wastewaters is performed through the excreted urine of chemotherapy patients as the other pharmaceuticals [5]. The anti-

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cancer agents by which excreted through urine may damage [1,3,8] the genetic and cell structure of living organisms in the aquatic environment [9,10] since they have potential to show carcinogenic, teratogenic, mutagenic and adverse effects on normal and immune system cells. Therefore, the physical and biological removal of anti-cancer drugs from wastewaters should be performed, but this process is rather difficult [9] because these drugs are poorly biodegradable and are not fully metabolized in the human body [1].

Al-Ahmed and Kümmerer reported that among pharmaceuticals, drugs used for cancer treatment, referred to as anticancer or antineoplastic drugs, are suspected to represent a specific risk for aquatic non-target species [11]. Data on the toxicity of anti-cancer agents suggest that some of these drugs are toxic at three-fold or higher concentrations than that of their known environmental concentrations [5, 12]. Environmental risk assessment of anti-cancer drugs should be done to determine biodegradability (biodegradation period) and behaviors (total removal (%), total biodegradation (%), total sludge adsorption (%)) of these drugs in sewage treatment plants (STPs) due to the toxic effects of these agents to the aquatic environment. Additionally, physicochemical properties of anti-cancer drugs should be investigated for understanding the potential risks of these drugs to the environment. During the chemotherapy medication, physicochemical parameters of anti-cancer drugs (polarity, non-volatile, solubility, etc..) can increase with the entering of these drugs to waste waters through hospital effluents and domestic dwellings [1]. This case can cause environmental risk for aquatic media. So, researching some critical physicochemical properties of anti-cancer drugs is crucial to get information whether it would be difficult to remove them from aquatic environment or not when they have penetrated it [5].

Generally, only limited studies have been performed on the ecotoxicity of both cytotoxic and cytostatic drugs. Until now, a detailed study has not been reported on the environmental significance of most frequently used anti-cancer drugs in Turkey in respect to predicting and assessing environmental risks due to the restricted and lower consumption compared to other pharmaceuticals. Furthermore, based on the tendency in the increasing usage of anti-cancer drugs in different fields (cancer treatment of pets, other treatments excluding cancer, etc.) [5]. In several countries, extra consumption data of these agents should be accounted. In this case, the existence of these drugs into the environment will be expected to increase further and there will be more need to the environmental risk assessment of anti-cancer drugs in the future.

In the present study, the calculations have been performed in order to assess the environmental risks of anti-cancer drugs as theoretically. The programme of EPA is used in the calculations. In these calculations, the structural analysis and the physical properties of anti-cancer drugs have been estimated. Due to the reason of increasing consumption of these anti cancer drugs, determining the environmental risks of these drugs is critical in future time. So, this study is original for this point of view.

2. Materials and Methods

In the present study, the consumption data (number of boxes/units) of imported oncology drugs by pharmacological firms were taken from IMS-Health (Intercontinental Marketing Services Health) Turkey for the year of 2017. Totally 13 anti-cancer drugs, widely used in Turkey, were selected for getting knowledge about fate and behaviors of these drugs, since examination of a group of anti-cancer drugs having high consumption as detailed is worthy. In this study, all calculations have been carried out using EPI SuiteTM (Estimation Programs Interface) program which includes physical/chemical and environmental fate estimation suites (BCFWIN, KOWWIN, KOCWIN, HENRYWIN, AEROWIN, ECOSAR, BIOWIN, STPWIN) developed by EPA's and Syracuse Research Corp. (SRC) [13]. EPI Suite program is based on Quantitative Structure Activity Relationships (QSARs) methodologies which are used in estimation of toxicity measures of chemicals from the physical properties based on their molecular structures and in prediction of the effects of chemicals on biota [13].

The Predicted Environmental Concentration (PEC) and the Predicted No Effect Concentration (PNEC) values of selected drugs have been calculated to obtain the PEC/PNEC ratios which indicate the risks of drugs. Risk assessment, assigned as insignificant, low, moderate and high depending on PEC/PNEC ratios, has been performed according to Stockholm Council Report and given in Table 1. PNEC values have been calculated by using Effective Concentration (EC50) and Lethal Concentration (LC50) values which are computed by Ecological Structure-Activity Relationships (ECOSAR) Interface of EPA's [13]. As physicochemical parameters of anti-cancer drugs, Bioconcentration factor (BCF), Octanol-water partition coefficient (log Kow), Organic carbon-normalized sorption coefficient (log Koc), vapour pressures and Henry Law constants have been

calculated by employing BCFWINTM, KOWWINTM, KOCWINTM, AEROWINTM and HENRYWINTM suites of EPA, respectively [13]. In addition, the biodegradability of drugs under aerobic and anaerobic conditions has been estimated by using the BIOWIN 3, BIOWIN 5 and BIOWIN 7 modules of the Biodegradation Probability Program (BIOWIN) which estimates the probable biodegradation of chemicals as rapidly or slowly . EPI Suite User Guide [13] has been used in the evaluation of the results obtained from BIOWIN output data. Also, STPWIN interface of EPA/EPI Suite [13] has been applied to evaluate the biological behaviors (total removal, total biodegradation and total sludge adsorption) of ACDs in STPs.

Among the BIOWIN modules, the results of BIOWIN 3, BIOWIN 5 and BIOWIN 7 have been evaluated heavily in this study. The ultimate biodegredation time has been calculated by BIOWIN 3, if the aerobic biodegredation occurs or not has been discussed by the way of the results of BIOWIN 5 and the anaerobic biodegredation conditions have been informed by BIOWIN 7. Due to the similar results of BİOWİN 1 and BIOWIN 2 modules with BIOWIN 3, also the insufficient information about biodegredation time, the non-linearity of BIOWIN 6 compared to BIOWIN 5, the primary biodegredation time obtained by BIOWIN 4 instead of ultimately, it is not required to evaluate the BIOWIN 1, BIOWIN 2, BIOWIN 4 and BIOWIN 6.

Also, total removal, total biodegradation and total sludge adsorption parameters that determine biological treatability of drugs in STPs have been calculated using STPWIN interface of EPA/EPI Suite [13]. Generally, PEC values of pharmaceuticals have been calculated according to Equation 1 (Eq.1) that following formula is given below with the explanations of parameters [14, 15].

$$PEC\ (\mu g/L)\ = \frac{Ax10^9x(100-R)}{365\frac{day}{year}xPxVxDx100} \quad (1)$$

A: The amount of annual use of pharmaceuticals (kg)

R: Removal rate of pharmaceuticals before mixing with the water bodies by using different processes (adjusted as 0) [14].

P: Population of Turkey (80810525 persons) [16].

V: The amount of wastewater produced by per person per day (180 L/person/day [17])

D: Environmental dilution factor (usually 10) [14,15].

In calculation of PNEC values of pharmaceuticals, toxicological dose descriptors (EC50/LC50/NOECs) obtained by toxicity studies are usually divided by different assessment factors. In that study, the PNEC values of the selected ACDs have been determined by dividing computed EC50 and LC50 values to the assessment factor taken as 1000. The following equation (Eq.2) has been used in the calculation of PNEC values [18].

PNEC = Lowest Acute (EC50 or LC 50)/Assessment Factor (2)

Bioconcentration factors (BCF) for the selected drugs, predicted with EPI Suite BCFWIN interface, have been calculated in order to get information about bioaccumulation potentials of ACDs on living organisms. BCF parameter, given in the following equation (Eq.3), can be expressed as the ratio between the concentrations of chemical in organism and aquatic media [19].

BCF=Concentration Biota/Concentration Water (3)

Concentration Biota = Concentration of a chemical in an organism

Concentration Water= Concentration of a chemical in an aquatic media.

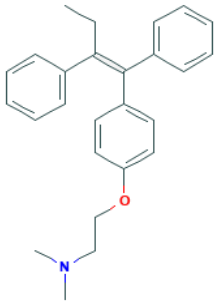
Kd values have been used to verify the adsorption capacities of pharmaceuticals on surfaces.The following equation (Eq.4) has been used in the calculation of Kd value of each drug [20].

Kd = 10(0.58 log Kow + 1.14) (4)

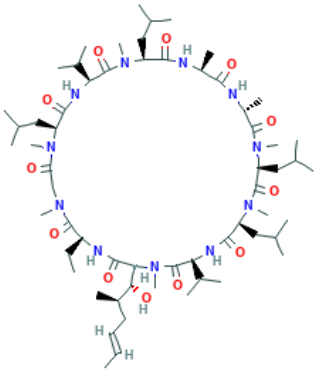
Herein, Kow and Kd parameters express octanol-water partition coefficient and particle-water distribution ratio of pharmaceuticals, respectively [20].

Totally 13 anti-cancer drugs, widely used in Turkey, were selected for getting knowledge about fate and behaviors of these drugs. The two-dimensional representation and chemical structure of the ACDs used in this study are shown in Figure 1.

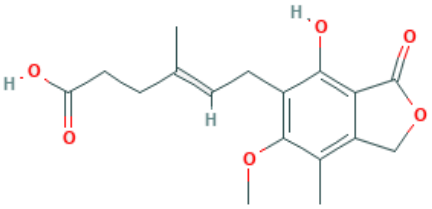
Tamoxifen



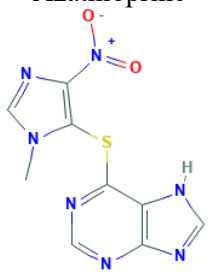
Ciclosporin



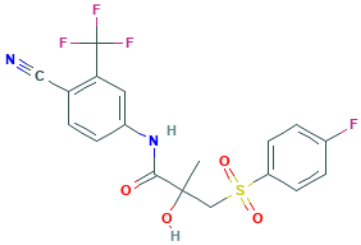
Mycophenolic acid



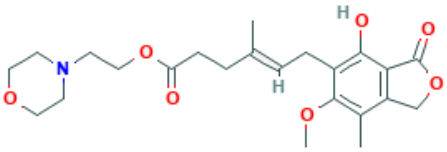
Azathioprine



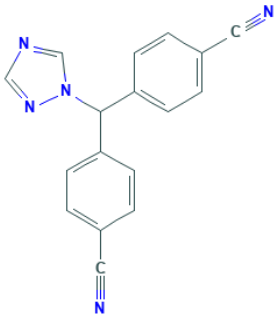
Bicalutamide



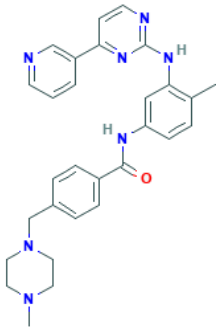
Mycophenolate mofetil



Letrozole

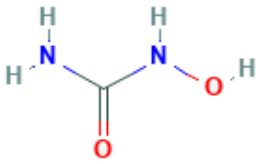


Imatinib

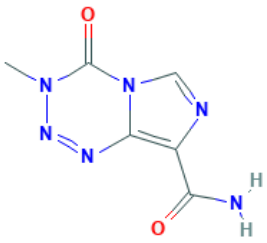


Capecitabine

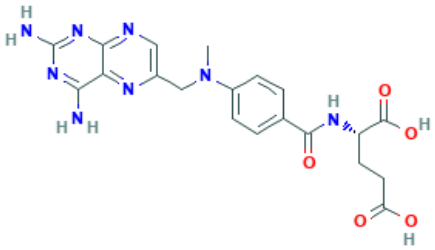
Hydroxycarbamide



Temozolomide



Methotrexate



5-Fluorouracil

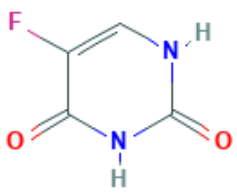


Figure 1. Chemical structure of the ACDs

3. Results and Discussion

3.1. Environmental risk assessment of ACDs

Predicted Environmental Concentration (PEC), Predicted No Effect Concentration (PNEC) and PEC/PNEC values have been calculated to assess the environmental risks of pharmaceuticals. [14, 21-24]. The following criteria that define the PEC and PEC / PNEC values is considered in the assessment of the environmental risks of pharmaceuticals.

- PEC<0.01 µg/L: There is no need to have done some tests and researches.
- 0.01µg/L <PEC<0.1µg/L: PEC/PNEC ratio should be considered and investigated.
- PEC/PNEC >1: Pharmaceutical can lead serious risks in environment, so precautions should be taken to avoid environmental risks [23].

To classify the risk groups of ACDs and to specify the environmental risks of them, the data taken from Stockholm Country Council report was used in that study. In this report, the potential risk groups determined to PEC/PNEC values are as follows; PEC/PNEC<0.1: Insignificant, 0.1<PEC/PNEC<1: Low, 1<PEC/PNEC<10: Moderate PEC/PNEC>10: High [22].

In the present study, the environmental risk assessment of 13 ACDs has been done by the aid of calculated PEC, PNEC and PEC/PNEC values which are given in Table 1.

Table 1. Environmental risk assessment of the selected ACDs

Drug Name	PEC (µg/L)	PNEC (µg/L)	Lowest Effect Level Toxicity Test /Test Organism/ECOSAR Class	PEC/PNEC	Risk Assessment	
					This Study*	Others [1,4,5]
Mycophenolic acid	0.0078	1.8750	LC_{50} /Daphnid/Neutral Organic	0.00414	Insignificant	-
Ciclosporin	0.0315	47.5790	EC_{50}/Green Algae/Amides	0.00066	Insignificant	-
Mycophenolate mofetil	0.2707	0.4290	EC_{50}/ Green Algae/ Aliphatic Amines	0.63091	Low risk	-
Azathioprine	0.0267	1.2710	EC_{50}/ Green Algae/Imidazoles	0.02103	Insignificant	-
Bicalutamide	0.0161	2.6430	EC_{50}/ Green Algae/Amides	0.00611	Insignificant	Need to confirm its presence in environment.
Tamoxifen	0.0178	0.0060	EC_{50}/ Green Algae/Aliphatic Amines	2.96350	Moderate	Potential risk
Letrozole	0.0006	7.7720	EC_{50}/ Green Algae/Triazoles	0.00008	Insignificant	-
Capecitabine	0.1262	0.9880	EC_{50}/ Green Algae/Carbamate Esters	0.12774	Low risk	Potential risk
Methotrexate	0.0014	34.9260	LC_{50}/Daphnid/Anilines	0.00004	Insignificant	No need to assess
Temozolomide	0.0036	1.8180	EC_{50}/ Green Algae/Imidazoles	0.00199	Insignificant	No need to assess
Hydroxycarbamide	0.1014	318.00	LC_{50} /Earthworm/Neutral Organic	0.00032	Insignificant	Potential risk
Imatinib	0.0122	1.0880	EC_{50}/ Green Algae/Amides	0.01120	Insignificant	Need to confirm its presence in environment
5-Fluorouracil	0.0031	0.0100	EC_{50}/ Green Algae/Carbonyl Ureas	0.31418	Low risk	Need to confirm its presence in environment

* Risk assessment for the selected ACDs was performed based on the criteria of Stockholm County Council report. According to this report, environmental risks are determined by taken into account PEC/PNEC values (If PEC/PNEC<0.1: Insignificant; if PEC/PNEC 0.1-1.0: Low; if PEC/PNEC 1-10: Moderate; if PEC/PNEC >10: High).

Among 13 ACDs given in Table 1. Tamoxifen, included in Endocrine Therapy class, was considered to be the most toxic drug for environment due to the calculated highest PEC/PNEC (2.96350) and the lowest PNEC (0.0060(µg/L)) values. According to the risk assessment report of Stockholm Country Council [21], Tamoxifen was assessed as moderate risky. On the other hand, Mycophenolate Mofetil, 5-Fluorouracil and Capecitabine were classified as ''low risk'' depending on PEC/PNEC values (0.63091, 0.31418, 0.12774) in descending order, respectively. Although, these three drugs are in low risk group, the potential risk levels may increase as to the increment in the amounts of use. The other ACDs excluding from Tamoxifen, Mycophenolate Mofetil, 5-Fluorouracil and Capecitabine have been considered as ''insignificant'' in terms of their risk assessment due to their calculated PEC/PNEC values lower than 0.1 (PEC/PNEC<0.1).

3.2. Biodegradation times of ACDs with their behaviors in STPs

The estimated biodegradation times of totally 13 ACDs, given in Table 2, were calculated by using BIOWIN suite involving BIOWIN 3, BIOWIN 5 and BIOWIN 7 models [13].

Table 2. Estimation of biodegradation times of the selected ACDs with their behaviors in sewage treatment plants.

	*Estimated Biodegradation Times Of ACDs						*Estimated Behaviors Of ACDs In Sewage Treatment Plants (STPs) (%)		
Drug Name	BIOWIN 3		BIOWIN 5		BIOWIN 7				
	Cal.* ratings	Complete B.D.* time units	Cal.* values	Readily B.D.*	Cal.* values	Rapid B.D.*	Total Rem.*	Total B.D.*	Total S.A.*
Mycophenolic acid	2.8446	Weeks	0.9028	Yes	0.7719	Yes	99.39	85.88	13.51
Ciclosporin	0.4035	Recalcitrant	-0.2050	No	-8.5487	No	5.07	0.12	4.95
Mycophenolate mofetil	2.1067	Months	0.5660	No	-1.0032	No	48.06	46.25	1.81
Azathioprine	2.4169	Weeks to Months	-0.0318	No	0.2562	No	21.99	20.54	1.45
Bicalutamide	0.9795	Recalcitrant	0.1007	No	-0.7876	No	2.64	0.10	2.54
Tamoxifen	2.1092	Months	0.0803	No	-1.1212	No	97.24	25.74	71.5
Letrozole	2.4039	Weeks to Months	0.0357	No	-0.0851	No	23.49	21.46	2.03
Capecitabine	2.9679	Weeks	0.3146	No	0.5557	Yes	75.09	74.46	0.63
Methotrexate	2.3452	Weeks to Months	0.1288	No	-1.6667	No	21.97	20.53	1.44
Temozolomide	2.7159	Weeks to Months	0.3183	No	0.0932	No	21.97	20.53	1.44
Hydroxycarbamide	3.0311	Weeks	0.4344	No	0.8361	Yes	75.06	74.44	0.62
Imatinib	1.1206	Recalcitrant	-0.5364	No	-3.6976	No	5.77	0.12	5.65
5-Fluorouracil	2.9117	Weeks	0.3981	No	0.7626	Yes	75.06	74.44	0.62

* Biowin/EPA draft method is used in order to assign biodegradation time of compounds [13], Cal: Calculated, B.D: Biodegradation, Rem: Removal, S.A: Sludge Adsorption

Each model predicts different biodegradation periods of drugs (i.e. complete biodegradation, ready for biodegradation, fast or slow biodegradation). BIOWIN 3 model estimates the time required for complete biodegradation of compound in a typical aquatic environment under aerobic conditions. Boethling and Sabljic have been rated the ultimate biodegradation of compounds as a scale of 1-5 according to the calculated numerical values by employing BIOWIN 3 model [25]. In this study, the calculated ratings have been attributed to the biodegradation time units of compounds (5: Hours, 4: Days, 3: Weeks, 2: Months, 1: Longer). If the calculated rating is a decimal value changing in the range of 1-5, it is considered that the ultimate biodegradation time of the compound cannot be determined exactly, that means the compound can

biodegrade completely in an uncertain time (i.e. days to weeks, weeks to months, etc..). As to BIOWIN 3 results, the calculated ratings of 0.4035, 0.9795, 1.1206, respectively for Ciclosporin, Bicalutamide and Imatinib, indicated these drugs being highly persistent in environment and resistant against biodegradation. Therefore, these drugs were called as ''Recalcitrant''. BIOWIN 5, which is one of several models of BIOWIN suite, is utilized to estimate whether the compounds are ready for biodegradability or not under aerobic conditions [13]. In predicting ''ready biodegradability'' of compounds, the results obtained from both BIOWIN 3 and BIOWIN 5 models are evaluated as common. With respect to the approach described by [26], if BIOWIN 3 result is defined as ''Weeks'' or faster than weeks (i.e. "Days", "Days to Weeks", or "Weeks") and BIOWIN 5 value is higher than 0.5, then the compound is considered as ''ready for biodegradation''; if not so the compound is considered as ''not ready for biodegradation''. Considering BIOWIN 3 results, Mycophenolic acid, Capecitabine, Hydroxycarbamide and 5-Fluorouracil have been evaluated as easily biodegradable drugs due to the shorter biodegradation time which are described as "Weeks". Among these 4 drugs, Mycophenolıc acid is considered as "ready for biodegradation" drug because of the calculated BIOWIN 5 value (0.9028) that is higher than that of 0.5. BIOWIN 7, an anaerobic biodegradation model, estimates the probability of rapid biodegradation under anaerobic conditions [13]. The calculated values by BIOWIN 7 higher than that of 0.5 (>0.5) indicate that compounds can biodegrade rapidly [13]. In this context, Hydroxycarbamide, Mycophenolıc acid, 5-Fluorouracil and Capecitabine ACDs can biodegrade rapidly under anaerobic conditions in respect to the calculated values of 0.8361, 0.7719, 0.7626 and 0.5557, respectively.

It is essential to know the behaviors of pharmaceuticals in sewage treatment plants due to the probable toxic effects of these drugs. The estimated behaviors of 13 ACDs in sewage treatment plants (STPs), total removal (%), total biodegradation (%) and total sludge adsorption (%) were given in Table 2. It was noted that the total removal efficiencies of Bicalutamide, Ciclosporin and Imatinib in STPs were found to be lower than the other ACDs in Table 2 due to the lower calculated values as 2.64, 5.07 and 5.77, respectively. This result indicates that the giant proportion of Bicalutamide, Ciclosporin and Imatinib can enter to aquatic media without treatment. Although these ACDs were considered to be non-risky according to the low PEC/PNEC ratios calculated as 0.00611(Bicalutamide), 0.00066 (Ciclosporin) and 0.01120 (Imatinib); their potential to enter in receiving water was rather high due to their lower removal efficiencies. The calculated values of total sludge adsorption as 2.54, 4.95 and 5.65 for Bicalutamide, Ciclosporin and Imatinib, respectively indicate that the large amount of these ACDs were removed from wastewater by being adsorbed to sludge based on their lower calculated removal efficiencies (2.64, 5.07 and 5.77) and this case can cause hazardous waste for environment. The calculated total biodegradation values for Bicalutamide, Ciclosporin and Imatinib as 0.10, 0.12 and 0.12, respectively showed that these ACDs were poorly biodegrade in aquatic media. This estimation is also in harmony with the predicted BIOWIN results since the results from BIOWIN explain that these ACDs are "Recalcitrant" against biodegradation and posses longer biodegradation time. On the other hand, even if Tamoxifen is the most risky agent depending on the highest PEC/PNEC ratio (2.96350); the amount of 97.24% for Tamoxifen can be removed from aquatic media. Although the total removal efficiency of Tamoxifen is rather high, the considerable portion of this amount (71.50%) is adsorbed on the treatment sludge causing to compose hazardous waste. Hence, the sludge adsorption of Tamoxifen is an undesired case due to its toxicity, leading environmental risk.

3.3. Physicochemical properties of ACDs

In combination with environmental risk assessment of pharmaceuticals, it should be required to investigate also the physicochemical properties of them which inform us for how difficult it would be remove these drugs from the aquatic environment when they have entered it. In the present study, the physicochemical parameters calculated by applying different suites of EPA, have been presented as collectively in **Table 3** for 13 ACDs. The chemical structures of the related ACDs, given as Supplementary Data, contribute in the assessment of some critical physicochemical parameters such as solubility, Kow, Kd.

Considering that most of the pharmaceuticals possess lipophilic character, namely dissolved in membrane lipids, it should be required to be investigated the bioaccumulation of drugs on organisms, in terms of their toxicity. In this context, bioconcentration factor (BCF), described as the ratio between the concentrations of chemical in living organism and in aquatic media, provides us to understand whether these drugs are causing accumulation or not in the organisms.

Table 3. Physicochemical properties of the selected ACDs

Drug Names	BCF (L/kg)	Log K_{ow}	Log K_{oc}	K_d (L/g)	Vapour Pressure (Pa)	Henry's Law Constant (Pa-m^3/mole)	Water Solubility (mg/L) 25°C
Mycophenolic acid	3.162	4.22	2.647	3869	3.15E-007	3.87E-007	22.07
Ciclosporin	39.23	2.92	1.729	682	*NC	*NC	4.239E-005
Mycophenolate mofetil	17.27	2.38	2.177	331	6.05E-009	5.59E-01	680.1
Azathioprine	3.162	0.10	2.395	16	7.48E-008	2.68E-010	272.3
Bicalutamide	15.23	2.30	2.177	298	2.33E-010	2.85E-010	11.75
Tamoxifen	6689	6.30	4.400	62230	2.31E-005	4.55E-005	0.1916
Letrozole	13.58	2.22	3.010	268	5.05E-005	2.01E-006	102.8
Capecitabine	3.162	0.56	0.173	29	1.35E-008	2.96E-014	1821
Methotrexate	3.162	-1.85	-0.387	1	1.23E-013	1.56E-026	2600
Temozolomide	3.162	-1.32	0.554	2	1.51E-005	8.10E-009	1.148E+004(11480)
Hydroxycarbamide	3.162	-1.80	-0.081	1	0.585	5.49E-006	2.242E+005(224200)
Imatinib	45.18	3.01	2.762	769	8.41E-012	8.17E-019	2.103
5-Fluorouracil	3.162	-0.89	0.442	4	0.0068	1.68E-005	2.59E+004 (25900)

*NC: non calculated

Eq.3 explains that there is a proportion between the calculated BCF value and the concentration of pharmaceutical on biota that means in the case of BCF value increases, tendency for bioaccumulation of pharmaceutical within the tissue will increase. Tamoxifen, with the calculated BCF value of 6689 L/kg, has the highest BCF value, compared to others, that means Tamoxifen extremely tends to accumulate in organisms due to its high concentration. Lipophilicity, a key physicochemical parameter associated with solubility, membrane permeability, and hence drug absorption and distribution with route and rate of clearance, is a measure of interaction with lipids [27]. From the structural point of view, apolar (non-polar) or lipophilic groups found in molecular structure of compound, makes molecule more lipophilic due to low water solubility of these fragments. Herein, Tamoxifen is considered as highly lipophilic since the structure of Tamoxifen is composed mostly of apolar groups, such as aromatic (C_6H_5-) and aliphatic groups (-CH_3, -CH_2-,H_2C=CH_2), which enhance the lipophilicity of Tamoxifen. So, Tamoxifen may cause toxic effect on the organisms by accumulating in the lipid part of the cell membranes. On the other hand, Mycophenolic acid, Azathioprine, Capecitabine, Methotrexate, Temozolomide and Hydroxycarbamide are unlikely to be expected for accumulation due to their low BCF values calculated as 3.162 L/kg for all.

Looking at the solubility of ACDs, Hydroxycarbamide has the highest aqueous solubility ($2.242x10^5$ mg/L). Presence of many deprotonated forms, (-HN-CO-NHOH), (H_2N-CO-N(OH)-), (H_2N-CO-N(H)O^-) and consisting of ionizable functional groups (primer, secondary amine and hydroxyl) make Hydroxycarbamide, more soluble in water, hence render it more hydrophilic. As different from other ACDs, Ciclosporin, a polypeptide consisting of 11 amino acid moieties with their hydrophobic aliphatic groups, has a complex structure. Amino acids, possessing hydrophobic -R groups, are found in the interior part of the polypeptide where does not come into contact with water [28]. Ciclosporin has low water solubility ($4.239x10^{-5}$) due to the presence of hydrophobic CH_3 and CH_2 groups binding to amino acid units of polypeptide. Kow is defined as a concentration ratio of compound, distributed between n−octanol and aqueous phase. In order to estimate the sorption efficiencies of ACDs, the following general statements [5, 29, 30], defining the sorption potentials of these drugs according to the calculated Kow values, were taken in consideration. A.P. Toolaram et al. have suggested that the pharmaceuticals having log Kow values below 1 (log Kow<1) are highly mobile in the aquatic media, therefore they remain in liquid phase in contrast to sorption of them onto particles, sediments or sludge [5]. Based on that survey, the drugs of Azathioprine (0.10), Capecitabine (0.56), Methotrexate (-1.85), Temozolomide (-1.32), Hydroxycarbamide (-1.80) and 5-Fluorouracil (-0.89)

are considered to remain in the aqueous phase and to show weak tendency for sorption due to their low log Kow values. The values given in parenthesis above represent the calculated log Kow values for the related drug. In another study, have determined the effectiveness of adsorption for pharmaceuticals using the following criteria [29, 31]

- log Kow< 2.5: low adsorption potential;
- 4.0< log Kow>2.5: moderate adsorption potential;
- log Kow>4.0: high adsorption potential;

According to the explanation above, Tamoxifen (6.30) and Mycophenolıc acid (4.22) are considered to have higher adsorption potentials than the other ACDs due to the calculated log Kow values above 4.0. In Tamoxifen, the hydrophobic interactions between, aromatic (benzene rings), alkyl (-CH_3, -CH_2-) groups and lipid fractions of sludge, may be efficient in sorption due to the highly lipophilic character of these groups. Imatinib and Ciclosporin have moderate adsorption potentials with the calculated log Kow values of 3.01 and 2.92, respectively. Excluding Tamoxifen, Mycophenolıc acid, Imatinib, and Ciclosporin, the sorption of other ACDs on the activated sludge is rather poor. The pharmaceuticals possessing log Kow values higher than 4.5, are considered as bioaccumulative according to the European Medicines Agency's (EMA) guideline associated with the environmental risk assessment of medicinal products [5, 32]. In this context, Tamoxifen is supposed to have tendency in terms of persistency and bioaccumulation due to its high calculated log Kow value.

Since ACDs are complex molecules which possess different functional groups, involving acidic and/or basic groups within the same molecule, it is difficult to determine if molecules may be sorbed onto surface or not. Log Kow data is not sufficient in the assessment of sorption behaviors due to the several factors affecting sorption process, such as pH, redox potential, chemical nature of sorbent and sorbed molecules, etc [31]. Hence, in order to clarify sorption of pharmaceuticals exactly, experimental studies have to be done accompanied with theoretical studies. The theoretical data from this study will guide the experimental studies to be carried out on this subject.

K_d, defined as solid-water distribution coefficient, is used to understand the sorption capacities of pharmaceuticals on surfaces. All K_d values are obtained by using calculated Kow values, previously. The relation between K_d and K_{ow} is given as a mathematical expression in **Eq.4.** From the results of K_d, it can be concluded that Tamoxifen has the highest capacity for sorption due to its considerable high K_d value calculated as 2230. Mycophenolıc acid with the calculated K_d value of 3869 is in the second order after Tamoxifen in terms of its sorption capacity. Methotrexate, Temozolomide, Hydroxycarbamide and 5-Fluorouracil are considered to exhibit extremely weak sorption potential with their rather low K_d values calculated as 1, 2, 1 and 4 L/g, respectively.

Henry's Law constant, defined as a fixed ratio between the concentration of a compound in water and its partial pressure in air, is proportional with vapour pressure. [33]. That means, the lower Henry's Law constant indicates the lower vapour pressure, hence slightly volatilization of compounds. Generally, vapour pressures and Henry's Law constants of pharmaceuticals are changing in the range of 10^{-7}-10^{-2} Pa and 10^{-10} to 10^{-5} Pa-m^3/mol, respectively [1]. In this study, Methotrexate's vapour pressure and hence Henry's Law constant were calculated as $1.23*10^{-13}$Pa and $1.56*10^{-26}$Pa-m^3/mole respectively, as the lowest values of all, that indicates unlikely to volatilize of Methotrexate from aqueous media at ambient temperatures. Furthermore, the existence of ionisable functional groups in Methotrexate's structure, such as carboxylic acid (COOH) and amino (R-NH_2) groups, increase hydrophilicity of it, so Methotrexate may be considered to present mostly in dissolved phase instead of gaseous.

4.Conclusion

In the present study, the environmental risk assessment has been done for widely used ACDs in Turkey. Although there are many studies related to the estimation of environmental risks of ACDs in many countries, that study is the first for Turkey. Of the 13 ACDs mostly used in Turkey, Tamoxifen was recognized as the most risky for environment due to its high PEC / PNEC ratio (2.96350) compared to others. Although the 97.24% of Tamoxifen seems to be removed in STPs, the giant portion of this amount (71.5%) is sorbed into the treatment sludge, that means the micro-pollutant is not removed from environment completely, but just changes its physical phase. In other words 71.5% of Tamoxifen is passing from the aquatic phase to the sludge phase. According to the BIOWIN results, Ciclosporin, Bicalutamide and Imatinib are considered to biodegrade as poorly due to their high persistency in environment. Also, the removal of these drugs in STPs is rather difficult when compared to other ACDs. Although these ACDs have been found to be non-risky according to the calculated

PEC/PNEC ratios; their potential to enter in receiving water is considered to be rather high due to their low removal efficiencies in STPs. In other words, the giant amount of these drugs may enter to aquatic media without treatment, causing toxic effect for environment.

Bioaccumulation of drugs on organisms is an important task in investigation of drugs with respect to their toxicity. In that study, Tamoxifen was found to have the biggest tendency to accumulate in the lipid fragments of cell membranes in the organisms due to its high BCF value (6689 L/kg) and high lipophilic character. Compared to other ACDs, the sorption potentials of Tamoxifen and Mycophenolıc acid on sludge were considered as high due to their high Kow and Kd values. Although the huge portion (85.88%) of Mycophenolıc acid can be removed from environment by biodegradation, Tamoxifen could not biodegrade due to its partially metabolized and the large amount of it (71.5%) was sorbed to sludge composing hazardous waste for environment. Based on the results in that study, it can be concluded that more precautions should be taken for reducing the release of Tamoxifen into the environment.

Conflicts of interest

The author state that did not have conflict of interests

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