Journal of Hazardous Materials 166 (2009) 297–308

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Appraisal of potential environmental risks associated with human antibiotic consumption in Turkey

F. Ilter Turkdogan, Kaan Yetilmezsoy*

Department of Environmental Engineering, Yildiz Technical University, 34349 Yildiz, Besiktas, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 14 September 2008
Received in revised form 9 November 2008
Accepted 10 November 2008
Available online 17 November 2008

Keywords:
Antibiotic
Medication
Environmental risk
Risk assessment
Wastewater treatment plant

ABSTRACT

A comprehensive analysis of Turkish antibiotic data was conducted to evaluate potential environmental risks associated with antibiotic consumption in Turkey for year 2007. Antibiotics were defined for systemic use or group J01 of the WHO Anatomical Therapeutic Chemical (ATC) classification system. Total emissions and prescriptions for each ATC group were classified separately into 17 different J01 categories and three forms of medication (capsule/tablets, injectables and suspensions). Capsules and tablets were found as the most emitted form of medication in year 2007, with a total emission rate of about 585.5 tons/year (76%). Total antibiotic emission rates including all forms of medications were determined to be about 664.2 tons/year (86%) and 110.1 tons/year (14%) for adult and pediatric patients, respectively. An environmental risk assessment of 8 human antibiotics was conducted according to the EU draft guidance (CEC/III/5504/94, draft 6, version 4) and the risk was indicated by the ratio of predicted environmental concentration (PEC) to predicted no effect concentration (PNEC) for the aquatic environment. Available acute and chronic toxicity data were collected from the open peer-reviewed literature to derive PNEC. Risk quotients (PEC/PNEC) were then calculated for 8 pharmaceutical substances. PEC/PNEC ratio exceeded 1.0 for β-lactams (cephalosporins and penicillins), fluoroquinolones, macrolides and aminoglycosides. The findings of this study concluded that the release of these compounds from wastewater treatment plants may potentially be of an important environmental concern based on today's use of antibiotics in Turkey.

1. Introduction

Antibiotic consumption has received a lot of attention in the media in the last several years due to the increasing numbers of diseases and infections becoming resistant to traditional treatments for both humans and animals. However, after administration to humans and animals in hospitals or by prescription, a high percentage of antibiotics (up to 90%) are excreted unchanged via urine and/or feces into domestic sewage, and are discharged to wastewater treatment plants (WWTPs) without a second thought [1–5]. The resultant higher concentrations of antibiotics and other pharmaceutical products in urban waste streams have substantial impacts on the environment and human health, which are very difficult to control using conventional practices. More importantly, in WWTPs, these pharmaceutical compounds are only partially removed and there is a potential for residues of antibiotics to be released through the WWTP effluents into the aquatic environment [3]. Therefore, urgent risk assessment and proper risk management are needed to ensure a robust and resilient control of antibiotic emissions for both developed and developing countries.

The main sources of antibiotics are homes, hospitals, nursing homes (medical treatment, disposal of unused medication), poultry and livestock feeding operations (growth promotion), and pharmaceutical manufacturers [6]. Kümmerer [7] has reported that if antibiotics used for veterinary purposes or as growth promoters in animal husbandry, they seep through the soil from manure and enter ground water. In addition, antibiotics may reach surface water and ground water, and potentially drinking water if they are not degraded or removed during sewage treatment, in soil or in other environmental compartments [7]. Although some antibiotics such as penicillins and ampicillin can be easily biodegraded in the aquatic environment, however, many antibiotics such as tetracyclines, erythromycin, metronidazole and sulphamethoxazole may not be readily destroyed by conventional wastewater treatment tecniques [6,8]. In addition, various antibiotics such as sulphonamides bind strongly to sludge, soil, sediments and manure, and may show a recalcitrant behaviour to a possible further biodegradation. Furthermore, many antibiotics are designed to be persistent and lipophilic, so that they can retain their chemical structure long enough to do their therapeutic work [4]. Because of aquatic contamination by these persistent chemicals, bacteria

* Corresponding author. Tel.: +90 212 3833033; fax: +90 212 2619041.
E-mail address: yetilmez@yildiz.edu.tr (K. Yetilmezsoy).

0304-3894/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jhazmat.2008.11.012

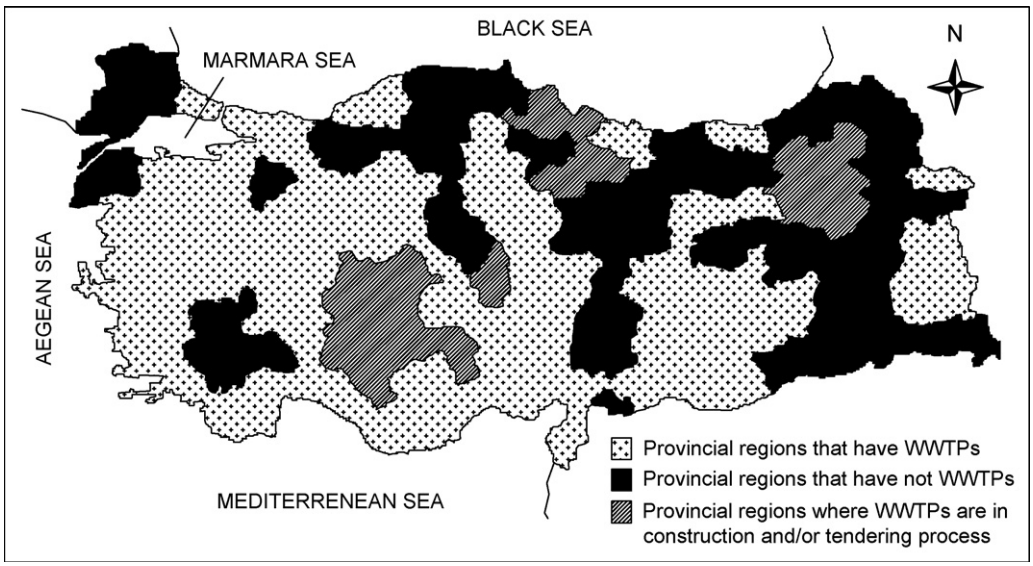

Fig. 1. Distribution of provincial regions according to the availability of WWTPs in Turkey.

and other microorganisms in the aquatic environment can become more resistant to these chemicals. This results in the development of more antibiotic resistant and virulent pathogens in the environment [4]. Therefore, Mowery and Loganathan [4] have indicated that the persistence of pharmaceutical chemicals in the environment has become a global problem. Similarly, Kümmerer [7] has reported that biodegradation of persistent antibiotics in seweage treatment plants and other conventional environmental compartments may not be an option for the reliable removal of these recalcitrant pharmaceutical substances and this needs more detailed investigation.

In recent years, several papers have addressed the determination of antibiotics in surface water and urban wastewater using different analyzing methods and techniques such as liquid chromatography (LC) combined with electrospray tandem mass spectrometry [3], on-line solid-phase extraction (SPE) with LC mass spectrometry (MS) [9,10], SPE and high-performance chromatography (HPLC) [11], off-line SPE and HPLC coupled with a diode-array ultraviolet detector and a fluorescence detector [8], LC–electrospray tandem MS combined with SPE and silica cartridge cleanup [12], capillary zone electrophoresis with UV-diode-array detection [13], and solid phase microextraction [14]. Although such monitoring studies in surface waters or wastewaters have been published more and more in recent years, however, there are a limited number of experimental studies investigating the efficiency of distinct wastewater treatment processes for the elimination of antibiotics [1,15–20]. Furthermore, detailed fate and behavior studies associated with antibiotics entering the environment after being used in human and veterinary medicine have only been reported a few in the literature, as previously reported by Göbel et al. [21]. Even though these compounds have been evaluated as safe for human and veterinary use, this is not adequate to ensure the protection of many ecosystems that may be exposed to these substances [22]. Therefore, a comprehensive analysis specifically devoted to a study of the appraisal of potential environmental risks associated with antibiotic consumption has become an important field of investigation to develop a continuous control strategy and to achieve an optimum management of these compounds.

Considering the above-mentioned facts, the specific objectives of this study were: (1) to assess the total amount of antibiotics used in Turkey for the year 2007; (2) to evaluate adult and pediatric consumptions and corresponding emission rates for each form of medication; (3) to examine existing capacities of wastewater treatment plants currently in Turkey for the possible removal of antibiotics from urban waste streams; and (4) to appraise the potential environmental risks associated with antibiotic consumption in Turkey.

2. Materials and methods

2.1. Analysis of antibiotic consumption in Turkey

In this study, antibiotics were defined for systemic use or group J01 of the WHO Anatomical Therapeutic Chemical (ATC) classification system. Sales data of antibiotics for the year 2007 were collected from Pharmaceutical Manufacturers Association of Turkey (IEIS) and IMS Health Inc. Antibiotic data were then imported into spreadsheets of Microsoft Excel® 2000 used as ODBC (open database connectivity) data sources for further calculations.

To calculate the total emission rate of antibiotics, dosages (g) and/or number of tablets in boxes were multiplied by the corresponding absolute number of antibiotics including injectable or oral drugs (capsules/tablets and suspensions) sold in Turkey in year 2007. Total emissions and total consumptions for each ATC group were then classified separately into 17 different J01 categories: D1, D2, F0, K0, E0, M0, A0, B0, P1, P2, P3, G1, G2, C1, C2, X1, and X9. Moreover, the total use of injectable and oral drugs were also determined for each J01 category to evaluate the form of antibiotic medication prescribed in Turkey in year 2007. Finally, adult and pediatric consumptions and corresponding emission rates were evaluated for each form of medication (capsules/tablets, injectables and suspensions) based on the present sales data of year 2007.

2.2. Existing capacities of WWTPs in Turkey

According to the Turkish Ministry of Environment and Forestry [23], about 88% of province municipalities in the Aegean Region and about 75% of province municipalities in the Mediterranean Region have WWTPs currently in operation. These are followed by the Marmara and Central Anatolia Regions with 55 and 54%, respectively. However, presently, only about 39% of province municipalities in the Black Sea Region and about 36% of province municipalities in the East Anatolia Region have WWTPs currently in operation. The distribution of provincial regions according to the availability of WWTPs is depicted in Fig. 1. As shown in Fig. 1, additional investments and specific developments appear to be needed for the construction

Table 1
Removal of some of the most commonly used groups of antibiotics in conventional and advanced treatment processes [27].

Type of antibiotic	PR (%)[a] (conventional treatment)				PR (%)[a] (advanced treatment)		
	PST	BR	FST	Overall	MF	RO	Overall
β-lactams (cephalosporins, penicillins)	14	Up to 100	−200[b]	99	100	–[c]	Up to 100
Quinolones (norfloxacin, ciprofloxacin)	−30[b]	88	−10[b]	83	55	75	91
Lincosamides	8	21	−21[b]	11	56	0	91
Macrolides	–[c]	–[c]	–[c]	–[c]	52	85	91
Tetracyclines	–[c]	–[c]	–[c]	–[c]	Up to 100	–[c]	Up to 100
Polyether ionophores	50	88	−234[b]	81	78	100	Up to 100
Sulphonamides	−35[b]	62	−46[b]	25	−18	100	Up to 100
Other (trimethoprim)	−9[b]	92	−67[b]	85	44	94	94
Overall	−6[b]	92	−23	89	43	89	94

PST, primary settling tank; BR, bioreactor; FST, final settling tank; MF, microfiltration; RO, reverse osmosis.
[a] Proportion removed of previous step.
[b] Negative values result from an observed increase of loads from inflow to outflow of the respective treatment step.
[c] No results available because of analytical interferences.

of new WWTPs, particularly in northern, eastern and northeastern parts of the country.

Presently, the total amount of wastewater generated and discharged into the sewerage systems is about 2.92 billion m^3/year in Turkey. Although 65.1% of the total discharged wastewater (1.90 billion m^3/year) is subjected to treatment in WWTPs (56.3% of biological treatment, 31.5% of physical treatment and 12.2% of advanced treatment), however, remaining (1.02 billion m^3/year, 34.9%) is directly discharged into receiving water bodies without any treatment [23].

2.3. Treatability of antibiotics by different treatment processes

Most of antibiotics are metabolized only incompletely or eliminated by patients after administration, and a high percentage of antibiotics (between 30 and 90%) are excreted unchanged via urine and/or feces into the municipal sewage and enter sewage treatment plants [24,25]. Hernando et al. [26] have reported that drugs, such as carbamazepine, atenolol, metoprolol, trimethoprim or diclofenac are partially removed (<10% for most of them and 10–39% for diclofenac) in conventional sewage treatment plants. Therefore, recently, different treatment technologies have been introduced for the removal of antibiotics from wastewaters. For instance, Watkinson et al. [27] assessed the removal of 26 human and veterinay antibiotics in a conventional (activated sludge) and advanced (microfiltration/reverse osmosis) WWTP system. They reported that both treatment plants (activated sludge and MF/RO) significantly reduced antibiotic concentrations with an average removal rate from the liquid phase of 92%. Table 1 summarizes several performance data [27] of different treatment configurations on the removal of some of the most commonly used groups of antibiotics in the world.

Kosutic et al. [16] have recently conducted experimental studies on the removal of antibiotics by reverse osmosis/nanofiltration (RO/NF) from a model wastewater of a manufacturing plant producing pharmaceuticals for veterinary use. The authors concluded that the rejection of the examined antibiotics (levamisole, sulfaguanidine, sulfhamethazine, trimethoprim, praziquantel, enrofloxacin and oxytetracycline (OTC)) by the selected RO and the tight NF membranes was acceptably high, exceeding in most cases 98.5%. Another membrane system including RO and ultrafiltration (UF) was proposed and evaluated by Li et al. [19] for the treatment of an OTC waste liquor. In the study, with additional treatment of ultrafiltration by 3K membranes, OTC crystallization and recovery from the RO retentate were significantly improved with a recovery ratio of more than 60% and a purity of higher than 80%. The authors concluded that the RO/UF membrane process could be developed as an effective alternative for the treatment of antibiotic wastewater as well as the recovery of antibiotics from the waste liquor.

In addition to above-mentioned membrane and advanced oxidation processes, the performance of a biological treatment system (up-flow anaerobic stage reactor, UASR) treating pharmaceutical wastewater containing macrolide antibiotics (tylosin and avilamycin) has also been recently investigated by Chelliapan et al. [18]. In the study, at a total hydraulic retention time (HRT) of 4.0 days and organic loading rate of 1.86 kg COD/(m^3 day), COD reduction was found to be 70–75%. Furthermore, an average of 95% tylosin reduction was achieved in the UASR, indicating that this antibiotic could be degraded efficiently in the anaerobic reactor system. The authors have concluded that the UASR can be used as an attractive process for the pretreatment of pharmaceutical wastewaters that contain tylosin and avilamycin macrolide antibiotics.

2.4. Estimation of risk quotients (PEC/PNEC) according to the EU draft guidance

The risk to aquatic organisms is calculated as the ratio between the predicted environmental concentration (PEC), and the predicted no effect concentration (PNEC). The PEC in water can be calculated according to the EU draft guidance (CEC/III/5504/94, draft 6, version 4) from the following equation [22,28]:

$$\mathrm{PEC(g/L)} = \frac{A \times (1 - R/100)}{365 \times P \times V \times D} \quad (1)$$

where A is the predicted amount used per year in the relevant geographic area (kg), R is the removal rate (due to loss by adsorption to sludge particles by volatilisation, hydrolysis, biodegradation or other naturally occurring processes), P is the number of inhabitants of the geographic area considered, V is the volume of wastewater per capita and day (m^3) (normally between 0.15 and 0.3 m^3 in the EU), and D is the dilution factor of wastewater by surface water flow [22,28].

Although most regulatory agencies have recommended the use of a 10-fold dilution factor (D) when estimating the PEC, however, there is an uncertainty with using D, as effluent discharges do not always benefit from dilution [29]. For instance, Heberer et al. [30] have reported that during the summer months in some places of the Platt River in the US, the flow consists almost entirely of effluent from WWTPs. Thus, environmental exposure in such areas would not dilute 10-fold and could present a greater risk to aquatic environment [29]. Considering potential environmental risks, Thompson [22] has suggested that the estimate should be conducted for the EU country with the maximum A/P ratio, and assuming the worst case conditions such as no losses ($R = 0$) and no dilution ($D = 1$).

Thompson [22] has reported that if the PEC is less than 0.01 μg/L, no further action is required. However, if the PEC is greater than this value, then the ratio PEC/PNEC should be calculated. For aquatic

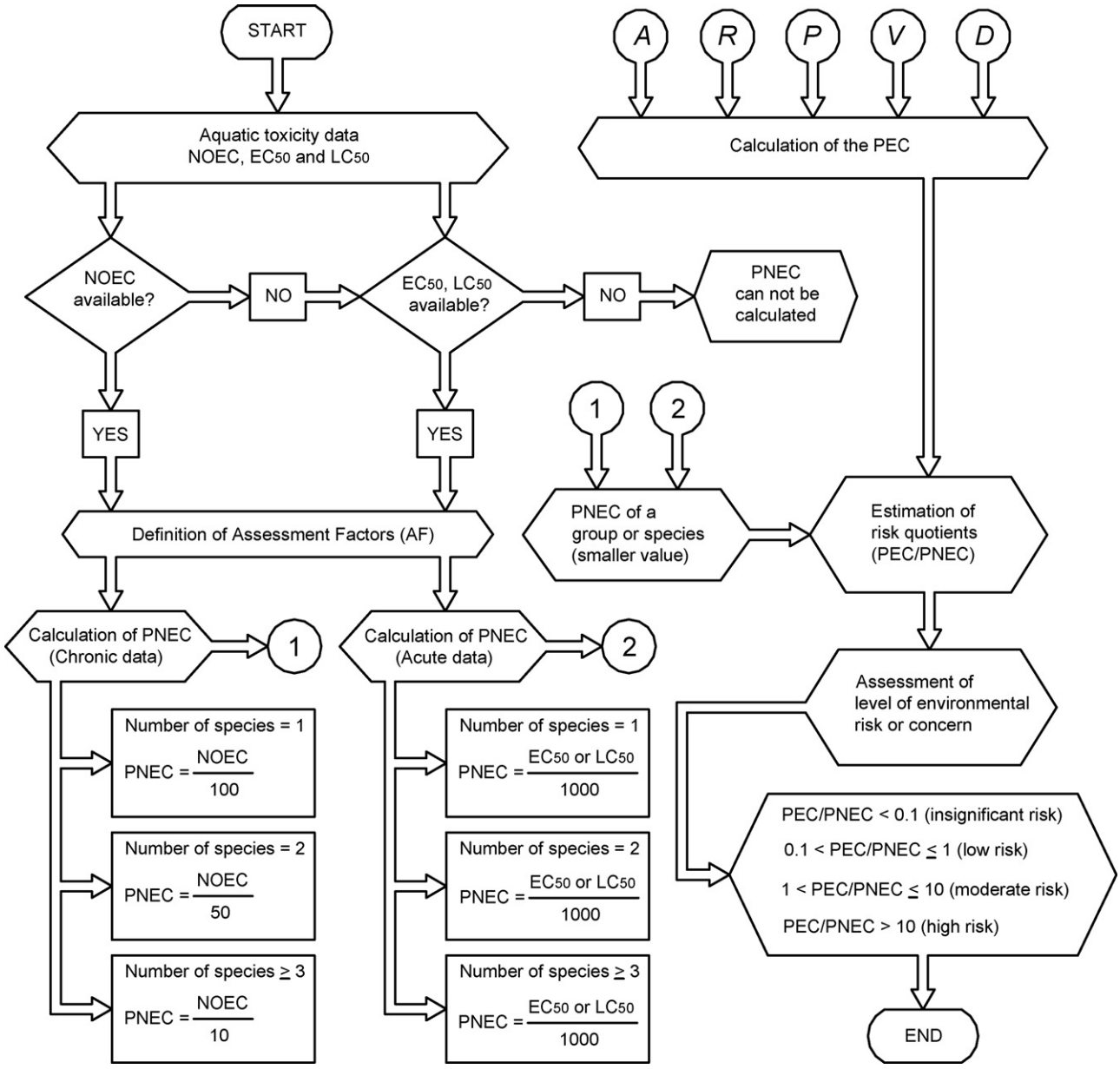

Fig. 2. A detailed schematic of the methodology used for evaluating the level of environmental risk or concern associated with antibiotic consumption.

organisms, it is necessary to be able to predict the concentration at which no effect will be observed in a particular organism [22]. For this purpose, the PNEC (μg/L or g/L) is derived by dividing the NOEC and EC_{50} (or LC_{50}) by a suitable assessment factor (AF) for the availability of chronic and acute toxicity data. The assessment factors used in the calculation of the PNEC is given in Table 2 [31]. In this study, available acute and chronic toxicity data were obtained from the open peer-reviewed literature to derive PNEC. Thereafter, PEC/PNEC ratios were estimated, and the level of environmental risk or concern was evaluated for each type of antibiotic depending on the estimated risk quotients (PEC/PNEC). On the basis of the above-mentioned calculation steps, a detailed schematic of the methodology used in this study for evaluating the level of environmental risk or concern associated with antibiotic consumption is shown in Fig. 2.

Table 2
Assessment factors used in the calculation of the PNEC [31].

Endpoint	Type of test	Number of species	AF [d]
NOEC [a]	Chronic	≥3	10
NOEC [a]	Chronic	2	50
NOEC [a]	Chronic	1	100
EC_{50} [b] or LC_{50} [c]	Acute	≥3	1000
EC_{50} [b] or LC_{50} [c]	Acute	2	1000
EC_{50} [b] or LC_{50} [c]	Acute	1	1000

[a] No observed effect concentration (μg/L or mg/L).
[b] Concentration where an effect is observed in 50% of the test organisms (μg/L or mg/L).
[c] Concentration resulting in 50% of test organism lethality (μg/L or mg/L).
[d] Assessment factor.

3. Results and discussion

3.1. Antibiotic emissions

The total emission rate of antibiotics (ATC group J01 for systemic use) consumed in Turkey in year 2007 was determined to be about 774.3 tons/year. The distribution of total antibiotic emissions

depending on the form of medication is shown in Fig. 3(a). As seen in Fig. 3(a), capsules and tablets were found as the most emitted form of medication in year 2007, with a total emission rate of about 585.5 tons/year (76%). The number of total antibiotics consumed in the form of both injectable or oral medication was determined to be about 200 millions in Turkey in year 2007. The distribution of total antibiotic consumptions depending on the form of medication is depicted in Fig. 3(b). As seen in Fig. 3(b), capsules/tablets (47%) and injectable (33%) antibiotics were more prescribed than suspension antibiotics (20%) in the past year. To evaluate the form of antibiotic medication prescribed in Turkey in year 2007, total emissions and total consumptions were determined for each individual antibiotic group. Results are summarized in Table 3.

On the basis of the present sales data of antibiotics, capsules/tablets was consisted of 12 J01 categories: D2, D1, F0, G1, E0, M0, A0, B0, P3, C1, C2, and X9 (Table 3). As seen in Table 3, penicillins (J01C1) had the highest emission rate or percentage (330.5 tons/year, 56.5%) among other J01 categories of capsules and tablets. This was followed by fluoroquilones (J01G1), cephalosporins (J01D1) and macrolides (J01F0) with emission rates of 92.1 tons/year (15.7%), 85.9 tons/year (14.7%) and 44.1 tons/year (7.5%), respectively. Amoklavin was found as the most emitted drug (about 49.6 tons/year, 15%) in the category of capsules and tablets. This drug is generally introduced among treatment options for common upper airways (such as otitis media and sinusitis) and lower airways (such as acute and chronic bronchitis) infections, as well as for skin and soft tissue and for urogenital infections [32]. Therefore, obtained results can be attributed to the fact that people in Turkey have mainly complained about respiratory symptoms in year 2007. Moreover, a detailed analysis of the most emitted category of

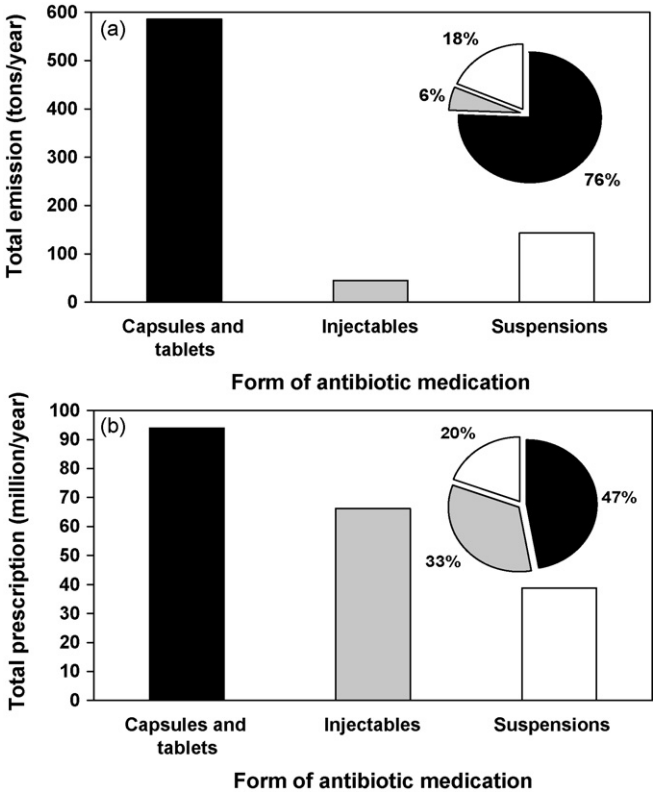

Fig. 3. Distribution of total antibiotic emissions and prescriptions depending on the form of medication.

Table 3
Detailed analysis of all J01 categories according to the form of medications prescribed in Turkey in year 2007.

Form of medication and J01 category	Name of the most emitted drug	Total emissions (tons/year)		Total prescriptions (millions/year)	
		Overall	The most emitted	Overall	The most emitted
Capsules and tablets					
J01D2 cephalosporins	Unacefin	4.10	1.30	5.40	1.65
J01D1 cephalosporins	Sef	85.9	14.9	17.0	1.05
J01F0 Macrolides	Klacid	44.1	5.8	11.5	1.00
J01G1 fluoroquinolones	Cipro	92.1	25.7	16.1	3.35
J01E0 trimethoprim	Metoprim	12.9	6.2	1.36	0.36
J01M0 rifampicin/rifamycin	Rifcap	1.3	1.1	0.27	0.22
J01A0 tetracyclines	Tetra	6.9	2.8	2.8	0.42
J01B0 choloramphenicols	Urfamycin	2.1	1.9	0.27	0.23
J01P3 carbacephems	Lorabid	0.97	0.97	0.29	0.29
J01C1 penicillins	Amoklavin	330.5	49.6	34.85	5.07
J01C2 penicillins	Alfasid	2.7	1.02	3.74	1.59
J01X9 all others	Stafine	1.9	1.86	0.25	0.24
Injectable antibiotics					
J01D2 cephalosporins	Iespor	32.6	13.1	40.05	16.22
J01F0 macrolides	Lincocin	4.8	1.75	6.86	2.91
J01K0 aminoglycosides	Genta	1.73	0.73	8.38	6.57
J01E0 trimethoprim	Bactrim	–[a]	–[a]	–[a]	–[a]
J01M0 rifampicin/rifamycin	Rif	0.6	0.42	3.04	2.12
J01B0 choloramphenicols	Tiofen	–[a]	–[a]	–[a]	–[a]
J01P2 penems and carbapenems	Meronen	0.38	0.21	0.53	0.21
J01G2 fluoroquinolones	Tavanic	0.095	0.037	0.28	0.074
J01X1 glycopeptide	Targocid	0.13	0.059	0.27	0.16
J01P1 monobactams	Azactam	–[a]	–[a]	–[a]	–[a]
J01C2 penicillins	Ampisid	5.38	1.58	6.7	2.40
Suspension antibiotics					
J01D1 cephalosporins	Kefsid	22.02	4.33	9.28	1.11
J01F0 macrolides	Deklarit	12.97	3.25	5.61	1.16
J01E0 trimethoprim	Metoprim	3.5	3.25	2.04	0.22
J01M0 rifampicin/rifamycin	Rifcap	0.03	0.005	0.02	0.0034
J01B0 choloramphenicols	Lorabid	1.31	0.79	0.51	0.41
J01C1 penicillins	Augmentin	103.3	22.6	21.31	3.76

[a] No results available.

Table 4
Detailed analysis of the most emitted category of capsules and tablets (J01C1 penicillins) used in Turkey in year 2007.

Name of drug	Total emissions (tons/year)	Total prescriptions (millions/year)
Amoklavin	49.6	5.07
Augmentin	43.9	4.45
Klamoks	30.1	3.02
Croxilex	17.8	2.01
Combicid	5.6	0.97
Largopen	46.2	3.32
Bioment	17.6	1.78
Sulcid	6.2	1.12
Alfasid	6.2	1.04
Amoksilav	15.6	1.70
Devasid	5.7	0.98
Duocid	3.5	0.93
Klavunat	9.9	1.04
Sultamat	4.7	0.85
Alfoxil	20.5	1.68
Nobecid	3.2	0.51
Ampisid	2.6	0.47
Alfasilin	9.8	0.92
Duobaktam	1.4	0.25
Ampisina	6.9	0.53
Klavupen	2.6	0.26
Atoksilin	5.8	0.44
Remoxil	5.2	0.38
Sultibac	0.6	0.11
Amoksina	3.9	0.31
Bakamsilin	2.3	0.31
Penbak	1.8	0.22
Duobak	0.3	0.08
Silina	0.5	0.04
Dentamax	0.6	0.04
Sultasid	0.03	0.005
Xibac	0.03	0.004
Total consumption	330.5	34.85

capsules/tablets (J01C1 penicillins) was also carried out to evaluate the type of oral drugs used in Turkey in year 2007 (Table 4). As seen in Table 4, Amoklavin emission was followed by Largopen, Augmentin and Klamoks with emission rates of 46.2 tons/year (14%), 43.9 tons/year (13.3%) and 30.1 tons/year (9.1%), respectively. Similar to indications of Amoklavin, these drugs are also used to treat upper and lower airways infections such as otitis media, sinusitis and bronchitis [32]. Therefore, these results may support that respiratory symptoms are still among the most common complaints for which patients in Turkey seek medical care.

Based on the present sales data of year 2007, the total emission rate of injectable antibiotics was determined for 11 different J01 categories: D2, F0, K0, E0, M0, B0, P1, P2, G2, X1, and C1 (Table 4). Results showed that the total emission rate of injectable antibiotics was about 45.1 tons/year. As seen in Table 3, cephalosporins (J01D2) had the highest emission rate or percentage (32.6 tons/year, 71.3%) among other injectable antibiotics consumed in year 2007. This was followed by penicillins (J01C2) and macrolides (J01F0) with emission rates of 5.38 tons/year (11.8%) and 4.8 tons/year (10.5%), respectively. Iespor was found as the most emitted drug (about 13.1 tons/year, 40.2%) in the category of injectable antibiotics. This drug is mainly prescribed for the treatment of pulmonary and chronic respiratory symptoms such as acute and subacute bronchitis, bronchiectasis and bronchopneumonia [32]. This result also proves that pulmonary and respiratory diseases are highly prevalent among people living in Turkey in year 2007. Furthermore, a detailed analysis of the most emitted category of injectable antibiotics (J01D2 cephalosporins) was also conducted to evaluate the type of injectable drugs used in Turkey in year 2007, as similarly done for capsules/tablets (Table 5). As listed in Table 5, Iespor emission was followed by Cefozin and Cezol with emission rates of

Table 5
Detailed analysis of the most emitted category of injectable antibiotics (J01D2 cephalosporins) used in Turkey in year 2007.

Name of drug	Total emissions (tons/year)	Total prescriptions (millions/year)
Iespor	13.1	16.22
Cefozin	4.1	4.18
Sefazol	2.8	3.71
Cezol	3.3	3.99
Multisef	2.2	3.45
Cefamezin	2.5	2.66
Novosef	1.3	1.61
Aksef	0.7	0.91
Desefin	0.7	0.88
Cefaday	0.5	0.64
Baktisef	0.3	0.40
Cefridem	0.3	0.34
Sulperazon	0.3	0.27
Iesef	0.1	0.19
Cefizox	0.1	0.13
Sefotak	0.1	0.16
Fortum	0.1	0.10
Maxipime	0.06	0.07
Sefagen	0.04	0.07
Maksiporin	0.05	0.05
Equiceft	0.01	0.012
Iesetum	0.01	0.012
Total consumption	32.6	39.93

4.1 tons/year (12.6%) and 3.3 tons/year (10.1%), respectively. The use of these drugs also revealed that pulmonary and respiratory symptoms were among the most important health issues in Turkey in year 2007.

To determine the total emission rate of suspension antibiotics, six different J01 categories (D1, F0, E0, M0, B0, C1) were analyzed (Table 3). Results indicated that the total emission rate of suspension antibiotics was determined to be about 143.1 tons/year. As found for capsules and tablets, penicillins (J01C1) had also the highest emission rate or percentage (103.3 tons/year, 72.2%) among other suspension antibiotics consumed in Turkey in year 2007. This category (J01C1) was followed by cephalosporins (J01D1) and macrolides (J01F0) with emission rates of about 22 tons/year (21.3%) and 13 tons/year (12.6%), respectively. Augmentin was found as the most emitted drug (about 22.6 tons/year, 21.9%) in the category of suspension antibiotics. As previously done for other forms of medication (capsules/tablets and injectables), a detailed analysis of the most emitted category of suspension antibiotics (J01C1 penicillins) was also conducted to evaluate the type of suspension drugs used in Turkey in year 2007 (Table 6). Table 6 shows that Augmentin emission was followed by Klamoks and Amoklavin with emission rates of 15.3 tons/year (14.8%), and 14.3 tons/year (13.8%), respectively. As previously reported, overall results concluded that pulmonary and respiratory infections were found to be an important cause of antibiotic use in patients living in Turkey in the past year. These findings may also indicate that there are still various possible problems in the country, such as nourishment problems, cigarette addiction and also air pollution-based problems that can lower of the body's resistance against invading pathogens.

Finally, adult and pediatric consumptions and corresponding emission rates were analyzed for each form of medication based on the present sales data of the past year. The distribution of percentages are illustrated in Fig. 4. Results indicated that capsules/tablets and injectable antibiotics were mostly emitted and consumed by adult patients. As expected, suspension antibiotics were mainly consumed by pediatric patients (29.2 millions/year, 75%) compared to adult patients (9.6 millions/year, 25%). However, it can be noted that since pediatric dosages are quite lower than those of adults, emissions of suspension antibiotics were

Table 6
Detailed analysis of the most emitted category of suspension antibiotics (J01C1 penicillins) used in Turkey in year 2007.

Name of drug	Total emissions (tons/year)	Total prescriptions (millions/year)
Augmentin	22.6	3.76
Amoklavin	14.3	2.67
Klamoks	15.3	2.98
Croxilex	8.5	1.68
Combicid	2.8	0.085
Largopen	7.9	1.45
Biomент	6.2	1.20
Sulcid	1.9	0.65
Alfasid	1.7	0.59
Amoksilav	5.1	1.01
Devasid	1.4	0.43
Duocid	3.1	0.95
Klavunat	3.8	0.73
Sultamat	0.8	0.27
Alfoxil	4.4	1.11
Nobecid	0.6	0.19
Ampisid	0.4	0.13
Alfasilin	0.6	0.16
Duobaktam	0.2	0.06
Ampisina	0.4	0.10
Klavupen	0.6	0.012
Atoksilin	0.1	0.033
Remoxil	0.1	0.020
Sultibac	0.1	0.042
Amoksina	0.2	0.050
Duobak	0.2	0.074
Total consumption	103.3	21.30

found to be closer to each other (64.3 and 78.9 tons/year for adult and pediatric patients, respectively), even though there was a noticeable difference between groups in terms of consumed units.

Based on the present sales data of year 2007, total antibiotic emission rates including all forms of medications were determined to be about 664.2 tons/year (86%) and 110.1 tons/year (14%) for adult and pediatric patients, respectively. Similarly, total antibiotic prescriptions were 140.4 millions/year (70.6%) and 58.5 millions/year (29.4%) for adult and pediatric patients, respectively. According to Turkish Statistical Institute's (TURKSTAT) data [33] for year 2007, about 26.4% of total population (about 71 millions people) consists of pediatric age group and remaining (73.6%) are adults. Therefore, average antibiotic emissions per age group were determined to be about 5.8 and 12.8 g/(year person) for pediatrics and adults, respectively. Considering the total population of Turkey in 2007, the average antibiotic emission of the country was found as 10.9 g/(year person).

3.2. Estimation of antibiotic emissions entering into receiving water bodies and PEC values

For the risk assessment performed in this study, we assumed that the entire amount of anbiotics sold in Turkey in year 2007 (774.3 tons/year) was consumed, and that amount was evenly distributed over the year and throughout the population. According to the Turkish Ministry of Environment and Forestry [23], the total amount of wastewater presently generated and discharged into the sewerage systems in Turkey in year 2007 was considered to be 2.92 billion m^3/year. Therefore, the volume of wastewater per capita and day was calculated to be about 113 L ($V = 0.113\ m^3$/day, $P = 71$ millions).

About 10% of the total antibiotic emission (about 77.5 tons/year) was assumed to be metabolized by patients, and remaining (696 tons/year) was considered to be entirely excreted through urine and/or feces into domestic sewage. Although the WWTP removal rate was set to zero in some studies dealing with this topic [28], however, in the present study, treatment performances of biological and advanced WWTPs were included into our scenario to assess existing capacities of WWTPs in Turkey for the possible removal of antibiotics, but no further losses by adsorption, volatilisation or hydrolysis were assumed for the effluent from WWTPs. Based on a representative experimental data [27] given in Table 1, antibiotic removals were selected as 90 and 95% in determination of present final emissions discharged from biological and advanced WWTPs, respectively.

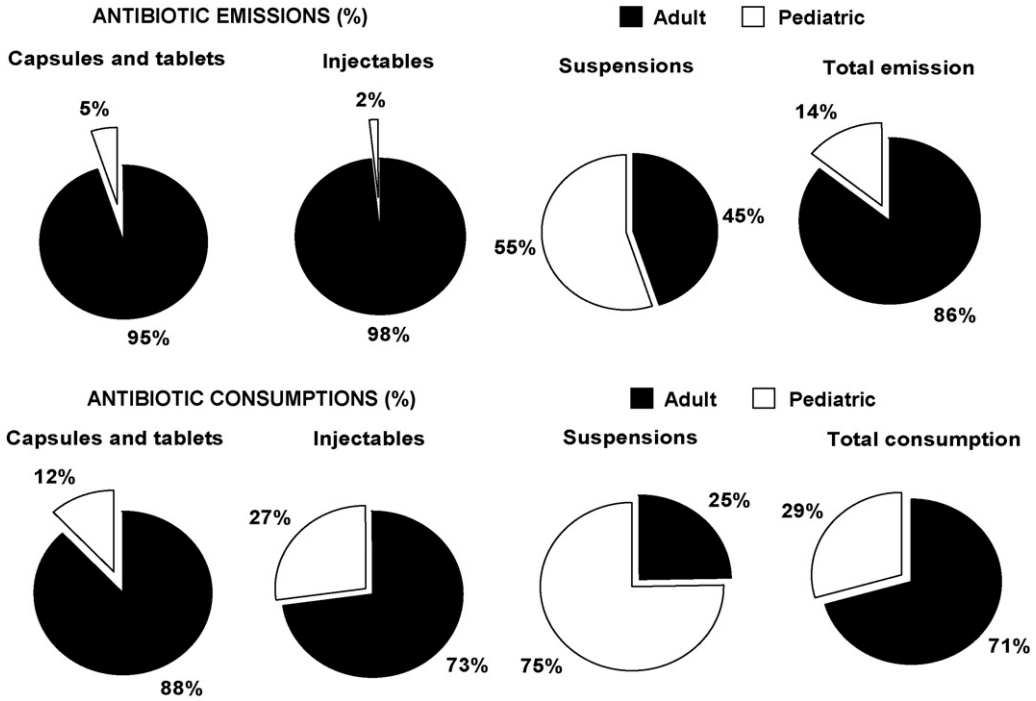

Fig. 4. Distribution of percentages depending on adult and pediatric consumptions and corresponding emission rates.

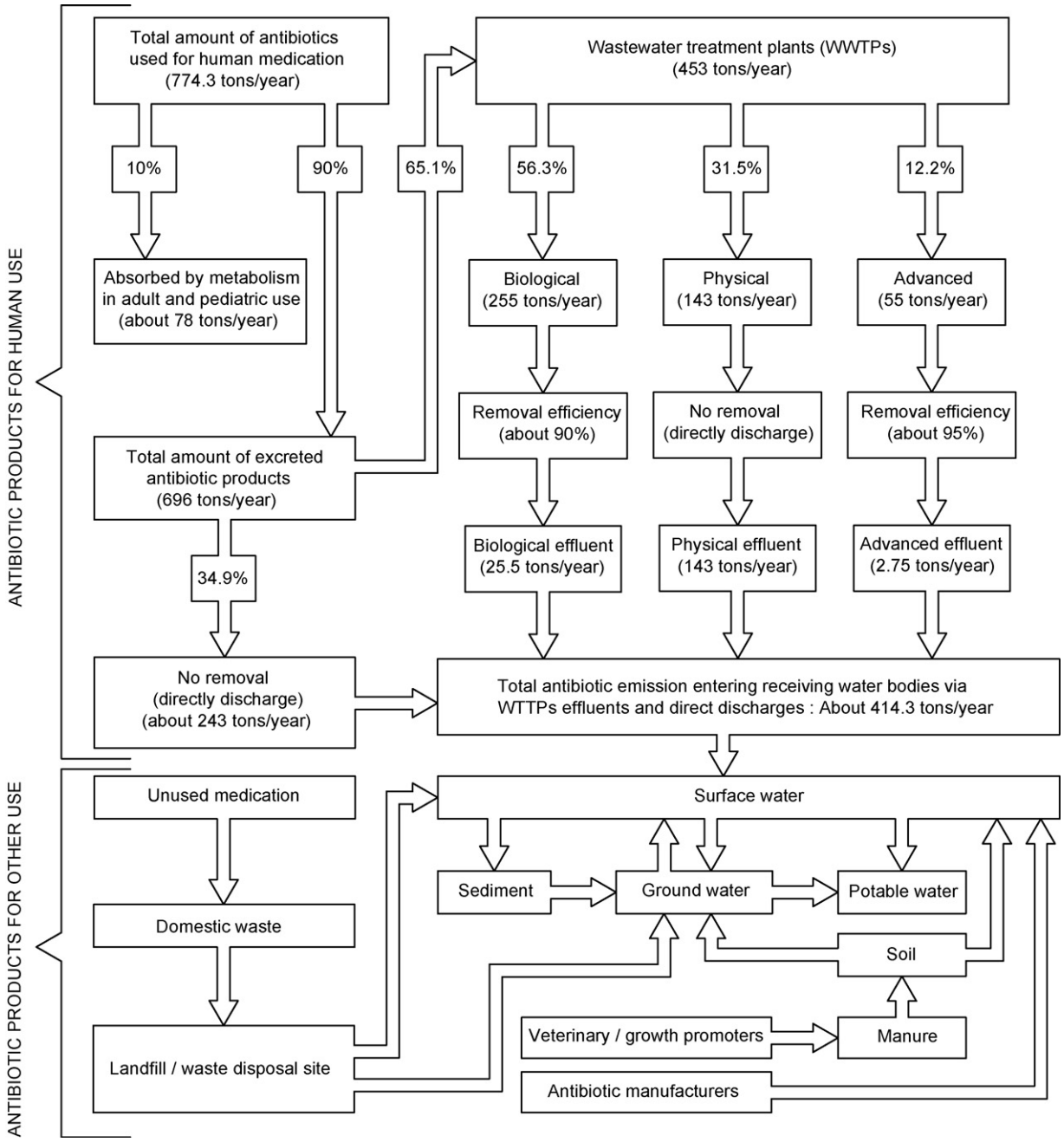

Fig. 5. Possible sources and primary pathways for the occurrence of antibiotic residues in the aquatic environment.

The possible sources and primary pathways for the occurrence of antibiotic residues in the aquatic environment are depicted in Fig. 5. Results showed that a significant portion (53.5%, 414.3 tons/year) of the total amount of antibiotics used for human medication entered into receiving water bodies via WWTPs effluents and improper discharges (Fig. 5). Although an environmental risk assessment was performed for only human medication in this study, as seen in Fig. 5, it can also be clearly noted that this amount will be much higher when unused medications, veterinary purposes and pharmaceutical manufacturers are taken into account.

Considering the present Turkish antibiotic data, existing capacities of WWTPs in Turkey and also the above-mentioned assumptions, antibiotic emissions released from WWTPs into receiving water bodies were estimated for each compound. Thereafter, the PEC values were derived separately for each type of antibiotic according to Eq. (1). Results are summarized in Table 7. As seen in Table 7, since the PEC of each compound was determined to be greater than 0.01 μg/L, in the next step, PEC/PNEC ratios were then calculated as a further action in this study.

3.3. Estimation of risk quotients (PEC/PNEC)

Available acute and chronic toxicity data obtained from the open peer-reviewed literature to derive the PNEC values are summarized in Table 8. To assess the worst-case scenario, risk quotients (PEC/PNEC) were estimated for undiluted ($D = 1$) conditions, as previously suggested by others [22,29]. Then, the level of risk or concern derived for a specific type of antibiotic. Estimated risk quotients and corresponding levels of potential risks to the environment are summarized in Table 9.

As seen in Table 9, our estimations showed that β-lactams (cephalosporins and penicillins), fluoroquinolones, macrolides and

Table 7
Estimated antibiotic emissions released from WWTPs into receiving water bodies and corresponding PEC values.

Compound	ATC code	Emission (tons/year)	Percentage in the total discharged load (%)	PEC (μg/L), D = 1 (no dilution), V = 0.113 m^3/(day person), P = 71 millions (inhabitants)
Cephalosporins	J01D1(D2)	77.39	18.68	26.50
Macrolides	J01F0	33.10	7.99	11.34
Aminoglycosides	J01K0	0.91	0.22	0.31
Trimethoprims	J01E0	8.78	2.12	3.01
Fluoroquinolones	J01G2	49.34	11.91	16.90
Rifampicin/rifamycin	J01M0	1.04	0.25	0.36
Tetracyclines	J01A0	3.69	0.89	1.26
Choloramphenicols	J01B0	1.82	0.44	0.62
Penems and carbacephems	J01P2(P3)	0.70	0.17	0.24
Penicillins	J01C1(C2)	236.44	57.07	80.97
Glycopeptide	J01X1	0.08	0.02	0.03
All others	J01X9	1.04	0.24	0.36
Total values		414.33	100	141.90

aminoglycosides possessed both acute and chronic risks in the aquatic environment with risk quotients (PEC/PNEC) greater that the trigger level of 1.0. For fluoroquinolones, it was found that lomefloxacin was strongly toxic to the duckweed (*Lemna gibba*) (7 d NOEC wet weight <0.1–0.3 mg/L) chronically with a PEC/PNEC ratio of 16.89 (AF = 100). In another study on the environmental risk of antibiotics, Halling-Sørensen et al. [34] similarly reported that the risk quotient of fluoroquinolones (ciprofloxacin) was found in the level of high environmental risk (PEC/PNEC = 12.7 > 10) for the cyanobacterium (*Microcystis aeruginosa*) based on the acute exposure (EC_{50} = 5–60 μg/L).

For macrolides, the risk quotient of tylosin was estimated as 8.217 against the blue-green algae (*Selenastrum capricornutum*) for short-term data (72 h EC_{50} = 1.38 mg/L). Similar to tylosin, amoxycillin (penicillins) possessed a PEC/PNEC ratio of 8.097 against the duckweed (*L. gibba*) for long-term data (7 d NOEC wet weight < 1 mg/L). This was followed by ciprofloxacin (fluoroquinolones) with PEC/PNEC ratios of 5.630 and 5.687 against the duckweed (*L. gibba*) and the blue-green algae (*S. capricornutum*) for long-term data (7 d NOEC wet weight <0.3 mg/L) and short-term data (EC_{50} = 2.97 mg/L), respectively.

According to the present assumptions, results showed that cephalexin (cephalosporins), ofloxacin (fluoroquinolones) and streptomycin (aminoglycosides) possessed PEC/PNEC ratios of 2.65, 3.653 and 2.346 against the the duckweed (*L. gibba*), the green algae (*Pseudokrichneriella subcapitata*) and the blue-green algae (*S. capricornutum*), respectively. However, results indicated that trimethoprims, tetracyclines and choloramphenicols possessed PEC/PNEC values ranging from 0.001 to 0.574, which were below the trigger level of 1.0. Therefore, estimated risk quotients did not represent that there were subtantial risks associated with the release of these compounds (trimethoprims, tetracyclines and choloramphenicols). On the other hand, our estimations clearly indicated that the release of five human antibiotics (cephalosporins, penicillins, fluoroquinolones, macrolides and aminoglycosides) from WWTPs may potentially be of a significant environmental concern based on today's use of antibiotics in Turkey (Table 9). It can also be noted that although the risk quotients of lomefloxacin (PEC/PNEC = 8.445, AF = 50), tylosin (PEC/PNEC = 8.217, AF = 1000) and amoxycillin (PEC/PNEC = 8.097, AF = 100) were estimated in the level of moderate environmental risk (1 < PEC/PNEC ≤ 10), however, they were found to be potentially closer to the level of high

Table 8
Open peer-reviewed literature data considered in estimation of risk quotients (PEC/PNEC).

Type of antibiotic			Aquatic toxicity data			
Compound	Chemical name	Species	Common type	Type of test	Endpoint concentration (mg/L)	References
Cephalosporins	Cephalexin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Macrolides	Erythromycin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Macrolides	Tylosin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 0.3 mg/L	[35]
Macrolides	Erythromycin	*Daphnia magna*	Water flea	Acute	48 h EC_{50} = 30.5 mg/L	[36]
Macrolides	Tylosin	*S. capricornutum*	Blue-green algae	Acute	72 h EC_{50} = 1.38 mg/L	[37]
Fluoroquinolones	Ciprofloxacin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 0.3 mg/L	[35]
Fluoroquinolones	Lomefloxacin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 0.1 mg/L	[35]
Fluoroquinolones	Norfloxacin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Fluoroquinolones	Ciprofloxacin	*S. capricornutum*	Blue-green algae	Acute	EC_{50} = 2.97 mg/L	[37]
Fluoroquinolones	Lomefloxacin	*Scenedesmus vacuolatus*	Green algae	Acute	EC_{50} = 58 mg/L	[37]
Fluoroquinolones	Norfloxacin	*S. vacuolatus*	Green algae	Acute	EC_{50} = 69.6 mg/L	[38]
Fluoroquinolones	Ofloxacin	*P. subcapitata*	Green algae	Acute	96 h EC_{50} (growth) = 4.74 mg/L	[39]
Penicillins	Amoxycillin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Penicillins	Amoxycillin	*Oncorhynchus mykiss*	Rainbow trout–hepatocytes	Acute	24 h EC_{50} (cytotoxicity) > 182.7 mg/L	[40]
Penicillins	Amoxycillin	*Rhodomonas saline*	Marine microalgae	Acute	EC_{50} (growth) = 3108 mg/L	[36]
Trimethoprim	Trimethoprim	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Trimethoprim	Trimethoprim	*R. saline*	Marine microalgae	Acute	EC_{50} = 16 mg/L	[36]
Trimethoprim	Trimethoprim	*S. capricornutum*	Blue-green algae	Acute	EC_{50} = 110 mg/L	[37]
Aminoglycosides	Neomycin	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Aminoglycosides	Streptomycin	*M. aeruginosa*	Blue-green algae	Chronic	35 d NOEC (growth) < 0.28 mg/L	[41]
Aminoglycosides	Streptomycin	*S. capricornutum*	Blue-green algae	Acute	72 h EC_{50} = 0.133 mg/L	[42]
Tetracyclines	Tetracycline	*L. gibba*	Duckweed	Chronic	7 d NOEC Wet weight < 1 mg/L	[35]
Tetracyclines	Tetracycline	*S. capricornutum*	Blue-green algae	Acute	72 h EC_{50} = 2.2 mg/L	[37]
Choloramphenicols	Choloramphenicol	*D. magna*	Water flea	Acute	24 h EC_{50} = 543 mg/L	[43]

Table 9
Estimated risk quotients and corresponding levels of potential risks to the environment.

Compound	Chemical name	PEC (μg/L), $D = 1$ (no dilution)	Type of test	AF	PNEC (μg/L)	PEC/PNEC	LER
Cephalosporins	Cephalexin	26.50	Chronic	10	100	0.265	Low Moderate
				50	20	1.325	Moderate
				100	10	2.650	
Macrolides	Erythromycin	11.34	Chronic	10	100	0.113	Low
				50	20	0.567	Low
				100	10	1.134	Moderate
Macrolides	Tylosin	11.34	Chronic	10	30	0.378	Low Moderate
				50	6	1.890	Moderate
				100	3	3.780	
Macrolides	Erythromycin	11.34	Acute	1000	30.5	0.372	Low
Macrolides	Tylosin	11.34	Acute	1000	1.38	8.217	Moderate
Fluoroquinolones	Ciprofloxacin	16.90	Chronic	10	30	0.563	Low Moderate
				50	6	2.815	Moderate
				100	3	5.630	
Fluoroquinolones	Lomefloxacin	16.90	Chronic	10	10	1.689	Moderate
				50	2	8.445	Moderate
				100	1	16.89	High
Fluoroquinolones	Norfloxacin	16.90	Chronic	10	100	0.169	Low
				50	20	0.845	Low
				100	10	1.689	Moderate
Fluoroquinolones	Ciprofloxacin	16.90	Acute	1000	2.97	5.687	Moderate
Fluoroquinolones	Lomefloxacin	16.90	Acute	1000	58	0.291	Low
Fluoroquinolones	Norfloxacin	16.90	Acute	1000	69.6	0.243	Low
Fluoroquinolones	Ofloxacin	16.90	Acute	1000	4.74	3.563	Moderate
Penicillins	Amoxycillin	80.97	Chronic	10	100	0.810	Low Moderate
				50	20	4.049	Moderate
				100	10	8.097	
Penicillins	Amoxycillin	80.97	Acute	1000	182.7	0.443	Low
Penicillins	Amoxycillin	80.97	Acute	1000	3108	0.026	Insignificant
Trimethoprim	Trimethoprim	3.01	Chronic	10	100	0.030	Insignifcant
				50	20	0.151	Low
				100	10	0.301	Low
Trimethoprim	Trimethoprim	3.01	Acute	1000	16	0.188	Low
Trimethoprim	Trimethoprim	3.01	Acute	1000	110	0.027	Insignifcant
Aminoglycosides	Neomycin	0.31	Chronic	10	100	0.003	Insignifcant
				50	20	0.016	Insignifcant
				100	10	0.031	Insignifcant
Aminoglycosides	Streptomycin	0.31	Chronic	10	28	0.001	Insignifcant
				50	5.6	0.006	Insignifcant
				100	2.8	0.011	Insignifcant
Aminoglycosides	Streptomycin	0.31	Acute	1000	0.133	2.346	Moderate
Tetracyclines	Tetracycline	1.26	Chronic	10	100	0.013	Insignifcant
				50	20	0.063	Insignifcant
				100	10	0.126	Insignifcant
Tetracyclines	Tetracycline	1.26	Acute	1000	2.2	0.574	Low
Choloramphenicols	Choloramphenicol	0.62	Acute	1000	543	0.001	Insignifcant

PEC, predicted environmental concentration; AF, assessment factor; PNEC, predicted no effect concentration; LER, level of environmental risk.

environmental risk or concern. Therefore, these compounds may be remarkable pollutants to give an environmental risk in the water, thus it is worthwhile to pay attention to detect them in our surface waters.

Although 10% of drug metabolism and 90–95% of removal efficiencies were considered in the present scenario, however, our estimations indicated that β-lactams (cephalosporins and penicillins), fluoroquinolones, macrolides and aminoglycosides still possessed high risk quotients for both short-term and long-term exposure in the aquatic environment. Consequently, increasing concentrations of these pollutants in the surface waters may cause persistent exposure due to their continuous infusion into aquatic media via WWTP effluents and improper discharges. Although antibiotics can reach surface waters in trace concentrations ranging from nanograms to micrograms per liter, however, results of this study clearly concluded that potential risks of antibiotics cannot be ignored due to their adverse effects on non-target organisms in the ecosystem.

Based on the present environmental risk assessment, the present study also concluded that existing wastewater treatment facilities in Turkey are still not sufficiently and specifically designed to reduce antibiotic emissions, which has become one of the most critical environmental and health hazard problems in the country. Therefore, urgent treatment solutions and risk management strategies are needed to ensure a resilient control of antibiotic emissions in Turkey. For this purpose, all improper wastewater discharges should be first prohibited and strict liability should be imposed by legislation. In addition, existing capacities of WWTPs in Turkey should be modernized, and more importantly, physical treatment steps should be combined with effective biological and/or advanced treatment technologies such as up-flow anaerobic stage reactor, combined anaerobic–aerobic system, membrane processes (RO/NF, RO/UF), advanced oxidation processes (O_3 and O_3/H_2O_2), and electro-oxidation processes. Furthermore, automated online sampling systems should be integrated into existing WWTPs, as well as into various discharge points, to develop a sustainable water quality monitoring in terms of antibiotic emissions in Turkey.

4. Conclusions

The total emission rate of antibiotics consumed in Turkey in year 2007 was determined to be about 774.3 tons/year. Detailed analyses of the most emitted J01 categories clearly indicated that pulmonary and chronic respiratory symptoms were an important

cause of antibiotic use in patients living in Turkey in the past year. Average antibiotic emissions associated with adult and pediatric consumptions were calculated to be about 5.8 and 12.8 g/(year person) for pediatrics and adults, respectively. Considering the total population of Turkey in 2007, the average antibiotic emission of the country was determined to be about 10.9 g/(year person).

An important objective was to assess the potential risks associated with human antibiotic consumption in Turkey. Therefore, an environmental risk assessment of 8 human antibiotics was performed according to the EU draft guidance, and risk quotients were estimated based on available acute and chronic toxicity data gathered from the open peer-reviewed literature. Results of the risk assessment indicated that β-lactams (cephalosporins and penicillins), fluoroquinolones, macrolides and aminoglycosides mainly possessed moderate risk quotients ($1 < PEC/PNEC \leq 10$) for both short-term and long-term exposure in the aquatic environment. The findings of this study confirmed that the release of these compounds from WWTPs may potentially become an important environmental concern in Turkey.

Although antibiotic consumption has gained a lot of attention in the media in recent years, however, there is still no extensive regulation and/or requirements implemented for the environmental assessment of antibiotics in Turkey. Considering other waste flows associated with antibiotic emissions (unused medications, veterinary medications and pharmaceutical manufacturers), it is obvious that the overall antibiotic emission could present more serious and greater risks to aquatic environment for both short-term and log-term health complications. Consequently, urgent environmental strategies supported by legislations and regulations are needed for a resilient control of antibiotic emissions, as well as for a sustainable surface water resource management Turkey. From the engineering point of view, additional investments are also required for the construction of new WWTPs, particularly in northern, eastern and northeastern parts of the country. Furthermore, existing capacities of WWTPs in Turkey should be modernized and physical treatment steps should be combined with effective biological and/or advanced treatment technologies for an efficient removal of antibiotics from urban waste streams.

References

[1] I. Akmehmet Balcioglu, M. Otker, Treatment of pharmaceutical wastewater containing antibiotics by O_3 and O_3/H_2O_2 processes, Chemosphere 50 (2003) 85–95.
[2] W. Osenga, Antibiotics in the environment, UWT J. Environ. 2 (2004) 1–12.
[3] J.M. Cha, S. Yang, K.H. Carlson, Trace determination of β-lactam antibiotics in surface water and urban wastewater using liquid chromatography combined with electrospray tandem mass spectrometry, J. Chromatogr. A 1115 (2006) 46–57.
[4] H.R. Mowery, B.G. Loganathan, persistent organic compounds in wastewater: Azithromycin and urobilin concentrations in wastewater treatment plant samples from Murray, Kentucky, USA, Final Paper, Department of Chemistry and Center for Reservoir Research, Murray State University, Murray, KY, pp. 1–4.
[5] X. Peng, J. Tan, C. Tang, Y. Yu, Z. Wang, Multiresidue determination of fluoroquinolone, sulfonamide, trimethoprim, and chloramphenicol antibiotics in urban waters in China, Environ. Toxicol. Chem. 27 (2008) 73–79.
[6] J. Kulis, D. McQuillan, T. Chapman, D. Mawhinney, R. Meyerhein, Antibotics in New Mexico wastewater and ground water, Reporting Status or Progress, New Mexico, September 22, 2003.
[7] K. Kümmerer, Significance of antibiotics in the environment, J. Antimicrob. Chemother. 52 (2003) 5–7.
[8] B. Halling-Sorensen, S. Nors Nielsen, P.F. Lanzky, F. Ingerslev, H.C. Holten Lutzhoft, S.E. Jorgensen, Occurrence, fate and effects of pharmaceutical substances in the environment—a review, Chemosphere 36 (1998) 357–393.
[9] K.J. Choi, S.-G. Kim, C-W. Kim, S.-H. Kim, Determination of antibiotic compounds in water by on-line, SPE-LC/MSD, Chemosphere 66 (2007) 977–984.
[10] W. Ben, Z. Qiang, C. Adams, H. Zhang, L. Chen, Simultaneous determination of sulfonamides, tetracyclines and tiamulin in swine wastewater by solid-phase extraction and liquid chromatography–mass spectrometry, J. Chromatogr. A 1202 (2008) 173–180.
[11] S. Reverte, F. Borrull, E. Pocurull, R.M. Marce, Determination of antibiotic compounds in water by solid-phase extraction–high-performance liquid chromatography–(electrospray) mass spectrometry, J. Chromatogr. A 1010 (2003) 225–232.
[12] H. Chang, J. Hu, M. Asami, S. Kunikane, Simultaneous analysis of 16 sulfonamide and trimethoprim antibiotics in environmental waters by liquid chromatography–electrospray tandem mass spectrometry, J. Chromatogr. A 1190 (2008) 390–393.
[13] M.I. Bailon-Perez, A.M. Garcia-Campana, C. Cruces-Blanco, M. del Olmo Iruela, Trace determination of β-lactam antibiotics in environmental aqueous samples using off-line and on-line preconcentration in capillary electrophoresis, J. Chromatogr. A 1185 (2008) 273–280.
[14] V.K. Balakrishnan, K.A. Terry, J. Toito, Determination of sulfonamide antibiotics in wastewater: a comparison of solid phase microextraction and solid phase extraction methods, J. Chromatogr. A 1131 (2006) 1–10.
[15] A. Gulkowska, H.W. Leung, M.K. So, S. Taniyasu, N. Yamashita, Leo W.Y. Yeung, Bruce J. Richardson, A.P. Lei, J.P. Giesy, Paul K.S. Lam, Removal of antibiotics from wastewater by sewage treatment facilities in Hong Kong and Shenzhen, China, Wat. Res. 42 (2008) 395–403.
[16] K. Kosutic, D. Dolar, D. Asperger, B. Kunst, Removal of antibiotics from a model wastewater by RO/NF membranes, Sep. Purif. Technol. 53 (2007) 244–249.
[17] C. Carlesi Jara, D. Fino, V. Specchia, G. Saracco, P. Spinelli, Electrochemical removal of antibiotics from wastewaters, Appl. Catal. B: Environ. 70 (2007) 479–487.
[18] S. Chelliapan, T. Wilby, P.J. Sallis, Performance of an up-flow anaerobic stage reactor (UASR) in the treatment of pharmaceutical wastewater containing macrolide antibiotics, Wat. Res. 40 (2006) 507–516.
[19] S.-Z. Li, X.-Y. Li, D.-Z. Wang, Membrane (RO-UF) filtration for antibiotic wastewater treatment and recovery of antibiotics, Sep. Purif. Technol. 34 (2004) 109–114.
[20] P. Zhou, C. Su, B. Li, Y. Qian, Treatment of high-strength pharmaceutical wastewater and removal of antibiotics in anaerobic and aerobic biological treatment processes, J. Environ. Eng. 132 (2006) 129–136.
[21] A. Göbel, C.S. McArdell, A. Joss, H. Siegrist, W. Giger, Fate of sulfonamides, macrolides, and trimethoprim in different wastewater treatment technologies, Sci. Total Environ. 372 (2007) 361–371.
[22] A. Thompson, The fate and removal of pharmaceuticals during sewage treatment, Ph.D. Thesis, School of Industrial and Manufacturing Science, Department of Water Sciences, Cranfield University, Cranfield, UK, 2005.
[23] The Turkish Ministry of Environment and Forestry, Activity Report of Current Situation Water and Wastewater, Water and Soil Management Department, Ankara, Turkey, 2007.
[24] R. Hirsch, T. Ternes, K. Haberer, K.-L. Kratz, Occurrence of antibiotics in the aquatic environment, Sci. Total Environ. 225 (1999) 109–118.
[25] N.N.A. AL-Hadithi, Determination of drugs and metabolites in water by use of liquid membrane systems and HPLC, Ph.D. Thesis, Department of Chemistry, Faculty of Science, University of Paderborn, Paderborn, North Rhine-Westphalia, Germany, 2007.
[26] M.D. Hernando, M. Mezcuaa, A.R. Fernandez-Alba, D. Barcelo, Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments, Talanta 69 (2006) 334–342.
[27] A.J. Watkinson, E.J. Murby, S.D. Costanzo, Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling, Wat. Res. 41 (2007) 4164–4176.
[28] M. Grung, T. Kallqvist, S. Sakshaug, S. Skurtveit, K.V. Thomas, Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline, Ecotoxicol. Environ. Saf. 71 (2007) 328–340.
[29] K. Bergh, Ecological risk assessment of pharmaceuticals and personal care products in surface water, M.Sc. Thesis, Department of Biological Science, Simon Fraser University, Burnaby, BC, Canada, 2005.
[30] Th. Heberer, K. Schmidt-Bäumler, H.-J. Stan, Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part I. Drug residues and other polar contaminants in Berlin surface and groundwater, Acta Hydrochim. Hydrobiol. 26 (1998) 272–278.
[31] P. Saling, R. Maisch, M. Silvani, N. König, Assessing the environmental-hazard potential for life cycle assessment, eco-efficiency and SEEbalance®, Int. J. Life Cycle Assess. 10 (2005) 364–371.
[32] The Turkish health and medical web site, www.turkmedikal.net, 2008.
[33] Turkish Statistical Institute's (TURKSTAT), Prime Ministry Republic of Turkey, Population, Housing and Demography, Bakanliklar, Ankara, Turkey, 2007.
[34] B. Halling-Sørensen, H.C. Holten Lutzhøft, H.R. Anderson, F. Ingerslev, Environment risk assessment of antibiotics: comparison of mecillinam, trimethoprim and ciprofloxacin, J. Antimicrob. Chemother. 46 (2000) 53–58.
[35] R.A. Brain, D.J. Johnson, S.M. Richards, H. Sanderson, P.K. Sibley, K.R. Solomon, Effects of 25 pharmaceutical compounds to *Lemna gibba* using a seven-day static-renewal test, Environ. Toxicol. Chem. 23 (2004) 371–382.
[36] H.C. Holten Lutzhøft, B. Halling-Sørensen, S.E. Jørgensen, Algal toxicity of antibacterial agents applied in Danish fish farming, Arch. Environ. Contam. Toxicol. 36 (1999) 1–6.
[37] B. Halling-Sørensen, Algal toxicity of antibacterial agents used in intensive farming, Chemosphere 40 (2000) 731–739.
[38] T. Backhaus, M. Scholze, L.H. Grimme, The single substance and mixture toxicity of quinolones to the bioluminescent bacterium *Vibrio fisheri*, Aquat. Toxicol. 49 (2000) 49–61.
[39] B. Ferrari, N. Paxeus, R.L. Giudice, A. Pollio, J. Garric, Exotoxicological impact of pharmaceuticals found in treated wastewater: study of carbamezapine, clofibric acid, and diclofenac, Environ. Toxicol. Environ. Saf. 55 (2003) 359–370.

[40] N. Laville, S. Ait-Aissa, E. Gomez, C. Casellas, J.M. Porcher, Effects of human pharmaceuticals on cytotoxicity, EROD activity and ROS production in fish hepatocytes, Toxicology 196 (2004) 41–55.
[41] M.C. Harrass, A.C. Kindig, F.B. Taub, Responses of the blue-green and green algae to streptomycin in unialgal and paired culture, Aquat. Toxicol. 6 (1985) 1–11.
[42] T. Backhaus, L.H. Grimme, The toxicity of antibiotic agents to the luminescent bacterium Vibrio fisheri, Chemosphere 39 (1999) 3291–3301.
[43] H. Lilius, B. Isomaa, T. Holmstrom, A comparison of the toxicity of 50 reference chemicals to freshly isolated rainbow trout hepatocytes and *Daphnia magna*, Aquat. Toxicol. 30 (1994) 47–60.