Environmental Risk Assessment of Selected Antibiotics in Iran

Alighardashi. A[1], Rashidi.A[1], Neshat. A. A[2], Golsefatan.H.R[1]*

1) Power & Water University of Technology (PWUT)
2) Zabol University of Medical sciences and Power & Water University of Technology

Author for Correspondence: en.neshat@gmail.com

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ABSTRACT

In recent years the increasing use of pharmaceuticals and personal-care products (PPCPs), especially antibiotics, has become a particular concern because of their undesirable potential ecological and human health effects. This study presents an environmental risk assessment for the aquatic environment of some frequently used antibiotics in Iran in three stages including; a short literature review about antibiotic consumption in Iran, a comprehensive estimation regarding acute toxicity of selected antibiotics and finally calculation of Risk Quotient (RQ) using the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC). According to recently published data, the consumption of antibiotics in Iran is several times greater than European countries and in case of antibiotics (e.g. Penicillin) is approximately 10 times greater than Scandinavian region. The calculated PECs were ranged from 0.0071 to 0.8570 and the PNECs value based on ecotoxicity data was found for all studied antibiotics (varied from 0.0037 to 177). The RQ exceeded one for Amoxicillin, Penicillin G, Sulfamethoxazole, and Erythromycin. Amoxicillin has the highest risk to aquatic organisms based on this study. With respect to the emergence of microbial resistance, it is important to begin monitoring the most frequently used antibiotics

Keywords: Antibiotics, Iran, Environmental risk, water pollution, Environmental toxicity

INTRODUCTION

Emerging contaminants (ECs) in the environment are a rapidly growing field of research. Within this field, pharmaceuticals and personal-care products (PPCPs) is an important subclass that are gaining interest in recent years [1]. Antibiotics are the most important groups of PPCPs being used in medicine, veterinary medicine, farming and aquaculture for the prevention and treatment of diseases [2]. After intake, pharmaceutically active compounds undergo metabolic processes in organisms. Significant fractions of the parent compound are excreted in unmetabolized form or as metabolites (active or inactive) into raw sewage and wastewater treatment systems [3-6]. Municipal sewage treatment plant effluents are discharged to water bodies or reused for irrigation, and produced biosolids are reused in agriculture as a soil amendment or disposed to landfill [7]

Based on published data, the rate of antibiotic prescription in developed countries (e.g.15.3% in the USA) is much more than developing countries varying from 17.5% in Lebanon to 60% in Jordan [8]. In Iran, about 37.3% of urban households are connected to 136 sewage treatment plant (STP) via 42390 km municipal sewers [9]. There is no national program or regulation for the collection of unused or expired drugs. However, it seems that many households dispose their drugs into toilets or garbage bins which ultimately end up in water bodies. In many countries the risk and effects of pharmaceuticals in the environment is known and some countries have regulations to limit their effects on the environment [10]. Despite the high consumption rate of PPCPs in Iran [11] there is no study on the risk assessment of PPCPs or antibiotics. This study aims to evaluate the environmental risk assessment for aquatic environments of some frequently used antibiotics in Iran.

MATERIALS AND METHODS

This study was conducted in three stages including; a short literature review about antibiotic consumption in Iran, a comprehensive estimation on the acute toxicity of selected antibiotics, and finally calculating the Risk Quotient (RQ) using predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC).

The sold drug data were analyzed to determine the most used drugs in Iran using the data sheet published by the Iranian Ministry of Health [11]. Furthermore, a comprehensive review of the literature was done to find the most prescribed drugs.

The environmental risk assessment is based on the EU draft guideline document for medicinal products for human use [10], and an RQ was calculated between the PEC or measured environmental concentration (MEC) and the PNEC. The concentration of the active substance in the water (PEC_w) was calculated as equation1. [10, 12, 13]:

$$PEC_w = \frac{A \times (100 - R)}{365 \times P \times V \times D \times 100} \quad (1)$$

Where, A is the amount used per year (kg/yr), R is the removal in percent (set to zero when information on biodegradation in the environment is missing or when worst-case conditions are assessed), P the number of inhabitants in Iran; 75000000 in 2011 [14], V the volume of wastewater per day per capita (0.165 m3) and D is the dilution factor in the environment (a default factor of 10 is used).

Acute toxicity data were made by the PNEC value from a short literature review as well as by using Structure Activity Relationships (SARs) predicted model ECOSAR (ECOWIN v1.11). To evaluate baseline toxicity for each antibiotic separately using the ECOSAR model, physicochemical properties of each antibiotic was evaluated from Estimation Program Interface (EPI) Suite software (USEPA) and then these values were imputed to ECOSAR model. Most SAR calculations in the ECOSAR Class Program are based upon the Octanol/water partition coefficient (K_{ow}) and then to all other physicochemical parameters. The PNEC value was obtained by considering the lowest EC_{50} or LC_{50} [15]. The RQ is an indicator for ecotoxicological risk and is a ratio between PEC and PNEC for each substance. In cases that RQ is greater than 1, ecotoxicological risk for the aquatic environment is expected. Otherwise, the values of RQ less than 1 indicate no ecotoxicological risk for the specific aquatic environment [16].

RESULTS

Antibiotics consumption in Iran:

Based on the research study, compared to three European countries (Denmark, Sweden, and Norway), the antibiotic consumption in Iran is several times higher (table 1) [17].

According to a published report about prescribed drugs in six large cities of Iran, the maximum and average number of prescribed drugs was 12.5 and 3.2 respectively, while the patients who took the antibiotics varied from 47-59% [18]. A study conducted in Iran showed that in the first 6 months of 2000 and 2005, the antibiotic consumption was 95.4 and 124 Defined Daily Dosis per 100 beds per day (DDD/100 bed-days) respectively [19]. Other studies also confirm that the antibiotic prescription rate is as high as 50 % (table 2).

Table1: Consumption of some antibiotics in Iran and three European countries (No./1000 habitation year) [17]

Pharmaceutical	Denmark	Sweden	Norway	Iran
Penicillin	7.3	8	7.5	76.25
Cephalosporins	<0.05	-	0.366	2.71
Trimethoprim Sulfamethoxazole	0.8	0.9	1.45	8.95
Aminoglicozide	<0.05	<0.1	0.05	60

According to the Iranian Ministry of Health, the used active compound in terms of gram per capita and year ranged from 0.04-5.02 and the 7 primary used antibiotics in 2011 were consumed more than 10 tons per year (table 3).

Results of acute toxicity data

For the selected antibiotics, acute toxicity data (i.e. PEC, PNEC and RQ values) were found with a very short comprehensive literature review. In some cases, these data were calculated using ECOSAR software (table 4). The toxicity of Amoxicillin, Penicillin G and Azithromycin were reported for just algae [24,25] and for cephalexin the test organism wasn't mentioned in the related paper. In another study, Clavulanic Acid acute toxicity was reported 13.3 without any appointment to test organism [26]. Jones et al (2002) reported acute toxicity of Penicillin V for Daphnia test [27]. ECOSAR software was used for calculating the toxicity of the other active compounds (i.e. Trimethoprim, Sulfamethoxazole and Erythromycin) (table 4). As it was obvious, the maximum and minimum RQ were 232 and 0.00028 for Amoxicillin and 0.00028 for penicillin V, respectively.

Table 2: Some conducted studies about antibiotics consumption pattern in Iran

No of studied prescriptions	City / Province	Results	Reference
8019328	Ghazvin	4 of 10 first prescribed drugs were antimicrobials, and Penicillin was the first	[20]
25700000	West Azerbaijan	Amoxicilin500 mg, Ceftriaxone 1 g and metronidazole 250 mg to 94.7, 67.4, and 23.4%, respectively, were among the first 10 prescribed drugs	[21]
12852901	Tehran	More than **45%** of prescriptions had at least 1 antibiotic. Cephalosporin, Penicillin and Macrolides were the top 3 prescribed drugs respectively. They found that 5-10 drugs that had the most consumption in 2011 were antibiotics.	[22]
2000	Ardebil	The total number of prescribed drugs was 7158. The average number of drugs for every prescription was 3.58. Antibiotics were the top prescribed drugs with a frequency of **52.8%**.	[23]
4463710	Isfahan	**51.25%** of the patients received an antibiotic. Amoxicillin (5.9%) and Penicillin 6-3-3 (5.53%), followed by Cefixime (3.62%) and Azithromycin (2.74%) were among the top prescribed drugs	[8]

Table 3: The 7 most used Antibiotics in Iran in 2011 [11]

No	Active compound	CAS-no.	An amount Active compound used (Kg/year)	An amount Active compound used (g/capita/year)
1	Amoxicillin	026787-78-0	387,095 [a]	5.02
2	Cephalexin	015686-71-2	109,227	1.41
3	Co-Amoxiclav:		48,104	0.62
	Amoxicillin	026787-78-0	32,069	0.41
	Clavulanic Acid	058001-44-8	16,035	0.20
4	Penicillin V	000087-08-1	24,135	0.31
	Penicillin G	001538-09-6	14,763	0.19
5	Co-Trimoxazole:		22,968	0.29
	Trimethoprim	738-70-5	3,190	0.04
	Sulfamethoxazole	723-46-6	19,140	0.24
6	Azithromycin	83905-01-5	17,654	0.22
7	Erythromycin	000114-07-8	10,402	0.13

a: including the value in Co-Amoxiclav (row no.3)

DISCUSSION

The calculated PECs ranged from 0.0071 to 0.8570 and the PNECs value based on ecotoxicity data was found for all studied antibiotics (varied from 0.0037 to 177).

The environmental risk assessment of the 7 most used antibiotics in Iran was done by calculating the risk quotient. As shown in the table 4, the RQ of Amoxicillin was 232. Moreover, according to Kümmerer (2008) it can cause an ecotoxicological risk to the aquatic environment [2]. This judgment was confirmed by Technical Guidance Document criteria [16].

The RQ exceeded one for Amoxicillin, Penicillin G, Sulfamethoxazole, and Erythromycin and was below one for Cefalexin, Penicillin V, Clavulanic Acid, Trimethoprim, and Azithromycin. According to Technical Guidance Document (2003) criteria for 4 of 7 studied antibiotics, ecotoxicological risk can be expected [16]; while based on Kümmerer (2008) classification Trimethoprim, Penicillin V, and Cefalexin had insignificant risks, Azithromycin had lower risks, Penicillin G, Sulfamethoxazole, and Erythromycin had moderate risks and finally Amoxicillin had a high risk for aquatic organisms [2]. Some antibiotics (and more specially the studied antibiotics in this study), are sold over the counter and without any prescription. As a result, the consumption of these antibiotics may be higher in Iran.

Excretion rates for the unchanged active compound in the antibiotics that are excreted into wastewater unchanged have varying ranges of 30 to 60 percent [32]. On average, if the volume of all the antibiotics used is totaled, the metabolic rate is 30% [3]. Therefore, if we consider it for just Amoxicillin, it equals to more than 270 tons per year in Iran. Moreover, Amoxicillin is suspected to have direct toxicity to certain aquatic organisms such as algae. It is reported that the photosynthesis mechanism of algae Synechocystis sp is inhibited by the toxic effects of this compound. Amoxicillin

accumulates within single organisms (i.e. Pathogenic bacteria) and increase its resistance leading to higher dosage needed or even its incapability to treat conventional diseases [33]. Our results are only related to antibiotics consumed by humans. If we take the total antimicrobial use into account, the antibiotics that are released into the environment will be higher.

Table 4: Top 7 Antibiotics ecotoxicological test results and PNECs

Pharmaceutical	Toxicity		References	PEC	PNEC	RQ
	Test organism	Concentration				
Amoxicillin	Algae	EC 50, 0.0037 EC 50 ,0.1	[24] [25]	0.8570	0.0037	232
Cephalexin	-	2.5	[25]	0.2418	2.5	0.096
Co-Amoxiclav: **Amoxicillin** **Clavulanic Acid**	Algae - 	 EC 50, 0.0037 EC 50 ,0.1 -	 [24] [25] [26]	0.8570 0.0355	0.0037 13.3	232 0.0027
Penicillin: **Penicillin V:** **Penicillin G:**	Daphnia EC50 Algae	EC50, 177 EC50, 0.006	 [27] [24]	0.0534 0.0327	 177 0.006	0.00028 5
Co-Trimoxazole: **Trimethoprim**	Fish Daphnia Algae Fish Daphnia Daphnia Algae Bacteria	LC50 ECOSAR, 798 LC50 ECOSAR, 4.5 EC50 ECOSAR, 2.6 EC50 ECOSAR, 795 EC50 ECOSAR, 121 EC50, 123 EC50 ECOSAR, 2.6 EC50 (15 min), 177	Authors Authors Authors [28] [29] [24] [28] [29]	0.0071	2.6	0.0038
Sulfamethoxazole	DAPHNIA DAPHNIA ALGAE FISH FISH DAPHNIA BACTERIA ALGAE ALGAE ALGAE	EC50 ECOSAR 4.5 LC50 ECOSAR, 1.87 EC50 ECOSAR, 51 LC50 ECOSAR, 413 EC50 (96 h) 563 EC50 (48 h-mortality) >100 EC50 (15 min) 78.1 EC50 (96 h-growth) 0.15 EC50 (96 h-growth) 0.027 EC50 ECOSAR, 6.6	[28] Authors [28] Authors [29] [30] [29] [30] [30] Authors	0.0424	0.027	1.48
Azithromycin	Green Algae	EC50 , 0.15 mg/L	[25]	0.0391	0.15	0.26
Erythromycin	 Fish Fish Daphnia Algae Invertebrates Algae Daphnia Algae	 LC50 ECOSAR,2.84 EC50 ECOSAR 61 EC50 ECOSAR 7.8 EC50 ECOSAR 4.3 EC50 15 EC50 0.02 LC50 ECOSAR,3.8 EC50 ECOSAR,2.5	Authors [28] [28] [28] [31] [31] Authors Authors	0.023	0.02	1.15

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CONCLUSION

Finally, according to present study the antibiotics roll in the environmental toxicity is considerably so, with respect to the emergence of microbial resistance, it is important to begin monitoring the most frequently used antibiotics, especially those who have higher environmental risk, such as Amoxicillin. Using labels such as “harmful to the environment” could be useful. Moreover, public education and restrictions for the sale of drugs without prescription could be effective.

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