Integrated Environmental Assessment and Management — Volume 13, Number 5—pp. 832–839

Received: 6 September 2016 | Returned for Revision: 31 October 2016 | Accepted: 16 January 2017

Health & Ecological Risk Assessment

Prioritization of Pharmaceuticals Based on Risks to Aquatic Environments in Kazakhstan

Bakhyt Aubakirova,†‡ Raikhan Beisenova,† and Alistair BA Boxall‡*

†LN Gumilyov Eurasian National University, Astana, Kazakhstan
‡Environment Department, University of York, Heslington, York, United Kingdom

ABSTRACT

Over the last 20 years, there has been increasing interest in the occurrence, fate, effects, and risk of pharmaceuticals in the natural environment. However, we still have only limited or no data on ecotoxicological risks of many of the active pharmaceutical ingredients (APIs) currently in use. This is partly due to the fact that the environmental assessment of an API is an expensive, time-consuming, and complicated process. Prioritization methodologies, which aim to identify APIs of most concern in a particular situation, could therefore be invaluable in focusing experimental work on APIs that really matter. The majority of approaches for prioritizing APIs require annual pharmaceutical usage data. These methods cannot therefore be applied to countries, such as Kazakhstan, that have very limited data on API usage. The present paper therefore offers an approach for prioritizing APIs in surface waters in information-poor regions such as Kazakhstan. Initially data were collected on the number of products and active ingredients for different therapeutic classes in use in Kazakhstan and on the typical doses. These data were then used alongside simple exposure modeling approaches to estimate exposure indices for active ingredients (about 240 APIs) in surface waters in the country. Ecotoxicological effects data were obtained from the literature or predicted. Risk quotients were then calculated for each pharmaceutical based on the exposure and the substances were ranked in order of risk quotient. Highest exposure indices were obtained for benzylpenicillin, metronidazole, sulbactam, ceftriaxone, and sulfamethoxazole. The highest risk was estimated for amoxicillin, clarithromycin, azithromycin, ketoconazole, and benzylpenicillin. In the future, the approach could be employed in other regions where usage information is limited. *Integr Environ Assess Manage* 2017;13:832–839. © 2017 SETAC

Keywords: Active pharmaceutical ingredients   Ecotoxicity   Kazakhstan   Exposure modeling   Environmental risk

INTRODUCTION

Active pharmaceutical ingredients (APIs) can be released to the aquatic environment during their manufacture, following use, and as a result of disposal (Boxall et al. 2003). The major pathway is thought to be through excretion to the sewage system where they are then transported to wastewater treatment plants (WWTPs) (Boxall et al. 2012). Because many APIs are resistant to treatment in WWTPs, they ultimately are released in WWTP effluents into surface waters. A range of APIs has been detected in surface waters and wastewater effluents in several regions of the globe, including the Arctic (Besse et al. 2008; Brausch and Rand 2011). Approximately 160 different APIs have been detected in the aquatic environment, with the most common classes belonging to the antibiotic, analgesic, painkiller, and cardiovascular drug families (Kümmerer 2010).

A wide range of effects of pharmaceuticals on aquatic organisms has been reported (Hegelund et al. 2004; Porsbring et al. 2009; Shi et al. 2012). Chronic toxicity studies have shown effects at low concentrations in fish, invertebrates, algae, and bacteria. For example, diclofenac has been reported to have adverse histological impacts on kidney and gills of rainbow trout at concentrations of 5 μg/L in 28 d tests (Schwaiger et al. 2004). Acetaminophen, venlafaxaine, carbamazepine, and gemfibrozil at concentrations of 10 μg/L, 0.5 μg/L, and 10 μg/L respectively, had adverse reproductive impacts, inducing reproduction and changing kidney proximal tubule morphology (Galus et al. 2013). Concentrations of propranolol and fluoxetine seen in effluents have been shown to affect reproduction in aquatic organisms and the nervous system in fish (Kümmerer 2010).

Although a wealth of data is now available on the occurrence, fate, and effects of APIs in the natural environment, the knowledge of the risk of pharmaceuticals in water is still limited. One of the major challenges is that whereas more than 1500 APIs are in use, we have data on the environmental risks of only a few of these (Berninger et al. 2016). Therefore,

This article includes online-only Supplemental Data.
* Address correspondence to alistair.boxall@york.ac.uk
Published 25 January 2017 on wileyonlinelibrary.com/journal/ieam.

approaches are needed that cut down the number of pharmaceuticals to be studied in order to focus on substances that are likely to pose the greatest risk and and for which environmental risk should therefore be established using experimental testing (Besse et al. 2008; Guo et al. 2016).

Prioritization methods provide an approach to help focus research on APIs that really matter (Roos et al. 2012). A variety of approaches have therefore been proposed and applied for ranking of APIs. Mostly these approaches cover areas of Western Europe and North America (Besse et al. 2008; Roos et al. 2012; Guo et al. 2016). Typically, these approaches use information on API usage to assess likely exposure concentrations and compare these to predictions of potential toxicity. However, only a few studies have prioritized APIs in other regions of the world such as Eastern Europe, Africa, and South America (e.g., Al-Khazrajy and Boxall 2016). Prioritization of pharmaceuticals in these regions is more challenging because information on API usage is either limited or nonexistent.

It is however important to understand the risks of drugs in the environment in these other unstudied regions. For example, in Kazakhstan, the focus of the present study, the pharmaceutical market in the country is rapidly growing, and in 2012 more than 500 million packages of drugs were sold, corresponding to an average of 32 packages per person per year (Tashenov and Cherednichenko 2013). Medical substances are readily available in Kazakhstan, with most of them being freely available for purchase over the counter. According to the Ministry of Healthcare and Social Development of the Republic of Kazakhstan, there are 7713 registered medications and approximately 24% of these are available without a prescription (MHSD 2016). Also, wastewater treatment systems in Kazakhstan are old and employ dated technologies, so the treatment may not be as effective in removing APIs as it is in Western countries. Consequently, emissions of pharmaceuticals to the natural environment in Kazakhstan are expected to be high, and impacts could be greater than elsewhere in the world.

The aim of the present study was therefore to develop an approach for prioritizing pharmaceuticals in surface water in regions with limited data and to apply the approach to identify APIs in use in Kazakhstan that require further scrutiny in terms of the assessment of their potential risks to the aquatic environment of Kazakhstan.

METHODS

The present study aimed to identify those APIs most likely to lead to environmental impacts in Kazakhstan. The overall approach to prioritization is illustrated in Figure 1. The approach was designed to consider potential for impacts on apical endpoints (mortality, growth, and reproduction) in aquatic systems in Kazakhstan as well as impacts on possible nonapical endpoints corresponding to the therapeutic mode of action of an API.

Identification of pharmaceuticals in use in Kazakhstan and selection of APIs for detailed assessment

A list of APIs in use in Kazakhstan was constructed using the online directory of pharmaceutical products in use in Kazakhstan (Vidal-Kazakhstan LLP 2015). For each API, the number of products on the market was determined. Vitamins and vaccines were excluded from the analysis. To make the prioritization manageable, all compounds contained in fewer than 3 products were not considered further; it was assumed that exposure to these would be low, although in the future these compounds could also be assessed. For the remaining compounds, data on the recommended daily dose and treatment duration were obtained (Supplemental Data Table S1).

Environmental exposure

The relative exposure of those APIs in use in 3 or more products was characterized by estimating an exposure index for surface water (EI_{sw}). The EI was calculated by multiplying the number of products containing an API available on the market, the average daily dose, and the fraction of drug not metabolized by the patient and the fraction not removed by the WWTP. The fraction of unmetabolized API was obtained from peer-reviewed papers and available online databases (Wishart et al. 2006; FASS Allmanhet, 2011; Medsafe 2015; Drugs.com 2016) (Supplemental Data Table S2). The compounds without data were considered to be totally excreted from the body. The fraction not removed by the WWTP was estimated using an equation proposed by the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EC 2003), with slight modification (Eq.1):

$$F_{wwtp} = 1 - \frac{Sludge_{inhab} \times K_{oc} \times foc_{sludge}}{WasteW_{inhab} + (Sludge_{inhab} \times K_{oc} \times foc_{sludge})}, \quad (1)$$

where Fwwtp is the fraction of pharmaceutical released from the WWTP. Wastewater parameters were obtained from the EU Technical Guidance Document for risk assessment of chemicals (EC 2003) because these are widely recognized for use in risk assessment. $WasteW_{inhab}$ is the amount of wastewater per inhabitant per day, which was assumed to be 200 L/d (EC 2003). $Sludge_{inhab}$ was the mass of waste sludge per inhabitant per day (inh/d), which was assumed to be 0.074 kg inh/d (EC 2003). The focsludge (fraction of sludge OC) was assumed to be 0.326 (Struijs et al. 1991). The soil OC–water partitioning coefficient (Koc) value was estimated with the model established for ionizable organic chemicals proposed by Franco and Trapp (2008). This model estimates sorption using information on the hydrophobicity and degree of dissociation of a molecule using Equations 2 and 3:

$$\text{Log}\, K_{oc} = \log\left(\Phi n \times 10^{0.54\log Pn+1.11} + \Phi ion10^{0.11\log Pn+1.54}\right) \text{ for acids.} \quad (2)$$

$$\text{Log}\, K_{oc} = \log\left(\Phi n \times 10^{0.37\log Pn+1.70} + \Phi ion10pKa0.65 \times f0.14\right) \text{ for bases.} \quad (3)$$

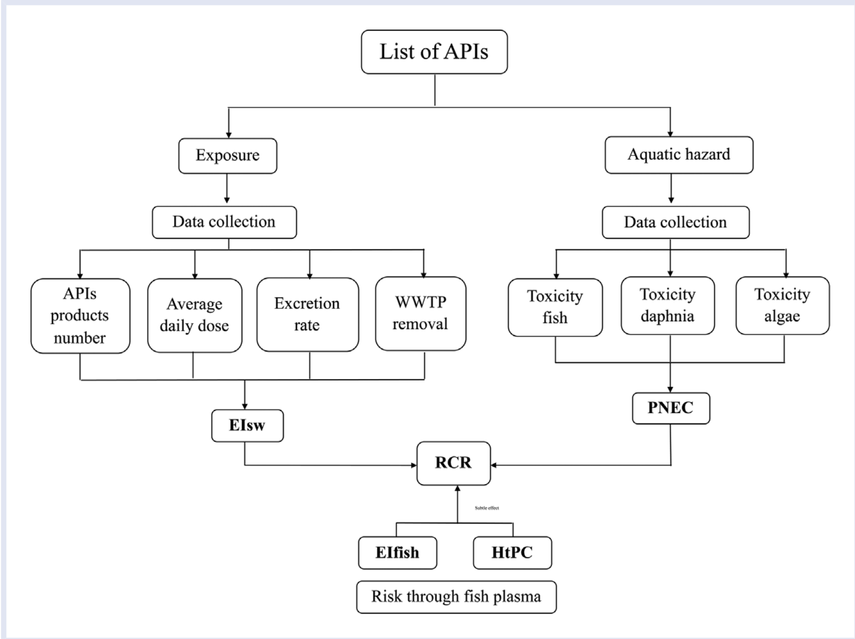

Figure 1. Outline of the prioritization approach for active pharmaceutical ingredients (APIs) in surface waters in Kazakhstan. APIs = active pharmaceutical ingredients; EI_{fish} = exposure index in fish plasma; EI_{sw} = exposure index for surface water; HtPC = human plasma therapeutic concentration; PNEC = predicted no-effect concentration; RCR = risk score ratio; WWTP = wastewater treatment plant.

An EI representing the internal exposure of APIs in fish plasma (EI_{fish}) was also determined by multiplying the EI_{sw} by the fish blood–water partition coefficient (Pbw) for each API. The calculation of Pbw was performed using Equation 4, proposed by Fick et al. (2010):

$$\mathrm{LogPbw} = 0.73 \times \mathrm{Log}K_{ow} - 0.88, \qquad (4)$$

where Pbw was aqueous phase and fish arterial blood partition coefficient and K_{ow} was octanol–water partition coefficient.

Apical effects assessment

Predicted no-effect concentrations (PNECs) were estimated for each API using Equation 5. In order to estimate PNECs, we collected all available experimental ecotoxicological data on the toxicity of APIs to apical endpoints in aquatic organisms from peer-reviewed papers, using Google scholar, Web of Knowledge, SCOPUS, and online datasets (FASS 2011) (Supplemental Data Table S3). The data contained acute and chronic ecotoxicity endpoints as LC50 or EC50 values and, because the aim of the present work is prioritization and not regulation, they were not quality assessed. For substances that did not have experimental ecotoxicity data, the quantitative structure activity relationships (QSARs) toolbox was used in order to fill all gaps (OECD 2009). This software helped to define potential analogs and construct a matrix of data based on them. Initially, we selected the protein-binding profile. Then, on the endpoints section we selected ecotoxicological information, which included growth, immobilization, and mortality. After that, on the category definition module we used the aquatic toxicity classification system by Ecological Structure Activity Relationships Predictive Model (ECOSAR). Finally, the toolbox processed data with a common structure (70%–90%). Where the toolbox identified predictions to be inaccurate, these predictions were not included in the prioritization analysis.

$$\mathrm{PNEC} = \frac{\mathrm{EcoTox}}{\mathrm{AF}}, \qquad (5)$$

where EcoTox is the most sensitive ecotoxicological data for the aquatic compartment, and AF is the safety factor. The AF was selected on the basis of recommendations in the technical guidance document on risk assessment (EC 2003).

Nonapical endpoints

In order to account for nonapical effects relating to the therapeutic mode of action of each API, we used a similar approach to that proposed by Huggett et al. (2003) and collated information on plasma therapeutic concentrations (HtPC) of each API in humans. The information on HtPC was obtained from online databases (FASS 2011; Medsafe 2015; Drugs.com 2016; Kim et al. 2016) (Supplemental Data Table S4).

Ranking APIs

The final step in the study was prioritization of the APIs. Risk scores were used to rank compounds. Basically, the score was estimated by dividing the exposure indices for water and fish by either the PNEC or the HtPC. The APIs with the highest ranking score were classified as the substances that should be in the list of concern.

 DOI: 10.1002/ieam.1895

RESULTS

In total, there are 7713 pharmaceutical products in use in Kazakhstan, containing 1684 APIs. When complex mixtures as well as vaccines and vitamins are excluded, 841 APIs remain. The top 20 APIs, based on product number containing the ingredient, are shown in Figure 2. Assuming product number is a surrogate for the extent of use, the most widely used compound is paracetamol (an analgesic) followed by hydrochlorothiazide (a diuretic used to treat high blood pressure, swelling, and fluid build-up) and metronidazole (an antibiotic).

When APIs in use in fewer than 3 products were excluded, a list of 237 APIs was obtained for further prioritization. Exposure indices for these substances are provided in Supplemental Data Tables S2 and S4. The highest exposure indices in surface water were seen for benzylpenicillin, metronidazole, sulbactam, ceftriaxone, and sulfamethoxazole, whereas the highest exposure indices in fish plasma were seen for lisinopril, orlistat, telmisartan, drotaverine, and terbinafine.

Experimental ecotoxicity data for *Daphnia* spp., fish, and/or algae were available for 154 of the 237 APIs, and HtPC data were available for 201 of these. Therefore, for the prioritization, experimentally based PNECs were used for 70% of compounds and QSAR-based PNECs were used for 66 compounds. The most highly ranked substances based on the apical ecotoxicological endpoints were amoxicillin, clarithromycin, azythromycin, ketoconazole, and benzylpenicillin, whereas the most highly ranked compounds based on the nonapical assessment were lisinopril, orlistat, estradiol valerate, drotaverine, and estradiol. Table 1 shows the top 5 ranked compounds broken down by classification of diseases. Classification of diseases was based on classes of illness cases registered in health care institutions in Kazakhstan in 2014 (MHSD 2015).

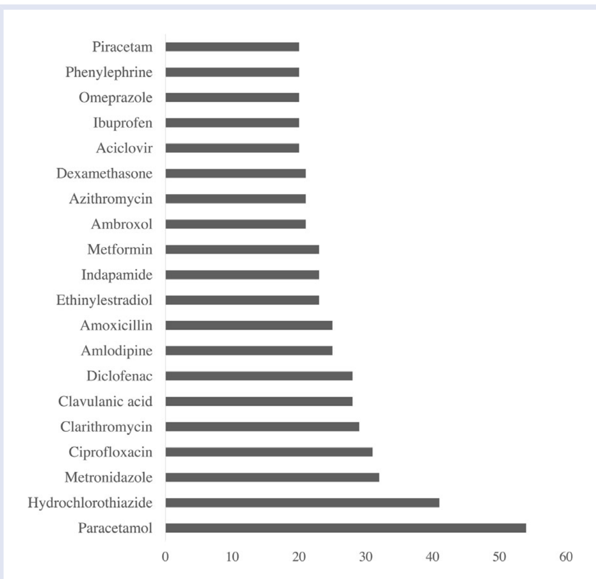

Figure 2. Top 20 active pharmaceutical ingredients in use in Kazakhstan, based on number of products containing an active pharmaceutical ingredient.

DISCUSSION

The objective of the present study was to develop a method for ranking pharmaceuticals in data-poor regions. The approach built on previous studies, but because usage amount data were not available for Kazakhstan, we used information on product numbers as the basis for the exposure characterization; the assumption was that APIs that were present in numerous products would be more widely used than APIs that were present in only a few products. During the study we found the main drugs of concern in Kazakhstan, based on a combination of risk to apical or nonapical endpoints, were amoxicillin, clarithromycin, azithromycin, ketoconazole, benzylpenicillin, terbinafine, drotaverine, diclofenac, benzathine benzylpenicillin, and telmisartan because these had the highest risk scores.

Even though the ranking used a different approach from previous studies, the results show that some of the top-ranked compounds in our study are also ranked highly by earlier prioritization research (Table 2). For example, amoxicillin, clarithromycin, diclofenac, and azithromycin, with the highest risk score, were defined as high priority in an ecotoxicological risk-based prioritization study performed in the United Kingdom by Guo et al. (2016). Moreover, amoxicillin was detected as a chemical with the highest hazard to aquatic organisms in the UK, France, Italy, Iran, Korea, and Spain (Table 2). Cooper et al. (2008) concluded that sulfamethoxazole, diclofenac, and clarithromycin were the pharmaceuticals of high risk in a US study. Ketoconazole was identified as one of the priority substances in a study by Roos et al. (2012) in Swedish aquatic systems. Lisinopril, orlistat, estradiol valerate, cinnarizine, drotaverine, estradiol, and clotrimazole were identified as having the potential to elicit subtle effects in fish. Estradiol was identified by Guo et al. (2016) as having the potential to cause subtle effects in fish.

Most of the pharmaceuticals that ranked high on our list are related to the treatment of infectious and parasitic diseases, so the majority of them are antibiotics. Currently, antibiotics are one of the most well-investigated pharmaceutical classes in terms of acute toxicity to aquatic organisms (Brausch and Rand 2011). Nevertheless, we still have a limited data set on chronic effects of many antibiotics to aquatic ecosystems. The majority of ecotoxicology studies have focused on acute toxicity of antibiotics to algal species, and the EC50s vary from 0.002 mg/L to 1283 mg/L (Guo et al. 2015).

Most drugs from our ranking list have been detected in monitoring studies around the world. This fact provides a level of confidence in the approach. For instance, amoxicillin was detected in concentrations of 28 μg/L and 82.7 μg/L in hospital wastewater in Germany during the daytime (Kümmerer 2001). Yasojima et al. (2006) showed clarithromycin and azithromycin at concentrations of 647 ng/L and 260 ng/L in wastewater effluents in Japan.

The majority of substances from the ranking list have been reported to cause toxicity to aquatic organisms. For instance, Shi et al. (2012) showed that clotrimazole can affect the development stage of *Xenopus tropicalis* larvae and can lead

Table 1. Summary of top-ranked APIs, by disease class, prioritized on the basis of apical effects and nonapical effects

Nr	Classification of diseases	Registered morbidity incidents in health care institutions in 2014 in Kazakhstan (per 100 000)	Top-ranked APIs	
			Apical effects (EI_{sw}:PNEC)	Nonapical effects (HtPC:EI_{fish})
1	Respiratory diseases	28 233.8	Xylometazoline Beclomethasone Chloropyramine Pheniramine Clemastine[a]	Loratadine Clemastine[a] Montelukast Dextromethorphan Fexofenadine
2	Diseases of blood circulatory system	13 472.7	Telmisartan[a] Atorvastatin Rutoside Losartan Captopril	Lisinopril Telmisartan[a] Amiodarone Rosuvastatin Amlodipine
3	Diseases of digestive system	8952.1	Drotaverine[a] Ursodeoxycholic acid Thioctic acid Bisacodyl Pioglitazone	Orlistat Drotaverine[a] Repaglinide Loperamide Hyoscine butylbromide
4	Disease of urino-genital system	7250.8	Ketoconazole[a] Levonorgestrel Nystatin Miconazole[a] Drospirenone	Estradiol valerate Estradiol Miconazole[a] Ethinylestradiol Ketoconazole[a]
5	Diseases of the eye and its appendages	5516.3	Neomycin[a] Betaxolol[a] Tropicamide[a]	Betaxolol[a] Neomycin[a] Tropicamide[a]
6	Diseases of the blood-forming organs and certain	4965.9	Clopidogrel[a]	Clopidogrel[a]
7	Diseases of the nervous system	4471.6	Cinnarizine[a] Paracetamol Betahistine Carbamazepine Gabapentin	Cinnarizine[a] Fentanyl Acetylsalicylic acid Tramadol Valproic acid
8	Diseases of the musculoskeletal system and connective tissue	4093.1	Diclofenac Etofenamate Ketoprofen[a] Clodronic acid Naproxen	Methyl salicylate Diclofenac Indomethacin Benzydamine Ketoprofen[a]
9	Infectious and parasitic diseases	2296	Amoxicillin Clarithromycin Azithromycin[a] Benzylpenicillin Terbinafine[a]	Clotrimazole Isotretinoin Disulfiram Terbinafine[a] Azithromycin[a]
10	Tumors	1657.	Oxaliplatin Cisplatin Mycophenolic acid[a] Capecitabine Paclitaxel	Paclitaxel Mycophenolic acid[a] Imatinib Anastrozole Topotecan
11	Mental and behavioral disorders	1270.6	Citicoline Piracetam Fluoxetine[a] Clozapine Sertraline	Sertraline Fluoxetine[a] Chlorpromazine Risperidone Clozapine

APIs = active pharmaceutical ingredients; EI_{fish} = exposure index in fish plasma; EI_{sw} = exposure index for surface water; HtPC = human plasma therapeutic concentration; PNEC = predicted no-effect concentration.
[a]Compounds that have been identified as priority using both risk ratios.

Table 2. Defined top-priority APIs in surface water of Kazakhstan, United Kingdom, France, United States, Sweden, Iran, Korea, and Italy

Kazakhstan	United Kingdom (Guo et al. 2016)	France (Besse et al. 2008)	United States (Cooper et al. 2008)	Sweden (Roos et al. 2012)	Iran (Alighardashi et al. 2014)	Korea (Kim et al. 2008)	Italy (Zuccato et al. 2005)
Amoxicillin	Amitriptyline	Amoxicillin	Erythromycin	Ethyinylestradiol	Amoxicillin	Amoxicillin	Amoxicillin
Clarithromycin	Amoxicillin	Acetylsalicylic acid	Oxytetracycline	Atovaquone	Cephalexin	Apramycin	Atenolol
Azithromycin	Atorvastatin	Ofloxacin	Sulfamethoxazole	Sertraline	Clavulanic acid	Bromhexine	Hydrochlorothiazide
Ketoconazole	Azithromycin	Propranolol	Fluoxetine	Estradiol	Penicillin	Ciprofloxacin	Ranitidine
Benzylpenicillin	Carbamazepine	Carbamazepine	Nitroglycerin	Mycopphenolate mofetil	Trimethoprim	Diclazuril	Clarithromycin
Terbinafine	Ciprofloxacin	Furosemide	Clofibrate	Propranolol	Sulfamethoxazole	Dihydrostreptomycin	Ceftriaxone
Drotaverine	Clarithromycin	Clarithromycin	Ibuprofen	Acetylsalicylic acid	Azithromycin	Doxycycline	Furosemide
Diclofenac	Diclofenac	Diclofenac	Acetominophen	Naproxen	Erythromycin	Enramycin	Bezafibrate
Benzathine benzylpenicillin	Estradiol	Sertraline	Estradiol	Felodipine		Erythromycin	Ciprofloxacin
Telmisartan	Metformin	Fluoxetine	Diclofenac	Ketoconazole		Fenbendazole	Enalapril
Disulfiram	Mezalazine	Fenofibrate	Caffeine	Acetaminophen		Flofenicol	Spiramycin
Oxytetracycline	Omeprazole	Paroxetine	Carvedilol	Amitriptyline		Fluvalinate	Omeprazole
	Orlistat	Fluvoxamine	Metronidazole	Fluoxetine		Ivermectin	
			Trimethoprim	Dipyridamole		Monensin	
			Tetracycline	Chlorprothixene		Norfloxacin	
			Propranolol	Bromhexine		Oxytetracycline	
			Gemfibrozil	Entacapone			
			Naproxen	Fulvestrant			
			Diazepam	Galantamine			
			Paroxetine				
			Clarithromycin				

APIs = active pharmaceutical ingredients.

to mortality of *Xenopus tropicalis* even at a low concentration (0.1 μg/L). In 2008 Porsbring et al. (2009) conducted a toxicity assessment of clotrimazole to natural microalgal communities. The results of the research showed that this compound causes growth inhibition of algal communities, and it can alter their pigment profiles and physiology (Porsbring et al. 2009). Hegelund et al. (2004) investigated the response of fish to ketoconazole. Their results showed that this compound had effects on rainbow trout and killifish at 12 mg/kg and 100 mg/kg, because it suppressed cytochrome enzyme activity of fish (Hegelund et al. 2004). Halling-Sorensen (2000) showed that benzylpenicillin was toxic to *Microcystis aeruginosa*, with an EC50 value of 0.005 mg/L. A large volume of published studies describes the risk of clarithromycin to the environment. For instance, Oguz and Mihciokur (2014) studied the environmental risks of drugs in Turkey and concluded that clarithromycin can cause potential hazard to living organisms because of its high bioconcentration factor. Furthermore, the substance with the highest concentration in Italian rivers was clarithromycin at a concentration of 0.02 μg/L (Calamari et al. 2003). A considerable amount of literature has been published on the toxicity and occurrence of diclofenac in the last decades. Recent research by Acuna et al. (2015) has reported that the occurrence of diclofenac was mentioned in 142 papers, which covered 38 countries. Moreover, there were 156 reports about the ecotoxicological effects of this substance (Acuna et al. 2015).

LIMITATIONS

The prioritization results in the present study are based on information on the number of products because we were not able to obtain information on annual mass usage data. The use of consumption data of drugs could give us more precise results but simply is not available in countries such as Kazakhstan. In the future, we recommend that more efforts be put into the development of databases on annual usage of pharmaceuticals (and other) chemicals in Kazakhstan and other regions with lack of data. In order to calculate PNEC, ecotoxicological data were collected from different sources and were not rated for data quality. Moreover, the majority of pharmaceuticals excreted to WWTPs would be in the form of metabolites. The present paper did not consider these for ranking, even though in some instances they could pose a risk to the environment.

CONCLUSIONS

The population of Kazakhstan is increasing, so it is likely that consumption of medicines in the country will grow too. Pharmaceuticals are readily available in Kazakhstan, with most of them being freely available for purchase over the counter. Wastewater treatment systems in the country are old and employ old technologies, so the treatment may not be as effective as in Western countries. Consequently, emissions of pharmaceuticals to the natural environment in Kazakhstan are expected to be high, and impacts could be greater than elsewhere in the world. Overall, the present assessment prioritized the human prescription APIs that are most likely to be present in Kazakhstan surface waters and that could pose the greatest risk to living organisms. We recommend that these compounds be considered in future research to monitor concentrations of the APIs in the Kazakhstan environment and to establish the level of risk to ecosystems in the country. It would be interesting to consider the effect of mixtures of these pharmaceuticals on surface water. While the present paper has focused on prioritization of pharmaceuticals in use in Kazakhstan, the design of the approach means that it can be applied in other countries with limited data on API use. The approach could therefore be invaluable in determining the wider impacts of APIs across the globe.

Data Accessibility—The data presented in this paper are available publicly. Readers may obtain all data collected in spreadsheets by writing to corresponding author Alistair Boxall at alistair.boxall@york.ac.uk.

SUPPLEMENTAL DATA

Table S1. List of active pharmaceutical ingredients (APIs) with number of products

Table S2. List of prioritized active pharmaceutical ingredients with the exposure and effect data

Table S3. List of prioritized active pharmaceutical ingredients with fish plasma data

ORCID

Bakhyt Aubakirova http://orcid.org/0000-0001-5286-2540

REFERENCES

Acuna V, Ginebreda A, Mor JR, Petrovic M, Sabater S, Sumpter J, Barcelo D. 2015. Balancing the health benefits and environmental risks of pharmaceuticals: Diclofenac as an example. *Environ Int* 85:327–333.

Al-Khazrajy OSA, Boxall ABA. 2016. Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. *Environ Sci Pollut Res* 23(15): 15712–15726.

Alighardashi A, Rashidi A, Neshat A, Folsefatan H. 2014. Environmental risk assessment of selected antibiotics in Iran. *IJHSE* 1(3):132–137.

Berninger JP, LaLone CA, Villeneuve DL, Ankley GT. 2016. Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large-scale mammalian pharmacological dataset. *Environ Toxicol Chem* 35(4):1007–1020.

Besse JP, Kausch-Barreto C, Garric J. 2008. Exposure assessment of pharmaceuticals and their metabolites in the aquatic environment: Application to the French situation and preliminary prioritization. *Hum Ecol Risk Assess* 14(4):665–695.

Boxall ABA, Kolpin DW, Halling-Sorensen B, Tolls J. 2003. Are veterinary medicines causing environmental risks? *Environ Sci Technol* 37(15): 286A–294A.

Boxall ABA, Rudd MA, Brooks BW, Caldwell DJ, Choi K, Hickmann S, Innes E, Ostapyk K, Staveley JP, Verslycke T, et al. 2012. Pharmaceuticals and personal care products in the environment: What are the big questions? *Environ Health Persp* 120(9):1221–1229.

Brausch JM, Rand GM. 2011. A review of personal care products in the aquatic environment: Environmental concentrations and toxicity. *Chemosphere* 82(11):1518–1532.

Calamari D, Zuccato E, Castiglioni S, Bagnati R, Fanelli R. 2003. Strategic survey of therapeutic drugs in the rivers Po and Lambro in northern Italy. *Environ Sci Technol* 37(7):1241–1248.

 DOI: 10.1002/ieam.1895

Cooper ER, Siewicki TC, Phillips K. 2008. Preliminary risk assessment database and risk ranking of pharmaceuticals in the environment. *Sci Total Environ* 398(1–3):26–33.

Drugs.com. 2016. Database for drugs. Auckland (NZ): The Drugsite Trust. [cited 2015 Nov 1]. https://www.drugs.com/

[EC] European Commission. Technical guidance document on risk assessment 2003. Luxembourg. [cited 2016 Feb 10]. https://echa.europa.eu/documents/10162/16960216/tgdpart2_2ed_en.pdf

FASS Allmanhet. 2011. Swedish environmental classification of pharmaceuticals database. Stockholm. [cited 2015 Oct 1]. http://www.fass.se/LIF/startpage

Fick J, Lindberg RH, Tysklind M, Larsson DGJ. 2010. Predicted critical environmental concentrations for 500 pharmaceuticals. *Regul Toxicol Pharm* 58(3):516–523.

Franco A, Trapp S. 2008. Estimation of the soil-water partition coefficient normalized to organic carbon for ionizable organic chemicals. *Environ Toxicol Chem* 27(10):1995–2004.

Galus M, Kirischian N, Higgins S, Purdy J, Chow J, Rangaranjan S, Li HX, Metcalfe C, Wilson JY. 2013. Chronic, low concentration exposure to pharmaceuticals impacts multiple organ systems in zebrafish. *Aquat Toxicol* 132:200–211.

Guo JH, Boxall A, Selby K. 2015. Do pharmaceuticals pose a threat to primary producers? *Crit Rev Env Sci Tec* 45(23):2565–2610.

Guo JH, Sinclair CJ, Selby K, Boxall ABA. 2016. Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. *Environ Toxicol Chem* 35(6):1550–1559.

Halling-Sorensen B. 2000. Algal toxicity of antibacterial agents used in intensive farming. *Chemosphere* 40(7):731–739.

Hegelund T, Ottosson K, Radinger M, Tomberg P, Celander M. 2004. Effects of the antifungal imidazole ketoconazole on cyp1a and cyp3a in rainbow trout and killifish. *Environ Toxicol Chem* 23(5):1326–1334.

Huggett DB, Cook JC, Ericson JF, Williams RT. 2003. A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. *Hum Ecol Risk Assess* 9(7): 1789–1799.

Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker BA, et al. 2016. PubChem substance and compound databases. *Nucleic Acids Res* 44(D1):D1202–1213.

Kim Y, Jung J, Kim M, Park J, Boxall ABA, Choi K. 2008. Prioritizing veterinary pharmaceuticals for aquatic environment in korea. *Environ Toxicol Phar* 26(2):167–176.

Kümmerer K. 2001. Emission and biodegradability of pharmaceuticals, contrast media, disinfectants and aox from hospitals. In: Kümmerer K, editor. Pharmaceuticals in the environment: Sources, fate, effects, and risks. Heidelberg (DE): Springer. p 29–41.

Kümmerer K. 2010. Pharmaceuticals in the environment. In: Gadgil A, Liverman DM, editors. Annual review of environment and resources, Vol 35. Palo Alto (CA): Annual Reviews. p 57–75.

Medsafe. 2015. Classification of medicines - Classification process. Wellington, New Zealand. [cited 2015 Oct 25]. http://www.medsafe.govt.nz/

[MHSD] The Ministry of Healthcare and Social Development of the Republic of Kazakhstan. 2015. Health of the Republic of Kazakhstan and the activities of the Healthcare Organization in 2014. Statistical compilations. Astana, Kazakhstan. [cited 2016 May 10]. https://pda.mzsr.gov.kz/sites/default/files/sbornik_2014.pdf

[MHSD] The Ministry of Healthcare and Social Development of the Republic of Kazakhstan. 2016. Sale of medical drugs by prescription is no novelty. Astana, Kazakhstan. [cited 2016 June 1]. http://www.mzsr.gov.kz/en/node/335602

[OECD] Organisation for Economic Co-operation and Development. 2009. The guidance document for using the OECD (Q)SAR Application Toolbox to develop chemical categories according to the OECD Guidance on Grouping Chemicals. OECD Series on Testing and Assessment. Nr 102. Paris, France. [cited 2016 Feb 20]. http://www.oecd.org/officialdocuments/public displaydocument pdf/?doclanguage=en&cote=env/jm/mono(2009)5

Oguz M, Mihciokur H. 2014. Environmental risk assessment of selected pharmaceuticals in turkey. *Environ Toxicol Phar* 38(1):79–83.

Porsbring T, Blanck H, Tjellstrom H, Backhaus T. 2009. Toxicity of the pharmaceutical clotrimazole to marine microalgal communities. *Aquat Toxicol* 91(3):203–211.

Roos V, Gunnarsson L, Fick J, Larsson DGJ, Ruden C. 2012. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Sci Total Environ* 421:102–110.

Schwaiger J, Ferling H, Mallow U, Wintermayr H, Negele RD. 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac part 1: Histopathological alterations and bioaccumulation in rainbow trout. *Aquat Toxicol* 68(2):141–150.

Shi HH, Sun Z, Liu Z, Xue YG. 2012. Effects of clotrimazole and amiodarone on early development of amphibian (*Xenopus tropicalis*). *Toxicol Environ Chem* 94(1):128–135.

Struijs J, Stoltenkamp J, van de Meent D. 1991. A spreadsheet-based box model to predict the fate of xenobiotics in a municipal wastewater treatment plant. *Water Res* 25(7):891–900.

Tashenov A, Cherednichenko N. 2013. Development prospects for the pharmaceutical market of the single economic space. Almaty (KZ): Eurasian Development Bank. [cited 2015 Sep 22]. http://www.eabr.org/general/upload/docs/AU/%D0%90%D0%A3%20-%20%D0%98%D0%B7%D0%B4%D0%B0%D0%BD%D0%B8%D1%8F%20-%202013/OBZOR_18_rus.pdf

Vidal-Kazakhstan LLP. 2015. Directory Vidal – Pharmaceuticals in Kazakhstan. Astana, Kazakhstan. [cited 2015 Nov 1]. http://www.vidal.kz/

Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. 2006. DrugBank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res* 34(Databaseissue): D668–672.

Yasojima M, Nakada N, Komori K, Suzuki Y, Tanaka H. 2006. Occurrence of levofloxacin, clarithromycin and azithromycin in wastewater treatment plant in Japan. *Water Sci Technol* 53(11):227–233.

Zuccato E, Castiglioni S, Fanelli R. 2005. Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment. *J Hazard Mater* 122(3):205–209.

