Prioritisation of Pharmaceuticals Based on Risks to Aquatic Environments in Kazakhstan

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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. Prioritisation methodologies, that 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 prioritising APIs require annual pharmaceutical usage data. These methods cannot therefore be applied to countries, such as Kazakhstan, which have very limited data on API usage. This paper therefore presents an approach for prioritising 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 modelling 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 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 are limited.

Key words: active pharmaceutical ingredients, ecotoxicity, Kazakhstan, exposure, environmental risk

INTRODUCTION

Active pharmaceuticals 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). As many APIs are resistant to treatment in WWTPs, they are ultimately 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). Around 160 different APIs have been detected in the aquatic environment with the most common classes being detected belonging to the antibiotic, analgesic, painkiller and cardiovascular drug families (Kummerer 2010).

A wide range of effects of pharmaceuticals on aquatic organisms have 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 days (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 an 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 (Kummerer 2010).

While 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 while over 1500 APIs are in use, we only have data on the environmental risks of a few of these (Berninger et al. 2016). Therefore,

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 to focus research on APIs that really matter (Roos et al. 2012). A variety of approaches have therefore been proposed and applied for ranking of activated pharmaceutical ingredients (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 prioritised 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 as information on API usage is either limited or non-existent for many of these regions.

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 this study, the pharmaceutical market in the country is rapidly growing, and in 2012 more than 500 million packages of drugs were sold in the country 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). Wastewater treatment systems in Kazakhstan are also old and employ old technologies so the treatment may not be as effective in removing APIs 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.

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

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

A list of APIs in use in Kazakhstan was constructed using the online directory of pharmaceutical products in use 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 prioritisation manageable, all compounds contained in fewer than 3 products were not considered further as 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 the recommended daily dose and treatment duration was obtained (Supporting information, Table 1).

Environmental exposure

The relative exposure of those APIs in use in three or more products was characterised 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 fraction of drug not-metabolised by the patient and the fraction not removed by the WWTP. The fraction of unmetabolised API was obtained from peer-reviewed papers and available online databases (Wishart et al. 2006; FASS 2011; Medsafe 2015; Drugs.com 2016) (Supporting information, Table 2). 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 (ECA 2003), with slight modification (Eqn.1):

$$F_{wwtp} = 1 - \frac{Sludgeinhab * Koc * focsludge}{WasteWinhab + (Sludgeinhab * Koc * focsludge)} \quad \text{(Eqn. 1)}$$

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) as these are widely recognised for use in risk assessment. WasteWinhhab is the amount of wastewater per inhabitant per day, that was assumed to be 200 L/day (ECA 2003). Sludgeinhab was mass of waste sludge per inhabitant per day which was assumed to be 0.074 kg inh/day (ECA 2003). The focsludge (fraction of sludge organic carbon) was assumed to be 0.326 (Struijs et al. 1991). The soil organic carbon-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 the following equations:

$$\text{Log } K_{oc} = \log (\Phi_n X 10^{0.54 \log Pn + 1.11} + \Phi_{ion} 10^{0.11 \log Pn + 1.54}) \quad \text{for acids (Eqn. 2)}$$

$$\text{Log } K_{oc} = \log (\Phi_n X 10^{0.37 \log Pn + 1.70} + \Phi_{ion} 10^{pKa^{0.65}} Xf^{0.14}) \quad \text{for bases (Eqn. 3)}$$

An Exposure Index 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 the equation proposed by Fick et al. (2010) (Eqn. 4):

$$\text{LogPbw} = 0.73 * \text{LogKow} - 0.88 \quad \text{(Eqn. 4)}$$

Where Pbw was aqueous phase and fish arterial blood partition coefficient and Kow was Octanol/water partition coefficient.

Apical effects assessment

Predicted no-effect concentrations (PNEC) 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 and SCOPUS, and online datasets (FASS 2011) (Supporting information, Table 3). The data contained acute and chronic ecotoxicity endpoints as LC/EC50 values and, as the aim of this work for priotisation and not regulation, were not quality assessed. For substances that did not have experimental ecotoxicity data, the quantitative structure activity relationships (QSAR) toolbox was used in order to fill all gaps (OECD 2009). This software helped to define potential analogues and construct a matrix of data based on them. Initially, we selected the protein-binding profile. Then, on endpoints section we selected ecotoxicological information, that included growth, immobilisation and mortality. After that, on the category definition module we used the aquatic toxicity classification system by

ECOSAR. Finally, the toolbox processed data with a common structure (70-90%). Where the toolbox identified predictions to not be accurate, these predictions were not included in the priotization analysis.

$$\text{PNEC} = \frac{\text{EcoTox}}{\text{AF}} \quad \text{(Eqn. 5)}$$

Where PNEC is the predicted no-effect concentration, EcoTox is the most sensitive ecotoxicological data for the aquatic compartment and AF was the safety factor. The AF was selected based on recommendations in the Technical guidance document on risk assessment (ECA 2003).

Non-Apical Endpoints

In order to account for non-apical 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 of HtPC was obtained from online databases (FASS 2011; Medsafe 2015; Drugs.com 2016; Kim et al. 2016) (Supporting information, Table 4).

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. APIs with the highest ranking score were classified as the substances that should be in the list of concern.

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 remained. 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 three products were excluded, a list of 237 APIs was obtained for further prioritisation. Exposure indices for these substances are provided in the Supporting Information(Supporting information Tables 2 and 4). 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, fish and/or algae was available for 154 of the 237 APIs and human plasma therapeutic concentration data were available for 201 of these. Therefore, for the prioritisation, 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 non-apical assessment were lisinopril, orlistat, estradiol valerate, drotaverine and estradiol. Table 1 shows the top five ranked compounds broken down by classification of diseases. Classification of diseases was based on classes of illness cases registrated in health care institutions in Kazakhstan in 2014 (MHSD 2015).

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, as usage amount data were not available for Kazakhstan, used information on product numbers as the basis for the exposure characterisation. The assumption being that APIs which were

present in numerous products would be more widely used than APIs present in only a few products. During the study we found the main drugs of concern, based on a combination of risk to apical or non-apical endpoints, in Kazakhstan were amoxicillin, clarithromycin, azithromycin, ketoconazole, benzylpenicillin, terbinafine, drotaverine, diclofenac, benzathine benzylpenicillin and telmisartan as these had the highest risk scores.

Even though the ranking approach 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 UK by Guo et al. (2016). Moreover, amoxicillin was detected as a chemical with the highest hazard to aquatic organisms in the United Kingdom, 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 substance 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 effect in fish. Estradiol was identified by Guo et al. (2016) as having the potential to cause subtle effects in fish.

Most of the pharmaceuticals ranked highly 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 dataset on chronic effects of many antibiotics to aquatic ecosystems. The majority of ecotoxicology studies have been focusing 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 of drugs from our ranking list have been detected in monitoring studies around the world. This 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 (Kummerer 2001). Yasojima et al. (2006) showed clarithromycin and azithromycin at concentrations 647 ng/L and 260 ng/L in the 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 X. tropiclalis larvae and can lead to mortality of X. tropiclalis 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, 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 to rainbow trout and killifish at 12 and 100 mg/kg, as it suppressed cytochrome enzyme activity of fish (Hegelund et al. 2004). Halling-Sorensen (2000) showed that benzylpenicillin was toxic to M.aeruginasa, with an EC_{50} value of 0.005 mg/L. There is a large volume of published studies describing 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 as 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 like Kazakhstan. In future, we recommend that more efforts are 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 paper did not consider these for ranking even though in some instances they could pose a risk to the environment.

CONCLUSION

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 also 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 which 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

about the effect mixture pharmaceuticals on surface water. While the paper has focused on prioritisation 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 usage. The approach could therefore be invaluable in determining the wider impacts of APIs across the globe.

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Figure captions

Figure 1. Outline of the prioritization approach for active pharmaceutical ingredients (APIs) in surface waters in Kazakhstan. APIs – active pharmaceuticals ingredients; WWTP – wasterwater treatment plant; EIsw – exposure index for surface water; PNEC – predicted no-effect concentration; RCR – risk score ratio; EIfish – exposure index in fish plasma; HtPC – human plasma therapeutic concentration.

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

Table 1. Summary of top ranked APIs, by disease class, prioritised based on apical effects (EIsw:PNEC) and non-apical effects (HtPC:EIfish). Compounds in bold have been identified as priority using both methods.

#	**Classification of diseases**	**Registered morbidity incidents in health care institutions in 2014 in Kazakhstan (per 100000)**	**Top ranked APIs (EIsw:PNEC)**	**Top ranked APIs (HtPC:EIfish)**
1	Respiratory diseases	28233.8	Xylometazoline Beclomethasone Chloropyramine Pheniramine **Clemastine**	Loratadine **Clemastine** Montelukast Dextromethorphan Fexofenadine
2	Diseases of blood circulatory system	13472.7	**Telmisartan** Atorvastatin Rutoside Losartan Captopril	Lisinopril **Telmisartan** Amiodarone Rosuvastatin Amlodipine
3	Diseases of digestive system	8952.1	**Drotaverine** Ursodeoxycholic acid Thioctic acid	Orlistat **Drotaverine** Repaglinide Loperamide

			Bisacodyl Pioglitazone	Hyoscine butylbromide
4	Disease of urino-genital system	7250.8	**Ketoconazole** Levonorgestrel Nystatin **Miconazole** Drospirenone	Estradiol valerate Estradiol **Miconazole** Ethinylestradiol **Ketoconazole**
5	Diseases of the eye and its appendages	5516.3	**Neomycin** **Betaxolol** **Tropicamide**	**Betaxolol** **Neomycin** **Tropicamide**
6	Diseases of the blood-forming organs and certain	4965.9	**Clopidogrel**	**Clopidogrel**
7	Diseases of nervous system	4471.6	**Cinnarizine** Paracetamol Betahistine Carbamazepine Gabapentin	**Cinnarizine** Fentanyl Acetylsalicylic acid Tramadol Valproic acid
8	Diseases of the musculoskeletal system and connective tissue	4093.1	Diclofenac Etofenamate **Ketoprofen** Clodronic acid Naproxen	Methyl salicylate Diclofenac Indomethacin Benzydamine **Ketoprofen**

9	Infectious and parasitic diseases	2296	Amoxicillin Clarithromycin **Azithromycin** Benzylpenicillin **Terbinafine**	Clotrimazole Isotretinoin Disulfiram **Terbinafine** **Azithromycin**
10	Tumors	1657.	Oxaliplatin Cisplatin **Mycophenolic acid** Capecitabine Paclitaxel	Paclitaxel **Mycophenolic acid** Imatinib Anastrozole Topotecan
11	Mental and behavioral disorders	1270.6	Citicoline Piracetam **Fluoxetine** Clozapine Sertraline	Sertraline **Fluoxetine** Chlorpromazine Risperidone Clozapine

Note: Bold highlighted pharmaceuticals show their common appearance in top ranking of drugs on both risk ratios. APIs – activated pharmaceuticals ingredients; EIsw – exposure index for surface water; PNEC – predicted no-effect concentration; HtPC – human plasma therapeutic concentration; EIfish – exposure index in fish plasma.

Table 2. Defined top priority APIs in surface water of Kazakhstan, UK, France, US, Sweden, Iran, Korea and Spain

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	Acetyl salicylic 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	Mycophenolate mofetil	Trimethoprim	Diclazuril	Clarithromycin
Terbinafine	Ciprofloxacin	Furosemide	Clofibrate	Propranolol	Sulfamethoxazole	Dihydrostreptomycin sulfate	Ceftriaxone
Drotaverine	Clarithromycin	Clarithromycin	Ibuprofen	Acetylsalicylic acid	Azithromycin	Doxycycline	Furosemide
Diclofenac	Diclofenac	Diclofenac	Acetominophen	Naproxen		Enramycin	Bezafibrate
Benzathine benzylpenicillin	Estradiol	Sertraline	Estradiol	Felodipine		Erythromycin	Ciprofloxacin
Telmisartan	Metformin	Fluoxetine	Diclofenac	Ketoconazole		Fenbendazole	Enalapril
	Mesalazine		Caffeine				

Disulfiram Oxytetracycline	Omeprazole Orlistat	Fenofibrate Paroxetine Fluvoxamine	Carvedilol Metronidazole Trimethoprim Tetracycline Propranolol Gemfibrozil Naproxen Diazepam Paroxetine Clarithromycin	Acetaminophen Amitriptyline Fluoxetine Dipyridamole Chlorprothixene Bromhexine Entacapone Fulvestrant Galantamine	Erythromyc in	Florfenicol Fluvalinate Ivermectin Monensin sodium Norfloxacin Oxytetracycline	Spiramycin Omeprazole

Figure 1

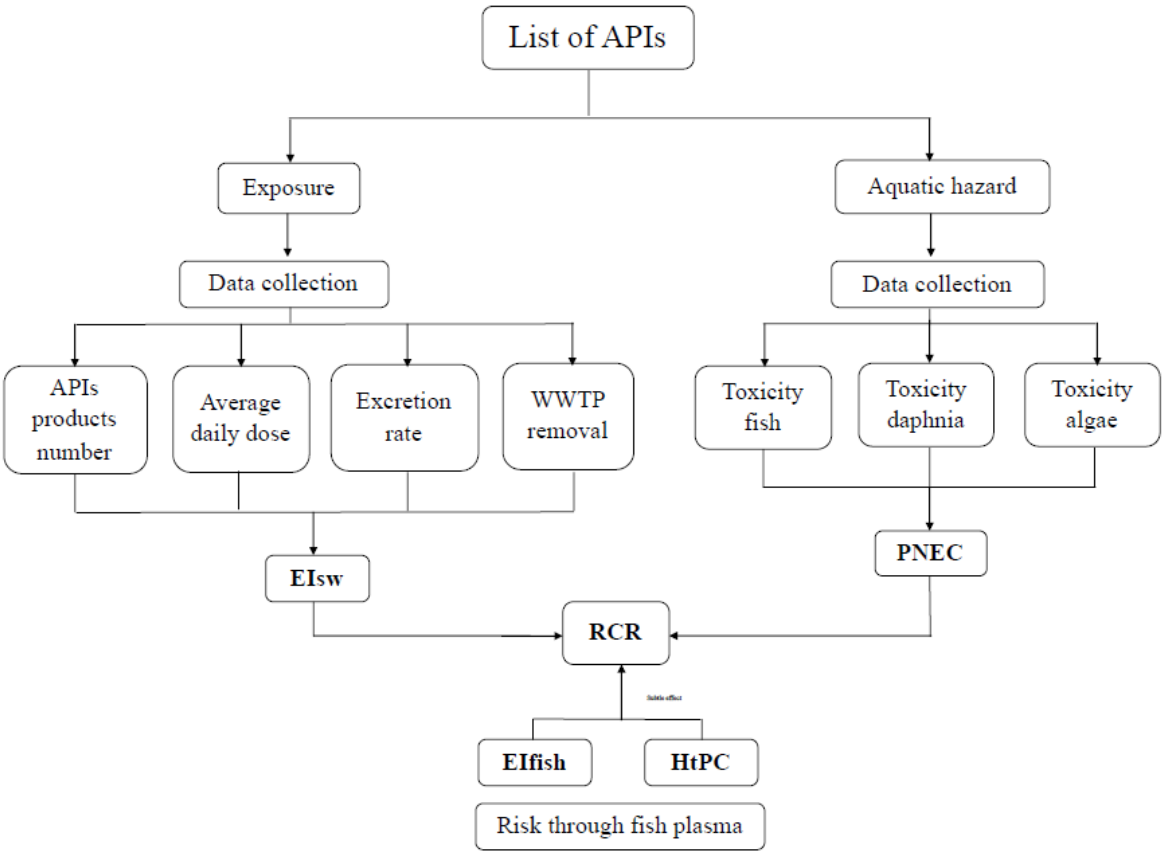
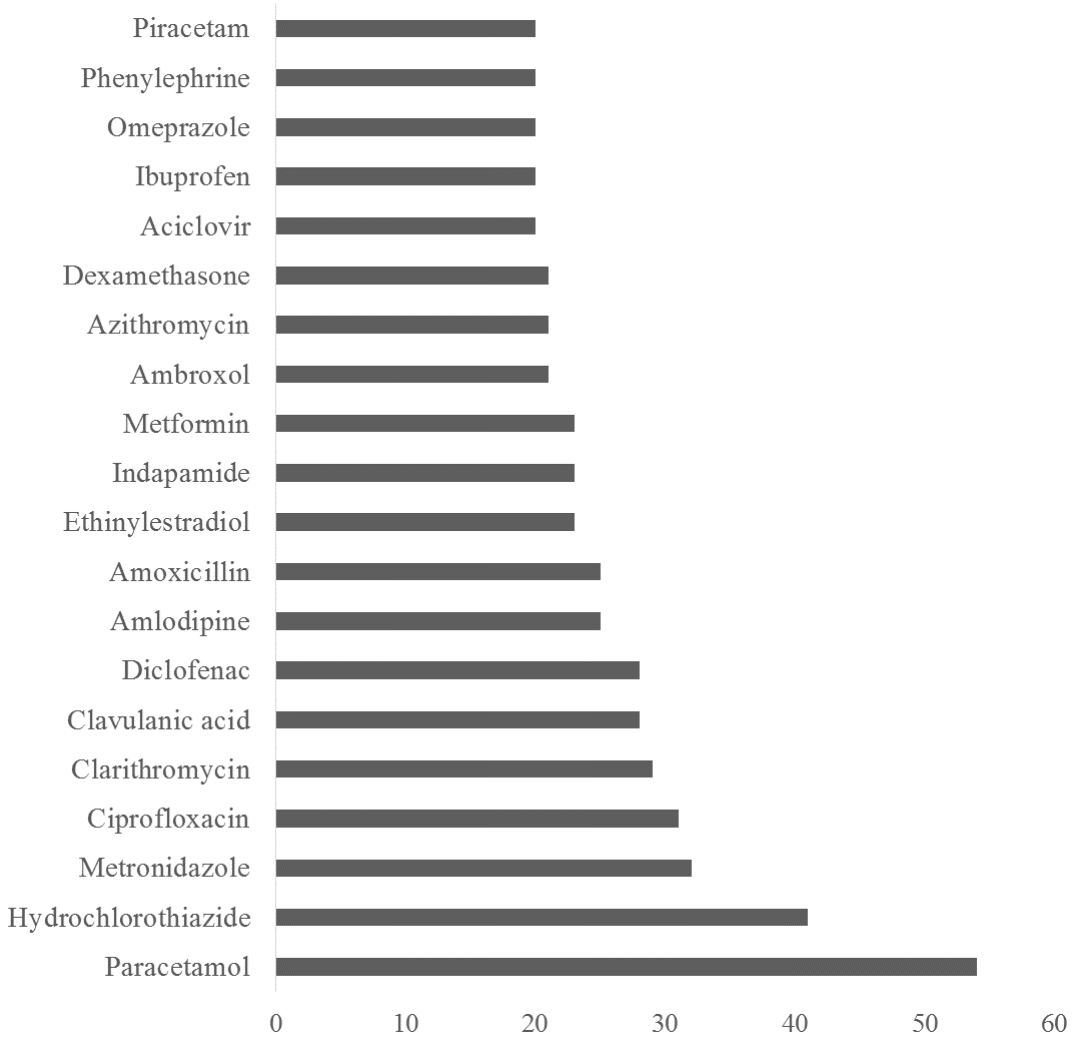

List of APIs
Exposure
Aquatic hazard
Data collection
Data collection
APIs products number
Average daily dose
Excretion rate
WWTP removal
Toxicity fish
Toxicity daphnia
Toxicity algae
PNEC
EIsw
RCR
EIfish
HtPC
Risk through fish plasma

Figure 2


Piracetam
Phenylephrine
Omeprazole
Ibuprofen
Aciclovir
Dexamethasone
Azithromycin
Ambroxol
Metformin
Indapamide
Ethinylestradiol
Amoxicillin
Amlodipine
Diclofenac
Clavulanic acid
Clarithromycin
Ciprofloxacin
Metronidazole
Hydrochlorothiazide
Paracetamol
0
10
20
30
40
50
60