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**Prioritisation of Pharmaceuticals Based on Risks to Aquatic Environments in
Kazakhstan**

Running head: Prioritisation of Pharmaceuticals in Kazakhstan

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1 **ABSTRACT**

2 Over the last 20 years, there has been increasing interest in the occurrence, fate,
3 effects and risk of pharmaceuticals in the natural environment. However, we still have
4 only limited or no data on ecotoxicological risks of many of the active pharmaceutical
5 ingredients (APIs) currently in use. This is partly due to the fact that the environmental
6 assessment of an API is an expensive, time-consuming and complicated process.
7 Prioritisation methodologies, that aim to identify APIs of most concern in a particular
8 situation, could therefore be invaluable in focusing experimental work on APIs that really
9 matter. The majority of approaches for prioritising APIs require annual pharmaceutical
10 usage data. These methods cannot therefore be applied to countries, such as Kazakhstan,
11 which have very limited data on API usage. This paper therefore presents an approach for
12 prioritising APIs in surface waters in information-poor regions such as Kazakhstan.
13 Initially data were collected on the number of products and active ingredients for different
14 therapeutic classes in use in Kazakhstan and on the typical doses. These data were then
15 used alongside simple exposure modelling approaches to estimate exposure indices for
16 active ingredients (about 240 APIs) in surface waters in the country. Ecotoxicological
17 effects data were obtained from the literature or predicted. Risk quotients were then
18 calculated for each pharmaceutical based on the exposure and the substances ranked in
19 order of risk quotient. Highest exposure indices were obtained for benzylpenicillin,
20 metronidazole, sulbactam, ceftriaxone and sulfamethoxazole. The highest risk was
21 estimated for amoxicillin, clarithromycin, azithromycin, ketoconazole and
22 benzylpenicillin. In the future, the approach could be employed in other regions where
23 usage information are limited.

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

26 INTRODUCTION

27 Active pharmaceutical ingredients (APIs) can be released to the aquatic
28 environment during their manufacture, following use and as a result of disposal (Boxall et
29 al. 2003). The major pathway is thought to be through excretion to the sewage system
30 where they are then transported to wastewater treatment plants (WWTPs) (Boxall et al.
31 2012). As many APIs are resistant to treatment in WWTPs, they are ultimately released in
32 WWTP effluents into surface waters. A range of APIs has been detected in surface waters
33 and wastewater effluents in several regions of the globe, including the Arctic (Besse et al.
34 2008; Brausch and Rand 2011). Around 160 different APIs have been detected in the
35 aquatic environment with the most common classes being detected belonging to the
36 antibiotic, analgesic, painkiller and cardiovascular drug families (Kummerer 2010).

37 A wide range of effects of pharmaceuticals on aquatic organisms have been reported
38 (Hegelund et al. 2004; Porsbring et al. 2009; Shi et al. 2012). Chronic toxicity studies have
39 shown effects at low concentrations in fish, invertebrates, algae and bacteria. For example,
40 diclofenac has been reported to have adverse histological impacts on kidney and gills of
41 rainbow trout at concentrations of 5 µg/L in 28 days (Schwaiger et al. 2004).
42 Acetaminophen, venlafaxine, carbamazepine and gemfibrozil at concentrations of 10
43 µg/L 0,5 µg/L and 10 µg/L respectively, had an adverse reproductive impacts, inducing
44 reproduction and changing kidney proximal tubule morphology (Galus et al. 2013).
45 Concentrations of propranolol and fluoxetine seen in effluents have been shown to affect
46 reproduction in aquatic organisms and the nervous system in fish (Kummerer 2010).

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

51 approaches are needed that cut down the number of pharmaceuticals to be studied in order
52 to focus on substances that are likely to pose the greatest risk and and for which
53 environmental risk should therefore be established using experimental testing (Besse et al.
54 2008; Guo et al. 2016).

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

65 It is however important to understand the risks of drugs in the environment in these
66 other unstudied regions. For example, in Kazakhstan, the focus of this study, the
67 pharmaceutical market in the country is rapidly growing, and in 2012 more than 500
68 million packages of drugs were sold in the country corresponding to an average of 32
69 packages per person per year (Tashenov and Cherednichenko 2013). Medical substances
70 are readily available in Kazakhstan with most of them being freely available for purchase
71 over the counter. According to the Ministry of Healthcare and Social Development of the
72 Republic of Kazakhstan, there are 7713 registered medications and approximately 24% of
73 these are available without a prescription (MHSD 2016). Wastewater treatment systems in
74 Kazakhstan are also old and employ old technologies so the treatment may not be as
75 effective in removing APIs as in western countries. Consequently, emissions of

76 pharmaceuticals to the natural environment in Kazakhstan are expected to be high and
77 impacts could be greater than elsewhere in the World.

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

82 **METHODS**

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

88 *Identification of pharmaceuticals in use in Kazakhstan and selection APIs for detailed* 89 *assessment*

90 A list of APIs in use in Kazakhstan was constructed using the online directory of
91 pharmaceutical products in use Kazakhstan (Vidal-Kazakhstan LLP 2015). For each API,
92 the number of products on the market was determined. Vitamins and vaccines were
93 excluded from the analysis. To make the prioritisation manageable, all compounds
94 contained in fewer than 3 products were not considered further as it was assumed that
95 exposure to these would be low, although in the future these compounds could also be
96 assessed. For the remaining compounds, data on the the recommended daily dose and
97 treatment duration was obtained (Supporting information, Table 1).

98 *Environmental exposure*

99 The relative exposure of those APIs in use in three or more products was
100 characterised by estimating an Exposure Index for surface water (EI_{sw}). The EI was

101 calculated by multiplying the number of products containing an API available on the
 102 market, the average daily dose and fraction of drug not-metabolised by the patient and the
 103 fraction not removed by the WWTP. The fraction of unmetabolised API was obtained
 104 from peer-reviewed papers and available online databases (Wishart et al. 2006; FASS
 105 2011; Medsafe 2015; Drugs.com 2016) (Supporting information, Table 2). The
 106 compounds without data were considered to be totally excreted from the body. The
 107 fraction not removed by the WWTP was estimated using an equation proposed by the
 108 Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use
 109 (ECA 2003), with slight modification (Eqn.1):

110

$$111 \quad F_{wwtp} = 1 - \frac{\text{Sludgeinhab} \cdot \text{Koc} \cdot \text{focsludge}}{\text{WasteWinhab} + (\text{Sludgeinhab} \cdot \text{Koc} \cdot \text{focsludge})} \quad (\text{Eqn. 1})$$

112

113 Where, F_{wwtp} is the fraction of pharmaceutical released from the WWTP.
 114 Wastewater parameters were obtained from the EU Technical Guidance Document for risk
 115 assessment of chemicals (EC, 2003) as these are widely recognised for use in risk
 116 assessment. $WasteWinhab$ is the amount of wastewater per inhabitant per day, that was
 117 assumed to be 200 L/day (ECA 2003). $Sludgeinhab$ was mass of waste sludge per
 118 inhabitant per day which was assumed to be 0.074 kg inh/day (ECA 2003). The $focsludge$
 119 (fraction of sludge organic carbon) was assumed to be 0.326 (Struijs et al. 1991). The soil
 120 organic carbon-water partitioning coefficient (Koc) value was estimated with the model
 121 established for ionizable organic chemicals proposed by Franco and Trapp (2008). This
 122 model estimates sorption using information on the hydrophobicity and degree of
 123 dissociation of a molecule using the following equations:

124

$$125 \quad \text{Log } K_{oc} = \log (\Phi_n \times 10^{0.54 \log P_n + 1.11} + \Phi_{ion} 10^{0.11 \log P_n + 1.54}) \quad \text{for acids (Eqn. 2)}$$

126 $\text{Log } K_{oc} = \log (\Phi_n X 10^{0.37 \log P_n + 1.70} + \Phi_{ion} 10^{pK_a^{0.65}} X f^{0.14})$ for bases (Eqn. 3)

127

128 An Exposure Index representing the internal exposure of APIs in fish plasma (EI_{fish})
129 was also determined by multiplying the EI_{sw} by the fish blood-water partition coefficient
130 (P_{bw}) for each API. The calculation of P_{bw} was performed using the equation proposed
131 by Fick et al. (2010) (Eqn. 4):

132

133
$$\text{Log } P_{bw} = 0.73 * \text{Log } K_{ow} - 0.88 \quad (\text{Eqn. 4})$$

134

135 Where P_{bw} was aqueous phase and fish arterial blood partition coefficient and K_{ow}
136 was Octanol/water partition coefficient.

137 ***Apical effects assessment***

138 Predicted no-effect concentrations (PNEC) were estimated for each API using
139 Equation 5. In order to estimate PNECs, we collected all available experimental
140 ecotoxicological data on the toxicity of APIs to apical endpoints in aquatic organisms from
141 peer-reviewed papers, using Google scholar, Web of Knowledge and SCOPUS, and online
142 datasets (FASS 2011) (Supporting information, Table 3). The data contained acute and
143 chronic ecotoxicity endpoints as LC/EC50 values and, as the aim of this work for
144 prioritisation and not regulation, were not quality assessed. For substances that did not have
145 experimental ecotoxicity data, the quantitative structure activity relationships (QSAR)
146 toolbox was used in order to fill all gaps (OECD 2009). This software helped to define
147 potential analogues and construct a matrix of data based on them. Initially, we selected the
148 protein-binding profile. Then, on endpoints section we selected ecotoxicological
149 information, that included growth, immobilisation and mortality. After that, on the
150 category definition module we used the aquatic toxicity classification system by

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

154

$$155 \quad \text{PNEC} = \frac{\text{EcoTox}}{\text{AF}} \quad (\text{Eqn. 5})$$

156

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

161 *Non-Apical Endpoints*

162 In order to account for non-apical effects relating to the therapeutic mode of action
163 of each API, we used a similar approach to that proposed by Huggett et al. (2003) and
164 collated information on plasma therapeutic concentrations (HtPC) of each API in humans.
165 The information of HtPC was obtained from online databases (FASS 2011; Medsafe 2015;
166 Drugs.com 2016; Kim et al. 2016) (Supporting information, Table 4).

167 *Ranking APIs*

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

172 **RESULTS**

173 In total, there are 7713 pharmaceutical products in use in Kazakhstan containing
174 1684 APIs. When complex mixtures as well as vaccines and vitamins are excluded, 841
175 APIs remained. The top 20 APIs, based on product number containing the ingredient, are

176 shown in Figure 2. Assuming product number is a surrogate for the extent of use, the most
177 widely used compound is paracetamol (an analgesic) followed by hydrochlorothiazide (a
178 diuretic used to treat high blood pressure, swelling and fluid build up) and metronidazole
179 (an antibiotic).

180 When APIs in use in fewer than three products were excluded, a list of 237 APIs
181 was obtained for further prioritisation. Exposure indices for these substances are provided
182 in the Supporting Information(Supporting information Tables 2 and 4). The highest
183 exposure indices in surface water were seen for benzylpenicillin, metronidazole,
184 sulbactam, ceftriaxone and sulfamethoxazole, whereas the highest exposure indices in fish
185 plasma were seen for lisinopril, orlistat, telmisartan, drotaverine and terbinafine.

186 Experimental ecotoxicity data for daphnia, fish and/or algae was available for 154 of
187 the 237 APIs and human plasma therapeutic concentration data were available for 201 of
188 these. Therefore, for the prioritisation, experimentally-based PNECs were used for 70% of
189 compounds and QSAR-based PNECs were used for 66 compounds. The most highly
190 ranked substances based on the apical ecotoxicological endpoints were amoxicillin,
191 clarithromycin, azythromycin, ketoconazole and benzylpenicillin, whereas the most highly
192 ranked compounds based on the non-apical assessment were lisinopril, orlistat, estradiol
193 valerate, drotaverine and estradiol. Table 1 shows the top five ranked compounds broken
194 down by classification of diseases. Classification of diseases was based on classes of
195 illness cases registrated in health care institutions in Kazakhstan in 2014 (MHSD 2015).

196 **DISCUSSION**

197 The objective of the present study was to develop a method for ranking
198 pharmaceuticals in data-poor regions. The approach built on previous studies but, as usage
199 amount data were not available for Kazakhstan, used information on product numbers as
200 the basis for the exposure characterisation. The assumption being that APIs which were

201 present in numerous products would be more widely used than APIs present in only a few
202 products. During the study we found the main drugs of concern, based on a combination of
203 risk to apical or non-apical endpoints, in Kazakhstan were amoxicillin, clarithromycin,
204 azithromycin, ketoconazole, benzylpenicillin, terbinafine, drotaverine, diclofenac,
205 benzathine benzylpenicillin and telmisartan as these had the highest risk scores.
206 Even though the ranking approach used a different approach from previous studies, the
207 results show that some of the top ranked compounds in our study are also ranked highly by
208 earlier prioritization research (Table 2). For example, amoxicillin, clarithromycin,
209 diclofenac and azithromycin, with the highest risk score, were defined as high priority
210 in an ecotoxicological risk-based prioritization study performed in the UK by Guo et al.
211 (2016). Moreover, amoxicillin was detected as a chemical with the highest hazard to
212 aquatic organisms in the United Kingdom, France, Italy, Iran, Korea and Spain (Table 2).
213 Cooper et al. (2008) concluded that sulfamethoxazole, diclofenac and clarithromycin were
214 the pharmaceuticals of high risk in a US study. Ketoconazole was identified as one of the
215 priority substance in a study by Roos et al. (2012) in Swedish aquatic systems. Lisinopril,
216 orlistat, estradiol valerate, cinnarizine, drotaverine, estradiol and clotrimazole were
217 identified as having the potential to elicit subtle effect in fish. Estradiol was identified by
218 Guo et al. (2016) as having the potential to cause subtle effects in fish.

219 Most of the pharmaceuticals ranked highly on our list are related to the treatment of
220 infectious and parasitic diseases, so the majority of them are antibiotics. Currently,
221 antibiotics are one of the most well investigated pharmaceutical classes in terms of acute
222 toxicity to aquatic organisms (Brausch and Rand 2011). Nevertheless, we still have a
223 limited dataset on chronic effects of many antibiotics to aquatic ecosystems. The majority
224 of ecotoxicology studies have been focusing on acute toxicity of antibiotics to algal
225 species and the EC50s vary from 0.002 mg/L to 1283 mg/L (Guo et al. 2015).

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

232 The majority of substances from the ranking list have been reported to cause toxicity
233 to aquatic organisms. For instance, Shi et al. (2012) showed that clotrimazole can affect
234 the development stage of *X. tropiclaialis* larvae and can lead to mortality of *X. tropiclaialis*
235 even at a low concentration (0.1 µg/L). In 2008 Porsbring et al. (2009) conducted a
236 toxicity assessment of clotrimazole to natural microalgal communities. The results of the
237 research showed that this compound causes growth inhibition of algal communities, it can
238 alter their pigment profiles and physiology (Porsbring et al. 2009). Hegelund et al. (2004)
239 investigated the response of fish to ketoconazole. Their results showed, that this
240 compound had effects to rainbow trout and killifish at 12 and 100 mg/kg, as it suppressed
241 cytochrome enzyme activity of fish (Hegelund et al. 2004). Halling-Sorensen (2000)
242 showed that benzylpenicillin was toxic to *M.aeruginasa*, with an EC₅₀ value of 0.005
243 mg/L. There is a large volume of published studies describing the risk of clarithromycin to
244 the environment. For instance, Oguz and Mihciokur (2014) studied the environmental
245 risks of drugs in Turkey and concluded that clarithromycin can cause potential hazard to
246 living organisms because of its high bioconcentration factor. Furthermore, the substance
247 with the highest concentration in Italian rivers was clarithromycin at a concentration of
248 0.02 µg/L (Calamari et al. 2003). A considerable amount of literature has been published
249 on the toxicity and occurrence of diclofenac in the last decades. Recent research by Acuna
250 et al. (2015) has reported that the occurrence of diclofenac was mentioned in 142 papers,

251 which covered 38 countries. Moreover, there were 156 reports about the ecotoxicological
252 effects of this substance (Acuna et al. 2015).

253 **LIMITATIONS**

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

264 **CONCLUSION**

265 The population of Kazakhstan is increasing so it is likely that consumption of
266 medicines in the country will grow too. Pharmaceuticals are readily available in Kazakhstan
267 with most of them being freely available for purchase over the counter. Wastewater treatment
268 systems in the country are also old and employ old technologies so the treatment may not be
269 as effective as in Western countries. Consequently, emissions of pharmaceuticals to the
270 natural environment in Kazakhstan are expected to be high and impacts could be greater than
271 elsewhere in the world. Overall, the present assessment prioritized the human prescription
272 APIs, that are most likely to be present in Kazakhstan surface waters and which could pose
273 the greatest risk to living organisms. We recommend that these compounds be considered in
274 future research to monitor concentrations of the APIs in the Kazakhstan environment and to
275 establish the level of risk to ecosystems in the country. It would be interesting to consider

276 about the effect mixture pharmaceuticals on surface water. While the paper has focused on
277 prioritisation of pharmaceuticals in use in Kazakhstan, the design of the approach means that
278 it can be applied in other countries with limited data on API usage. The approach could
279 therefore be invaluable in determining the wider impacts of APIs across the globe.

280

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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 – wastewater treatment plant; EIs_{sw} – 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:Elfish). 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:Elfish)
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; EIs_w – 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 (Alighardas hi et al. 2014)	Korea (Kim et al. 2008)	Italy (Zuccato et al. 2005)
Amoxicillin	Amitriptyline	Amoxicillin	Erythromycin	Ethynyl estradiol	Amoxicillin	Amoxicillin	Amoxicillin
Clarithromycin	Amoxicillin	Acetyl salicylic acid	Oxytetracycline	Atovaquone	Cephalexin	Apramycin	Atenolol
Azithromycin	Atorvastatin		Sulfamethoxazole	Sertraline	Clavulanic acid	Bromhexine	Hydrochlorothiazide
Ketoconazole	Azithromycin	Ofloxacin	Fluoxetine	Estradiol	Penicillin	Ciprofloxacin	Ranitidine
Benzylpenicillin	Carbamazepine	Propranolol	Nitroglycerin	Mycophenolate mofetil	Trimethoprim	Diclazuril	Clarithromycin
Terbinafine	Ciprofloxacin	Carbamazepine	Clofibrate	Propranolol	Sulfamethoxazole	Dihydrostreptomycin sulfate	Ceftriaxone
Drotaverine	Clarithromycin	Furosemide	Ibuprofen	Acetylsalicylic acid	Sulfamethoxazole	Doxycycline	Furosemide
Diclofenac	Diclofenac	Clarithromycin	Acetaminophen	Naproxen	Azithromycin	Enramycin	Bezafibrate
Benzathine	Estradiol	Diclofenac	Estradiol	Felodipine	in	Erythromycin	Ciprofloxacin
benzylpenicillin	Metformin	Sertraline	Diclofenac	Ketoconazole		Fenbendazole	Enalapril
Telmisartan	Mesalazine	Fluoxetine	Caffeine				

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

Figure 1

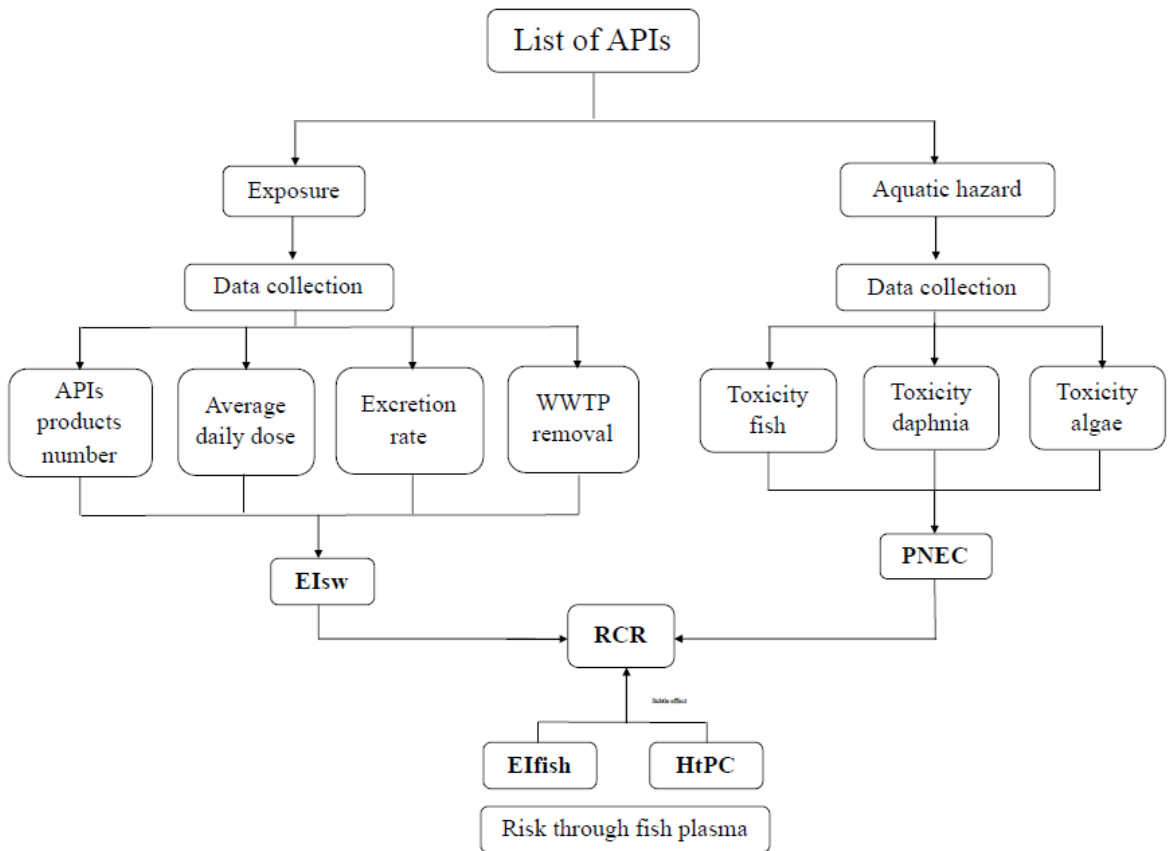


Figure 2

