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Environmental risk analysis and prioritization of pharmaceuticals in a developing world context

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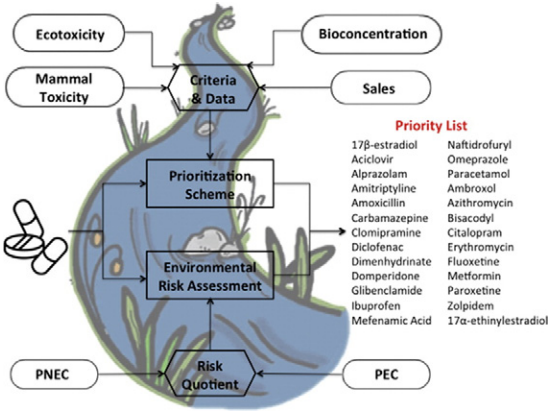
HIGHLIGHTS

- 69 pharmaceuticals are prioritized using a multi criteria decision analysis approach.
- Environmental risk analysis is performed on 84 pharmaceuticals.
- Metformin and amoxicillin have the highest predicted environmental concentrations.
- A priority list of 26 pharmaceuticals is identified for potential monitoring purposes.
- The priority list is dominated by nervous system and alimentary tract pharmaceuticals.

GRAPHICAL ABSTRACT



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ABSTRACT

The impact of residual pharmaceuticals on the aquatic environment has gained widespread attention over the past years. Various studies have established the occurrence of pharmaceutical compounds in different water bodies throughout the world. In view of the absence of occurrence data in a number of developing world countries, and given the limited availability of analytical resources in these countries, it is prudent to devise methodologies to prioritize pharmaceuticals for environmental monitoring purposes that are site specific. In this work, several prioritization approaches are used to rank the 88 most commonly consumed pharmaceuticals in Lebanon. A simultaneous multi-criteria decision analysis method utilizing the exposure, persistence, bioaccumulation, and toxicity (EPBT) approach is applied to a smaller subset of the original list (69 pharmaceuticals). Several base cases are investigated and sensitivity analysis is applied to one of these base case runs. The similarities and differences in the overall ranking of individual, and classes of, pharmaceuticals for the base cases and the sensitivity runs are elucidated. An environmental risk assessment (ERA), where predicted environmental concentrations (PEC) and risk quotients (RQ) are determined at different dilution factors, is performed as an alternative method of prioritization for a total of 84 pharmaceuticals. The ERA results indicate that metformin and amoxicillin have the highest PECs while 17β-estradiol, naftidrofuryl and dimenhydrinate have the highest RQs. The two approaches, EPBT prioritization and ERA, are compared and a priority list consisting of 26 pharmaceuticals of various classes is developed. Nervous system and alimentary tract and metabolism pharmaceuticals (9/26 and 5/26 respectively) constitute more than half of the numbers on the priority list with the balance consisting of anti-

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infective (4/26), musculo-skeletal (3/26), genito-urinary (2/26), respiratory (2/26) and cardiovascular (1/26) pharmaceuticals. This list will serve as a basis for the selection of candidate compounds to focus on for future monitoring campaigns.

1. Introduction

The number of pharmaceutically active compounds, for human and veterinary use, that are being prescribed globally is not known with any degree of certainty. Caldwell et al. (2014) have reported the number to be 3500, Boxall et al. (2012) have given a figure of 4000, Hughes et al. (2013) have reported a figure of 5000 for Europe only and a much higher value of 10,000 has been reported by Dong et al. (2013) for the US market. The number of pharmaceutical compounds that have been detected in water bodies is also subject to debate; Hughes et al. (2013) have reported a total number of 203 compounds detected worldwide, whereas Kuster and Adler (2014) have reported a worldwide number of 600.

In the Middle East and North Africa (MENA), and in the developing world in general, the number of investigations and the number of pharmaceuticals detected in water bodies are much smaller than those reported in the developed countries (Hughes et al., 2013; Segura et al., 2015). To date, and to the authors' knowledge, the total number of investigations performed in the MENA region is limited to 12 where studies were conducted in six countries only (Israel, Jordan, Lebanon, Palestine, Tunisia and Saudi Arabia) and out of the 42 compounds investigated 28 have been detected in surface and ground water bodies. These studies are summarized in Table S1 of the supplementary material and the appropriate references given in Table S11. It is worth noting that for the vast majority of these studies, the choice of pharmaceuticals has not been clearly stated and, when stated, was based on the most frequently dispensed pharmaceuticals or obtained from occurrence data recorded in water bodies of the developed world.

Whilst there is an extensive and ever growing body of literature on the occurrence, fate, removal and toxicological effects of pharmaceuticals in the environment, there are currently no statutory regulations anywhere in the world defining maximum safe contaminant levels of pharmaceutical compounds in drinking water and sewage effluent discharges (Straub and Hutchinson, 2012). This absence of regulation appears to be changing with the recent issuance of Directive 2013/39/EU of the European Union amending earlier directives on priority substances in the field of water policy (EC, 2013). This directive calls for the inclusion of 17-α-ethinylestradiol, 17-β-estradiol and diclofenac, onto "the first watch list, in order to gather monitoring data for the purpose of facilitating the determination of appropriate measures to address the risk posed by those substances" (EC, 2013).

In view of the large number of pharmaceutical compounds currently in use, several prioritization methodologies have been proposed to identify a manageable and smaller subset of substances of high relative concern (Boxall et al., 2012; Guillen et al., 2012; Kuzmanovic et al., 2013; Roos et al., 2012). This list of priority substances allows for an effective deployment of resources for environmental and human health risk assessment, monitoring and regulatory purposes (Boxall et al., 2012).

Criteria used for the prioritization of pharmaceuticals include:

(a) sales figures,
(b) exposure data which incorporates measured or predicted occurrence in the environment,
(c) toxicity data, derived from acute or chronic experiments, or through quantitative structural activity relations (QSAR), that a particular pharmaceutical will have on specific types of organisms, fauna, flora and on the environment,
(d) pharmacological attribute which encompasses sub-attributes such as enzymatic induction or inhibition, metabolic inactivation, nature of effects, dose dependency,
(e) physico-chemical properties such as molecular weight, chemical structure, partitioning coefficients, e.g. octanol-water, K_{OW}, or organic carbon-water, K_{OC}, half-life, vapor pressure, water solubility, Henry's constant, degradation coefficients, bioconcentration factor (BCF), and other biochemical properties,
(f) literature based where a compound is considered a priority if it has been listed in a number of previous studies,
(g) sewage treatment plant (STP) removal efficiency to determine the extent of or the potential for environmental contamination and
(h) specific miscellaneous guidelines such as analytical measurement feasibility, expert judgment, removal by advanced treatment processes.

A considerable number of the methodologies combine elements of exposure and hazard effects (see Table 1). Hazard effects are related to the intrinsic properties of the pharmaceutical compounds and are characterized by persistence (P), bioaccumulation (B) and toxicity (T) either individually or in the combined PBT approach.

Another commonly used prioritization approach, which utilizes some aspects of the exposure and PBT approach is the environmental risk assessment (ERA) methodology proposed initially as a discussion paper and then developed, after several iterations, into a guideline document for approving newly introduced pharmaceutical products (EMEA/CPMP, 2001; EMEA/CHMP, 2006). This two-step methodology combines an exposure element with an effect element. The exposure element is determined by a predicted environmental concentration (PEC) or a measured environmental concentration (MEC). On the other hand, the exposure element is determined by a toxicity (T) attribute. This approach has been used by several researchers and regulatory authorities (Carlsson et al., 2006; FASS, 2012; Grung et al., 2008) to rank pharmaceuticals according to their risk quotient, RQ.

A number of prioritization methods employed elements of the ERA, whether based on MEC or PEC, in combination with one or more of the criteria detailed above to propose hybrid sequential or hybrid simultaneous prioritization methodologies (Table 1).

A summary of the main prioritization methodologies discussed above, primarily those involving at least two criteria and not restricted to ERA investigations, along with the criteria used for each individual methodology are presented in Table 1. It can be seen from Table 1 that almost all of the prioritization studies have been conducted in North America, Europe and China, the exception being a single South African study by Ncube et al. (2012). Whilst prioritization methodologies developed in North America, Europe and China can be applied to other regions in the world, the priority lists generated by these methodologies may not be applicable to countries in the developing world. This is primarily due to the differing environmental and climatic conditions, the levels of wastewater collection and treatment (or absence thereof), the type of pharmaceuticals used, and the usage pattern and quantities of pharmaceuticals consumed.

A "criteria map" is shown in Fig. 1 where the relationships between exposure, persistence, bioaccumulation and toxicity and the various criteria discussed above are elucidated graphically.

In view of the dearth of prioritization studies in the developing world and the lack of extensive occurrence data in the MENA region the objectives of this study are as follows: (a) to perform a prioritization

Table 1
Summary of prioritization studies.

Authors	Country	No. of drugs	Criteria							
			Sales	Exposure	Toxicity	Pharma	Physico-chemical	Guide-lines	Literature	STP removal
Ashton et al. (2004)	UK	12	+	+	+					+
Besse et al. (2008)	France	120		+	+	+	+	+	+	+
Booker et al. (2014)	UK	65	+	+			+			+
Castiglioni et al. (2006)	Italy	26	+	+					+	
Christen et al. (2010)	EU	20			+	+		+		
Cooper et al. (2008)	USA	287	+	+	+		+			
Coutu et al. (2012)	Switzerland	58			+		+	+	+	
Daginnus et al. (2011)	Europe	151	+	+	+					
Daouk et al. (2015)	Switzerland	71	+	+	+		+			+
de Voogt et al. (2009)	Europe	153	+	+	+		+	+	+	+
Diamond et al. (2011)	USA	144		+	+		+			
Dong et al. (2013)	USA	200	+	+	+			+		+
Donnachie et al. (in press)	UK	21	+	+	+				+	
Ginebreda et al. (2012)	Spain	43		+	+			+		
Gotz et al. (2010)	Switzerland	44		+			+	+	+	
Helwig et al. (2013)	Europe	15	+	+	+				+	+
Howard and Muir (2011)	USA & Canada	674	+	+	+		+			
Jean et al. (2012)	France	70	+	+	+		+			
Jin and Peldszus (2012)	Canada	101	+	+	+		+	+		
Kumar and Xagoraraki (2010)	USA	55		+	+					+
Li et al. (2014)	China	51		+	+		+			+
Morais et al. (2014)	Europe	82		+	+		+			+
Ncube et al. (2012)	S. Africa	46		+	+			+	+	
Oldenkamp et al. (2013)	Europe	18	+	+	+			+		+
Olsen et al. (2013)	USA	406	+	+	+		+		+	
Ortiz de Garcia et al. (2013)	Spain	84	+	+	+		+			
Perazzolo et al. (2010)	Switzerland	58	+	+	+	+	+	+		+
Roos et al. (2012)	Sweden	582	+	+	+	+	+	+		
Sanderson et al. (2004)	Canada	2986			+	+		+		
Sui et al. (2012)	China	39	+		+		+	+		+
von der Ohe et al. (2011)	Europe	21			+	+		+		
Wennmalm and Gunnarsson (2010)	Sweden	153		+	+		+			
Zhou et al. (2014)	China	126	+		+		+		+	

study for the pharmaceuticals sold in the Lebanese market using the exposure-hazard approach so as to rank these pharmaceuticals in a descending order of priority; (b) to carry out an environmental risk assessment to predict the environmental concentrations and risk quotients, RQ, of pharmaceuticals in Lebanese surface water bodies and (c) to compare the results of the two methods, and to determine their robustness in the face of uncertainties. The ultimate objective of this study is to prepare a list of priority pharmaceuticals that may serve as a basis for the selection of candidate compounds for future monitoring campaigns in Lebanese water bodies.

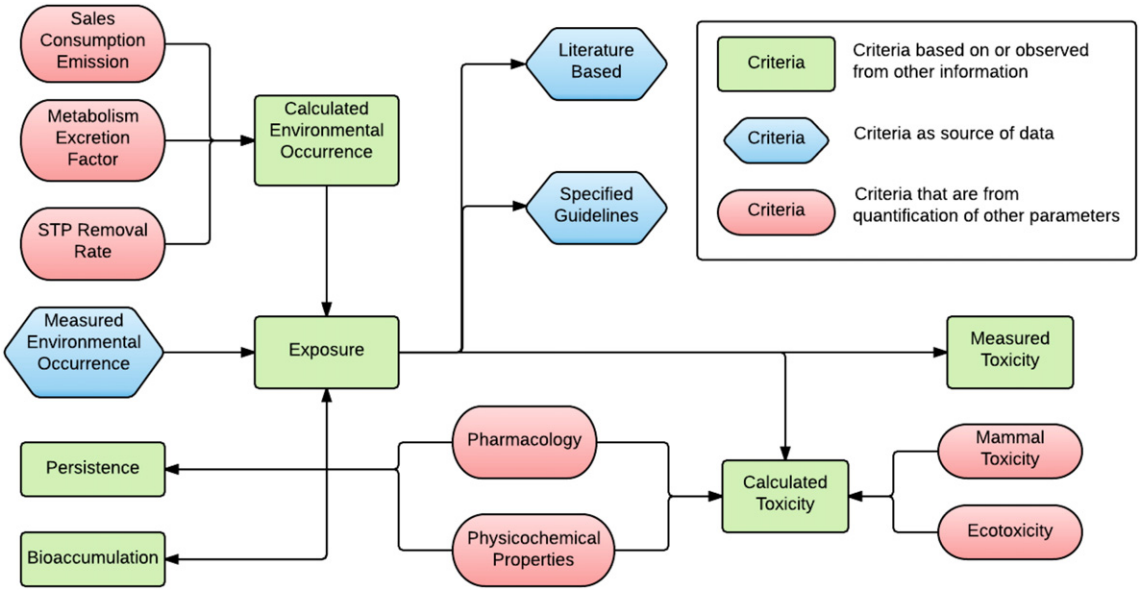

Fig. 1. A summary diagram of the criteria used for previous prioritization studies.

2. Materials and methods

2.1. Analysis of Lebanese situation

2.1.1. Pharmaceutical consumption

Lebanon is an upper-middle income country (World Bank, 2015). The expenditure on pharmaceuticals was $1.3 billion for the year 2012 (BANKMED, 2013). Sales data in terms of the number of units (boxes or packages) sold for a particular medicine containing injectable, oral (capsules, tablets, suspensions) and other forms for the year 2012 were collected from IMS Health. This data includes the sales quantities of all prescribed and over the counter pharmaceuticals delivered to pharmacists and hospitals in Lebanon. This information was then converted into mass of pharmaceutical using the following equation:

$$M = \frac{\left(\sum_i^j p_i * n_i * A_i\right)}{10^6} \quad (1)$$

where:

M	the total amount of pharmaceutical sold annually, in kg
i	the active ingredient being considered, dimensionless
j	the number of different forms of the active ingredient, dimensionless
p_i	the number of packages sold of active ingredient i, dimensionless
n_i	the number of tablets (or other form of administration), dimensionless
A_i	the amount of active ingredient i in each tablet, in mg
10^6	the conversion factor from mg to kg, dimensionless.

2.1.2. Wastewater treatment

Lebanon has a small number of small and medium sized wastewater treatment plants that are currently operational. There are, however, several large sized plants that have been constructed but, due to a variety of reasons, are not yet operational (Massoud et al., 2010; World Bank, 2011). The volume of wastewater that is currently treated in Lebanon is low compared to other countries in the region and well below treatment levels attained in the developed world (WHO, 2005; World Bank, 2012). The volumes of wastewater treated in Lebanon are subject to debate with some reports claiming that <10% is treated (MOE/EU/UNDP, 2014), others claiming 19% (World Bank, 2011) and the most optimistic study reporting a 26% treatment level (ACWUA, 2010).

Almost all of the wastewater generated on the Lebanese coastline, which represents approximately 65% of the total wastewater generated in the country, is discharged into the Mediterranean Sea with preliminary treatment only (MOE/EU/UNDP, 2014; World Bank, 2012). On the other hand, a large percentage of non-coastal towns and villages lack wastewater infrastructure (MOE/UNDP/ECODIT, 2011) and rely on open sewers, septic tanks, cesspools or simply discharge wastewater directly into the environment (WHO, 2005; World Bank, 2011). These practices have resulted in severe contamination of water bodies in Lebanon as evidenced by very high counts of fecal and total coliforms, organic and inorganic pollutants recorded in rivers, watersheds and ground water (El-Fadel et al., 2000; Massoud et al., 2010).

2.2. Prioritization

2.2.1. Criteria

The prioritization procedure applied to the list of pharmaceuticals consumed in Lebanon is in line with previous studies in that it utilizes the exposure-hazard (PBT) approach. However, unlike the majority of methods employed in the literature where the prioritization proceeds sequentially, the prioritization method proposed in this work utilizes a simultaneous multi-criteria decision analysis, a methodology employed previously by a smaller number of workers (Kumar and Xagoraraki, 2010; Li et al., 2014; Sui et al., 2012) to rank a list of pharmaceuticals in a descending order of priority.

The exposure criterion is based on the amounts released to the environment determined by multiplying the mass sold by the excretion factor. The bioconcentration factor (BCF), which is a function of K_{OW}, is used for bioaccumulation (EPA, 2013). Two sub-criteria are used for persistence: the organic carbon-water, K_{OC}, partition coefficient and percentage removal of pharmaceutical in sewage treatment plants (STP). Eco and mammalian toxicities are used for the toxicity criterion. The criteria, sub-criteria as well the interpretation of each sub-criterion are shown in Table 2. A pharmaceutical compound will feature very high on the list of priority compounds if it has a high sales figure, high excretion factor, low STP removal, low partitioning coefficient, low concentration values for eco and mammalian toxicities.

2.2.2. Database compilation

Physical property data is gathered for the criteria listed above and compiled into a comprehensive database. The bioconcentration factor (BCF), adsorption constant (K_{oc}), and sewage treatment plant (STP) removal data are obtained from the EPISuites software (EPA, 2013) and ChemSpider (ChemSpider, 2015); it should be noted that the STP removal data are for the conventional extended aeration activated sludge process and are applicable to the Lebanese situation. The ecological structure activity relationship (ECOSAR) software is used to obtain ecotoxicity values, where the lowest value amongst green algae, daphnid, and fish ecotoxicity values is used (EPA, 2012). The ChemIDPlus database is used for the mammalian LD_{50} values; the lowest value amongst rat and mice toxicities is used (ChemIDplus, 2015). The excretion factor values are collected from several sources and databases. The database, and references used to obtain the data sets, can be found in Tables S2 and S11, respectively, of the supplementary material.

Based on the highest selling pharmaceuticals in Lebanon in 2012, a list consisting of a total of 88 pharmaceuticals was initially considered. However, the absence of mammalian toxicity data, excretion factors and sewage treatment plant removal for a number of pharmaceuticals led to their exclusion from the prioritization study. In view of this, the base list used for the prioritization runs was reduced to a total of 68/69 pharmaceuticals with/without the STP removal criterion.

2.2.3. Ranking and scoring

A multi-criteria decision analysis (MCDA) algorithm is used to get a final priority list of pharmaceuticals. The “Logical Decisions” software is used to prioritize the list of pharmaceuticals according to the set of criteria discussed above (Logical Decisions, 2014). The software uses the multiple criteria values inputted for each alternative, or pharmaceutical, to generate an overall utility score, according to which they are ranked in terms of priority. It should be noted that for each criterion, the pharmaceuticals are ranked in an ascending or descending order of priority depending on the assigned values. The highest priority is assigned to compounds that pose the greatest environmental risk to the water compartment.

The “alternatives” (pharmaceuticals) are entered into the software along with the respective values for each criterion. The log form of all criteria data, except for excretion factor and STP removal values, are used. This is due to the large range of values for the raw criteria values, which drastically affects the utility distribution. The log form of values provides a more even and clearer distribution between values. For each criterion, most and least preferred values are assigned based on how each criterion contributes to the pharmaceutical's behavior in the environment. For some criteria, the most preferred value, i.e. that which contributes to ranking the substance as that of greater priority, is the maximum value in the range; for other criteria, the most preferred value is the minimum value, as observed in Table 2. For a particular criterion each pharmaceuticals is then given a numerical score between 0

Table 2
Criteria, sub-criteria, and preferred values used for the prioritization methodology.

Criteria	Sub-criteria	Most preferred value[a]	Least preferred value[a]	Interpretation
Exposure	Sales figures	High	Low	The higher the sales, the more likely it is for pharmaceutical to be present in the environment.
	Excretion factor	High	Low	The higher the excretion, the more likely it is for pharmaceutical to be present in the environment.
Bioaccumulation	Bio Concentration Factor (BCF)	High	Low	The higher the BCF, the more likely it is for pharmaceutical to bioconcentrate.
Persistence	STP removal	Low	High	The lower the % of pharmaceutical removed, the higher its concentration in effluent water.
	Log K_{oc}	Low	High	The lower the K_{oc}, the lower the sorption to soil/sediment, and the faster the migration to groundwater.
Toxicity	Eco	Low	High	The lower the value, the less concentration needed to induce a toxic effect.
	Mammalian	Low	High	The lower the value, the less concentration needed to induce a toxic effect.

[a] The most and least preferred values refer to where the criterion falls on the priority scale with respect to environmental risk in the water compartment. A criterion with a high most preferred value indicates that the higher the value of that criterion, the greater risk it poses to the water environment. On the other hand, a high least preferred value indicates the higher the value the lower the priority, i.e. the lower the risk it poses to the water environment.

and 1, which is determined on the basis of the specific value for that pharmaceutical relative to the range of values for the criterion.

The overall rank score, $R_{i,total}$, for a pharmaceutical, i, varies between 0 and 1 with a value closer to 1 indicating a high priority. The overall rank score is calculated from:

$$R_{i,total} = \sum_{j=1}^{N_C} W_{j,i} \times R_{j,i} \quad (2)$$

where $W_{j,i}$ is the weight of criterion j, $R_{j,i}$, is the numerical score (between 0 and 1) of pharmaceutical i for the j criterion and N_C is the total number of criteria used in a particular run.

Three "base" cases are chosen. Table 3 details the criteria used for each base case along with the weight for each criterion with and without the incorporation of the STP removal criterion. For case A, six criteria are selected, one criterion for exposure, consisting of sales multiplied by excretion factor, two for persistence, one for bioaccumulation, and two for toxicity. For base case B, five criteria are selected, while four criteria are selected for base case C (the classic (E)PBT approach). For each base case, there are two runs, one with the STP removal criterion and one without where for the runs without the STP criterion the number of criteria are reduced to 5, 4, and 3 for cases A, B and C, respectively. The base case runs with the STP removal criterion reflect an optimistic case while the runs without the STP criterion represent a more realistic reflection of the current Lebanese situation.

2.2.4. Sensitivity analysis

To determine the effect of individual criterion on the overall prioritization ranking, the weight of each criterion is shifted through a series of runs derived from the base case 'B', described above. Base case B is used as it is the most representative of the objectives of this study, which caters to the prioritization of pharmaceuticals in the water compartment; for this purpose, the K_{OC} criterion is deemed relatively unimportant. It is noted that two sets of runs are performed to account for the exclusion (T runs) and inclusion (S runs) of the STP removal criterion.

In the base run T_0 (S_0 with STP removal criterion), all criteria have equal weighting; i.e. the results will be identical to those for base case B. Modifying the weights is done via a swing method, where the number of points (out of 100) is changed to reflect the significance of the criterion, with 100 being most significant. Thus, all criteria are assigned 50 points in the base run. Then, one by one, each of the remaining criteria are increased to 100 points individually (in different runs). As the other criteria remain at 50 points, one criterion has higher weighting, which demonstrates the sensitivity of prioritization to that criterion. Thus 5 additional simulations are performed for the T runs and 4 additional simulations for the S runs giving a total of 11 runs. The resulting weighting scheme is presented in Table S3 of the supplementary material.

2.3. Environmental risk assessment (ERA)

The procedure for environmental risk assessment is based on the EMEA guidelines (EMEA/CPMP, 2001) and consists of a step-wise tiered procedure. In the first step, a predicted environmental concentration (PEC) in surface water is calculated using the following equation (Besse et al., 2008; Carlsson et al., 2006):

$$\mathrm{PEC} = \frac{A \times E \times (100-R) \times 10^6}{365 \times P \times V \times DF \times 100} \quad (3)$$

where PEC is in μg/L,

A	the amount of pharmaceutical used per year, in kg
R	the removal rate of the pharmaceutical during wastewater treatments, in %
P	the number of inhabitants dimensionless
E	the excretion factor of the pharmaceutical, dimensionless fraction
V	the volume of waste water generated per day per capita, in m^3/day
DF	is the dilution factor of wastewater by surface water (dimensionless)

Table 3
Applicable criteria and weights used for the base case prioritization runs.

Base case	Criteria used	Weight ($W_{j,i}$)[a] (without STP removal)	Weight ($W_{j,i}$)[a] (with STP removal)
A	BCF, K_{oc}, LD_{50} (mammal), ecotoxicity, sales-excretion	0.2	0.167
B	BCF, LD_{50} (mammal), ecotoxicity, sales-excretion	0.25	0.2
C	BCF, ecotoxicity, sales-excretion	0.33	0.25

[a] The weights are calculated from 1/(total number of criteria). BCF: bioconcentration factor; K_{oc}: adsorption constant; LD: lethal dose.

100 the conversion factor for percentage, dimensionless
365 the number of days in a year, dimensionless
10^6 the conversion factor from g/L to μg/L, dimensionless.

The assumptions underlying Eq. (3) are: (a) all of the pharmaceuticals that are sold are consumed, (b) the predicted amount used is evenly distributed throughout the year, (c) there is no breakdown of the pharmaceutical in the sewage system, (d) pharmaceuticals do not absorb to organic or inorganic colloidal material or bacterial biomass in sewage treatment plants or natural water. For Lebanon, the number of inhabitants, *P*, was assumed to be equal to 4,924,257 (UN, 2015) and *V* was assumed to be equal to 0.15 m^3/day (El-Fadel et al., 2000).

Three scenarios are considered in this work:

PEC_0: worst case scenario where the excretion factor is set to 1 and the removal rate is set to zero.

PEC_A: a more realistic scenario for the conditions prevalent in Lebanon, where the excretion factor is taken into account but the removal rate is set to zero.

PEC_B: a more optimistic scenario, where both the excretion factor and the removal rate are taken into account; this scenario, through the use of R, may under or over-estimate a number of the attenuation processes (such as volatilization, adsorption/absorption, photolysis) that will inadvertently occur post discharge.

For the PEC calculations several dilution factors (DFs) are used. The three DFs considered are: 3, 6.6, and 10. The selection of the DF = 3 and DF = 6.6 is based on two studies where different values for DF were given for Lebanon (Keller et al., 2006; Keller et al., 2014); whereas, the DF of 10 is included as it is the most commonly used dilution factor (Besse et al., 2008; Carlsson et al., 2006; FASS, 2012; Grung et al., 2008), and is representative of a more optimistic scenario.

If the value of PEC for any of the pharmaceuticals is <0.01 μg/L, it is assumed that this pharmaceutical is unlikely to present a risk to the environment (Agerstrand et al., 2015; Christen et al., 2010; EMEA/CPMP, 2001) and no further assessment is deemed necessary. On the other hand, for all pharmaceuticals with a PEC value > 0.01 μg/L, a phase II environmental fate and effect analysis is performed (Christen et al., 2010) whereby a predicted no effect concentration (PNEC) for each pharmaceutical is determined and a risk quotient, RQ (Carlsson et al., 2006; Escher et al., 2011; Iatrou et al., 2014), is calculated from the following equation:

$$RQ = \frac{PEC}{PNEC}. \quad (4)$$

Several methodologies have been proposed for the determination of PNEC. The EMEA guidelines (EMEA/CHMP, 2006) recommend the use of standard long term (chronic) toxicity tests on algae, daphnia and fish in conjunction with an appropriate assessment factor (AF). On the other hand, several workers, citing the paucity of experimental acute toxicological data for a large number of pharmaceuticals, have opted for the use of ecological structure activity relationships (ECOSAR) class program (Dong et al., 2013; Escher et al., 2011), acute and chronic experimental toxicity data (Grung et al., 2008) or both ECOSAR and experimental toxicological values (Iatrou et al., 2014).

In this work, the approach adopted by Escher et al. (2011) will be used whereby the ecotoxicity data is obtained from ECOSAR. For each pharmaceutical three PNEC values are calculated from the ratio of the ecotoxicity for each of the three taxa (green algae, daphnid and fish) to an assessment factor of 1000, as seen in the formula below. The ecotoxicity values for the three taxa can be found in the supplementary material (Table S1).

$$PNEC = \frac{Ecotoxicity_{green\ \ algae}}{1000} \text{ and } \frac{Ecotoxicity_{daphnid}}{1000} \text{ and } \frac{Ecotoxicity_{fish}}{1000} \quad (5)$$

According to EMEA the risk is based on a binary ecological classification where for an RQ ≥ 1, a likely appreciable risk exists for the environment while for an RQ < 1, the risk is unlikely (EMEA/CHMP, 2006). Hernando et al. (2006), on the other hand, propose three levels of risk to the environment: a "low" level for the range 0.01 ≤ RQ ≤ 0.1, a "medium" level from 0.1 ≤ RQ ≤ 1, and a "high" level for RQ > 1. FASS (2012) proposes four levels of risk: an "insignificant" level for RQ ≤ 0.1, a "low" level for the range 0.1 ≤ RQ ≤ 1, a "moderate" level for the range 1 ≤ RQ ≤ 10, and a "high" level for RQ > 10. In this work, the approach proposed by FASS (2012) is used for the risk categorization. Two RQ values are reported, RQ_A, corresponding to PEC_A, defined above (i.e. the STP removal term is assumed to be zero), and RQ_B, corresponding to PEC_B (i.e. the STP removal value is incorporated).

It should be noted that the absence of excretion data and ECOSAR based PNEC data for a number of pharmaceuticals reduced the data set from the original 88 down to 84 for the PEC calculations and to 71 for the RQ calculations.

3. Results

3.1. Consumption of pharmaceuticals in Lebanon

A complete list of the sales data for the top 88 pharmaceuticals sold in Lebanon can be found in Table S2 in the supplementary materials. The top five selling pharmaceuticals in Lebanon are paracetamol (nervous system-analgesic), metformin (alimentary tract and metabolism-antidiabetic), amoxicillin (anti-infective), ibuprofen (musculo-skeletal-anti-inflammatory), and acetylsalicylic acid (nervous system-analgesic). The anatomical therapeutic chemical (ATC) classification system proposed by WHO (WHO, 2013) is used to classify the pharmaceuticals considered in this work into various categories. Of the top 15 selling pharmaceuticals (selling over a ton annually), the majority are of the musculo-skeletal category (40%) followed by the nervous system (30%) category; there are also two anti-infectives, one cardiovascular, and one alimentary pharmaceutical.

It is worth noting that the per capita consumption of pharmaceuticals in Lebanon is approximately 49 g per capita which is well above the worldwide average per capita consumption of 15 g (Zhang et al., 2008) and almost in line with the developed countries' value of 50–150 g per capita (Zhang et al., 2008).

3.2. Prioritization results - base case analysis

Table 4 lists the top 30 pharmaceuticals of highest priority for the three base case simulation runs (A, B and C) with and without the STP removal criterion. The complete set of prioritization results can be found in Table S4 of the supplementary material.

As can be seen from Table 4, the results for base case A indicate that for the top 30 pharmaceuticals, there are only 11 pharmaceuticals in common for the two runs (with/without STP removal criterion). However, with the exception of metformin, the pharmaceuticals constituting the top 10 are entirely different for the two runs. The highest priority pharmaceuticals for each run: amitriptyline (without STP removal criterion) and amoxicillin (with STP removal criterion) belong to different classes, and are unique to each run. Another particular effect of the inclusion of STP removal criterion is that some of the highest selling pharmaceuticals such as mefenamic acid, acetylsalicylic acid, ibuprofen, and tiaprofenic acid, which appear near the top of ranking in run A (without the STP removal criterion) are not amongst the top 30 list for run A with the STP removal criterion.

As for base case B, 15 of the top 30 pharmaceuticals are common to both runs (with and without the STP removal criterion). The highest priority pharmaceuticals are naftidrofuryl and amoxicillin without/with STP removal criterion respectively. On the other hand, for base case C runs there are 23 pharmaceuticals that are in common between the runs with/without STP removal criterion. Bisacodyl and naftidrofuryl

Table 4
Ranking of the top 30 pharmaceuticals for prioritization base cases A, B, and C, with/without the STP removal criterion.

Base case A				Base case B				Base case C			
Without STP removal	$R_{i,total}$	With STP removal	$R_{i,total}$	Without STP removal	$R_{i,total}$	With STP removal	$R_{i,total}$	Without STP removal	$R_{i,total}$	With STP removal	$R_{i,total}$
Amitriptyline	0.67	Amoxicillin	0.75	Naftiduryl	0.81	Amoxicillin	0.74	Naftiduryl	0.92	Bisacodyl	0.74
Naftidrofuryl	0.65	Cefixime	0.71	Amitriptyline	0.78	17β-Estradiol	0.73	Glibenclamide	0.81	17β-Estradiol	0.73
Metformin	0.62	Metformin	0.70	Clomipramine	0.71	Bisacodyl	0.73	Amitriptyline	0.81	Naftidrofuryl	0.73
Clomipramine	0.62	Aciclovir	0.70	Glibenclamide	0.66	Domperidone	0.72	Clomipramine	0.78	Citalopram	0.73
Sulfadiazine	0.62	Bisacodyl	0.69	Paroxetine	0.65	Ambroxol	0.70	17β-Estradiol	0.73	Paroxetine	0.72
Dimenhydrinate	0.61	17β-Estradiol	0.69	Sertraline	0.64	Celecoxib	0.69	Fenofibrate	0.71	Ambroxol	0.72
Paroxetine	0.59	Ambroxol	0.69	Fluoxetine	0.63	Aciclovir	0.69	Paroxetine	0.70	Celecoxib	0.72
Paracetamol	0.59	Erythromycin	0.68	Citalopram	0.61	Glibenclamide	0.69	Domperidone	0.69	Domperidone	0.72
Allopurinol	0.59	Ampicillin	0.68	Zolpidem	0.61	Omeprazole	0.68	Citalopram	0.68	Fluoxetine	0.72
Bisoprolol	0.58	Domperidone	0.68	Sulfadiazine	0.61	Erythromycin	0.68	Fluoxetine	0.68	Alprazolam	0.72
Azithromycin	0.58	Ciprofloxacin	0.67	Fenofibrate	0.61	Carbamazepine	0.68	Hydroxyprogesterone	0.68	Zolpidem	0.71
Acetylsalicylic acid	0.57	Azithromycin	0.66	Mefenamic acid	0.59	Cefixime	0.68	Zolpidem	0.68	Omeprazole	0.71
Fluoxetine	0.57	Phloroglucinol	0.66	Allopurinol	0.58	Azithromycin	0.67	Sertraline	0.68	Carbamazepine	0.71
Diosmin	0.56	Carbamazepine	0.66	17β-Estradiol	0.58	Albendazole	0.66	Azithromycin	0.67	Albendazole	0.70
Sertraline	0.55	Ofloxacin	0.66	Propranolol	0.58	Citalopram	0.66	Bisacodyl	0.67	Erythromycin	0.70
Citalopram	0.55	Captopril	0.65	Azithromycin	0.57	Testosterone	0.66	Celecoxib	0.65	Diltiazem	0.70
Alprazolam	0.55	Atenolol	0.65	Dimenhydrinate	0.57	Carvedilol	0.66	Progesterone	0.64	Glibenclamide	0.69
Glibenclamide	0.55	Omeprazole	0.65	Progesterone	0.57	Ampicillin	0.66	Atorvastatin	0.64	Amoxicillin	0.69
Propranolol	0.55	Alprazolam	0.64	Paracetamol	0.57	Phloroglucinol	0.66	Mefenamic acid	0.63	Paracetamol	0.69
Diltiazem	0.55	Celecoxib	0.64	Diltiazem	0.57	Alprazolam	0.65	Ambroxol	0.63	Azithromycin	0.69
Zolpidem	0.54	Testosterone	0.64	Alprazolam	0.56	Indapamide	0.65	Carvedilol	0.62	Metformin	0.69
Mefenamic acid	0.54	Indapamide	0.64	Bisoprolol	0.56	Zolpidem	0.65	Alprazolam	0.62	Progesterone	0.69
17β-Estradiol	0.54	Furosemide	0.63	Domperidone	0.55	Metformin	0.64	Omeprazole	0.61	Amitriptyline	0.68
Ciprofloxacin	0.54	Albendazole	0.63	Celecoxib	0.55	Progesterone	0.64	Carbamazepine	0.61	Dimenhydrinate	0.68
Erythromycin	0.54	Carvedilol	0.63	Hydroxyprogesterone	0.55	Naftidrofuryl	0.64	Albendazole	0.60	Propranolol	0.67
Ambroxol	0.54	Citalopram	0.62	Bisacodyl	0.54	Fluoxetine	0.64	Erythromycin	0.60	Testosterone	0.66
Tiaprofenic acid	0.53	Paracetamol	0.62	Clonixin	0.54	Paroxetine	0.63	Amoxicillin	0.59	Indapamide	0.66
Ibuprofen	0.52	Doxycycline	0.62	Ibuprofen	0.54	Furosemide	0.62	Diltiazem	0.59	Allopurinol	0.65
Fenofibrate	0.52	Ranitidine	0.61	Albendazole	0.53	Ciprofloxacin	0.62	Paracetamol	0.59	Phloroglucinol	0.65
Ranitidine	0.52	Dimenhydrinate	0.61	Ambroxol	0.53	Atenolol	0.62	Propranolol	0.59	Aciclovir	0.65

$R_{i,total}$ is the overall numerical score for a pharmaceutical i, between 0 and 1, such that a value closer to 1 indicates higher priority.

are the highest-ranking priority pharmaceuticals in the former and latter cases, respectively.

It can be observed from Table 4 that a number of pharmaceuticals can be found consistently across all three base case runs with or without STP removal. For example, clomipramine, sertraline, mefenamic acid, and fenofibrate appear in all the base case runs (A, B, and C) without the STP removal criterion. On the other hand, aciclovir, testosterone, indapamide, and phloroglucinol appear in all the base case runs with the STP removal criterion. Azithromycin, citalopram, alprazolam, and 17β-estradiol appear across all the base case runs with and without the STP removal criterion, but at different rankings for each run.

Fig. 2(a) shows the comparison of the ATC pharmaceuticals classes for the base case runs A, B and C without the STP removal criterion where it can be seen that the nervous system pharmaceuticals account for the largest share of the pharmaceuticals across all the runs, with the cardiovascular pharmaceuticals coming in second. On the other hand, for the base case runs A, B and C with the STP removal criterion, Fig. 2(b) shows that anti-infective pharmaceuticals account for a majority of the pharmaceuticals in runs A and C, but nervous system pharmaceuticals dominate for run C. All three runs have the same amount of alimentary tract and metabolism pharmaceuticals, which is the second largest category. Cardiovascular pharmaceuticals come in third for runs A and B.

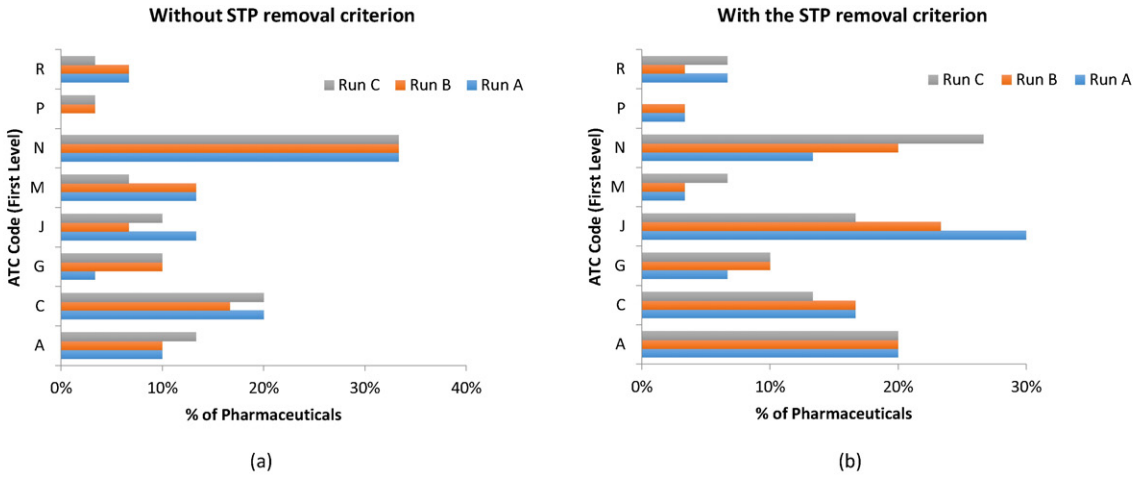

Fig. 2. Therapeutic class distribution of the top 30 ranked pharmaceuticals from base case runs A,B, and C: (a) without the STP removal criterion and (b) with the STP removal criterion.

3.3. Sensitivity analysis

Complete results for both sets of sensitivity analysis can be found in Table S5 (without the STP removal criterion, the T_0–T_4 runs) and Table S6 (with the STP removal criterion, S_0–S_5 runs) of the supplementary material. On the other hand, Table S7 lists all of the pharmaceuticals that have appeared in the top 15 for the T (without STP removal) and S (with STP removal) runs, respectively, and details the number of times a particular pharmaceutical appears across the runs.

For both sets of sensitivity runs a total of 38 unique priority pharmaceuticals are identified, where nervous system, anti-infective, and alimentary tract and metabolism pharmaceuticals account for approximately 26%, 18%, and 16%, respectively, of all pharmaceuticals. There are 27 pharmaceuticals that appear in the top 15 across the five T sensitivity runs, the most consistent of which are amitriptyline, citalopram, clomipramine, fluoxetine, glibenclamide, naftidrofuryl, and paroxetine. On the other hand, a total of 24 pharmaceuticals appear in the top 15 of the six S sensitivity runs, the most consistent of which are 17β-estradiol, ambroxol, bisacodyl, domperidone, and erythromycin.

It is worth noting that in comparing the sensitivity results with/without STP removal, the pharmaceuticals consistent in each case differ quite substantially. However, nine pharmaceuticals are common to both sets of sensitivity runs (the T and S runs): 17β-estradiol, azithromycin, citalopram, domperidone, glibenclamide, metformin, naftidrofuryl, paroxetine, and zolpidem with the most significant amongst these are 17β-estradiol and glibenclamide which appear consistently throughout the S and T sensitivity runs.

3.4. Environmental risk assessment

The results for all the PEC calculations, PEC_0, PEC_A and PEC_B, for the 84 pharmaceuticals can be found in Tables S8 for all three dilution factor values. Similarly, the RQ calculations, RQ_A and RQ_B, for the 71 pharmaceuticals for all three taxa, can be found in Tables S9. The discussion below is focused primarily on the PEC and RQ calculations at a dilution factor of 3 as this is the most conservative of the three values and appears to be more representative of the situation in Lebanon, in terms of how much pharmaceuticals are expected to be released into the environment.

Fig. 3 presents the results of the PEC_A and PEC_B calculations. Given that the difference between PEC_A and PEC_B is the inclusion of the STP removal coefficient, which varies from one pharmaceutical to another, the environmental risk, or otherwise, posed by a particular pharmaceutical is expected to differ between PEC_A and PEC_B. The calculations indicate that there are 30 pharmaceuticals that have a PEC_A, ≥0.01 μg/L and 29 pharmaceuticals that exhibit values of PEC_B, ≥0.01 μg/L with metformin and amoxicillin at the top of the priority list for both PEC_A and PEC_B.

Fig. 4 shows the pharmaceuticals across all environmental risk levels, according to the RQ guidelines discussed above for all three taxa: green algae, daphnid and fish.

For the green algae taxa, 16 pharmaceuticals have exhibited RQ_A values that are considered to pose some form of environmental risk. Three of these pharmaceuticals, 17β-estradiol, naftidrofuryl and dimenhydrinate have the highest risk quotients posing, in accordance with the FASS (FASS, 2012) classification of risk, a high level of risk. On the other hand there are 15 pharmaceuticals that have RQ_B values that are considered to pose an environmental risk with 17β-estradiol and dimenhydrinate posing a high level of environmental risk. On the other hand, for the RQ values based on daphnid ecotoxicity, ten pharmaceuticals are considered to pose an environmental risk for RQ_A and 7 for RQ_B. For RQ_A, one pharmaceutical, naftidrofuryl is of high risk, two, paracetamol and mefenamic acid, are of moderate risk, and the remaining ones are of low risk. RQ_B has no "high" risk pharmaceuticals, two, naftidrofuryl and mefenamic acid, moderate risk pharmaceuticals, and 5 low risk ones. The number of priority drugs drops for the fish taxon, resulting in 6 and 5 compounds for RQ_A and RQ_B, respectively. For RQ_A, two drugs, naftidrofuryl and mefenamic acid, are of "moderate" risk, while the remaining ones are of low priority including clonixin, which did not appear as a risk for the other two taxa. As for RQ_B, all pharmaceuticals are of low risk.

The number of pharmaceuticals that constitute an environmental risk decreases with increasing dilution factors where, for a dilution factor of 6.62 the number of pharmaceuticals posing any form of environmental risk reduces to 12 for RQ_A (10 for RQ_B) for PNECs based on the green algae taxa.

There are a number of uncertainties associated with the use of the ERA methodology. These include (a) incorrect sales quantities; (b) inaccurate or incorrect values for a number of the parameters used

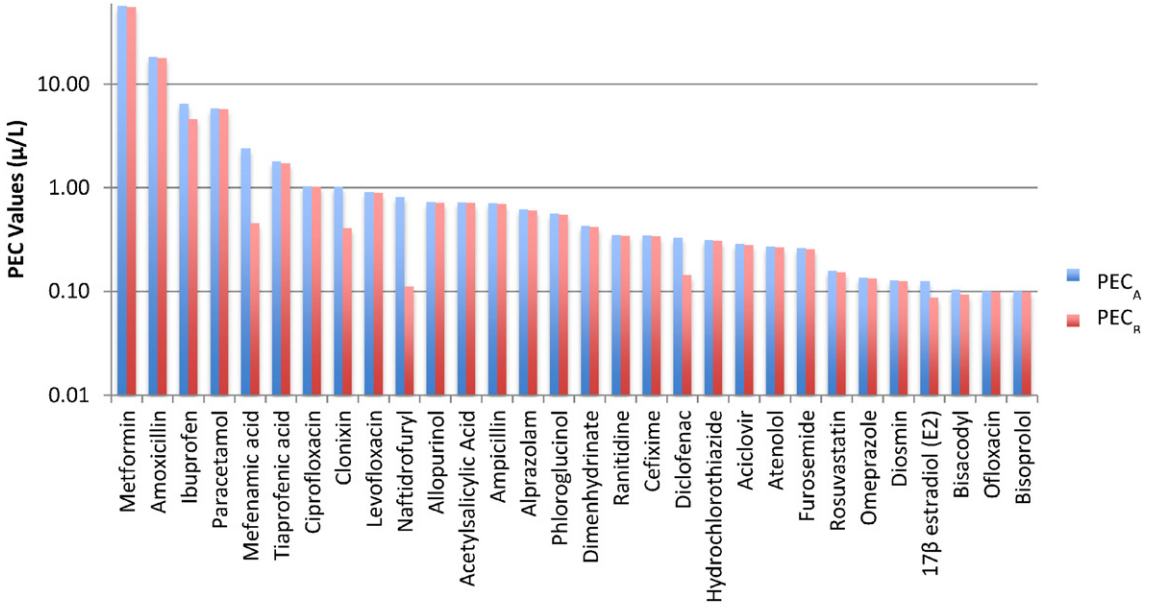

Fig. 3. Predicted environmental concentrations (PEC) of the top 30 pharmaceuticals in Lebanese surface water.

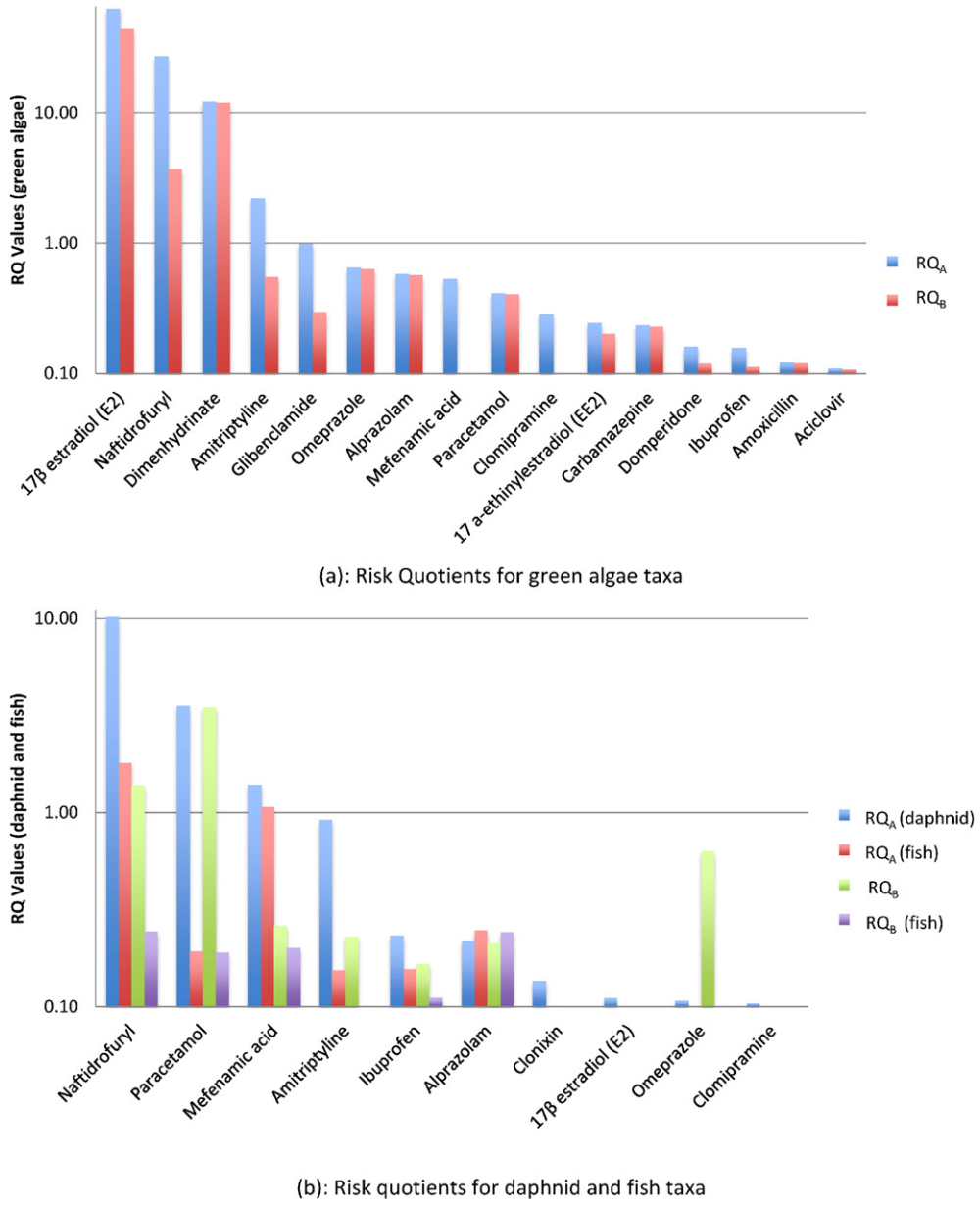

Fig. 4. Risk quotients (RQ) for priority pharmaceuticals calculated using PNECs for: (a) green algae and (b) daphnid and fish.

for the calculation of PEC; (c) unaccounted for attenuation, degradation or metabolism mechanisms in sewer, rivers and surface water (Besse et al., 2008; Verlicchi et al., 2014).

3.5. Comparison between the prioritization methodology and the ERA results

With the exception of 17α-ethinylestradiol, all of the other 16 pharmaceuticals that constitute any level of environmental risk, according to the RQ analysis, are also found in the top 30 ranking pharmaceuticals of at least one of the base case runs A, B, and C, regardless of whether it is for the results with or without STP removal criterion. 17α-ethinylestradiol does not appear in the top 30 of any of the three base case prioritization runs. 17β-estradiol and alprazolam are the only two pharmaceuticals that appear consistently across all prioritization runs and are of risk according to ERA at a dilution factor of 3. Of the 17 priority pharmaceuticals, as determined by the RQ analysis, three compounds appear in the runs where the STP removal criterion is not accounted for: mefenamic acid, clorixan and clomipramine, while aciclovir appears only in the runs when the STP removal criterion is included. The remaining 11 pharmaceuticals appear differently across the runs, as can be seen in Table 5.

Table 5 shows that base case C runs, with and without STP removal criterion, have the most overlap with the results of the RQ risk at DF = 3. The overlap is not surprising given that in base case C the exposure criteria, sales-excretion factor, has the highest weighting factor amongst the other three base cases and will therefore yield a priority list which matches very closely the priority list generated by the environmental risk assessment method.

While the ERA approach is capable of generating a list of priority pharmaceuticals, it suffers from a number of disadvantages: it relies exclusively on consumption and ecotoxicity parameters, does not account for other important parameters such as persistence, and bioaccumulation, often results in a very small number of priority compounds and may not identify compounds that are toxic to other forms of taxa.

Table 5
Priority pharmaceuticals that appear in the prioritization runs and the ERA approach.

Base case run A		Base case run B		Base case run C	
No STP	With STP	No STP	With STP	No STP	With STP
Amitriptyline	Amoxicillin	Naftidrofuryl	Amoxicillin	Naftidrofuryl	17β-estradiol
Naftidrofuryl	Aciclovir	Amitriptyline	17β-estradiol	Glibenclamide	Nafitdrofuryl
Clomipramine	17β-estradiol	Clompiramine	Domperidone	Amitriptyline	Domperidone
Dimenhydrinate	Domperidone	Glibenclamide	Aciclovir	Clomipramine	Alprazolam
Alprazolam	Carbamazepine	Mefenamic Acid	Glibenclamide	17β-estradiol	Omeprazole
Glibenclamide	Omeprazole	17β-estradiol	Omeprazole	Domperidone	Carbamazepine
Mefenamic Acid	Alprazolam	Dimenhydrinate	Carbamazepine	Mefenamic Acid	Glibenclamide
17b-estradiol	Paracetamol	Paracetamol	Alprazolam	Alprazolam	Amoxicillin
Ibuprofen	Dimenhydrinate	Alprazolam	Naftidrofuryl	Omeprazole	Paracetamol
		Domperidone		Carbamazepine	Amitriptyline
		Clorixin		Amoxicillin	Dimenhydrinate
		Ibuprofen		Paracetamol	Aciclovir

The prioritization approach developed in this work is, on the other hand, much more comprehensive in that it combines several important criteria, such as bioaccumulation, persistence and mammalian toxicity, proceeds in a simultaneous fashion and results in a large ranked list of pharmaceuticals as opposed to the small number of compounds generated in the ERA approach. Furthermore, the application of the sensitivity analysis procedure captures a number of additional, potentially elusive, compounds that may have been missed initially and proffers an additional level of thoroughness.

3.6. Comprehensive priority list

Having compared the two approaches of prioritization and ERA, a comprehensive list of the most significant priority pharmaceuticals, a total of 26 pharmaceuticals, is presented in Table 6. The first 16 pharmaceuticals are those that are common between the top 30 pharmaceuticals in all three base case prioritization runs and the results of the ERA for RQ values at DF = 3. The next 9 pharmaceuticals are those appearing consistently throughout the T and S sensitivity runs, while 17α-ethinylestradiol is included as it appears in the RQ assessment.

4. Discussion

To the authors' knowledge, there have been only two publications that have considered the occurrence of pharmaceuticals in Lebanon (Doummar et al., 2014; Zhang and Geiben, 2010). Both research papers considered a single pharmaceutical, the anti-epileptic nervous system pharmaceutical carbamazepine, where Zhang and Geiben (Zhang and Geiben, 2010) reported a PEC value of 780 ng/L in the sewage effluent while Doummar and co-workers (Doummar et al., 2014) reported measured values in the range of 10–30 ng/L in spring water. It is worth noting that in this work, the PEC for carbamazepine was in the range of 900–3000 ng/L; the lower value calculated at a dilution factor of 10 and the higher value for a dilution factor of 3.

Table 6
Complete list of priority pharmaceuticals.

Pharmaceuticals common to both prioritization and ERA	Pharmaceuticals from the prioritization sensitivity analysis	Pharmaceuticals from the ERA only
17β-estradiol (G)	Ambroxol (R)	17-α-Ethinylestradiol (G)
Aciclovir (J)	Azithromycin (J)	
Alprazolam (N)	Bisacodyl (A)	
Amitriptyline (N)	Citlopram (N)	
Amoxicillin (J)	Erythromycin (J)	
Carbamazepine (N)	Fluoxetine (N)	
Clomipramine (N)	Metformin (A)	
Clonixin (M)	Paroxetine (N)	
Dimenhydrinate (R)	Zopilidem (N)	
Domperidone (A)		
Glibenclamide (A)		
Ibuprofen (M)		
Mefenamic Acid (M)		
Naftidrofuryl (C)		
Omeprazole (A)		
Paracetamol (N)		

A: alimentary tract and metabolism, C: cardiovascular, G: genito-urinary/sex hormone, J: anti-infective, M: musculo-skeletal, N: nervous system, P: antiparasitic, and R: respiratory.

The absence of pharmaceuticals such as 17α-ethinylestradiol and diclofenac from the high-ranking pharmaceuticals in the prioritization study, suggests that there may have been inaccuracies in the original data set used. These inaccuracies may arise from the use of predicted physicochemical properties and ecotoxicity values, instead of measured experimental ones. The disparity between measured and predicted toxicity and physical property data and the paucity of data for a considerable number of pharmaceuticals has been highlighted in several previous studies (Cooper et al., 2008; Escher et al., 2011). However, it is worth noting that the combined methods, prioritization and ERA, have resulted in identifying two (17β-estradiol and 17α-ethinylestradiol) out of the three pharmaceuticals currently placed on the EU's first watch list (EC, 2013); the third being diclofenac.

While the use of the individual chemical-to-chemical approach has been adopted in most prioritization and ERA studies, pharmaceuticals do not occur individually or in isolation in water bodies but rather as mixtures, often in the presence of other substances such as heavy metals, pesticides and other anthropogenic pollutants (Diamond et al., 2011; Escher et al., 2011; Kostich et al., 2010). Therefore, in these situations the mixture-effect approach for the pharmaceuticals, where it on the basis of concentration addition or independent action, is more appropriate (Escher et al., 2011; Vasquez et al., 2014). This approach has come into focus very recently (Vasquez et al., 2014) and is used to determine the risk quotient of the various pharmaceutical classes discussed in this work. Calculations are based upon the common mode of action between pharmaceuticals belonging to the same pharmaceutical class where the sum of individual risks (the concentration addition approach) reflects the total environmental risk of that pharmaceutical class. Table S10 presents the cumulative RQ values for DFs 3, 6.6, and 10. Three ATC classes, genito-urinary-sex hormone class, cardiovascular and respiratory pharmaceuticals pose considerable environmental risks at all dilution factors.

One major uncertainty that may arise from the results of the prioritization and ERA runs is the exclusion of environmentally relevant pharmaceuticals due to low sales figures, incorrect, inaccurate, or unavailable toxicological data (Christen et al., 2010) and to the Mathew Effect (Daughton, 2014) where bias towards pharmaceuticals that have been considered in previous studies may lead to their inclusion at the expense of other less investigated ones.

The occurrence of pharmaceuticals in water bodies, where it in terms of concentrations or types of pharmaceuticals, can vary significantly at different geographical locations (Ortiz de Garcia et al., 2013)

Table 7
Comparison of prioritization results with other literature studies.

Pharmaceutical	Coutu et al. (2012)	de Voogt et al. (2009)	Kumar and Xagoraraki (2010)	Li et al. (2014)	Ortiz de Garcia et al. (2013)	Roos et al. (2012)	Sui et al. (2012)	Zhou et al. (2014)	Number of studies
17α-Ethinylestradiol	+				+	+			3
17β-Estradiol			+		+				2
Aciclovir									0
Alprazolam					+				1
Ambroxol						+			1
Amitriptyline						+		+	2
Amoxicillin	+	+			+			+	4
Azithromycin			+		+			+	3
Bisacodyl									0
Carbamazepine		+	+	+	+	+	+	+	7
Citalopram	+			+		+			2
Clomipramine						+			1
Clonixin									0
Dimenhydrinate									0
Domperidone									0
Erythromycin	+	+	+	+	+		+	+	7
Fluoxetine	+	+	+		+	+			5
Glibenclamide								+	1
Ibuprofen	+	+	+	+	+	+	+	+	8
Mefenamic acid							+	+	2
Metformin	+	+		+		+			4
Naftidrofuryl									0
Omeprazole						+		+	2
Paracetamol		+				+			2
Paroxetine					+	+		+	3
Zolpidem						+			1
Total[1]	7/20	7/28	6/20	5/20	11/25	12/32	4/17	10/27	

[1] The total is presented in the form of a/b, where "a" is the number of pharmaceuticals in common between the current study's method and the listed authors' method, while "b" is the total number of priority pharmaceuticals reported by the listed authors.

due to a number of factors including variations in consumption trends, dilution factors and attenuation mechanisms. Though this difference may render the comparison between the results of this work and other prioritization studies superfluous, it is perhaps worthwhile considering whether a commonality exists between the results of this work and other published literature. Table 7 presents a comparison between the results of this work and the results of eight recent publications (Coutu et al., 2012; de Voogt et al., 2009; Kumar and Xagoraraki, 2010; Li et al., 2014; Ortiz de Garcia et al., 2013; Roos et al., 2012; Sui et al., 2012; Zhou et al., 2014) where it can be seen that six out of the total 26 pharmaceuticals identified as priority in this work are not included in the results of other workers. These six pharmaceuticals are aciclovir (anti-infective), bisacodyl (alimentary tract and metabolism-constipation), clonixin (musculo-skeletal), dimenhydrinate (respiratory), domperidone (alimentary tract and metabolism-gastronomical) and naftidrofuryl (cardiovascular).

5. Conclusion

In this work, several prioritization approaches are used to rank the 88 most commonly consumed pharmaceuticals in Lebanon. A simultaneous multi-criteria decision analysis method utilizing the exposure, persistence, bioaccumulation, and toxicity (EPBT) approach is used to rank a subset of the original list (69 pharmaceuticals). Several base cases are investigated and sensitivity analysis is applied to one of these base case runs. An environmental risk assessment (ERA), where predicted environmental concentrations (PEC) and risk quotients (RQ) are determined at different dilution factors, is performed as an alternative method of prioritization for a total of 84 pharma ceuticals.

Results from the base case prioritization runs indicate a non-consistent ranking for any individual pharmaceutical. However, a number of pharmaceuticals appear throughout the base case runs: Azithromycin, Citalopram, Alprazolam, and 17β-estradiol. On the other hand, results of the sensitivity analysis yield nine pharmaceuticals that are common to both sets of sensitivity runs: 17β-estradiol, azithromycin, citalopram, domperidone, glibenclamide, metformin, naftidrofuryl, paroxetine, and zolpidem. Perhaps most significant amongst these are 17β-estradiol and glibenclamide. The ERA results indicate that metformin and amoxicillin have the highest PECs while 17β-estradiol, naftidrofuryl and dimenhydrinate have the highest RQs.

A priority list, generated from comparing the results of the ERA with the combined results of the prioritization methodology and sensitivity analysis, resulted in the inclusion of 26 pharmaceuticals of various classes. Nervous system and alimentary tract and metabolism pharmaceuticals (9/26 and 5/26 respectively) constitute more than half of the numbers on the priority list with the balance consisting of anti-infective (4/26), musculo-skeletal (3/26), genito-urinary (2/26), respiratory (2/26) and cardiovascular (1/26) pharmaceuticals.

The prioritization approach developed in this work is more comprehensive than ERA based approaches in that it combines several important criteria, such as bioaccumulation, persistence and mammalian toxicity with exposure to yield a ranked list of pharmaceuticals. Furthermore, the application of the sensitivity analysis procedure captures a number of additional, potentially elusive, compounds that may have been missed initially. With few minor modifications, such as the incorporation of specific local information (pharmaceutical sales figures, demographic figures, STP removal rates) the prioritization methodology developed in this work may be adapted and extrapolated for use in other developing countries.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.03.023.

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