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

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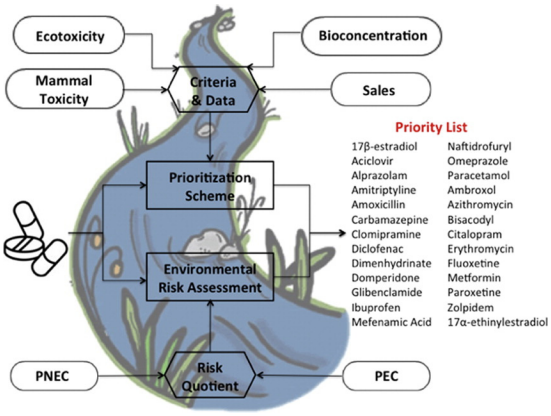
HIGHLIGHTS

- 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