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A critical evaluation of different parameters for estimating pharmaceutical exposure seeking an improved environmental risk assessment

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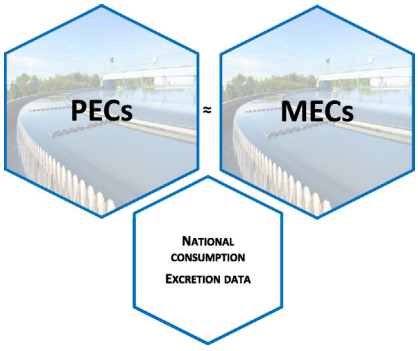
HIGHLIGHTS

- Several parameters were evaluated in PECs calculation for EMA guideline improvement.
- PECs were optimized through comparison with MECs in Portuguese wastewater effluents.
- PECs calculation should enclose national consumption and excretion data.
- A RQ higher than 1 was found for 7 pharmaceuticals when comparing PECs with PNECs.
- ERA should be performed each five years and for substances marketed before 2006.

GRAPHICAL ABSTRACT



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ABSTRACT

A critical evaluation of the European Medicines Agency (EMA) Guideline on Environmental Risk Assessment (ERA) was performed on 16 of Portugal's most consumed pharmaceuticals in wastewater effluents (WWEs), the main route for aquatic contamination. The predicted environmental concentrations (PECs) were formulated based on the Guideline, after incorporating several refinements. The best approach was selected by comparing the measured environmental concentrations (MECs) to the PECs in WWEs. Finally, risk was assessed by comparing PECs to predicted no-effect concentrations (PNECs).

The results showed that the default value of the penetration factor (Fpen) used by the EMA (0.01) was surpassed and that national consumption and excretion data were the two most important parameters for PEC calculations. The risk quotient between PECs and PNECs was higher than 1 for 12 pharmaceuticals, indicating a risk to all three trophic levels of aquatic organisms (algae, daphnids and fish).

To improve the current ERA framework, suggestions were made for incorporating consumption and excretion data, changing the default value of Fpen to 0.04 and adding a safety factor of 10. Moreover, this evaluation should be performed for pharmaceuticals already on the market, and future ERAs should incorporate a risk-benefit analysis, an important risk-management step.

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1. Introduction

The presence of human pharmaceuticals in the environment has raised concerns worldwide. Due to their increased consumption and their pharmacokinetic properties, pharmaceuticals can be excreted in their parent form or as metabolites and enter into aquatic systems mainly through wastewater treatment plant (WWTP) effluents. Due to their physicochemical and biological properties, as well as their low removal efficiencies in WWTPs, several hundred types of pharmaceuticals have been found in sewage water, surface water, groundwater and tap water in concentrations from sub-ng L^{-1} to more than μg L^{-1}, which has led to concerns about their potential to affect non-target species (Ågerstrand et al., 2015; Celle-Jeanton et al., 2014; European Commission, 2003; Kosma et al., 2014; Meisel et al., 2009; Zenker et al., 2014).

Based on this knowledge, the European Medicines Agency (EMA) issued its Guideline on Environmental Risk Assessment (ERA) of Medicinal Products for Human Use in 2006 (EMEA, 2006), predicting the possible impact that new marketing authorizations for medicinal products may have on the environment following their release (Ågerstrand et al., 2015; Bound and Voulvoulis, 2006).

Therefore, it is critical to evaluate the concentrations of pharmaceuticals in the aquatic environment to assess and manage the possible risk that these compounds pose to aquatic organisms (European Parliament, 2013). Pharmaceutical exposure assessments may be conducted by means of either laborious and exhaustive monitoring programs, which result in measured environmental concentrations (MECs), or by means of prediction models based on different parameters that can be used to calculate predicted environmental concentrations (PECs). Both approaches have advantages and disadvantages (Kugathas et al., 2012; Verlicchi et al., 2014); nonetheless, the number and variability of molecules that may enter the environment, together with the high costs of analysis, led to further development of theoretical models to estimate the PECs (Celle-Jeanton et al., 2014). Additionally, only a predictive model could be used to assess newly marketed pharmaceuticals because MECs can only be used to manage the risk related to substances that have already hit the market. However, a comparison between MECs and PECs that considers the calculation methods and particularly the parameters included in the calculation (consumption data, pharmacokinetic parameters and elimination rate) is required to assess the validity of the predicted approaches for the PECs (Celle-Jeanton et al., 2014).

The ERA Guideline (EMEA, 2006) consists of two phases. In Phase I, crude PECs for surface water are calculated and the octanol-water partition coefficient (K_{ow}) is measured. If the PEC is above 0.01 μg L^{-1}, a Phase II assessment is performed; if $\log K_{ow} > 4.5$, persistence, bioaccumulation potential and toxicity must be evaluated (Fig. 1). Pharmaceuticals that are known to have toxic activity at concentrations below 0.01 μg L^{-1} should also enter Phase II, following a tailored risk assessment strategy that addresses its specific mechanism of action. Phase II is divided into two tiers (A and B). Tier A involves a basic set of aquatic toxicity and fate tests to determine the predicted no-effect concentrations (PNECs) for three trophic levels (algae, daphnids and fish). Tier B consists of an extended assessment using refined values for PEC and PNEC calculations. At this stage, both a fate analysis and effect studies can be performed. The pharmaceutical is then assessed by generating a risk quotient (RQ) and evaluating the ratio between the PEC and the PNEC; when the ratio is below 1, no risk of the pharmaceutical to the aquatic environment is expected.

The EMA Guideline states that ERA does not constitute a valid criterion upon which to base the refusal of a market authorization of medicinal products for human use in the European Union (EU), although for veterinary medicines, this evaluation is included in the risk-benefit analysis. Furthermore, there is no publicly available record of ERAs (Kuster and Adler, 2014). Additionally, ERAs should also be performed for products that made it to the market before 2006 because there is no reason to believe that the risks posed by a substance, or the need for a risk assessment, would depend on the date of market approval (Ågerstrand et al., 2015). Nonetheless, of the approximately 4000 pharmaceuticals on the market today, only roughly 10% have sufficient data to perform a complete ERA, and 10% also have potential environmental risks (Ågerstrand et al., 2015; Holm et al., 2013; Kuster and Adler, 2014). Despite this awareness, legal limits have not yet been set for pharmaceuticals in water, although a "watch list" that includes 7 pharmaceuticals has been created recently (European Commission, 2015; European Parliament, 2013). The Guideline, and the PEC calculation, in particular, have been debated by scholars, some of whom argue that other parameters should also be incorporated, such as consumption data and excretion rates (Ågerstrand et al., 2015; Bound and Voulvoulis, 2006; Celle-Jeanton et al., 2014; Meisel et al., 2009).

The aim of the present work was to introduce, rationalize and discuss a general tiered approach for estimating the PECs based on the EMA Guideline, taking into account the Portuguese scenario for 16 of the most consumed pharmaceuticals (INFARMED, 2011). We also aimed to critically evaluate uncertainties in PEC calculations, compare the MECs with the appropriate PECs, adopt the best-suited model, assess which parameters included in the model are more crucial and suggest solutions to strengthen the EU legislation to improve the environmental exposure estimations.

2. Assessing the predicted environmental concentrations (PECs) of pharmaceuticals in wastewater effluents (WWEs) using different formulas

In the scope of the present manuscript, 16 pharmaceuticals, namely, alprazolam (ALP), lorazepam (LOR) and zolpidem (ZOL) (anxiolytics and hypnotics (Anx)), azithromycin (AZI) and ciprofloxacin (CIP) (antibiotics (Antib)), simvastatin (SIM), bezafibrate (BEZ) and gemfibrozil (GEM) (lipid regulators (Lip Reg)), citalopram (CIT), escitalopram (ESC), fluoxetine (FLU), paroxetine (PAR) and sertraline (SER) (selective serotonin reuptake inhibitors (SSRIs)), and ibuprofen (IBU), diclofenac (DIC) and paracetamol (PARA) (non-steroidal anti-inflammatories and analgesics (Anti-inf)) (Table S1, Supporting information) were selected for the assessments of the environmental exposure based on data regarding their national consumption rates (INFARMED, 2011). These consumption data were supported by two extensive Portuguese studies (Pereira et al., 2016; Silva et al., 2014). To perform this evaluation, the PECs were assessed in WWEs, by considering several different approaches, because, according to the Guideline, the PECs for surface water are derived from the PECs in WWEs after considering a dilution factor of 10 (EMEA, 2006). The first approach used to calculate the PECs for human pharmaceuticals was that advocated by the EMA Guideline for the ERA (EMEA, 2006), which derives the initial crude wastewater PEC for pharmaceuticals using a simple formula that multiplies the maximum daily dose (DOSEai) (mg/day) with a default penetration factor (Fpen) and dividing by the amount of wastewater per inhabitant per day (WASTEWinhab) (L/inh d) (Eq. (1)) (EMEA, 2006). This estimation of exposure uses certain default values: a Fpen of 0.01, which represents the percentage of the population being treated daily with a specific drug (1%) and was established based on German data obtained for 800 drug substances in 2001 (Table S2, Supporting information); the DOSEai, obtained from the Summaries of Product Characteristics; and the WASTEWinhab of 200 L/inh d, not factoring in any human metabolism or removal by the WWTPs.

$$PEC = \frac{DOSEai^{*} Fpen}{WASTEWinhab} \quad (1)$$

Our second approach replaced the DOSEai and the Fpen with data regarding the Portuguese consumption (PortCons) of the selected