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# Anticancer drugs in Portuguese surface waters – Estimation of concentrations and identification of potentially priority drugs

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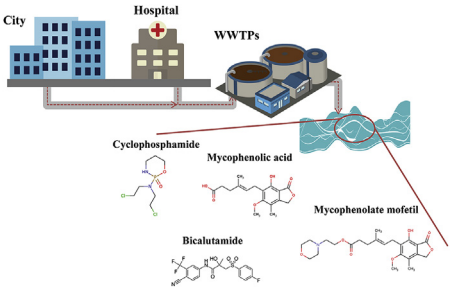
## HIGHLIGHTS

- 11 anticancer drugs were identified based on an exposure criteria.
- Mycophenolic acid and mycophenolate mofetil represent high risk to aquatic life.
- Moderate risk was associated to cyclophosphamide exposition.
- Bicalutamide is suspected to pose low risk to aquatic biota.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Anticancer drugs, used in chemotherapy, have emerged as new water contaminants due to their increasing consumption trends and poor elimination efficiency in conventional water treatment processes. As a result, anticancer drugs have been reported in surface and even drinking waters, posing the environment and human health at risk. However, the occurrence and distribution of anticancer drugs depend on the area studied and the hydrological dynamics, which determine the risk towards the environment.

The main objective of the present study was to evaluate the risk of anticancer drugs in Portugal. This work includes an extensive analysis of the consumption trends of 171 anticancer drugs, sold or dispensed in Portugal between 2007 and 2015. The consumption data was processed aiming at the estimation of predicted environmental loads of anticancer drugs and 11 compounds were identified as potentially priority drugs based on an exposure-based approach ($PEC_b$> 10 ng $L^{-1}$ and/or $PEC_c$> 1 ng $L^{-1}$). In a national perspective, mycophenolic acid and mycophenolate mofetil are suspected to pose high risk to aquatic biota. Moderate and low risk was also associated to cyclophosphamide and bicalutamide exposition, respectively. Although no evidences of risk exist yet for the other anticancer drugs, concerns may be associated with long term effects.



## 1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2

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million cancer-related deaths in 2012 (WHO, 2013). Cancer incidence in population is gradually increasing, being expected to rise by about 70% over the next 2 decades (WHO, 2013). Until now, chemotherapy with cytotoxic medicines has proved to be an important ally against cancer but the environmental implications have only recently been evidenced (CytoThreat, 2014).

Anticancer drugs are a broad of chemotherapy compounds that were designed to disrupt or prevent cellular proliferation, usually by interfering in some way with DNA synthesis. Their pharmacological potencies, along with their fetotoxic, genotoxic (mutagenic) and teratogenic properties, potentially make anticancer drugs the most dangerous contaminants of our water system (Rowney et al., 2009). However, a proportion of the medicines, that are consumed everyday by patients under chemotherapy, is excreted unmetabolized or as conjugates that may subsequently be reactivated into the wastewater treatment plants (WWTPs) (Franquet-Griell et al., 2016). Thus, these contaminants can reach water courses mainly through wastewater effluents from municipal treatment plants, hospital effluents and live-stock activities (Johnson et al., 2008; Ortiz de García et al., 2013). Many questions which lack of answer have arisen: what levels of contamination are expected according to consumption?; what is the extent of the threat posed by these chemicals?; what will be the impact in each country? Some countries have planned large-scale chemical and biological monitoring programs to assess their particular situation. Traces of anticancer drugs have been measured in hospital effluents (<0.9–124000 ng $L^{-1}$), influent WWTP wastewaters (<0.3–13100 ng $L^{-1}$), effluent WWTP wastewaters (<6–2900 ng $L^{-1}$) and surface waters (<0.5–41 ng $L^{-1}$) (Booker et al., 2014). However these monitoring programs are very expensive, time-consuming and quite limited. Actually, analytical limitations exist (concentrations of anticancer drugs in real waters are expected to be very low) and due to the high number of chemotherapy drugs, it is not conceivable to determine all molecules in the environment and evaluate their ecotoxicity. Therefore, it is imperative to rank anticancer drugs according to their environmental relevance and to identify priority molecules according to consumption trends prior to implement a monitoring program.

So far, the situation of Portugal is not evaluated concerning this matter (up to the authors' knowledge, no monitoring programs, no prioritization studies and no environmental risk assessments are carried out).

This work will provide for the first time:

- an overview of the consumption trends in Portugal. This temporal and regional analysis will be based on the consumption of anticancer drugs in each Portuguese region (*North*, *Center*, *Lisbon*, *Alentejo* and *Algarve*) between 2007 and 2015 (9 years);
- an estimation of the concentration of 171 anticancer drugs in surface waters;
- an identification of the potentially priority anticancer drugs in Portugal;
- an exposure-based classification of anticancer drugs according to Portuguese consumption patterns;
- a preliminary assessment of the risk by calculating the risk quotients.

## 2. Materials and methods

### 2.1. Anticancer drugs consumption in Portugal

The number of medicine units (pills, capsules or any formulation) consumed by patients under chemotherapy treatment, both in specialized hospitals and in pharmacies, was provided by *Instituto Nacional da Farmácia e do Medicamento, I.P* (INFARMED, I.P.). Consumption data was provided for 171 anticancer drugs in each Portugal NUTS level II region (*North*, *Center*, *Lisbon*, *Alentejo* and *Algarve*) over nine years (2007–2015) and corresponds to the sum of consumptions in pharmacies and hospitals. NUTS is the term used to define the common classification of national territorial zones for statistics. The list of anticancer drugs presented in Table S1 and S2 of the Supporting Information section was obtained as follows: (i) the number of units of each chemotherapy medicine was multiplied by the correspondent dose of active pharmaceutical ingredient; (ii) the different sources of the same active pharmaceutical ingredient were added to obtain the total consumption amount of a certain active substance in a given year and NUTS level II region. Most of the compounds are from the L group (Antineoplastic and Immunomodulating agents) of the Anatomical Therapeutic Chemical code. Cyproterone (G03HA01) and megestrol (H02AB07), a sex hormone and corticosteroid, respectively, are not antineoplastic drugs, but are widely used in cancer treatments.

### 2.2. Exposure-based classification

Exposure-based classification was implemented by Besse and Garric in 2008 as part of an approach to prioritize human pharmaceuticals in France (Besse and Garric, 2008). This methodology was based upon the premise that the pharmaceuticals used in higher amounts have a potential to reach the aquatic environment in greater quantities and therefore may represent a higher risk for the aquatic environment. The classification of compounds according to the exposure criteria results from the comparison of predicted environmental concentrations (PECs) with threshold values proposed by the US Food and Drug Administration (100 ng $L^{-1}$) (FDA, 1998) and the European Medicine Evaluation Agency (10 ng $L^{-1}$) (EMEA, 2006). Compounds are priority ranked according to the exposure criteria in six different classes as shown in Scheme 1 (Besse and Garric, 2008). Two PEC values were determined following Eqns (1) and (2). $PEC_a$ is an over-conservative PEC for surface water and assumes no metabolism in the body (i.e. 100% of the parent molecule excreted unchanged) and no removal in WWTPs. $PEC_b$ is a refinement of $PEC_a$ as it considers the excretion fraction of the unchanged compound.

$$\frac{PEC_a = consumption}{WWinhab \times inhab \times DF} \quad (1)$$

$$\frac{PEC_a = consumption \;\; F_{exc}}{WWinhab \times inhab \times DF} \quad (2)$$

where, Consumption (ng $yr^{-1}$) is the quantity of active pharmaceutical ingredient (or anticancer drug) consumed over one year in a defined zone; *WWinhab* (L $inhab^{-1}$ $yr^{-1}$) is the water consumption per person per year; *inhab* is the number of habitants of a defined zone; *DF* is the dilution factor from WWTP effluents to surface waters and $F_{exc}$ is the fraction of parent compound that is excreted unchanged.

The parameters of Eqns (1) and (2) were defined according to the following criteria:

- A water consumption default of 200 L $inhab^{-1}$ $day^{-1}$ (73000 L $inhab^{-1}$ $yr^{-1}$) is recommended in EMEA guidelines (EMEA, 2006). However, more accurate information was found in the 2011 Census database for each defined region (i.e. for the five NUTS II regions of Portugal) (CENSOS, 2011);
- The number of inhabitants in all NUTS II regions were also obtained from 2011 Census database;