Environmental Pollution 229 (2017) 505–515

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Anticancer drugs: Consumption trends in Spain, prediction of environmental concentrations and potential risks☆

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ARTICLE INFO

Article history:
Received 22 March 2017
Received in revised form
30 May 2017
Accepted 3 June 2017
Available online 16 June 2017

Keywords:
Anticancer drugs
Predicted environmental concentrations
Pharmacies
Risk assessment
River

ABSTRACT

This study presents the occurrence and impact of 78 anticancer drugs in Spanish river basins based on consumption data in pharmacies during the period 2010–2015 and calculation of the predicted environmental concentrations (PEC). The total consumption of anticancer drugs in Spanish pharmacies was of 23.4 tons in 2015, being mycophenolic acid and hydroxycarbamide the drugs with the highest prescription. Their PECs in river at national scale were up to 80 ng/L. However, the use of different dilution factors revealed major differences between hydrographic basins, and PEC_{river} rose up to 68,014 ng/L in highly populated rivers with low flows. Concerning acute toxicity, there was no expected risk for the aquatic environment. However, chronic toxicity tests revealed possible long-term mutagenic effects for aquatic organisms. This study provides the tools for the estimation of PEC at river basin scale using time trend consumption data compilation. This information is very useful for prioritization of compounds of concern and permit to focus resources in environmental monitoring and risk evaluation.

1. Introduction

Over the last years, concern on the presence of anticancer drugs, or cytostatic, in the environment has remarkably increased, associated with the high cancer incidence (estimated 14.1 million new cases in 2012 worldwide (Cancer Research UK)). These compounds are used in chemotherapy and administered in the order of tons per year (Besse et al., 2012; Franquet-Griell et al., 2015). After use, these pharmaceuticals are excreted through urine or feces as metabolites or as the parent compound and can reach the sewer system. For some of these drugs, it is known that their elimination in wastewater treatment plants (WWTP) is low (Negreira et al., 2014; USEPA, 2006; Zhang et al., 2013) and can reach surface waters (Kosjek and Heath, 2011). In fact, nowadays anticancer drugs have been reported as emerging contaminants in European river waters at concentrations up to hundreds of ng/L (Buerge et al., 2006; Coetsier et al., 2009; Ferrando-Climent et al., 2014; Franquet-Griell et al., 2017a,b; Giebułtowicz and Nałęcz-Jawecki, 2016; López-Serna et al., 2012; Martín et al., 2011). Studies considering short-term toxicity showed high lethal concentrations (Bristol-Myers, 2010; Parrella et al., 2014; Roche, 2014) and additionally interaction with DNA can represent long-term effects for the aquatic organisms (Besse et al., 2012). The environmental risk of these compounds can be high.

Anticancer drugs are classified by the World Health Organization (WHO) under the class L according to the organ or system in which they act. This group is divided in four subgroups: L01, which accounts for the antineoplastic agents; L02 classifies estrogens and progestogens used specifically in the treatment of neoplastic diseases; L03 for immunostimulants; and L04 for immunosuppressants (www.whocc.no/atcddd). The number of drugs listed in class L is up to 300 but this list is periodically revised and 18 new drugs are expected to be included in 2017 (WHOCC, 2016). Finally, G03 are sex hormones and modulators of the genital system and H02 are corticosteroids for systemic use, which are very often administered in cancer treatments and were also included.

Due to the large number of drugs currently used in the medical treatments, methods have been developed to prioritize those compounds expected to be detected in the environment. The European Medicines Agency (EMA) proposed the calculation of predicted environmental concentrations (PEC) (EMEA, 2006) and suggests to evaluate their presence, environmental fate and effects when PEC values in surface water are equal or above 10 ng/L. This

Abbreviations: DF, dilution factor; EMA, European Medicines Agency; NOEC, no-effect concentration; PEC, of predicted environmental concentrations; RQ, risk quotient; WWTP, wastewater treatment plants.

☆ This paper has been recommended for acceptance by Klaus Kummerer.

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http://dx.doi.org/10.1016/j.envpol.2017.06.011
0269-7491/

model takes into account the consumption of a specific drug in a given area, its excretion and its elimination in WWTP in order to calculate the predicted concentration. This method has been used to estimate the presence of a high number of pharmaceuticals including antibiotics, lipid regulators, antiphlogistics or fibrate regulators, among others (Carballa et al., 2008; Coetsier et al., 2009; Oosterhuis et al., 2013). It permits to prioritize pharmaceuticals in the environment (Guo et al., 2016) and is especially applicable when robust and local data on the system of interest are available and reflect source inputs (Burns et al., 2017). For the specific case of anticancer drugs, this is a suitable model as the consumption can easily be correlated with the sales of these drugs, because all prescribed amount will be taken by the patient. This information can be used to focus and optimize efforts and resources for the control of these pharmaceuticals in different environmental compartments, such as WWTP effluents and surface waters (Besse et al., 2012; Franquet-Griell et al., 2015). PEC for anticancer drugs have been calculated for a few preselected compounds in Germany (Kümmerer and Al-Ahmad, 2010; Kümmerer et al., 2016), France (Besse et al., 2012), several European countries (Johnson et al., 2013), NW-UK (Booker et al., 2014) and for all L ATC type drugs in Catalonia (NE Spain) (Franquet-Griell et al., 2015). In these studies, predicted concentrations for some drugs in surface waters were above the threshold of 10 ng/L for environmental risk assessment suggested by EMA, like hydroxycarbamide with 78 ng/L (Besse et al., 2012) or mycophenolic acid with 77 ng/L (Franquet-Griell et al., 2015). The prognostic is that concentrations will increase over the years. According to Kümmerer et al. (2016) consumption will presumably continue growing up due to the share and age of elderly people which increases the probability of suffering cancer, and the use of antineoplastics in palliative medicine.

Spain has 46.7 million people. In 2015, nearly a 200,000 new invasive cancer cases were diagnosed and the five most common cancers were colon–rectum, prostate, lung, breast and urinary bladder (Galceran et al., 2017). The incidence of cancer reverts in a high consumption of chemotherapeutic drugs, which inevitably are discharged to environmental waters. Spain has eight main hydrographic basins (Miño, Duero, Tajo, Guadiana, Guadalquivir, Segura, Júcar and Ebro) which cover 82% of the Spain surface and 57% of the population. River basins in Spain are highly populated areas affected by agricultural run-off, WWTP and industrial discharges. These discharges, together with the dynamics of the rivers (overall water scarcity, flood events, season linked flow variabilities) results in rivers markedly affected by organic contamination.

Given the large amount of anticancer drugs prescribed in Spain, the aim of this study was to prioritize and evaluate their risk by calculating PECs according to global consumption in pharmacies from 2010 to 2015. Raw consumption data from Spain were used to calculate PECs accordingly to population and dilution factor in the eight main river basins. The predicted concentrations were combined with available toxicological data including acute and chronic effects to identify compounds with potential risk for the aquatic environment.

2. Materials and methods

2.1. Consumption data

The consumption data of anticancer drugs in Spain was kindly provided by the Ministry of Health, Social Services and Equality, and corresponds to the billing of prescriptions from the Spanish National Health Service through pharmacies. During 2010–2015, a total of 78 different drugs belonging to L01-L04, G03 and H02 groups were administered in Spanish pharmacies. This information does not include consumption through mutual insurance companies neither the consumption in hospitals, as this data was not available at national scale. However, pharmacies have proved to be the main path of anticancer drug administration, as it represented 78–82% of the total administration according to previous studies (Besse et al., 2012; Franquet-Griell et al., 2015; Kümmerer et al., 2016). Therefore, PEC calculations considering only pharmacies administration will be slightly underestimated but will provide reliable data as it considers the most consumed drugs.

Consumption data was provided as the number of pills, capsules, injections or other presentations of a specific drug, as well as its concentration, from 2010 to 2015. Knowing the concentration of each activity, the total consumption in kg per year was calculated. This data was further normalized to μg/inhab/day to compare consumption patterns in Spain with other countries.

2.2. PEC calculations

To calculate the predicted environmental concentrations in WWTP effluents (PEC_{eff}) and surface waters (PEC_{river}), the following equation was used (Besse et al., 2008):

$$PEC\ (ng/L) = \frac{consumption \times\ Fexc\ \times\ (1 - Fwwtp)}{W \times\ inhab \times\ DF} \times 10^9 \qquad (1)$$

where.

- *Consumption* (g/day) is the quantity of each cytostatic delivered in Spanish pharmacies.
- *Fexc* is the excreted fraction of the unchanged drug, considering both urine and feces. Compounds with glucuronide metabolites, which are deconjugated in WWTP processes (Domènech et al., 2011), were also considered. When different values were reported in the bibliography, the highest one was used. Selected values ranged from negligible to >90% depending on the compound. For those drugs whose values could not be found, a default value of 0.5 was applied, considering that a pharmaceutical will not be totally excreted as parental compound (Drugbank database).
- *Fwwtp* is the removal fraction in WWTP. Here, when different data were obtained from the bibliography, the lowest value was applied. In the cases that no information was available a default value of 0 was used to consider the worst case scenario.
- *W* (L/inhab per day) is the water consumption per inhabitant per day as mean of Spanish values (in 2013, 130 L/inhab per day were reported) (INE, 2015).
- *Inhab* is the number of inhabitants in Spain (a mean of 46.6 million inhabitants during 2010–2015).

More details about the PECs calculation is given in a previous work (Franquet-Griell et al., 2015).

An important parameter in the equation is the dilution factor (DF) applied from WWTP effluents to surface waters, which is used in the PEC_{river} calculation. Changes in this value can vary the results more than 100-fold. Thus, PEC_{river} have been calculated using different values. Firstly, a DF of 25 suggested by Keller et al. (2014) as the median DF for Spain was used to obtain the PEC_{river} at national scale. This data was used to compare PECs with measured environmental concentrations (MEC) according to published data. Secondly, DFs for the main hydrographic basins in Spain were calculated to obtain a better representation of the contamination levels, taking into account the specific characteristics of flow and population. Studied basins were Duero, Ebro, Guadalquivir, Guadiana, Júcar, Miño, Segura and Tajo, which cover most of the peninsula area (basins information in Table 1). These new DFs were calculated adapting the formula from Keller et al. (2014):