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Consumption and occurrence of pharmaceutical and personal care products in the aquatic environment in Spain

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HIGHLIGHTS

- Consumption of pharmaceutically active compounds was estimated.
- The occurrence in the environment of PPCPs and metabolites was estimated.
- Predicted and measured environmental concentrations were compared.
- PECs were close to MECs for 64.7% of compounds.
- PECs are a useful tool for prioritizing the study of PPCPs in the environment.

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ABSTRACT

The occurrence of sixty pharmaceutically active compounds (PhACs), twenty metabolites and eight personal care products (PCPs) in the aquatic environment in Spain and their predicted environmental concentrations (PECs) were calculated and compared with measured environmental concentrations (MECs) obtained from relevant published research. The occurrence in the aquatic environment was calculated through a mass balance approach considering the following: the number of pharmaceutical prescriptions issued, the amount of pharmaceutical discharged without consumption, consumption, self-medication, pharmacokinetics, treatment in wastewater facilities and discharged to aquatic environment. The estimation of consumption of active compounds of pharmaceuticals was conducted by at least one of the following methodologies: number of commercial packages sold, data for the number of defined daily dose per 1000 inhabitants per day (DHD), and pattern of treatment. Comparison of these methodologies for some compounds showed similar estimated consumption ranges. The highest pharmaceutical occurrence in the aquatic environment was for acetaminophen glucuronide, Galaxolide®, Iso-E-super®, acetaminophen, valsartan, amoxicillin, 2-hydroxy-ibuprofen, iopromide, omeprazole, carbamazepine 10, 11-epoxide, iopamidol, salicylic β-D-O-glucuronide acid, Tonalide®, acetylsalicylic acid (ASA), clarithromycin and iohexol, with releases between 5 and 600 t y^{-1}. The relation of PEC/MEC was calculated for 58% of the compounds under study, and 64.7% of them had PEC/MEC ratios between 0.5 and 2. PEC values were mostly overestimated (57.4%). The predicted concentrations for pharmaceutical and personal care products (PPCPs) that had a high occurrence in the aquatic environment were very close to the measured concentrations. This research provides information that had not been calculated and analyzed previously, at least for Spain. Estimation of the PECs for pharmaceutical,

Abbreviations: AD, Average dose in milligrams per body surface area; ADDD, Amount of one defined daily dose for each pharmaceutically active compound; ATC, Anatomical Therapeutic Chemical Classification System; ASA, Acetylsalicylic acid; BSA, Body surface area; DDD, Defined daily dose; DHD, Number of defined daily dose per 1000 inhabitants per day; EAC, Estimation of pharmaceutical active compound consumption; ENH, Estimated excretion of natural hormones; EPA EPI Suite™, Estimation Programs Interface Suite™ developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation; IA, Estimate of total number of cases with probability to receive treatment; LOQ, Limit of quantitation; MAD, Mass of active ingredient per dose; ME, Amount of metabolite excretion; MECs, Measured environmental concentrations; NDC, Number of doses per cycle; NP, Number of packages; NPA, Number of people who used different types of antidepressants; NPP, Number of pills in the most commercialized package; NSAIDs, Non-steroidal anti-inflammatory drugs; OAE, Occurrence in aquatic environment; PA, Percentage of absorption; PCAU, Amount of parent compound absorbed but unmetabolized; PCPs, Personal care products; PECs, Predicted environmental concentrations; PFM, Percentage of formation of each metabolite; PhAC, Pharmaceutical active compound; PPCPs, Pharmaceutical and personal care products; PPEU, Percentage of pharmaceutical excreted unchanged; R, Ratio of the number of cases treated with a particular drug and the number of total cases receiving chemotherapy; SM, Self-medication; STPWIN™, Sewage treatment plant program in EPA EPI Suite™; TC, Treatment cycles in one year; UPC, Unabsorbed parent compound; WWTP, Wastewater treatment plant.

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personal care products and metabolites is a useful tool for identifying compounds that should be considered for environmental concern, and such estimations could be used to improve environmental risk assessment studies.

1. Introduction

Concerns about the presence and possible harmful effects of active pharmaceuticals and personal care products (PPCPs) in the environment, have arisen in recent years. Several studies have demonstrated adverse effects from longstanding, low-dose exposures in both aquatic and terrestrial wildlife, although human toxicity related to trace levels of pharmaceuticals in the water supply remains unknown (Strauch, 2011). It is now well-established that these compounds are introduced into the environment, mainly through wastewater effluent from municipal treatment plants, hospital effluents and livestock activities (Halling-Sorensen et al. 1998; Ternes, 1998; Hereber, 2002; Fent et al. 2006; Besse et al. 2008, 2012; Besse and Garric, 2009; Kümmerer and Al-Ahmad, 2010; Vulliet and Cren-Olivé, 2011; Brausch and Rand, 2011). Water effluents are then discharged into rivers, and sludge is spread on the soil as fertilizer, which means these compounds can reach all environmental compartments.

Physicochemical analyses have confirmed the presence of drug residues and their metabolites in all the different compartments of the aquatic environment: wastewater, groundwater, surface water, and drinking water (Houeto et al. 2012). These analyses require highly specialized equipment, and the time and costs associated are also relatively high.

The level of these compounds in the natural environment depends on many factors: their consumption pattern and use, the percentage of wastewater that is collected, the characteristics of the processes used for wastewater treatment and legislation. These features are characteristic of each population, although the trend in the use/consumption of major PPCPs worldwide tends to be similar due to the globalization of the chemical and pharmaceutical industries. Barral and Cohen (1998) claimed that a study of the pharmaceutical industry has shown an ever increasing globalization, particularly for the most innovative drugs. This global reorganization of the pharmaceutical industry is ongoing.

Besse et al. (2008) estimated the consumption of pharmaceutically active compounds (PhACs) and the excretion of some metabolites; they also calculated ratios of predicted environmental concentrations (PECs) with respect to measured environmental concentrations (MECs) in France. In other research, they provided an overview of the occurrence of anticancer drugs in the aquatic environment by calculating PECs based on French consumption data (Besse et al. 2012). Carballa et al. (2008) calculated consumption and excretion rates of some PhACs in Spain in 2003, Kasprzyk-Hordern et al. (2009) estimated the use of drugs in local communities, ter Laak et al. (2010) related environmental concentrations of pharmaceuticals to consumption for the river Rhine and Baran et al. (2011) reported the use and occurrence of sulfonamides in different countries. These studies yielded interesting results and showed that, due to the large amount of PPCP use, more research (experimental and theoretical) is needed.

Generally, the data for PPCP consumption are dispersed and this information is essential for calculating relevant PECs. Therefore, an objective of this work was the use of three different methodologies to estimate the consumption of PhACs: (1) use of the number of packages of PhACs sold based on information from the Ministry of Health and Social Policy (2010), (2) use of parameter "number of defined daily dose per 1000 inhabitants per day" (DHD), and (3) treatment patterns. Consumption of personal care products (PCPs) was estimated by extrapolating data for other countries and years. The first two methodologies have been used in other studies. Stuer-Lauridsen et al. (2000) calculated the annual consumption of pharmaceuticals in Denmark using the numbers of defined daily doses (DDD), Carlsson et al. (2006) used DDD to obtain the total weight of the 100 most sold active pharmaceutical ingredients for human use in Sweden in 2002, Carballa et al. (2008) performed a review of consumption of 17 pharmaceuticals, two musk fragrances and two hormones by the Spanish population in 2003 and ter Laak et al. (2010) calculated and predicted loads of pharmaceuticals in the river Rhine from pharmaceuticals sales. The third methodology is novelty.

The pharmacokinetics in humans, removal in different wastewater facilities and discharge to the aquatic environment for each PPCP were used to estimate their environmental occurrence and to calculate the PECs. These PECs were compared with MECs published in other studies to verify the estimated predictions from the different models.

Consequently, the goals of this work were (1) to use different methodologies to calculate yearly amounts of PPCPs and metabolites in aquatic environments in Spain, (2) calculation of PECs and (3) comparison of PECs with MECs to verify the validity of the selected methods.

This work includes relevant information about PPCPs, some of which have been poorly studied until now, at least in Spain and in many European countries, as well as updated data about consumption patterns, sampling campaigns and resource management.

2. Materials and methods

A diagram showing the methodological procedure used to estimate PPCPs and metabolites in the aquatic environment from their prescription, sale or excretion is shown in Fig. 1. PPCPs selected for this study were based on their human consumption in Spain and their occurrence in the aquatic European environment as shown in the literature. The compounds selected are presented in Tables 1–5.

2.1. Estimation of consumption of pharmaceutically active compounds (EACs)

2.1.1. Number of packages sold (EAC_{NP}) method

To estimate PhAC consumption, the following information was collected: the number of packages (NP) of each type of PhAC sold or dispensed in Spain in 2009 as charged to the National Health System (Ministry of Health and Social Policy, 2010), the number of pills in the most-often sold package (NPP) and the mass of active ingredient per dose (MAD), usually expressed as milligrams per pill. With these data, the estimated amount of PhACs prescribed (EAC_{NP}) was calculated, in kilograms per year, according to Eq. (1) for PhACs shown in Table 1.

$$EAC_{NP}\left(\text{kg y}^{-1}\right) = NP\left(\text{No.packages y}^{-1}\right) * NPP\left(\text{No.pills package}^{-1}\right) * MAD\left(\text{mg pill}^{-1}\right) * 10^{-6}\left(\text{kg mg}^{-1}\right). \quad (1)$$

In this study, the oral administration of PhACs in humans was considered for most compounds. The exception was for X-ray contrast media and cytostatics/cancer therapeutics (can use other routes of administration, e.g., parenteral).

The EAC_{NP} calculation varied for some PhACs that had more than one presentation, such as differing NPPs or MADs; in these cases, the EAC was calculated considering a range of values. EACs were calculated with Eq. (1) for the PhACs shown in Table 1.