Can source control of pharmaceuticals decrease the investment needs in urban wastewater infrastructure?

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Abstract

The source control of pharmaceuticals involves influencing the everyday consumption volume and compound choice. This paper evaluates how source control contributes to protecting the environmental health and decreasing the investment needs in urban wastewater infrastructure. Different levels of reduction in diclofenac consumption (as recommended by the European Medicines Agency) compensated by equivalent increases in naproxen consumption (a less environmentally harmful compound) are evaluated. The different loads of compounds are fed into a microcontaminant fate and transport model of the Llobregat catchment (Spain) to assess the investment needs in tertiary treatment to reach diclofenac and naproxen concentrations below environmental quality standards. The results show that, despite the implementation of source control measures, tertiary treatment upgrades are still required in every scenario evaluated. Even though source control of pharmaceuticals decreases the investment needs in urban wastewater infrastructure, apparent concentrations reductions (i.e. statistically significant differences relative to the reference situation) are only observed in drastic substitutions of diclofenac by naproxen (a reduction in the total diclofenac consumption by 73% and a corresponding increase in naproxen consumption). The results also show that Spain is well on track with regards to the substitution of diclofenac by naproxen (among the top 5 in Europe), and this paper shows how positive this substitution can be for the environment.

Abbreviations

defined daily dose (DDD); environmental quality standard (EQS); Microcontaminant Fate and Transport Model (MFT); non-steroidal anti-inflammatory (NSAID); over-the-counter (OTC); predicted no-effect concentration (PNEC); wastewater treatment plant (WWTP).

1. INTRODUCTION

Individual households are among the main sources of pharmaceutical release into the environment, particularly for human medicines in industrialized countries (Ebele et al., 2017). This release poses a threat to freshwater organisms (Richardson et al., 2018) as well as to the human health at environmentally relevant concentrations. Of the multiple possible approaches that can contribute to reducing the presence of pharmaceuticals in freshwater ecosystems, source control is recognized as having a large potential for reduction (Roig, 2010). Source control consists of finding solutions before pharmaceuticals are released into the environment by addressing the issues of the production, prescription, distribution and use of medicines. This paper focuses on influencing the everyday consumption volume and compound choice as two of the potential source-control measures suggested in Ternes and Joss (2007). The reduction in the consumption volume involves modifications in the prescription of medicines (lower dosages) and reduction in the over-the-counter (OTC) dispensing levels in pharmacies through public awareness (Daughton & Sue Ruhoy, 2013; Daughton, 2014; Interreg IV B Nopills project, 2015). The compound choice involves the substitution of medical prescriptions towards more environmentally benign drugs, that is, the prescription of pharmaceuticals that are better removed in conventional wastewater treatment plants (WWTPs) and pose less harmful effects to aquatic life and drinking water (Kümmerer, 2009). In addition to the consumption volume and compound choice, this paper also discusses how green or sustainable pharmacy represents a safe long-term solution for the environment (Kummerer et al., 2000; Sanderson, 2011). Green pharmacy applies to the manufacture of a new generation of pharmaceuticals that are i) environmentally less harmful while maintaining the pharmacological properties and therapeutic efficacy of molecules, ii) the production of new pharmaceuticals with similar therapeutic effects at lower doses, or iii) that are completely biodegraded in the human body, thereby minimizing the excretion of metabolites.

Even though source-control measures must be at the forefront (Courtier et al., 2019), end-of-pipe measures are still required to meet environmental quality standards (EQSs) for pharmaceuticals. These end-of-pipe measures involve the upgrade of WWTPs with tertiary treatment (e.g., ozonation followed by sand filtration). Hence, the future of environmental protection involves the combination of source control with end-of-pipe measures (Eggen et al., 2014; Hillenbrand et al., 2014; van Wezel et al., 2017; Kümmerer *et al.*, 2018). The cost and effectiveness of end-of-pipe measures to reach specific EQS has already been evaluated at a catchment level using model-based approaches (e.g., Gimeno et al., 2017; Kehrein et al., 2015; Ort et al., 2009). However, the effectiveness of source control measures in reducing needs for WWTP upgrading has been poorly addressed in the literature. To the best of our knowledge, Hillenbrand et al. (2014) is the only existing study on this topic; they concluded that a reduction by 20% in the consumption of 3 pharmaceuticals in a German catchment did not contribute to a significant reduction in the concentrations below the PNEC in freshwater ecosystems. Only upgrading every WWTP larger than 10,000 PE (Population Equivalents), regardless of whether the pharmaceutical consumption decreased or not, resulted in reductions in the concentrations below the PNEC in almost the entire basin. However, to date, no study has assessed whether pharmaceutical substitution by less environmentally harmful substances is an effective measure to significantly avoid WWTP upgrades in a catchment. The novelty of this paper is on addressing source-control of pharmaceuticals with the definition of realistic substitution scenarios based on EU databases on pharmaceuticals consumption, and their evaluation using state-of-the art fate and transport models. In this study, diclofenac is selected as the more environmentally harmful pharmaceutical and naproxen as the less environmentally harmful equivalent. The Llobregat river catchment (North East Iberian Peninsula) is the selected case study.

2. MATERIALS AND METHODS

2.1 The Llobregat river basin

The study area is the Llobregat river basin, which is the second longest river in Catalonia (North East of Iberian Peninsula). The main axis of the river extends 165 km from the Pyrenees to the Mediterranean Sea, draining an area of 4,948 km2, and the river has two main tributaries, the Cardener and Anoia rivers. The hydrology of the Llobregat river is characterized by a highly variable flow that is strongly influenced by seasonal rainfall. According to 2017 data from the Catalan Water Agency, the mean annual bulk precipitation is 3,330 hm^3, and the river has an annual average bulk discharge of 693 hm^3. The Llobregat river basin includes 56 WWTPs (54 conventional activated sludge, 1 aerated lagoon and 1 membrane bioreactor, with a PE ranging from 100 to 280,000), which collect and treat wastewater from 1,1 M inhabitants and discharge to the Llobregat river basin (Figure 1).

Figure 1. The Llobregat river basin, main tributaries (Cardener and Anoia) and location of the WWTPs. The WWTPs are ranked based on the population equivalent served.

2.2 Diclofenac and naproxen

2.2.1 Characteristics

Diclofenac is a common non-steroidal anti-inflammatory (NSAID) and anti-rheumatic drug. The average defined daily dose (DDD) for diclofenac used as an anti-inflammatory and anti-rheumatic drug in adults is 0.1 grams for any administration route (oral, parenteral or rectal; WHO, 2007). Diclofenac is dispensed in pharmacies with a prescription or OTC in the form of pills, eye drops, suppositories or a gel. Among NSAIDs, diclofenac increases the risk of cardiovascular events compared to other NSAIDs (McGettigan & Henry, 2013). The EQS proposed in Europe for diclofenac ranges from 10 $ng \cdot L^{-1}$ (European Medicines Agency, 2006) to 100 $ng \cdot L^{-1}$ (European Commission, 2012).

Naproxen is also an NSAID and anti-rheumatic drug. The average defined DDD for naproxen used as an anti-inflammatory and anti-rheumatic drug in adults is 0.5 grams (5 times higher than diclofenac; WHO, 2007). Naproxen is dispensed in pharmacies with a prescription or OTC in the form of pills. Among the NSAIDs, naproxen is associated with the lowest cardiovascular risk but increased gastrointestinal side effects are possible (Baigent et al., 2013). The EQS proposed in Europe for naproxen are also higher than diclofenac because they range from 640 ng·L^{-1} (LIF, 2005) to 1,700 ng·L^{-1} (Ecotox centre, 2017).

Additional information regarding the excretion and removal of diclofenac and naproxen in WWTPs and rivers can be found at SI, section 1.

2.2.2 Total consumption (purchased with a prescription and OTC) of diclofenac and naproxen

IQVIA (2018) provided the yearly total amount (kg) of diclofenac and naproxen that the wholesalers and the manufacturers supplied directly to pharmacies and hospitals in European countries from 2006 to 2016. We assumed that all of the amount that was supplied to the pharmacies was sold to customers in the same year and that the customers consumed 100% of the medicines. Hence, the values include the total amount of drugs purchased with a prescription and OTC. We standardized the quantity of pharmaceuticals purchased as DDD/1000 inhab/day using the average DDD for diclofenac and naproxen (0.1 g. and 0.5 g., respectively; WHO, 2007) and the population in Europe from 2006 to 2016 (World Bank, 2018).

The lowest consumptions of diclofenac in 2016 are found in the UK and the Netherlands (3.4 and 7.6 DDD·1000 inhab^{-1}·day^{-1}, respectively), and the highest values are in Estonia and Austria (35 and 33 DDD·1000 inhab^{-1}·day^{-1}, respectively, Figure 2a). In 2011, the European Medicines Agency recommended decreasing the prescription of diclofenac in patients with a high cardiovascular risk (EMA, 2012, 2013). Certain countries show a positive decline in diclofenac daily dosages between the period of 2011 to 2016 (Figure 2b); UK shows the largest reduction in diclofenac consumption (a reduction of 6.4 DDD·1000 inhab^{-1}·day^{-1}), followed by Ireland (4.5), Slovenia (4.5) and Spain (2.5). Other countries show a lower reduction or even an increase in the consumption of diclofenac. In certain cases, the decrease in diclofenac consumption coincides with the increase in naproxen consumption (27, 17 and 14 DDD·1000 inhab^{-1}·day^{-1} in Slovenia, UK and Spain, respectively, Figure 2c); for these cases we assume that diclofenac is substituted by naproxen (we are aware of the fact that substitution can be by a combination of NSAIDs). This was the case for UK, which shows the highest degree of substitution of diclofenac by naproxen, followed by Ireland, Norway, Romania and Spain (the degree of substitution calculated as the share of Naproxen vs the sum of naproxen and diclofenac in 2016 minus the share in 2011, Figure 2d). Other countries showed low or null levels of substitution due to a continued increase in diclofenac consumption or due to the potential substitution of diclofenac by another pharmaceutical (e.g., ibuprofen).

Figure 2. Diclofenac and naproxen consumption in different European countries and the level of substitution

Specific data for the prescribed amount of diclofenac and naproxen from 2000 to 2016 in Spain was provided by the Spanish agency of pharmaceuticals (AEMPS, 2014, 2017). This allowed to estimate the yearly diclofenac and naproxen purchased OTC in Spain as the difference between the total (IQVIA) and the prescribed amount (AEMPS). Then, the decreasing and increasing trends from 2006 to 2016 for the total and prescribed consumption of diclofenac and naproxen, respectively, can be observed (Figure S1).

2.3 The Microcontaminant Fate and Transport Model (MFT)

The model developed in Gimeno et al. (2017) was used to describe the fate and removal of diclofenac and naproxen in the Llobregat river basin. The tool integrates 3 submodels: 1) a substance-human consumption and excretion model, which estimates the diclofenac and naproxen loads that reach the influents of WWTPs; 2) a WWTP model, which estimates the effluent loads; and 3) a river model, which estimates the loads in every river stretch. Each submodel has a key parameter: 1) F is a lumped factor that includes the fraction of the diclofenac and naproxen parent compound that is excreted to toilets, discharged directly via sinks, washed off of skin or clothes and degraded in sewers; 2) k_{WWTP} is the reaction rate constant that incorporates the processes by which diclofenac and naproxen are eliminated in WWTPs; and 3)

k_{river} is the reaction rate constant that represents the natural diclofenac and naproxen elimination in rivers. The equations involved in each sub-model are included in the Supporting Information – section 3.

The parameter values for diclofenac and naproxen were calibrated as in Gimeno et al. (2017) using a Bayesian inference approach and measurements of both pharmaceuticals in the river and in WWTPs (Supporting Information- section 5). Experimental data include influent and effluent concentrations of 5 WWTPs over the period from 2006 to 2009 (Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011), the consumption of diclofenac and naproxen during same periods, and operational data (activated sludge solids concentrations and hydraulic retention time) from the same WWTP and river flows and velocities during September 2010 (when the sampling campaign for measuring the naproxen level in WWTPs and rivers was conducted).

Hence, the MFT model predicts the concentrations of diclofenac and naproxen in every river stretch, accounting for the uncertainty in the calibrated model parameters. The model predicts three different concentrations of diclofenac and naproxen: worst, median and best probable concentrations. The worst probable concentrations of diclofenac and naproxen, i.e. the highest probable concentrations, are simulated using the 97.5th percentile of F and the 2.5th percentiles of k_{WWTP} and $k_{river.}$ The best probable concentrations, i.e. the lowest probable concentrations, are simulated using the 2.5th percentile of F and the 97.5th percentiles of k_{WWTP} and $k_{river.}$ The median concentrations are simulated using the median value of the three parameters.

2.4 Source control scenarios

We evaluated the reduction in the diclofenac consumption volume and its equivalent substitution by naproxen. Different levels of diclofenac consumption volume reduction were evaluated based on real data on the amounts of diclofenac and naproxen purchased with a prescription and OTC in Spanish pharmacies and based on grey literature. We assumed that all the amounts purchased were consumed in the same year by the customers (we used the amounts purchased and amounts consumed interchangeably). The following four scenarios were evaluated (Table 1):

Scenario 1 or reference scenario. The real consumption volumes of diclofenac and naproxen in 2010, just before the implementation of the European Medicines Agency recommendation for decreasing diclofenac prescriptions.

Scenario 2. The real consumption volumes of diclofenac and naproxen in 2016, four years after the European Medicines Agency recommendation. The diclofenac consumption with a prescription had been reduced to 3.2 DDD·1000 $inhab^{-1}$·day^{-1} (2 times smaller) and the naproxen consumption had increased up to 9.9 DDD·1000 $inhab^{-1}$·day^{-1} (almost 2 times higher), compared to scenario 1. Although the amounts of both pharmaceuticals purchased OTC increased in S2, the total amount of diclofenac purchased in scenario 2 still decreased by 17% compared to scenario 1. With scenarios 1 and 2, we can evaluate the environmental effects (and potential investment cost changes) due to the implementation of the European Medicines Agency recommendation in 2011.

Scenario 3. The reduction in the diclofenac consumption through prescription went down to 1.9 DDD·1000 $inhab^{-1}$·day^{-1}, with the equivalent substitution by naproxen. These values corresponded to the maximum potential change in the diclofenac consumption of naproxen for the Netherlands as reported in Grinten et al. (2016). The volume of naproxen purchased with prescriptions increased by 1.3 DDD·1000 $inhab^{-1}$·day^{-1}. The amounts of diclofenac and naproxen purchased OTC remained the same as in scenario 2. Thus, the total amount of diclofenac purchased in scenario 3 was 27% smaller than that in scenario 1.

Scenario 4. The reduction in the total diclofenac consumption was down to 3.6 DDD·1000 $inhab^{-1}$·day^{-1}, which corresponded to the consumption level in the UK in 2016, the lowest consumption level observed in Europe (IQVIA, 2018). We kept the prescribed diclofenac consumption at 1.9 DDD·1000 $inhab^{-1}$·day^{-1} (the same as in scenario 3) but reduced the OTC consumption to 1.7 DDD·1000 $inhab^{-1}$·day^{-1}. The decrease in the OTC diclofenac consumption was compensated by an equivalent increase in the OTC naproxen consumption. Hence, the total amount of diclofenac purchased in scenario 4 decreased by 73% compared to scenario 1.

Table 1. Scenarios for the consumption of diclofenac and naproxen.

2.5 Optimization of the number of WWTPs requiring an upgrade

We used the Non-Sorting Genetic Algorithm NSGA-II (Deb et al., 2002) optimizer coupled to the MFT model as described in Gimeno et al. (2018) to obtain the optimal set of WWTPs that should be upgraded in the Llobregat basin to decrease the diclofenac and naproxen concentrations in the rivers. Two objective functions were defined: the minimization of the total EQS exceedance in the entire Llobregat basin and minimization of the total cost of the upgrades (the annual investment and operational cost). Ozonation was selected as the upgrade technology because it removes diclofenac and naproxen almost completely (close to 99%) at low ozone doses (Huber et al., 2005). The function that calculated the ozonation costs based on the treated flow and population equivalents was extracted from Gimeno et al. (2018). We assumed that ozonation could only be installed at WWTPs larger than 5000 PE (18 of 56 WWTPs in the catchment). Therefore optimization only searches for the optimal sub-set of WWTPs (among this set of 18) to be upgraded. Installing ozonation in WWTPs smaller than 5000 PE is not feasible because ozonation requires qualified permanent staff for their operation (Rossi et al., 2013). Moreover, the sum of PE corresponding to the WWTPs smaller than 5000 PE only represents 6% of the total PE in the Llobregat basin.

We ran the optimizer separately for diclofenac and for naproxen. The optimization for each compound was conducted 24 times, as a combination of four scenarios of the total consumption (section 2.4), three levels of uncertainty in the predicted concentrations (worst, median and best probable concentrations), two EQS levels (10 and 100 $ng \cdot l^{-1}$ for diclofenac; 640 and 1,700 $ng \cdot l^{-1}$ for naproxen) and two river flow conditions (the average flows in September 2010 and environmental or minimum river flows as defined in Gimeno et al., 2018). Rice and Westerhoff

(2017) demonstrates the relevance of wastewater discharges during low flow periods. For every optimization, we assumed the same river stretch configurations and WWTP operational variables as in Gimeno et al. (2017).

In the results section, we compare the investment costs of scenarios 2 to 4 with respect to scenario 1. Since uncertainty is considered, the result for each scenario is represented by a dispersion. We consider that an apparent reduction in the investment costs of a particular scenario with respect to scenario 1 is achieved if these dispersions do not overlap, i.e. there are statistically significant differences relative to the reference situation. The latter means that the cost of the upgrades in a particular scenario for the worst probable concentrations of diclofenac is lower than the cost in the reference scenario (scenario 1) for the best probable concentrations.

3. RESULTS

3.1 MFT model performance

After the Bayesian calibration of the integrated MFT model (Section 5 in SI), we obtained the posterior probability distributions for the parameters *F* (lumped factor to estimate loads at the WWTP influents), k_{WWTP} (rate of degradation in WWTP) and K_{river} (rate of degradation in rivers) for both naproxen and diclofenac (Section 6, 7 and 8 in SI for details). The calibrated parameters for naproxen and diclofenac are calculated as the median and the 2.5th and 97.5th percentiles of the probability distributions (Table 2).

Table 2. Calibrated model parameters for naproxen and diclofenac (latter one from Gimeno et al., 2017).

The calibrated model accurately predicts the naproxen loads measured at 9 points along the Llobregat River (r^2 = 0.88), we obtained a very good fit between the measured and predicted naproxen loads in the rivers (Figure 3). The predicted influent loads also matched the measured loads well at the Igualada and Manresa WWTPs. However, the model overestimated the measured effluent loads. The latter can be justified by either probable errors in the sampling campaign at the WWTPs or in the estimation of the inhabitants connected to these WWTPs (Gimeno et al., 2017). Indeed, the measured effluent concentration at the Igualada WWTP was lower than any measured effluent concentration at the other 5 WWTPs (Gros et al., 2007; Gros et al., 2010; Jelic et al., 2011), which were used to estimate the prior distributions of F and k_{WWTP}.

Figure 3. Model-predicted versus measured loads of naproxen at the river sampling points (black symbols) and in the influents and effluents of the Igualada and Manresa WWTPs (coloured symbols). Each prediction consists of 3 simulated values (circle = median loads, and bars = worst and best probably loads). Points located on the bisector indicate a perfect fit between the predicted and measured values. Predictions lie within the dashed lines parallel to the bisector if they do not deviate by more than ±50 from the corresponding measured value.

3.2 Effect of a decrease in diclofenac consumption on the WWTP upgrades

Overall, the costs of the WWTP upgrades decreased as the total diclofenac consumption decreased (Figure 4 and Figure 5). However, the apparent reductions in the number of WWTP upgrades and costs were only achieved when the consumption of diclofenac purchased with a prescription and OTC was drastically reduced by 73% (scenario 4) compared to the baseline (scenario 1). This is consistent for both EQS and average flows (Figure 4). For the average flows (Figure 4), this consideration translates into a reduction in the number of WWTP upgrades from 14 (scenario 1) down to 8 (scenario 4) for an EQS of 10 $ng \cdot L^{-1}$ and from 5 (scenario 1) down to 2 (scenario 4) for an EQS of 100 $ng \cdot L^{-1}$. For the minimum flows (Figure 5), the apparent reductions in the number of WWTP upgrades were only achieved for an EQS of 100 $ng \cdot L^{-1}$. For the EQS of 10 $ng \cdot L^{-1}$, every WWTP required an upgrade for the worst concentrations of diclofenac (even for scenario 4), so there was no apparent reduction in the WWTP upgrades or in the costs. Reducing the consumption of diclofenac by only reducing the prescriptions (scenarios 2 and 3) did not lead to apparent reductions in the WWTP upgrades and costs compared to the baseline (scenario 1) for both flow conditions. Great savings were obtained when reducing both the diclofenac prescriptions and OTC consumption (scenario 4): 4.2 M€·year^{-1} for an EQS of 10 ng·L^{-1}, average flows and median values and 4.3 M€·year^{-1} for an EQS of 100 ng·L^{-1}, minimum flows and median values. Therefore, source control became more relevant for lower levels of the EQS during average flows and for higher EQS values during minimum flows.

Figure 4. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid an EQS exceedance of 10 and 100 ng·L^{-1}, respectively, for diclofenac and 640 and 1,700 ng·L^{-1}, respectively, for naproxen for the average flows. These values are calculated for scenarios S1, S2, S3 and S4 for the consumption of diclofenac and naproxen as defined in Table 3. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen.

Figure 5. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid an EQS exceedance of 10 and 100 ng·L^{-1}, respectively, for diclofenac and 640 and 1,700 ng·L^{-1}, respectively, for naproxen for the environmental flows. These values are calculated for scenarios S1, S2, S3 and S4 for the consumption of diclofenac and naproxen as defined in Table 3. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen.

3.2 Effect of an increase in the naproxen consumption on the WWTP upgrades.

The substitution of diclofenac by naproxen in scenarios 2 and 3 did not lead to an increase in the number of WWTPs to be upgraded or the costs. Figure 4 and Figure 5 show that the limiting compound for upgrading WWTPs was diclofenac, regardless of the EQS or the river flow condition. If the decision would be based only on the naproxen concentrations, only 1 WWTP at most in scenario S3 would require an upgrade for the EQS of 1,700 ng·L^{-1} and between 3 (average flows) and 8 WWTPs (minimum flows) for an EQS of 640 ng·L^{-1} (considering the median values). The equivalent substitution in scenario 4 indicated an increase in the number of WWTPs to be upgraded for one particular case (an EQS of 100 ng·L^{-1} for diclofenac and EQS of 640 ng·L^{-1} for naproxen). This situation involved 1 additional WWTP to be upgraded under average flows and 3 additional WWTPs for environmental flows, on top of the upgrades required by the diclofenac EQS evaluations (2 and 6 WWTPs upgraded, respectively). The set of WWTPs requiring an upgrade for each EQS, uncertainty in the concentrations and river flow condition are included in the Supporting Information section 9. Interestingly, for the median and the best concentrations, the sets of WWTP upgrades required to reduce the diclofenac concentrations always contained WWTP upgrades to reduce the naproxen concentrations and vice versa. For the worst concentration, this finding held true except for scenario S4 and the minimum flows, in which the naproxen and diclofenac concentrations required the upgrade of different numbers of WWTPs (11 and 10 WWTPs, respectively). Thus, a combination of both solutions resulting in the upgrade of 12 WWTPs would be needed to reduce the EQS exceedance of diclofenac and naproxen concentrations together.

3.3 Substitution of pharmaceuticals and green pharmacy (sensitivity of the DDD and the excretion factor)

We used the integrated MFT model to evaluate the influence of green pharmacy on the urban water infrastructure upgrades. We assumed that diclofenac was substituted with a new drug with a DDD of 0.1 g (instead of 0.5 g for naproxen). Considering that the new drug had the same excretion factor, WWTP and river removal efficiencies as naproxen, only 2 WWTPs (instead of 5) would require an upgrade for the worst concentration, average river flow and EQS of 640 ng·L^{-1} in scenario 4 (the scenario that required a higher number of WWTP upgrades) (see Figure 4). When the evaluation involved environmental flows, only 5 WWTPs would require an upgrade as opposed to 11 WWTPs. Conversely, we assumed that diclofenac was substituted by a new drug with the same DDD, WWTP and river removal efficiency as naproxen but with an excretion factor of 7% (no glucuronide compounds would be excreted). For the worst concentration, the average flow and an EQS of 640 ng·L^{-1} in scenario 4, again only 2 WWTPs would require an upgrade as opposed to 5 WWTPs. For the environmental flows, 7 WWTP upgrades would be required. Therefore, efforts should not concentrate only in upgrading WWTP but also on designing pharmaceuticals in such a way that WWTP and the environment can cope with the challenge of pharmaceuticals (Kümmerer *et al.*, 2019).

4. DISCUSSION

4.1. Source control of pharmaceuticals and decrease in investment needs in urban wastewater infrastructure

Despite the implementation of source control measures, end-of-pipe upgrades were required in every scenario evaluated. The source control of pharmaceuticals decreased the investment needs in urban wastewater infrastructure, but the apparent reductions (when accounting for the model uncertainty) were only observed in the drastic substitutions of diclofenac by naproxen (a reduction in the total diclofenac consumption by 73% and a corresponding increase in the naproxen consumption). Looking further into detail, we estimated that the required decrease in the consumption to obtain apparent reductions in the investment costs with respect to scenario 1 would be 60% for the average flows and an EQS of 100 ng·L^{-1} and 90% for the environmental flows and an EQS of 10 ng·L^{-1}. The Llobregat River is a typical Mediterranean watercourse with an average flow in the mouth of 20 m^3·s^{-1}. The magnitude of wastewater effluents in the whole basin is approximately 3 m^{3}s^{-1}. The overall low dilution during average flows in the Llobregat explains the high concentrations of pharmaceuticals that significantly exceeded the EQS in particularly dry stretches. This finding justifies why a considerable decrease in diclofenac consumption was needed to avoid the upgrade of WWTPs and, hence, achieve the apparent reductions in the number of WWTP upgrades.

The results of this study are in line with the outcomes by Hillenbrand et al. (2014), where a 20% reduction in diclofenac consumption (on top of the upgrade of every WWTP with a level above 50,000 PE in the Neckar river basin, Germany) did not lead to a significant improvement in the EQS exceedance. Although the average diclofenac consumption in the Neckar river basin in 2016 was more than twice the consumption in the Llobregat river basin (25 DDD·1000 $inhab^{-1}\cdot day^{-1}$ and 11 DDD·1000 $inhab^{-1}\cdot day^{-1}$, respectively; IQVIA, 2018), the average flow in the mouth (145 $m^3\cdot s^{-1}$; Gisen et al., 2017) was approximately 10 times higher compared to the Llobregat. Hence, assuming a similar magnitude of wastewater effluents (a similar population was connected to the WWTPs in both basins), considerable reductions in the consumption of diclofenac were needed to significantly avoid WWTP upgrades in both catchments with high and low flows. In any case, this result still required a model-based evaluation because the optimal number of WWTPs that required an upgrade is a catchment-specific problem (Gimeno et al., 2018).

4.2 Degree of the substitution of diclofenac by naproxen in Spain compared to other European countries

Spain is among the top 5 countries in Europe substituting diclofenac (either by naproxen or by other NSAIDs). The results show that further substitution (down to UK levels, as described in scenario 4 from the results section) would lead to enhanced water quality and would imply a reduction in the investment needed to fulfil EU legislation in freshwater ecosystems. Actions can be taken on the physician side to reduce the consumption of “environmentally harmful” pharmaceuticals. There are already certain initiatives that aim to include the environmental aspects of the physician decision when prescribing two equivalent pharmaceuticals (e.g., at the national level in Sweden, LIF 2005). As summarized in Courtier et al. (2018), Van Rensselaer Potter’s original conceptualization of bioethics can be used to balance the obligations of clinicians to protect the individual, public, and environmental health Balch et al. (2017). Actions can be taken on the over-the-counter side by enhancing patient awareness. Particularly the compound choice, i.e., opting for the environmentally friendly choice in case of alternative compounds being available with a comparable effectiveness, can be addressed through classification and labelling schemes. In addition, patient awareness can be achieved by ensuring that pharmaceutical expertise is provided to patients when purchasing OTC diclofenac (Netherlands strategy; Interreg IV B - No-pills project, 2015) or limiting the diclofenac availability as prescribed only (UK strategy; Medicines and Healthcare products Regulatory Agency, 2015). The commercial advertising of naproxen might also have encouraged the increase in naproxen OTC consumption in the UK, which accounts for the highest consumption of this pharmaceutical in Europe. A reduction in the OTC consumption of diclofenac would be especially effective in countries showing high OTC consumption rates, e.g., in Spain and Sweden. For instance, the diclofenac purchased OTC represented 75% of the total consumption in Spain in 2016 (IQVIA, 2018; AEMPS, 2017), and 70% in Sweden in 2015 (IQVIA, 2018; Eriksen et al., 2017). Finally, initiatives in the direction of green pharmacy are extremely limited because of the low interest of the industry to modify existing molecules (expensive and without compensation) as well as the trend of new-generation molecules such as monoclonal antibodies (Roig and Touraud, 2010).

5. CONCLUSIONS

We have illustrated that source control can contribute to protecting the environmental health and decreasing the investment needs in urban wastewater infrastructure. Despite the implementation of source control measures, tertiary treatment upgrades are required in every scenario evaluated. For the particular case of the Llobregat catchment, the substitution of diclofenac by naproxen would potentially decrease the investment needs by approximately 4 M€·year^{-1} in urban wastewater infrastructure to keep the concentrations of both compounds below their respective environmental quality standards. This paper also shows that Spain is well on track with regards to the substitution of diclofenac by naproxen (among the top 5 in Europe) following the recommendations of the European Medicines Agency.

FIGURES AND TABLES

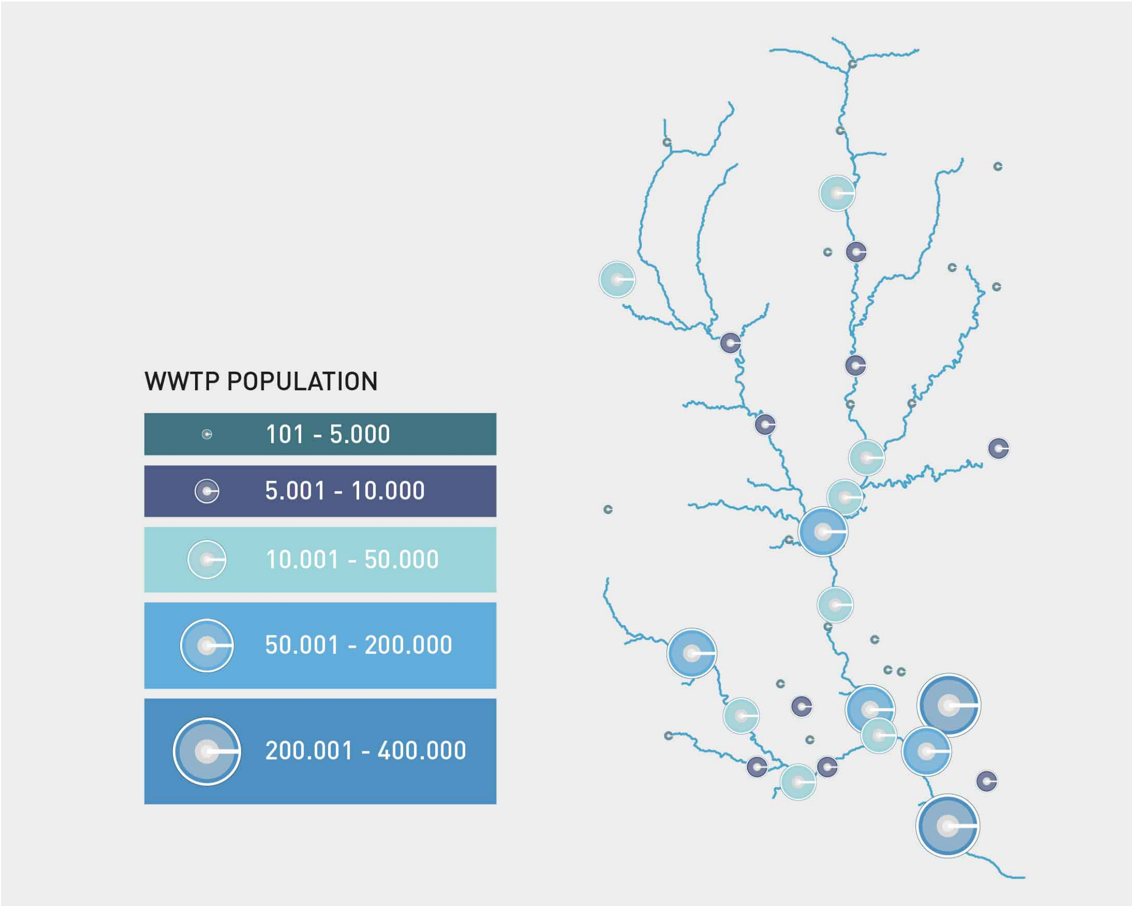

Figure 1. The Llobregat River catchment, main tributaries (Cardener and Anoia) and location of WWTPs. WWTPs are ranked based on the population equivalent served.

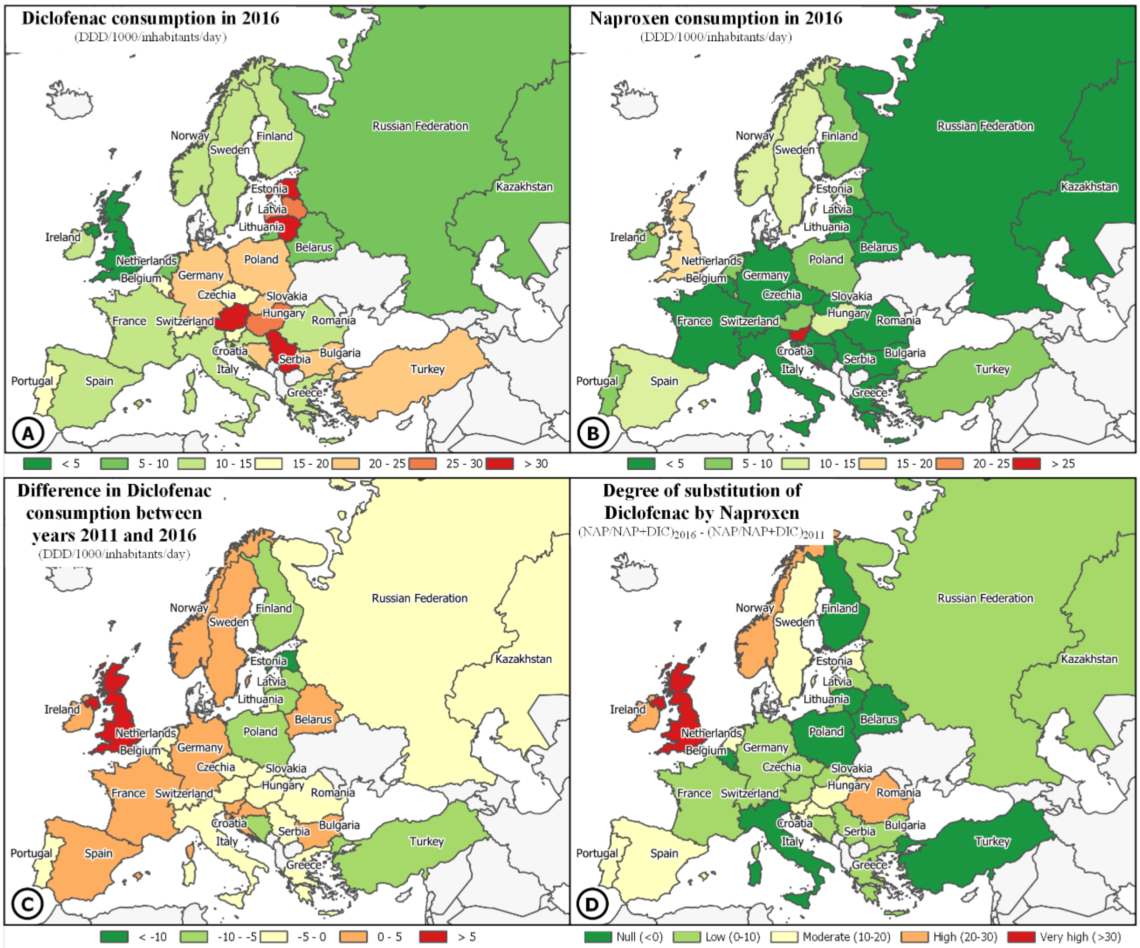

Figure 2. Diclofenac and naproxen consumption in different European countries and level of substitution (calculated as the share of NAP with respect to the sum of NAP and DIC in 2016 minus the share in 2011).

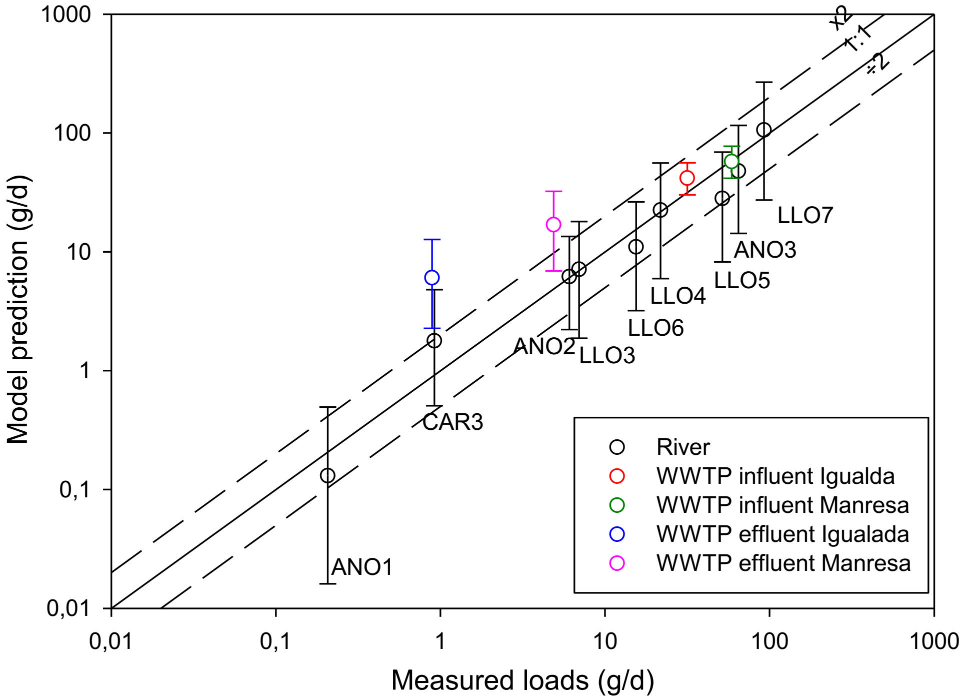

Figure 3. Model predicted versus measured loads of naproxen in the river sampling points (black symbols) and in the influents and effluents of the Igualada and Manresa WWTPs (colored symbols). Each prediction consists of 3 simulated values (circle = median loads, bars = worst and best probably loads). Points located on the bisector indicate a perfect fit between predicted and measured values. Predictions lie within the dashed lines parallel to the bisector if they do not deviate by more than ±50 from the corresponding measured value.

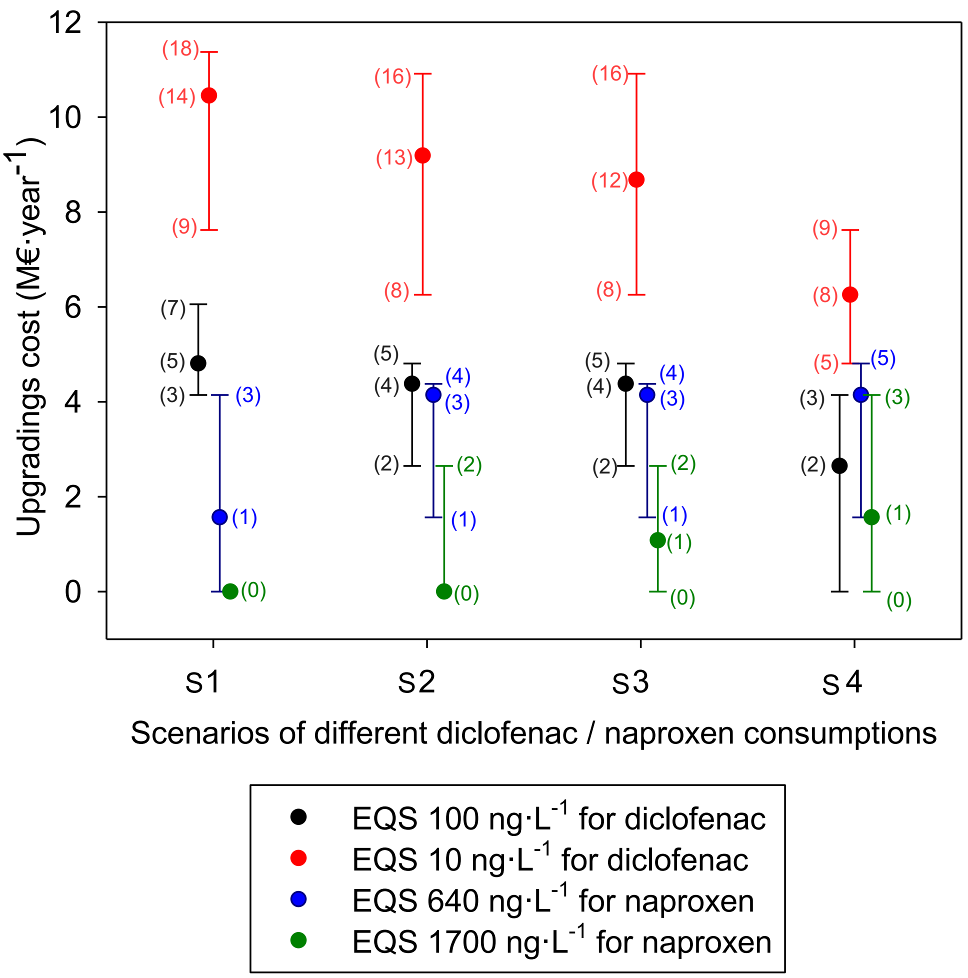

Figure 4. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid EQS exceedance of 10 and 100 ng·L^{-1} for diclofenac and 640 and 1,700 ng·L^{-1} for naproxen for the average flows. These are calculated for the scenarios S1, S2, S3 and S4 in the consumption of diclofenac and naproxen defined in table 3. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen.

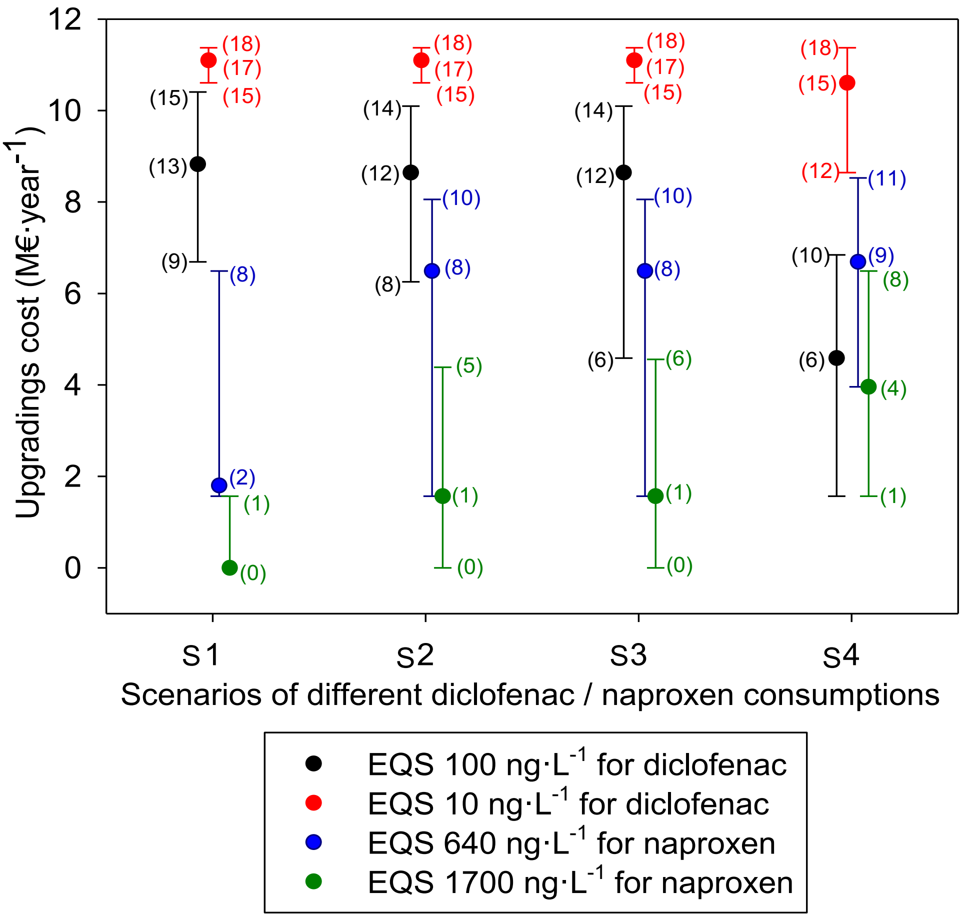

Figure 5. Number of WWTP upgrades (shown in brackets) and upgrading costs optimized to avoid EQS exceedance of 10 and 100 ng·L^{-1} for diclofenac and 640 and 1,700 ng·L^{-1} for naproxen for the environmental flows. These are calculated for the scenarios S1, S2, S3 and S4 in the consumption of diclofenac and naproxen defined in table 3. The number of WWTP upgrades and the costs are optimized for the median, worst and best concentrations of diclofenac and naproxen.

	Diclofenac (percentile)			Naproxen (percentile)		
	2.5th	50th	97.5th	2.5th	50th	97.5th
F	0.11	0.15	0.23	0.13	0.18	0.25
k_{WWTP}	0.12	0.25	0.70	0.72	1.25	2.61
WWTP Removal (%)	23	38	63	65	76	87
k_{river}	$1.4 \cdot 10^{-7}$	$3.0 \cdot 10^{-6}$	$1.5 \cdot 10^{-5}$	$2.2 \cdot 10^{-6}$	$9.4 \cdot 10^{-6}$	$2.4 \cdot 10^{-5}$

Table 1. Calibrated model parameters for naproxen and diclofenac (latter one from Gimeno et al., 2017).

Table 2. Scenarios for the consumptions of diclofenac and naproxen.

		Diclofenac			Naproxen		
Scenario	Description	Prescribed	OTC	Total	Prescribed	OTC	Total
S1	Consumption in 2010 Reference scenario	6.9	6.6	13.5	5.5	1.5	7
S2	Consumption in 2016 Substitution in S1 prescriptions Increase S1 OTC	3.2	8	11.2	9.9	3.9	13.8
S3	Substitution in S2 prescriptions S2 OTC remains the same.	1.9	8	9.9	11.2	3.9	15.1
S4	Substitution in S2 OTC and prescriptions (same as S3)	1.9	1.7	3.6	11.2	10.2	21.4
	Units: $DDD \cdot 1000 inhab^{-1} day^{-1}$;						

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