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Environmental impact assessment of pharmaceutical prescriptions: Does location matter?

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HIGHLIGHTS

- We present a method to compare environmental impacts of pharmaceutical prescriptions.
- Impacts on the aquatic environment and human are included in the method.
- Relative impacts of pharmaceutical prescriptions show spatial variation.
- Spatial variation in sewage sludge disposal mainly influences human health impacts.
- Spatial variation in sewage treatment techniques mainly influences aquatic impacts.

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ABSTRACT

A methodology was developed for the assessment and comparison of the environmental impact of two alternative pharmaceutical prescriptions. This methodology provides physicians with the opportunity to include environmental considerations in their choice of prescription. A case study with the two antibiotics ciprofloxacin and levofloxacin at three locations throughout Europe showed that the preference for a pharmaceutical might show spatial variation, i.e. comparison of two pharmaceuticals might yield different results when prescribed at different locations. This holds when the comparison is based on both the impact on the aquatic environment and the impact on human health. The relative impacts of ciprofloxacin and levofloxacin on human health were largely determined by the local handling of secondary sludge, agricultural disposal practices, the extent of secondary sewage treatment, and local food consumption patterns. The relative impacts of ciprofloxacin and levofloxacin on the aquatic environment were mostly explained by the presence of specific sewage treatment techniques, as effluents from sewage treatment plants (STPs) are the most relevant emission pathway for the aquatic environment.

1. Introduction

Several factors play a role in a physician's decision to prescribe a pharmaceutical, e.g. efficacy, tolerability (Benjamin et al., 2012), costs (Hart et al., 1997), and advertisement and promotion (Orlowski and Wateska, 1992). Additionally, environmental considerations have become of importance due to the increased awareness of the unintended impact of our pharmaceutical use on humans and the environment (e.g. Doerr-MacEwen and Haight, 2006). This environmental awareness is reflected in concepts such as green pharmacy and pharmaECOvigilance (e.g. Daughton and Ruhoy, 2011).

One way to support physicians to include environmental considerations in pharmaceutical prescription is the introduction of a decision support system. Vidaurre and Turcotte (2012) assessed the need for such a system amongst European physicians and other stakeholders. A publicly available classification system for pharmaceuticals has already been implemented on a national scale in Sweden (www.fass.se; LIF, 2008). This system is based on the voluntary risk-based Swedish Environmental Classification and Information System (Mattson, 2007), and consists of three levels of information. The first level contains a classification per substance (insignificant, low, moderate or high environmental risk), based on its PEC/PNEC ratio (PNECs according to ECB (2003); PECs according to EMA (2006)). The second level contains additional information on PBT properties (persistence, bioaccumulation, toxicity), and the third gives detailed environmental information underlying the calculations. However, the system provides only limited guidance to end-users who want to explore the need and possibility to substitute one pharmaceutical for another (Ågerstrand et al., 2009). Furthermore, the system shows shortcomings in its accuracy and consistency (Ågerstrand and Rudén, 2010), and data are often lacking or too scarce to enable a comparison that transcends a

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superficial comparison based on PBT properties (Wennmalm and Gunnarsson, 2009; Deblonde and Hartemann, 2013). Because of these shortcomings and because it is perceived as too complicated and time consuming, the Swedish classification system is not extensively used by individual physicians (Goetz et al., 2012).

Here, we present a methodology that can be used to compare two otherwise equivalent pharmaceutical prescriptions on the basis of their relative impact on both the aquatic environment and human health. It is based on a spatially explicit prioritization tool for human pharmaceuticals in the environment (Oldenkamp et al., 2013). Because the methodology is centered around the comparison to be made, it requires only limited end-user input, being (1) a selection of the pharmaceuticals to be compared, (2) the amounts intended to be prescribed, and (3) the region where the pharmaceuticals will be used. This straightforward approach ensures that complexity and time constraints are restricted. The spatially explicit nature of the methodology, as reflected in the third input requirement, enables an assessment of the influence of spatial variation on the comparison of alternative pharmaceuticals. In other words: does location matter in the choice between alternative pharmaceuticals? We will answer this question in a case study with two fluoroquinolone antibiotics: ciprofloxacin and levofloxacin.

2. Methodology

2.1. Description of the methodology

The methodology for the environmental decision support system is similar to the previously developed screening tool for policy prioritization (Oldenkamp et al., 2013), which is based on four consecutive steps: emission, fate, exposure and effect. It calculates regional (100 km^2 grid-scale) risk indicators throughout Europe for both the aquatic environment and human health. For a detailed description of the assumptions and calculations underlying the tool we refer to Oldenkamp et al. (2013). Furthermore, Appendix A contains a short summary of this publication and a visualization of the tool. Below, the adaptations are explained.

Contrary to the original prioritization tool, prescribed amounts instead of national consumption data form the starting point for the emission calculations. After all, the impact of one prescription cannot be deduced from the impact of the total consumption on a national level. By default, prescribed amounts are expressed in Defined Daily Doses (DDDs; WHO, 2012), which enables a comparison of different pharmaceuticals. Optionally, they can also be expressed in grams.

Furthermore, emissions are assumed to take place in a limited geographical region, i.e. the location of prescription. The end-user has to select the grid in which the pharmaceutical is prescribed. Consequently, the resulting emissions to surface water also take place in this grid. Emissions to agricultural soil depend on state-specific sludge disposal practices and are expressed as per km^2 agricultural soil. Under the assumption of a homogeneous disposal over the agricultural area in the Member State of concern, these emissions are therefore not restricted to the grid of prescription, but can occur in every grid that contains agricultural soil. The multimedia fate model SimpleBox (Hollander et al., 2007), adapted for ionizing substances and spatially parameterized with data from Pistocchi and Pennington (2006), subsequently calculates exposure concentrations in each grid where emissions take place. For each of these grids and for both pharmaceutical prescriptions, a grid-specific risk indicator is calculated, i.e. the ratio between the predicted exposure concentration and a reference value. Eqs. (1) and (2) specify this risk indicator for the aquatic environment and for human health, respectively:

$$I_{aq,i,j} = C_{sw,i,j}/HC_{50,i} \quad (1)$$

where $I_{aq,i,j}$ is a measure for the impact of pharmaceutical i on the aquatic environment in grid j, $C_{sw,i,j}$ is the surface water concentration of pharmaceutical i in grid j, and $HC_{50,i}$ is the hazardous concentration of pharmaceutical i at which at least 50% of the individuals in 50% of aquatic species is affected.

$$I_{hum,k,i,j} = D_{k,i,j}/HD_{50,i} \quad (2)$$

where $I_{hum,k,i,j}$ is a measure for the impact of pharmaceutical i on human exposure group k in grid j, $D_{k,i,j}$ is the dose of pharmaceutical i taken in by human exposure group k in grid j, and $HD_{50,i}$ is the hazardous dose of pharmaceutical i at which at least 50% of the individuals in 50% of mammalian species is affected.

When the impact is not limited to the grid of prescription, i.e. when agricultural disposal of sludge takes place, risk indicators for multiple grids need to be integrated. This can be done in different ways. Here, grid-specific aquatic risk indicators are integrated according to Eq. (3), and grid-specific risk indicators for human health according to Eq. (4).

$$I_{aq,i} = \sum_{j=1}^{n} (V_j/V_{MS} * C_{sw,i,j}/HC_{50,i}) \quad (3)$$

in which n is the number of grids in the Member State of concern, V_j is the surface water volume in grid j (excluding sea water), and V_{MS} is the total surface water volume in the Member State.

$$I_{hum,k,i} = \sum_{j=1}^{n} (P_j/P_{MS} * D_{k,i,j}/HD_{50,i}) \quad (4)$$

in which P_j is the population size in grid j, and P_{MS} is the total population in the Member State.

Previously, infants (0–1 years) that consume conventionally treated drinking water and locally produced foodstuffs were identified as the most sensitive human exposure group (Oldenkamp et al., 2013). They were therefore selected as the human exposure group most suitable for the calculation of the impact on human health.

Finally, relative impacts (I_{rel}) are calculated to compare the two alternative pharmaceutical prescriptions. These represent the contribution of a pharmaceutical prescription to the total impact in case both pharmaceuticals would have been prescribed, normalized to 100% (Eq. (5)). The calculation is the same for the aquatic environment and human health.

$$I_{rel,i} = I_i/(I_1 + I_2) * 100\% \quad (5)$$

2.2. Selection of substances

Ciprofloxacin and levofloxacin, two second-generation fluoroquinolone antibiotics, were selected to illustrate the methodology in a case study. Because of their relatively high risk quotients, both substances were identified from a larger set of antibiotics and antineoplastics as being amongst the most interesting for future policy focus (Oldenkamp et al., 2013). Additionally, ciprofloxacin and levofloxacin are comparable in terms of their medical application (Walker, 1999). Table 1 provides an overview of the data quality of the relevant substance-specific input parameters, based on a four-step procedure to select input data which descends from high to low quality:

1. Experimental or measurement data.
2. Extrapolation from related data (e.g. from degradation rates in other environmental media).
3. Structure or property based predictions (e.g. the use of QSARs).
4. Worst-case assumptions.