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Impact assessment of emission management strategies of the pharmaceuticals Metformin and Metoprolol to the aquatic environment using Bayesian networks

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HIGHLIGHTS

- An integrated impact assessment of drug emission management measures was developed.
- Drug emission management should comprehensively target the lifecycle of a substance.
- Only a broad range of measures can address a spectrum of drug characteristics.
- The model hints that an integrated emission management leads to stronger reduction.
- The model can function as a context-specific forecasting tool for drug pollution.

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ABSTRACT

The issue of pharmaceuticals in the environment has caused increasing concern in the recent years and various strategies have been proposed to tackle this problem. This work describes a Bayesian network (BN)-based socio-ecological impact assessment of a set of measures aimed at reducing the entry of pharmaceuticals in the aquatic environment. The measures investigated were selected across three sectors: public health market, environmental politics and drug design innovation. The BN model was developed for two drugs, Metformin and Metoprolol, and it models the distribution of the Predicted Environmental Concentration (PEC) values as a function of different measures. Results show that the sensitivity of the PEC for the two drugs to the measures investigated reflects the distinct drug characteristics, suggesting that in order to ensure the successful reduction of a broad range of substances, a spectrum of measures targeting the entire lifecycle of a pharmaceutical should be implemented. Furthermore, evaluation of two scenarios reflecting different emission management strategies highlights that the integrated implementation of a comprehensive set of measures across the three sectors results in a more extensive reduction of the contamination. Finally, the BN provides an initial forecasting tool to model the PEC of a drug as a function of a combination of measures in a context-specific manner and possible adaptations of the model are proposed.

1. Introduction

Pharmaceutical residues are ubiquitous in the aquatic environment and recent improvements in analytical methods have revealed the presence of an ever growing spectrum of these contaminants in surface waters (Bergmann, 2011; Daughton and Ternes, 1999; Kümmerer, 2010; Walz and Götz, 2014; Winker, 2009), raising concerns of potential risks for humans and for the environment (Brodin et al., 2013; Sumpter, 2010). Pharmaceuticals for human use mainly enter the wastewater stream through excretion and incorrect disposal through the sink or toilet and they reach the environment due to their incomplete removal at wastewater treatment plants (Kümmerer, 2010; Walz and Götz, 2014).

Until recently, efforts to prevent the entry of pharmaceuticals in the environment mainly concentrated on end-of-pipe measures, whether by improving wastewater treatment efficacy or by introducing take-back collection systems for unused drugs (Daughton, 2014). However, there has been growing emphasis on the importance of upstream preventive measures targeting drug prescription practice and drug design characteristics and in recent years the discussion has shifted towards tackling the problem of pharmaceuticals in the environment by addressing different sections of their life cycle (Daughton, 2014; Daughton and Ruhoy, 2013; ISOE, 2008). In fact, when discussing emission management alternatives, different options can be proposed. Strategies can either focus on a single phase of the life cycle, therefore targeting only drug design, drug use or drug release, or they can be the result of a combination of measures addressing the three phases. In an effort to identify a suitable

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emission management strategy to handle this issue, three main sectors were identified through a stakeholder participatory process as key areas where intervention could target the entry of pharmaceuticals in the environment (Kerber et al., 2014a): the public health market (including disease prevention, medical treatment and prescription practices), environmental politics (which addresses aspects of water and wastewater treatment as well as broader environmental regulatory frameworks) and drug design innovation (focusing on drug design guidelines and criteria for drug approval). Within these sectors, a number of measures were identified as either desirable or likely to be implemented in the coming years and their development in Germany until 2030 was outlined in two scenarios. One describes a likely course of events in the next two decades, where measures are implemented only to some extent and in an uncoordinated manner, and one proposes a more intensive and integrated effort to tackle the issue of pharmaceuticals in the environment (Kerber et al., 2014b).

The aim of the study presented here was to gain an overview of how the implementation of a comprehensive set of measures across the three aforementioned sectors can ensure an effective emission management strategy of a broad range of pharmaceutical substances. To achieve this we decided to focus on two drugs, the antidiabetic drug Metformin and the beta-receptor blocker Metoprolol, and to develop a social-ecological impact assessment using Bayesian networks (BNs) with two main goals: first, to evaluate how a selection of measures targeting a broad section of the lifecycle of these substances can affect their occurrence in the environment; second, to assess how the different measures address the drug-specific characteristics and can therefore be suitable to target a wide range of substances.

Given the diverse nature of the measures to be analyzed and their, until now, uncoordinated implementation under different (context-specific) conditions, we decided to develop this impact assessment using Bayesian networks. BNs are statistical multivariate models that combine a qualitative, graphical description of a system with a quantitative evaluation of the strength of the interdependencies between the variables of such system (Castelletti and Soncini-Sessa, 2007). BNs have a number of properties that are useful in the context of environmental modeling and that make them suitable for the purpose of this study: first of all, they allow to describe complex systems (such as e.g., the lifecycle of a pharmaceutical) in a transparent manner; second, they can incorporate different types of information, ranging from data to expert opinion, and can therefore be used in cases where there are limited data available or where a participatory modeling approach is desirable; third, they can be updated as new knowledge becomes available; finally, the probabilistic description of knowledge allows to explicitly represent uncertainties in the system (Aguilera et al., 2011; Bergmann et al., 2012; Cain, 2001; Pollino et al., 2007; Uusitalo, 2007).

BNs are a very versatile tool that can be used for different applications. BNs can for example be implemented for the qualitative description and conceptualization of a system by defining the interdependency of the variables under examination, as in the case of the model developed by researchers in the same team in the framework of the *start*$_2$ project (ISOE, 2010). On the other hand, BNs are often used in probabilistic inference to quantitatively model a system and can be implemented as decision support systems for the development of management strategies (Cain, 2001; Castelletti and Soncini-Sessa, 2007; Jensen and Nielsen, 2007; Kuikka et al., 1999). BNs have been increasingly applied in environmental modeling, particularly in the fields of water resource management and ecology (Aguilera et al., 2011; Bromley, 2005; Cain, 2001; Castelletti and Soncini-Sessa, 2007; Landuyt et al., 2013; Marcot et al., 2006; Pollino et al., 2007) and they have also been implemented for environmental exposure and risk assessment (Liu et al., 2012; Money et al., 2014; Tighe et al., 2013; Voie et al., 2010).

As to the pharmaceutical substances selected for this impact assessment, they are both representatives of wide-spread chronic diseases, whose prevalence is expected to increase in the coming years (Peters et al., 2010; Shaw et al., 2010), and they have a set of properties which was interesting to compare for the purpose of this study.

Metformin is an oral antidiabetic commonly used in the treatment of type 2 Diabetes mellitus. In 2011, Metformin prescription in Germany reached a total of 601 Mio defined daily doses (DDDs) (Schwabe and Pfaffrath, 2012), corresponding to over 1200 t per year (calculated for a DDD of 2 g (WHO Collaborating Centre for Drug Statistics Methodology, 2014a)). Individual annual prescription levels in Europe are in the range of 5.9–12.1 g/person (Oosterhuis et al., 2013; Roig, 2010) and prescription is likely to increase in the coming years given the expected increase in diabetes prevalence. The high consumption of Metformin, combined with a poor extent of metabolism in the human body (Bailey and Turner, 1996), results in high levels of metformin in wastewater, followed by its release in the aquatic environment due to incomplete removal during wastewater treatment (Scheurer et al., 2012; Scheurer et al., 2009; Trautwein et al., 2014; Trautwein and Kümmerer, 2011).

Metoprolol, on the other hand, is commonly used in the treatment of hypertension. In 2011 sales in Germany were over 135 t per year (Schwabe and Pfaffrath, 2012), equivalent to 901 Mio DDDs (DDD is 0.15 g (WHO Collaborating Centre for Drug Statistics Methodology, 2014b)), and the annual prescription level in Europe is between 0.04–1.0 g/person (Oosterhuis et al., 2013; Roig, 2010). Metoprolol has been detected in surface waters in Germany (Derksen and ter Laak, 2013; Ternes, 1998), though at lower levels compared to Metformin, and it provides an interesting comparison due to its higher extent of metabolism in the human body (Lienert et al., 2007) as well as its characteristic wastewater treatment removal efficiency profile (Margot et al., 2013).

Our analysis aims to show that addressing the issue of pharmaceuticals in the environment with a comprehensive set of measures allows to target a variety of drugs having different characteristics and results in a more efficient reduction of the contamination. Furthermore, we propose the BN developed in this study as a forecasting tool (which can be updated and modified) to model the occurrence of a drug in surface water in a context-specific manner.

2. Materials and methods

2.1. BN development and selection of variables

BNs consist of two main components. The directed acyclic graph (DAG) comprises a set of variables, also called nodes, connected by directed arrows which describe the cause and effect dependency between them. On the other hand, the conditional probability tables (CPTs) associated with each node define the strength of the relationship between the variables in the DAG (Cain, 2001).

To model the entry of pharmaceutical residues in the aquatic environment, the core of the BN was developed based on the equation of the Predicted Environmental Concentration (PEC) for surface water (European Medicines Agency, 2006). The PEC describes the calculated value of a chemical in surface water and its equation was adapted from that detailed in the guidelines for the environmental risk assessment of pharmaceuticals published by the European Medicines Agency (European Medicines Agency, 2006). The equation (see Eq. 1) is based on drug excretion, incorrect disposal (i.e., disposal of unused drugs through the toilet or sink), removal efficiency during wastewater treatment, population, wastewater production and dilution of the wastewater effluent in the environment.

The selection of the substances to be analyzed was based on the following criteria: it can be easily related to a single disease type; it allows to discuss different types of measures across the three sectors; there is sufficient literature data available concerning its use, pharmacokinetics, removal and detection in the environment; it should be currently in the