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Probabilistic environmental risk characterization of pharmaceuticals in sewage treatment plant discharges

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ABSTRACT

The occurrence of pharmaceuticals in different water bodies and the findings of effects on aquatic organisms in ecotoxicity tests have raised concerns about environmental risks of pharmaceuticals in receiving waters. Due to the fact that the amount of ecotoxicological studies has increased significantly during the last decade, probabilistic approaches for risk characterization of these compounds may be feasible. This approach was evaluated by applying it to 22 human-used pharmaceuticals covering both pharmaceuticals with a high volume and high ecotoxicity, using ecotoxicological effect data from laboratory studies and comparing these to monitoring data on the effluents from sewage treatment plants in Europe and pharmaceutical sales quantities. We found that for 19 of the 22 selected pharmaceuticals the existing data were sufficient for probabilistic risk characterizations. The subsequently modeled ratios between monitored concentrations and low-effect concentrations were mostly above a factor of 100. Compared to the current paradigm for EU environmental risk assessment where a safety factor of 10 or 100 might have been used it seems that for the modeled compounds there's a low environmental risk. However, similarly calculated ratios for five pharmaceuticals (propranolol, ibuprofen, furosemide, ofloxacin, and ciprofloxacin) were below 100, while ibuprofen and ciprofloxacin are considered to be of high concern due to lack of ecotoxicity studies. This paper shows that by applying probabilistic approaches, existing data can be used to execute a comprehensive study on probability of impacts, thereby contributing to a more comprehensive environmental risk assessment of pharmaceuticals.

1. Introduction

Sewage treatment plant (STP) effluent is generally considered to be the main point source of human pharmaceuticals to the aquatic environment (Zuccato et al., 2006; Ternes et al., 2007). The most obvious sources to pharmaceutical residues in municipal wastewater comprise excreted active ingredients, their water soluble conjugates and metabolites, and unused medicine being directly disposed, resulting in pharmaceuticals in river catchment areas. In several cases also hospital wastewater, landfill leachate and wastewater from pharmaceutical manufacturing are discharged to municipal STPs.

A rapidly increasing number of laboratory studies is available on the ecotoxicological effects of pharmaceuticals (Halling-Sørensen et al., 1998; Daughton and Ternes, 1999; Heberer, 2002; Fent et al., 2006; Zuccato et al., 2006). For this study, we used the current knowledge about pharmaceutical findings in STP effluents and the available ecotoxicological data to develop a probabilistic risk characterization method for the aquatic environment. By evaluation of existing studies, we tried to identify data gaps, future research priorities, and the identities of pharmaceuticals of primary environmental concern.

Different approaches has been suggested to be used to evaluate the risk of discharge of pharmaceuticals to the environment such as using specific relevant biomarkers in the risk assessment procedure as suggested by Ankley et al. (2007) and PEC/PNEC ratio calculations (Bound and Voulvoulis, 2006; Cooper et al., 2008; Kostich and Jazorchak, 2008). Attempts to use probabilistic modeling for risk characterization has also been suggested (Straub and Steward, 2007).

Probabilistic approaches have already been used on numerous occasions for a wide range of purposes in risk characterization of xenobiotics, mainly focusing on species sensitivity distributions in hazard evaluations (Hall et al., 2000; EUFRAM Report, 2006; Posthuma and de Zwart, 2006). For pharmaceuticals, probabilistic approaches in risk characterization are not commonly used. Most likely this is due to an assumed lack of data, both on measured concentrations and on ecotoxicological effects. However, the study by Straub and Steward, on naproxen demonstrated that sufficient data

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may be available for this type of risk assessment (Straub and Steward, 2007).

The probabilistic assessment procedure proposed in this paper is based on the continua of measured concentrations and effect concentrations, which are parameters closely related to PEC and PNEC, respectively, whereby the effects assessment step includes several species from different tropic levels. The characterization of risk can then be calculated as a ratio between effect concentrations and measured concentrations.

The aim of this study was to perform a probabilistic ecological risk analysis for 22 different selected human pharmaceuticals used in Europe, using an approach in which measured and predicted concentrations in sewage treatment plant effluents and ecotoxicological effects documented in laboratory tests were analyzed on a probabilistic basis. The assessment is limited to STP effluents, as these are the main point sources of human pharmaceuticals in the aquatic environment and because data on pharmaceutical concentrations is most abundant in STP effluents. STP sludge will not be considered in the current paper as focus is on effects to the aquatic environment.

2. Materials and methods

2.1. Data collection

Pharmaceutical use statistics, measured concentrations in STP effluents and laboratory ecotoxicity data were collected for the following 22 pharmaceuticals used in Europe belonging to nine different therapeutic classes: betablockers (atenolol, metoprolol, propranolol, sotalol), diuretic (furosemide), lipid modifying agent (simvastatin), selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine, sertraline), antiepileptic (carbamazepine), anxiolytics (diazepam, oxazepam), analgesic (paracetamol), antiinflammatorics (ketoprofen, naproxen, ibuprofen, dichlofenac) and antibiotics (ciprofloxacin, norfloxacin, ofloxacin, trimethoprim). The compounds were mainly selected in view of high usage and high ecotoxicity, while being limited to compounds for which information on effects and measured concentrations were available.

We collected data on pharmaceutical concentrations measured in STP effluent (MSTP) in Europe from national survey studies and studies published in scientific journals using cross referencing and the databases PubMed, SciFinder Scholar 2007 and ISI Web of Knowledge; combinations of the following search terms were used: sewage, effluent, compound name, waste water, environment and pharmaceutical. National survey studies were found using the search terms at www.google.com.

Results of aquatic ecotoxicological tests (EC50/LC50/NOEC/LOEC) for acute and chronic effects from both standardized and non-standardized studies were collected from the public databases www.fass.se, http://cfpub.epa.gov/ecotox/ and from papers in scientific peer reviewed journals using the above mentioned databases and cross referencing using combinations of the terms: compound name, ecotoxicity, acute, chronic, effect, environment and pharmaceutical.

For a number of European countries predicted concentrations of pharmaceuticals in STP effluent (PSTP) at the level of a region were calculated as worst case estimates thus neglecting metabolism in the patient and dissipation in STPs. These estimates were based on pharmaceutical sales statistics in 2005 for 11 countries. However, for several countries it was not possible to obtain this type of information either because the consumption is not registered or because the data is not accessible. For Denmark, Sweden, Finland and Estonia the sales cover both the primary (sold at pharmacies) and the secondary (hospitals and other health institutions) health care sector. For the following countries only sales in the primary health care sector were available: The Netherlands, Belgium, Italy, Germany, Spain and Czech Republic. Calculation of regional PSTP concentrations and references are given in Appendix II.

2.2. Ecotoxicological test data categorization

The ecotoxicological test data for each pharmaceutical was categorized according to availability and quality, assigning a score from A to F (see Table 1 and Appendix IV in the Supporting information). This score is comparing the estimated ratio between ecotoxicological effect concentrations and measured concentrations (EC_5/MC_{95}) to amount of available data in order to evaluate if lack of ecotoxicological data is so pronounced that environmental risk assessments will be affected. Ratios of EC_5/MC_{95} were estimated using the 95th percentile for MSTP values as this includes 95% of the lowest measurements (5% of the highest measurements are excluded) and the 5th percentile of ecotoxicological effects was selected as this includes 5% of the lowest ecotoxicological data. For detailed informations on the scorings system informations are available in the Supporting informations (Appendix IV).

2.3. Modeling procedure

In the probabilistic modeling the logarithmic normal distribution was separately fitted to aggregate data of measured STP concentrations (MSTP), predicted STP concentrations (PSTP) and ecotoxicological effect concentrations. Hereby, the quotient of two independent measurements following separate logarithmic normal distributions is easily described enabling estimations of confidence intervals for the quotients between MSTP, PSTP and effect concentrations. The basic assumption underlying the probabilistic modeling is that MSTP values for a given pharmaceutical belongs to the same logarithmic normal distribution. Similar assumptions are made for the PSTP values and ecotoxicological effect concentrations. The distribution of MSTP values is thus assumed to be a characterization of MSTP effluent concentrations across Europe, across urban/no-urban STPs, across high/low technology STPs, across time of measurement, type of sampling and across quality of analysis. The selected ecotoxicological effect concentrations that were used in the modeling reflect data across species, endpoints and test duration for acute and chronic effects in both standardized and non-standardized tests. In this way the fitted distributions summarize the available measurements ignoring their origin (which is partly unknown).

Likelihood analysis was used for estimation of the distribution parameters of each fitted model (Lehmann, 1983). For the MSTP effluent concentrations, different types of data are presented, i.e. individual and combined observations. The combined observations include mean and median values of a sample of size n and available information about maximum concentrations measured. For fixed values of the distribution parameters the mean correspond to a particular percentile, and the measurement of the mean is reinterpreted as the measurement of this percentile. Thus, the combined measurement of the median, mean and the maximum of a sample of size n, can be reinterpreted as the combined measurements of three percentiles in the sample distribution, and these can be given a joint likelihood in the probabilistic model. Such likelihoods are multiplied by the likelihoods for the individual measurements to give the joint likelihood. The information on the number of samples below quantification limit or detection limit was ignored since this could not easily be combined with the other measurements (Hecht and Honikel, 1995). Only data for parent compound measurements were included. Information on "not detected" was also ignored since this cannot be modeled by the logarithmic normal distribution. The joint likelihood was maxi-