Occurrence of Venlafaxine, other Antidepressants and selected metabolites in the Rhine catchment in the face of climate change

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Capsule Abstract

The fate of the antidepressants was determined in the Rhine catchment area with regard to the influence of climate change on the concentration of antidepressants in rivers.

Abstract

Fate and occurrence of 4 selective serotonin reuptake inhibitors, one serotonin-noradrenergic reuptake inhibitor and one noradrenergic-dopaminergic reuptake inhibitor and their human metabolites were determined in a German municipal wastewater treatment plant as well as in the Rhine River and selected tributaries. The enantiomeric fractions of venlafaxine and its metabolites were not altered during wastewater treatment and were similar in all river samples underlining that no appreciable biodegradation occurs. In the Rhine catchment area highest concentrations were detected for venlafaxine, citalopram and their human metabolites. Projected future climate change would lead to an increased portion of treated wastewater in rivers due to reduced discharges during low flow situations by the end of the 21st century. However, the effect of climate change on the pattern and concentrations of antidepressants is predicted to be of minor importance in comparison to altered consumption quantities caused by demographic developments and changes in life styles.

Keywords

Antidepressant, surface water, climate change, chiral separation, Rhine River

Introduction

The consumption of pharmaceuticals keeps on growing in developed countries. During the last decade, a wide range of these compounds has been discovered ubiquitously in the aquatic environment with subsequent potential risks for the biodiversity of rivers and streams (Daughton and Ternes, 1999). Pharmaceuticals enter the aquatic environment predominately via discharges from wastewater treatment plants (WWTPs), run-offs from agricultural fields, if they are fertilized with manure or sewage sludge or via leachates of landfill sites (Boxall et al., 2004, Schlüsener et al., 2006 and Halling-Sørensen et al., 1998).

More than 200 individual pharmaceuticals have already been detected in the aquatic environment. Among these are the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, citalopram, and sertraline and the serotonin-noradrenergic reuptake inhibitor (SNaRI) venlafaxine and the noradrenergic-dopaminergic reuptake inhibitor (NaDaRI) bupropion. In Germany, the prescribed quantities of these antidepressants increased significantly during the 6 years from 2007-2012 (Schwabe and Paffrath, 2008-2013) (Table 1). The annual consumptions of citalopram and venlafaxine were even doubled from 3.4 t and 6.2 t in 2007 to 6.8 t and 14.7 t in 2012, respectively, which may lead to increased concentrations in German rivers and streams.

Most of the antidepressants are converted (frequently demethylated) by patients to biologically active metabolites (Hiemke et al., 2000). Metcalfe et al. (2003, 2010) detected SSRIs and their demethylated metabolites in surface water downstream of WWTPs (900 ng/L venlafaxine; 1470 ng/L O-desmethylvenlafaxine). Schultz et al. (2008, 2010), Du et al., (2012) and Ramirez et al., (2009) identified them in rivers, wastewater, WWTP effluents, sediments and fish tissue. Only a few studies are published for Europe about the occurrence of selected antidepressants, so far comprising Spain (Lamas et al., 2004), Austria (Himmelsbach et al., 2006), Germany (Subedi et al., 2012 and Rúa-Gómez et al., 2013) Norway (Vasskog et al., 2006) and EU-wide (Loos et al. 2013). Also here, climate change may have an impact. As transformation is in part temperature dependent, changes of average and maximum water

temperatures may affect the concentrations of the original contaminants. Therefore, climate change may have an impact on the water concentrations of micropollutants.

Antidepressants are reported to adversely impact aquatic flora and fauna already close to environmental concentrations (Brooks et al., 2003, Fong, 1998, Johnson et al., 2007, Gaworecki and Klaine, 2008, Painter et al., 2009, Franzellitti et al., 2014, Weinberger and Klaper, 2014). Toxicological studies highlighted that fluoxetine and paroxetine induced spawning in zebra mussels at concentrations as low as 10^{-7} M, equivalent to ~ 30 $\mu\text{g/L}$ (Fong, 1998). Adverse effects to algae were observed at concentration levels ranging from 0.73 to about 13 mg/L (Johnson et al., 2007). Gaworecki and Klaine (2008) found a decrease in prey capture ability by hybrid striped bass exposed to fluoxetine concentrations ranging from 23 to 100 $\mu\text{g/L}$. Painter and co-workers (2009) identified a reduced predator avoidance performance in larval fathead minnows that are exposed to fluoxetine and venlafaxine at concentration levels ranging from 25 to 250 ng/L and from 500 to 5000 ng/L, respectively.

Future climate change may accelerate the increase of the antidepressant concentrations in rivers through intensification and prolongation of low flow situations during the summer months (e.g. Middelkoop and Kwadijk, 2001, Görgen et al., 2010, Hurkmans et al., 2010, Huang et al. 2010, Huang et al., 2013). Assuming constant emissions of treated water from WWTPs, concentrations of relevant substances may further rise under these conditions. Benotti et al. (2010) reported about studies that over several years the droughts in Lake Mead increased the concentrations of selected wastewater originated contaminants in the drinking water resources of Southern Nevada.

An estimate of climate change for the Rhine basin shows an average air temperature increase of 2-4°C until 2100 (Görgen et al., 2010). Since stream water temperature changes are closely related to air temperature changes (Langan et al., 2001), an increase in water temperature can be expected due to the projected climate change. Furthermore, in Europe the increase of air temperature, mainly be attributed to the emission of greenhouse gases, may cause more frequently heat periods in summer (Schär et al., 2004, Stott et al., 2004). With respect to precipitation, most climate projections show an increase in winter (+5% to +20%) and a decrease in summer (-10% to -30%) until the end of the 21st century in the Rhine basin. River discharge is expected to be higher under these conditions during the winter and reduced

during the summer due to lower precipitation quantities, increased evapotranspiration and reduced snow storage (Görger et al., 2010).

The aim of this study was (i) to determine the removal of 4 SSRIs, 1 SNaRI and 1 NaDaRI and their human metabolites (Figure 1) in a municipal WWTP, their occurrence in the Rhine catchment area and (ii) to estimate the impact of climate change scenarios on future concentrations of these substances in German rivers and streams based on assumptions about consumption quantities, proportion of wastewater, and river water temperatures.

Therefore, the antidepressants were analyzed in the river Rhine, selected tributaries of the river Rhine and two WWTPs. The persistence was ascertained by the longitudinal distribution of the enantiomeric fractions of venlafaxine and its metabolites in the river Ruhr and its behavior during WWTP treatment. The potential influence of climate change on the concentrations of antidepressants in rivers was estimated by extrapolating the annual average concentrations and loads measured in the river Rhine at the city of Koblenz, two kilometer upstream from the confluence of river Moselle, and Rhine (RKI, River Kilometer Index 590.3) to the future using a set of climate change models.

Experimental

Used chemicals, solid phase extraction methods, LC-MS analysis, chiral separation, and the calibration are described in the Supporting Information.

Sampling

Raw and treated wastewater were sampled from two municipal German WWTPs consisting of a grit-removal, a primary clarifier followed by nitrification/denitrification for nutrient removal and chemical phosphorous removal by Fe(II) addition. WWTP1 serves for about 330,000 population equivalents (PE) with a daily flow rate of approx. 60,000 m³. The activated sludge system is operated with a hydraulic retention time (HRT) and sludge retention time (SRT) of approx. 12 h and 10-12 d, respectively (results Table S4). WWTP2 treats approx. 250,000 m³ of wastewater per day and serves 1,350,000 PE. It consists of two biological treatment units in series. HRT and SRT of the first aerated COD removal unit are approx. 1h and 0.5 d, respectively. The second activated sludge unit consists of a stirred anaerobic compartment for denitrification followed by an aerated compartment for nitrification and is operated with a HRT and SRT of approx. 5 h and 18 d, respectively. Grab samples were taken from WWTP1, whereas 24 h composite samples over 5 consecutive days were taken from WWTP2 during

07.05.-11.05.2012 (results Table 2). Samples were acidified with 2.5 M sulfuric acid to pH 3, stored at 4°C and transported to the laboratory and extracted within 48h.

The Ruhr watershed, the river Rhine and the river Emscher were monitored. An overview of the sample locations is provided in Figure 2 and Table S1. Grab samples were taken in amber glass bottles during a dry weather period in September 2009. To determine the long time occurrence of the antidepressants in the river Rhine, 28d composite samples (n=21) were taken at the international monitoring stations of the ICPR (International Commission for the Protection of the Rhine) at RKI 590.3 near Koblenz, Germany, from 2011 to 2012. The water was stored at 4°C during the sampling period of 28d and extracted within 24h after sampling. All water samples were immediately transported to the laboratory (within 4-6 h), filtered through glass fiber filters (GF 6, <1 µm, diameter 55 mm from Schleicher and Schuell, Dassel, Germany) and acidified to pH 3 with 2.5 M sulfuric acid for sample preservation. All river samples were stored at 4°C in the dark until sample extraction (within 2-4 d).

Validation of the analytical method

The analytical method was validated by spiking 1 L of groundwater with the stock solutions to attain concentrations of 0.3, 1, 3, 10, 30, 100, 300 and 1000 ng/L. In addition, both WWTP influent and effluent were spiked with concentrations of 100 ng/L and 500 ng/L of each analyte. Sample preparation, extraction and detection were performed as described above and in the SI. Recovery experiments were carried out for eight concentration levels in triplicates. The limit of quantification (LOQ) was defined as a signal-to-noise ratio of 10:1 in the respective matrix.

Climate change simulations of the river Rhine

The effects of future climate change on aquatic systems are usually evaluated using chains of computer models (e.g. Middelkoop and Kwadijk, 2001; Hurkmans et al., 2010; Görgen et al., 2010 for the river Rhine). These chains begin with scenarios (plausible assumptions) of future greenhouse gas emissions. The resulting atmospheric concentrations are used to drive global climate models which project globally coherent fields of climate variables on relatively coarse spatial grids (often 200 km x 200 km; Meehl et al. 2007). As more spatial details are necessary to evaluate regional climate change effects within river basins such as the river Rhine basin, regional climate models are 'nested' in the global models to downscale the coarse fields of climate variables to resolutions of 10 km to 20 km (e.g. Van der Linden and Mitchell

2009). The resulting high resolution fields of climate variables (e.g. precipitation, air temperature, global radiation) are then used as input to hydrological, water temperature and other models which produce relevant variables describing potential reactions of aquatic systems on future climate change. As models are by definition only approximations of the real systems, simulations deviate from contemporaneous observations more or less systematically. Currently there is no single "best" model because different models perform variably well for different regions, seasons and statistical parameters. Any step of the described model chain adds uncertainty to the simulated change signal. To capture this uncertainty, it is advisable to carry out each modelling step several times using a variety of models (IPCC 2007). The resulting multi-model ensemble of simulations leads to a range of results that cover the current knowledge about possible climate change effects conditioned by the assumed greenhouse gas emissions and the modelling framework used.

Here, the potential effects of climate change were derived from an ensemble of 20 discharge simulations (Görgen et al., 2010) covering the period 1950 to 2100. The simulations were carried out based on plausible climate model chains combining three different emission scenarios, eight different global climate model runs and nine different regional climate models. Most of the climate simulations were provided by the EU-FP7 project ENSEMBLES (Van der Linden and Mitchell 2009) and forced by the emission scenario A1B (Nakicenovic et al., 2000). The model results (daily fields of air temperature, precipitation and global radiation) were corrected for biases between the simulated and observed values in the period 1961-1990 following a linear scaling approach as published e.g. by Lenderink et al. (2007). On that basis, hydrological simulations were carried out with the semi-distributive conceptual hydrological model HBV134 (Bergström et al., 1995, Eberle et al., 2005) and provided daily time series of discharge at various gauging stations in the catchment of the river Rhine. Here, we focus on the Middle Rhine (represented by gauge Kaub, RKI =546) close to the chemical measurement station Koblenz, RKI 590.3). Highest wastewater proportions are usually occurring during the summer, as in these months this river stretch typically shows the lowest flows of the year. Thus, 30 years mean changes of the lowest daily mean discharge in the hydrological summer (May-Oct) were used to describe relevant effects of future climate change as simulated by the 20 member ensemble.

Water temperature modelling was carried out using the water quality simulation model QSim of the German Federal Institute of Hydrology (Kirchesch and Schöl, 1999, Schöl et al., 2006). QSim is a deterministic, process based, one dimensional model which was already applied to calculate the water temperature of the rivers Main, Elbe and Saar (Brahmer et al., 2008,

Becker et al., 2010, Quiel et al., 2011). As input data, QSim requires daily discharge data at the gauging stations and meteorological data (air temperature, wind velocity, relative humidity, global radiation and cloudiness) at the weather stations. A model for the free-flowing German part of the Rhine was established (Hardenbicker et al., 2014). Due to computational restrictions, long-term simulations (30 year periods) could not be carried out for all 20 members of the ensemble of climate and discharge simulations. Therefore, five representative model chains were selected which cover a range of future low flow conditions for the Rhine catchment area (Fig. 3). The selected sub-ensemble is driven by the intermediate CO₂ emission scenario C20-A1B (Nakicenovic et al., 2000) and includes three different global climate models (GCMs HCQ0, EH5, BCM), five different regional climate models (RCMs HRQ0, RCA, REMO, RACMO, CLM24), one bias correction procedure (Linear scaling), one hydrological model (HBV134) and one water temperature model (QSim). Future changes in lowest daily flows and highest daily water temperatures were calculated by comparing the simulation results for two future periods (2021-2050 and 2071-2100) with the reference period (1961-1990). The selected model chains and the results are summarized in Figure 3.

The spread between the different simulations provides an estimate of the current level on uncertainty associated with the climate/discharge projections and of the robustness related to statements on the change in climate, hydrological, and river water temperature.

Results and Discussion

Validation of the method

Mean recoveries ($\pm$ 95% confidence interval) of the selected antidepressants ranged from 76 $\pm$ 6% to 106 $\pm$ 8% for groundwater, from 61 $\pm$ 18% to 121 $\pm$ 5% for surface water, and between 79 $\pm$ 8% and 110 $\pm$ 7% for WWTP effluents (Table S3, S6). The recoveries for WWTP influents ranged from 79 $\pm$ 4% to 117 $\pm$ 6%. Due to severe ion suppression in ESI the developed analytical method was inappropriate to determine bupropion in wastewater samples (Table S3).

Removal of antidepressants in municipal WWTPs

Highest concentrations in raw wastewater were measured for the SNaRI venlafaxine and its principle metabolites O-desmethylvenlafaxine and N,O-didesmethylvenlafaxine up to 260 $\pm$ 6 ng/L, 640 $\pm$ 14 ng/L and 150 $\pm$ 3 ng/L, respectively (Table 2). Similar concentrations of venlafaxine in wastewater were found by Schultz et al. (2010) (873 ng/L-930 ng/L), Lajeunesse et al. (2008) (176ng/L- 215 ng/L) and Loos et al. (2013) (average 119 ng/L, max. 548 ng/L). O-desmethylvenlafaxine and N,O-didesmethylvenlafaxine were not eliminated in the WWTP during the period monitored over 5 days, while for venlafaxine a low elimination (based on loads) of 17 $\pm$ 9% was calculated.

The SSRI citalopram and its metabolite desmethylcitalopram were eliminated in the WWTP from influent to effluent by 33 $\pm$ 7% and 41 $\pm$ 6 % and the SSRI fluoxetine, its principle metabolite norfluoxetine and paroxetine by 65 $\pm$ 4%, 90 $\pm$ 1% and 76 $\pm$ 3%, respectively. For the SSRI sertraline and its two metabolites eliminations from 40 $\pm$ 6% (desmethylsertraline) to 82 $\pm$ 2% (sertraline) were determined. Similar concentrations of citalopram, sertraline and fluoxetine in wastewater as measured in this study (Table 2) were determined by Vasskog et al. (2006), Lajeunesse et al. (2008), Schultz et al. (2010) and Loos et al. (2013). The concentrations of hydroxybupropion, the metabolite of the NaDaRI bupropion, were found to be reduced by 19 $\pm$ 8 %. To our knowledge, it is the first time that this metabolite was detected in wastewater.

Based on the monitoring study it cannot be excluded that during wastewater treatment the antidepressants were also microbially transformed into the metabolites excreted by humans and vice versa. However, it can be concluded that similar to other pharmaceuticals SSRIs,

SNaRI and NaDaRI are incompletely removed during biological wastewater treatment and are thus, continuously discharged via WWTPs into rivers and streams.

The concentrations detected are reflecting the prescribed quantities per person and year (Table 4). The elevated concentrations of venlafaxine and fluoxetine reported in the Canadian studies (Metcalf 2010) are caused by the 3-4 times higher Canadian consumption quantities of 672 mg/(cap a) in comparison to 179 mg/(cap a) in Germany for venlafaxine and 38 mg/(cap a) in comparison to 13 mg/(cap a) in Germany for fluoxetine. From 2009 to 2012 the consumption quantities of venlafaxine were roughly doubled in Germany. If this trend will proceed the next years, the venlafaxine loads might reach the Canadian levels in a few years.

Antidepressants in the Rhine and its catchment area

One kilometer after the spring of the river Ruhr (Ru_01) no antidepressants were detected, while already after the discharge of the first WWTP (Ru_02) five antidepressants were found at levels up to 5.3 ng/L. In both Ruhr and Rhine downstream of WWTP discharges elevated concentrations were found. For instance, fluoxetine and norfluoxetine were only detected directly after a WWTP discharge (Ru_28) with 3.8 ng/L and 9.1 ng/L, respectively. From the spring to the mouth of the river Ruhr the concentrations of the antidepressants increased slightly, leading to 56 ng/L of O-desmethylvenlafaxine, 26 ng/L of venlafaxine and around 10 ng/L of citalopram. In addition to venlafaxine, citalopram and their metabolites only bupropion, and in a few sampling stations fluoxetine and norfluoxetine were detected, while paroxetine, sertraline and its metabolites were not found at all above the LOQs (Table S4, Figure 4 and 5). The small streams Oelbach (Ru_24) and Emscher (Ru_33) exhibited the highest concentrations for all analytes with up to 400 ng/L for O-desmethylvenlafaxine. The portion of treated wastewater of both streams can be higher than 80%. The Emscher receives WWTP discharges from around 4.5 million people and the Oelbach receives the discharge of a WWTP near Bochum (300,000 PE; 35,000 m³/d) that flows directly into the Kemnader reservoir, a local recreation area.

The concentration ratios of O-desmethylvenlafaxine/venlafaxine (2.3 ± 0.8) and N,O-didesmethylvenlafaxine/venlafaxine (0.5 ± 0.2) remained constant in samples taken along the Ruhr. The ratios were equal to those detected in the WWTP effluents. In addition, the enantiomeric fractions (EF) with 0.49 ± 0.03 for venlafaxine (calibration standards: 0.47 ± 0.03 (n=14)); 0.48 ± 0.02 for O-desmethylvenlafaxine (calibration standards: 0.48 ± 0.02 (n=14)) and 0.51 ± 0.03 for N,O-didesmethylvenlafaxine (calibration standards: 0.51 ± 0.03 (n=14)) were not altered during wastewater treatment and were similar in all rivers. Thus, the constant concentration ratios of the metabolites and venlafaxine as well as the constant EF values from the spring to the mouth of the river Ruhr are strong indicators that there is no further biodegradation of venlafaxine and its metabolites in the river during the monitoring period.

In both rivers, Rhine and Ruhr, downstream of WWTP discharges elevated concentrations of the selected antidepressants were found. Thus, WWTP effluents are the primary source of antidepressants in rivers. From the spring to the mouth of the river Ruhr the concentrations of the antidepressants increased slightly, leading to 56 ng/L of O-desmethylvenlafaxine, 26 ng/L of venlafaxine and around 10 ng/L of citalopram. In addition to venlafaxine, citalopram and their metabolites only bupropion, was detected frequently, while the concentrations of paroxetine, sertraline and its metabolites were always < LOQ (Table S4, Figure 4 and 5).

Small streams that are fed mainly by wastewater (e.g. Oelbach, Ru_24 and Emscher, Ru_33) exhibited the highest concentrations for all analytes with up to 400 ng/L for O-desmethylvenlafaxine.

The analysis of the antidepressants in 28d composite samples of the river Rhine at Koblenz from 2011 and 2012 exhibited stable loads of citalopram (mean: 10 ± 2 kg/28d), venlafaxine (mean: 58 ± 9 kg/28d) as well as of the metabolites of both compounds (Table 3, S5), since elevated flow rates lead to lower concentrations of the antidepressants and vice versa. The concentrations of the antidepressants in the river Rhine are directly linked to the proportion of treated wastewater. High flow events caused by heavy rain falls or snow melts have no substantial influence on the antidepressant loads as they are only leading to a dilution of the water. The annual mean concentration of venlafaxine and human metabolites in 2012 was 51 ng/L at an annual mean flow rate of 1813 m³/s and a wastewater proportion of 5% (ICPR 2014), which gives a total annual load of venlafaxine (including metabolites) of 2.8 tons in the Rhine at Koblenz. The catchment area of the Rhine covers about 26 million people (including 5 million Swiss and 1.3 million French people) (ICPR 2014). In 2012 the per capita prescription of venlafaxine was reported to be 179 mg in Germany. This lead to an annual load of 4.7 tons, assuming that consumptions in Switzerland and France are comparable to Germany. Considering that about 18% are eliminated in municipal WWTPs, as shown in this study, and that a certain amount of the prescribed venlafaxine is disposed in domestic waste (ca 10-20%) 2.8 tons are a reasonable quantity. It has to be noted, that the uncertainties of these assumptions are high, but the comparison underlines the persistence of venlafaxine and its human metabolites under environmental conditions.

Potential impacts of climate change

Antidepressants and their metabolites are discharged in rivers and streams primarily via WWTPs (see above). Thus, the concentrations of the antidepressants in rivers are directly correlated to the portion of treated wastewater. Due to the elevated microbiological and chemical (e.g. hydrolysis) persistence of antidepressants, alterations of river flow rates caused by climate changes should have a direct influence on their concentrations. Climate change might lead in the case of droughts to intensified/longer low flow periods and increased water temperatures. Both phenomena can potentially influence the percentage of treated wastewater and alter the concentration levels and the pattern of antidepressants present in rivers and streams. An increased UV radiation can lead to a higher photodegradation of venlafaxine, Rúa-Gómez et al. (2013) reported a half-life of venlafaxine in natural river water

of 2.1 days for indirect photodegradation and 19.2 hours for O-desmethylvenlafaxine. Rühmland et al. (2014) investigated the photodegradation of venlafaxine and its metabolites in different depths of a constructed wetland. No photolysis was observed up to a depth of 20 cm and below over a 3 days period. Therefore, an appreciable direct or indirect photolysis of venlafaxine and its metabolites can be neglected in the river Rhine containing suspended solids with about 35 mg/L and a depth of about 5 m.

Low flow change: Extreme low flow situations have occurred throughout the past centuries in the Rhine catchment (e.g. 1921, 1949, 1972, 1976, 2003, 2011; e.g. Krahe and Larina, 2010). There is no indication that these situations have become more frequent or more intense (e.g. Belz et al., 2006). Also, for the next decades (until the mid of the 21st century), the discharge projections show no clear direction of change. Using as an indicator the lowest daily mean discharge during summer (May-Oct), most projections indicate changes ranging from +10% to -10% around the reference level (average of period 1961-1990) for the period 2021-2050 (Figure 3). For the end of the 21st century (2071-2100) the majority of projections points to decreasing discharges (-10% to -25%). Assuming constant discharges of treated wastewater, these situations would be associated with an increase of the wastewater portion from about 10% (average lowest discharge in reference period) to 14% (far future, low discharge scenarios). As compared to normal flow conditions of 1800 m³/s the antidepressant concentrations might be doubled or even tripled in the Rhine water (Table 5).

Also the durations of low flow situations are projected to increase. For example, a threshold undercut on 20 days in the reference period will be undershot on up to 40 days or more at the end of the 21st century, depending on the respective discharge projection (Nilson et al. 2012). Extreme hydrological droughts are known to cause reduced flow rates for a short period (several days or few weeks). For example, in the reference period 1961-1990 the average of the lowest daily discharge during summer months (May-Oct) was 900 m³/s, while the minimum was 550 m³/s (40% below average) in 1976. Under the low discharge scenarios selected in this study (HCQ0_HRQ0 and EH5r1_CLM24) the minimum daily flow during individual years in the distant future (2071-2100) are simulated to be 50 % and more below the reference value.

Unlike the above assumption, the prescribed and consumed quantities of the selected antidepressants are not constant over time. For instance, in 4 years from 2009 to 2012 the prescribed quantities of venlafaxine in Germany were nearly doubled from 7.5 to 14.7 t. Although this is an extreme example, the potential contributions of up to 10-40% increase

caused by climate change for the next 90 years are likely small in comparison to alterations of consumption quantities during such long periods and changes between normal and low flow conditions.

On the basis of three different future *consumption* scenarios of venlafaxine, i) “no change in consumption”: same consumption of venlafaxine in near and far future as in 2012; ii) “moderate increase”: linear increase of the consumption of 0.5 tons per year until 2050; iii) “Canadian consumption”: same per capita consumption in Germany as in Canada, the concentrations of venlafaxine in the river Rhine are projected for the near and far future (Table 5), as a worst case scenario. Since venlafaxine is a relative persistent compound, it can be assumed that considering the analytical uncertainty of about 20% the predicted increase of the water temperature in summer by about 1.3 °C in the near future (until 2050) and of about 2.8°C until 2100 has no measurable influence on its concentrations in German rivers and streams.

A reduced predator avoidance performance in larval fathead minnows that are exposed to venlafaxine was reported by Painter et al. (2009) at 500 ng/L. Currently, 51 ng/L of venlafaxine (including its human metabolites) are detected in the river Rhine at Koblenz containing an average portion of 5 % treated wastewater. If the consumption of venlafaxine will not change or moderately increase in the next years, the concentrations of venlafaxine in the river Rhine will not reach this ecotoxicological effect level of 500 ng/L. Only if the Canadian consumption levels will be reached and the wastewater portion increased to levels of higher than 14% this ecotoxicological effect level might be exceeded in the river Rhine in the far future. However, for small rivers like tributaries of the river Ruhr (e.g. Oelbach, Ru_24) with a wastewater portion of 40 % the ecotoxicological effect level will be surpassed if the flow rate of these rivers will be lowered by 25% (Table 5). Rivers with a wastewater portion of 50 % and higher surpass the ecotoxicological effect level already today (e.g. Emscher, Ru_33).

Water temperature change: As climate projections indicate further rising air temperatures under all emission scenarios (IPCC 2007, 2013), water temperatures may rise, too. Increased water temperatures are well known to improve the biodegradation of micropollutants. A temperature increase of 10°C nearly doubles or quadruples the microbial biodegradation rate of chemicals (Atkins 2009). The mean maximal increase of water temperature during the hydrological summer ranges between +0.4 to +1.3°C in the near future and between +2.3 to +2.8°C in the distant future. This increase of the water temperature can be assessed to be of

minor importance for the concentrations of venlafaxine, due to its very limited tendency for biodegradation as already seen by passing WWTPs. For the other antidepressants a higher water temperature will improve their biodegradation. The scenarios for the river Rhine indicate that the maximal heat period of successive days with water temperatures exceeding 25°C will increase from 10 to 39 days until 2050 and to more than 50 days until 2100 (Hardenbicker et al. 2014). The concentration of transformation products might become more relevant for these periods.

pH change: Climate change might also alter the pH of surface water, since increased water temperatures and increasing biomass could lead to a reduce dissolved CO₂ concentration and thus depending on the buffer capacity a slight increased pH-value cannot be ruled out. Currently at the Rhine no summer/winter trend of the pH was observed at the monitoring station Koblenz (Wasserblick, 2014). It is therefore very unlikely, that a temperature increase of up to 2.8°C will have impacts on the pH values of the river. However, it should be noted that the ecotoxicological potential of compounds such as sertraline are increasing if the pH exceed 8.5 (Valenti et al., 2009).

Conclusions

In the investigated German rivers and streams the most dominant antidepressants were venlafaxine, citalopram and their human metabolites. Venlafaxine and its metabolites were hardly removed in WWTPs. The influence of climate change leading to an increase of treated wastewater portion can be assessed as minor for the venlafaxine and citalopram concentrations in comparison to the expected consumption enhancement caused by demographic developments and changes in life styles. Since the German consumption quantities of the antidepressants increased permanently up to 30% in the last 6 years, the concentrations in German rivers and streams are increasing as well. If this will continue, it can be expected that in next years during droughts concentrations levels in small rivers are reached, that are causing ecotoxicological effects. Due to their increasing consumption and their relatively high environmental toxicity, it can be recommended to include the investigated antidepressants in environmental monitoring programs.

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Tables

Table 1: Prescribed antidepressants in Germany 2007-2012 according to Schwabe et al (2008-2013).

active pharmaceutical ingredient (API)	Substance class	prescribed DDD in Germany [Million]					Defined Daily Dose (DDD) [mg/day]	Estimated annual quantities prescribed [t]					Metabolism in human body [%]
		2007	2008	2009	2011	2012		2007	2008	2009	2011	2012	
Citalopram	SSRI	165.5	209.3	241.7	338.7	340.9	20	3.39	4.19	4.48	6.77	6.82	>80
Fluoxetine	SSRI	41.2	43.4	43.3	51.6	54.8	20	0.82	0.87	0.87	1.03	1.1	>90
Paroxetine	SSRI	32.3	37.9	42.3	43.5	46	20	0.65	0.76	0.85	0.87	0.92	>98
Sertraline	SSRI	39.2	51.6	55.1	64.4	82.6	50	1.96	2.58	2.75	3.22	4.13	>99
Bupropion	NaDaRI	-	4.4	6.5	12.3	15.5	300	-	1.32	1.95	3.69	4.65	>99
Venlafaxine	SNaRI	61.6	72.5	75.1	123.9	147	100	6.16	7.25	7.51	12.4	14.7	>90

Table 2: Antidepressants in influents and effluents of sampled WWTP2. Statistical uncertainties: 95% confidence intervals for concentration and loads; uncertainty of the elimination is based on Gaussian error propagation. Total treated wastewater was 1,070,100 m³/5d.

Analyte	WWTP2			WWTP2		
	Concentration [ng/L]		Elimination based on concentration [%]	Load [g/5d]		elimination based on loads [%]
	Influent (n=10)	Effluent (n=5)		Influent	Effluent	
Bupropion	-	-	-	-	-	-
Hydroxybupropion	74±2	57±6	23±8	76±2	61±6	19±8
Citalopram	180±4	120±22	36±7	190±4	127±13	33±7
Desmethylcitalopram	100±2	58±6	42±6	106±2	62±6	41±6
Fluoxetine	24±1	8±1	65±4	26±1	9±1	65±4
Norfluoxetine	13±0.3	1.0±0.1	90±1	14±0.3	1.4±0.1	90±1
Paroxetine	9.1±0.2	2.3±0.2	76±2	9.7±0.2	2.4±2	76±3
Sertraline	49±1	9.0±1.1	82±2	54±1	9.4±1	82±2
Desmethylsertraline	65±1	42±4	35±7	74±2	45±5	40±6
Desmethylhydroxysertraline	7.6±0.2	3.6±0.4	52±5	8.4±0.2	3.9±4	53±5
Venlafaxine	260±6	220±22	18±9	280±6	233±24	17±9
O-Desmethylvenlafaxine	640±14	610±62	5±10	667±15	657±67	2±10
N,O-Didesmethylvenlafaxine	150±3	140±14	11±9	154±3	146±15	5±10

Table 3: Load of 28d composite samples of antidepressants in river Rhine at RKI 590.3 including annual load of 2012.

Sampling period	Load [kg/28d]					
	Venlafaxine	Desmethyl-venlafaxine	Didesmethyl-venlafaxine	Citalopram	Desmethyl-citalopram	Hydroxy-bupropion
27.12.10 - 23.01.11	58	147	28	9		8
24.01.11 - 20.02.11	56	111	21	12	7	6
18.04.11 - 15.05.11	24	55	14	5	4	4
16.05.11 - 12.06.11	29	55	15	5	4	4
08.08.11 - 04.09.11	51	142	13	6	4	5
05.09.11 - 02.10.11	53	76	15	7	5	6
03.10.11 - 30.10.11	44	132	18	7	5	7
28.11.11 - 25.12.11	102	259	50	15	9	12
02.01.12 - 29.01.12	74	188	31	16	10	11
30.01.12 - 26.02.12	107	238	45	21	12	13
27.02.12 - 25.03.12	45	127	30	12	8	7
26.03.12 - 22.04.12	36	107	22	9	6	6
23.04.12 - 20.05.12	55	119	24	11	7	8
21.05.12 - 17.06.12	52	120	19	11	6	6
18.06.12 - 15.07.12	45	99	21	11	7	8
16.07.12 - 12.08.12	49	80	17	8	5	6
13.08.12 - 09.09.12	63	56	12	6	4	6
10.09.12 - 07.10.12	41	78	18	8	5	7
08.10.12 - 04.11.12	54	128	27	9	6	9
05.11.12 - 02.12.12	60	163	32	13	8	10
03.12.12 - 30.12.12	79	193	37	19	10	14
Annual load 2012 [kg/a]	759	1697	334	155	93	110

Table 4: Comparison of the annual per capita consumption of antidepressants in Germany, USA and Canada

active pharmaceutical ingredient (API)	German annual capita consumption [SP] [mg/(cap·a)]	US annual capita consumption [SC] [mg/(cap·a)]	Canadian annual capita consumption [ME] [mg/(cap·a)]
Citalopram	83	80	124
Fluoxetine	13	n.a	38
Paroxetine	11	7	73
Sertraline	50	131	143
Bupropion	56	322	412
Venlafaxine	179	167	672

n.a: not available, population USA: 308 million, Germany: 82 million, Canada: 33 million

[SP] Schwabe and Paffrath 2008-20013; [SC] Schultz et al. 2010; [ME] Metcalfe et al. 2010

Table 5: Concentration of venlafaxine in the river Rhine on the basis of three discharge change scenarios covering the range of results presented in Figure 3, a low flow reference scenario based of measured data from 1960-1990, and three consumption scenarios, “no change”: same consumption of venlafaxine in near and far future as in 2012; “moderate increase”: linear increase of the consumption of 0.5 tons per year until 2050; “Canadian consumption”: same per capita consumption in Germany as in Canada.

		Estimated portion of wastewater [%]	Consumption scenario: no change [ng/L]	Consumption scenario: moderate increase [ng/L]	Consumption scenario: Canadian consumption [ng/L]
Rhine (based on climate change scenarios)	Normal flow (1800 m ³ /s)	5	51	117	191
	Low flow reference (900 m ³ /s)	10	102	234	382
	Low flow change 2021-2050 (810 m ³ /s)	11	112	257	420
	Low flow change 2051-2100 (665 m ³ /s)	14	143	328	535
Tributary (projection)	Low flow (+/-0 %)	40	408	936	1530
	low flow change (-10%)*	44	446	1020	1670
	low flow change (-25%)	50	510	1170	1910

Figures

Figure 1: Chemical structure, monoisotopic mass, pKa values and CAS reg. no. of 4 SSRIs, 1 SNARI, 1 NaDaRI and 7 human metabolites

Substance	Chemical structure	Substance	Chemical structure
CAS number		CAS number	
monoisotopic mass		monoisotopic mass	
Fluoxetine		Norfluoxetine
54910-89-3		83891-03-6	
309.13 amu		295.12 amu	
pK _a : 10.1		pK _a : 9.1	
Sertraline		N-desmethyl sertraline
79617-96-2		87857-41-8	
305.07 amu		291.06 amu	
pK _a : 9.5		pK _a : 9.4	
Desmethyl hydroxysertraline		Venlafaxine
79560-19-3		93413-69-5	
291 amu		277.20 amu	
pK _a : n.a.		pK _a : 9.2	
O-desmethyl venlafaxine		N-O-Didesmethyl venlafaxine
93413-62-8		135308-74-6	
263.19 amu		249.17 amu	
pK _a : n.a.		pK _a : n.a.	
Citalopram		N-Desmethyl citalopram
59729-33-8		62498-69-5	
324.16 amu		310.15 amu	
pK _a : 9.6		pK _a : 10.5	
Bupropion		Hydroxybupropion
34911-55-2		119802-68-5	
239.11 amu		241.12	
pK _a : 7.9		pK _a : n.a.	

Paroxetine		Paroxetine-methoxyphenol	
61869-08-7		112058-90-9	
329.14 amu		331.16 amu	
pK _a : 10.3		pK _a : n.a.	

672 pK_a (Vaskoog 2006)

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674 Figure 2: Map and sampling stations of the river Ruhr and its major tributaries (Ru_01-

675 Ru_30) river Rhine -(Ru_31, 32, 34) and river Emscher (Ru_34).

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680 Figure 3: Left panel, change of the lowest daily flow during hydrological summer (May-Oct)
681 in the Middle Rhine River averaged for the near (2021-2050, red) and far (2071-2100, purple)
682 future as derived from a 20 member multi-model ensemble of discharge projections. The
683 reference value of 900 m³/s refers to the observations in period 1961-1990. Right panel,
684 change of the highest daily water temperatures averaged over the same periods based on a
685 selection of model chains that covers most of the low flow changes. The reference value of
686 25.5°C refers to the observations in period 1990-2009. The highlighted model chains were
687 selected to reflect the structure of the overall ensemble, i.e. the main clusters rather than the
688 overall range of outcomes. Acronyms of the model chains consist of two elements describing
689 the global climate model run (HCQ0 = HadCM3Q0, BCM, EH5r1/3 = ECHAM5 run 1 and
690 3), the regional climate model (HRQ0 = HadRM3Q0, RCA, RE-ENS = REMO, RACMO,
691 CLM24) used. All model chains were forced by the same greenhouse gas concentrations
692 (C20-A1B) and include the same hydrological model (HBV134). Data and procedures are
693 described in Görden et al. (2010) and Hardenbicker et al. 2014.
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Figure 4: Concentrations of selected antidepressants in the river Ruhr from spring to mouth and its major tributaries. Further details about sampling locations and detected concentrations are provided in Table S1 and Figure 2.

Figure 5: Concentrations of antidepressants in the river Rhine and river Emscher. The Emscher contains 80-99% treated wastewater. Further details about sampling locations and detected concentrations are provided in Table S1 and Figure 3.