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Exposure and ecotoxicological risk assessment of mixtures of top prescribed pharmaceuticals in Swedish freshwaters

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Abstract

Surface water concentrations of 54 pharmaceuticals were predicted for seven major Swedish rivers and the Stockholm City area basins using the STREAM-EU model. These surface water concentrations were used to predict the ecotoxicological impact resulting from the exposure of aquatic organisms to this mixture of 54 pharmaceuticals. STREAM-EU model results indicated that <10 substances were present at median annual water concentrations greater than 10 ng/L with highest concentrations occurring mostly in the more densely populated area of the capital city, Stockholm. There was considerable spatial and temporal variability in the model predictions (1-3 orders of magnitude) due to natural variability (e.g. hydrology, temperature), variations in emissions and uncertainty sources. Local mixture ecotoxicological pressures based on acute EC50 data as

well as on chronic NOEC data, expressed as multi-substance potentially affected fraction of species (msPAF), were quantified in 114 separate locations in the waterbodies. It was estimated that 5% of the exposed aquatic species would experience exposure at or above their acute EC50 concentrations (so-called acute hazardous concentration for 5% of species, or aHC5) at only 7% of the locations analyzed (8 out of 114 l*o*cations). For the evaluation based on chronic NOEC concentrations, the chronic HC5 (cHC5) is exceeded at 27% of the locations. The acute mixture toxic pressure was estimated to be predominantly caused by only three substances in all waterbodies: Furosemide, Tramadol and Ibuprofen. A similar evaluation of chronic toxic pressure evaluation logically demonstrates that more substances play a significant role in causing a higher chronic toxic pressure at more sites as compared to the acute toxic pressure evaluation. In addition to the three substances contributing most to acute effects, the chronic effects are predominantly caused by another five substances: paracetamol, diclofenac, ethinylestradiol, erythromycin and ciprofloxacin. This study provides regulatory authorities and companies responsible for water quality valuable information for targeting remediation measures and monitoring on a substance and location basis.

Keywords: Pharmaceuticals, Mixture toxicity, Exposure modelling, STREAM-EU model, Pharmaceuticals

1. Introduction

Currently, more than 5000 pharmaceutically active substances are reported to be available on the European market (Hughes et al., 2013). Hundreds of those substances have been detected in European surface waters, in concentrations ranging typically from ng/L to μg/L (IWW, 2014). Since pharmaceuticals are designed to have biological activity in order to achieve specific therapeutic effects, their presence in surface waters may have adverse effects in aquatic organisms. This has become apparent in reported effects, such as, endocrine disruption (Kidd et al., 2007); reproductive impairment (Nash et al., 2004); alterations in spawning (Lister et al.,

2009) and enhancement of resistance of microorganisms (Zhang et al., 2009). Moreover, hydrolysis, photolysis and biodegradation may yield transformation products with a separate toxicological profile (Hirte et al., 2016). Environmental impacts of pharmaceuticals on aquatic organisms are therefore an increasing concern (Boxall et al., 2012) leading to the European Medicines Agency (EMA) developing guidance documents for environmental risk assessment (EMA, 2006) and to the establishment of an ever-growing body of ecotoxicological data for pharmaceuticals (Fent et al., 2006; DeGarcia et al., 2014; Santos et al., 2010; Stuer-Lauridsen et al., 2000). The European Union (EU) has also acknowledged the potential harmful effects of these substances by including diclofenac, 17β-estradiol and 17α-ethinylestradiol in the Water Framework Directive (WFD) Watch List (EC, 2013) making them candidates for future regular monitoring. Nevertheless, apart from these three substances, other pharmaceuticals are not currently subject to environmental regulations by the EU, leading to very limited information on their occurrence. When environmental concentration measurements are not available they can be predicted with modelling tools. Models are particularly useful if there is a need to predict occurrence over time and for multiple locations (Schowanek et al., 2002), as existing data on pharmaceuticals in water rarely has a good spatial and temporal coverage (Petrie et al., 2015). In the present work the spatially and temporally resolved model STREAM-EU (Lindim et al, 2016a) was used to predict concentrations of multiple pharmaceuticals in several major Swedish waterbodies. These predicted environmental concentrations (PECs) were then used as a basis for evaluating the ecotoxicological risks of the pharmaceuticals. Previous studies have demonstrated that STREAM-EU can accurately quantify concentrations of organic contaminants in European surface waters, by predicting concentrations in close agreement with measurements for a range of substances in multiple catchments (Lindim et al., 2016a; Lindim et al., 2016c).

When environmental risk assessments for a large number of pharmaceuticals need to be performed, prioritization methods are generally applied to keep the work load within realistic limits and focus on a lower number of drugs (Boxall et al., 2012). However, many prioritization strategies for pharmaceuticals in the aquatic environment are based on the assumption that higher consumptions or higher emissions to the

69 environment imply higher concentrations in rivers which in turn imply higher risks for aquatic organisms
70 (Helwig et al., 2013; Daginnus et al., 2011). Such assumptions neglect cases of fast decaying and metabolizing
71 pharmaceuticals for which neither high emissions nor high consumptions necessarily imply high concentrations
72 in water; it also fails for substances that are biologically active at very low concentrations by underestimating
73 their risks. Risks can therefore not be inferred as having linear relations with consumption, emissions or
74 environmental concentrations. In principle, the read-across in silico models (Schüürmann et al., 2011; Kühne et
75 al., 2013) or QSAR (EPISUITE 2016) prediction of toxicity could aid in the risk assessment for aquatic organisms
76 (Schäfer et al., 2011; von der Ohe et al., 2011), but their applicability to pharmaceuticals is still limited, also
77 because the calculus is based on baseline toxicity and Mode of Action-specific QSARs have not been generated
78 for pharmaceuticals. Furthermore, because aquatic organisms are exposed to multiple pharmaceuticals
79 simultaneously, environmental risk assessments should evaluate the toxicity of the local mixture. Mixture
80 toxicity has important implications in terms of environmental toxicity and risk assessment outcomes. In many
81 cases, significant effects for mixtures were observed when toxic individual concentrations were negligible (Silva
82 et al., 2002; Cleuvers, 2003; Dietrich et al., 2010; Gonzalez-Pleiter et al., 2013). Several approaches have been
83 used for the prediction of mixture toxicity based on the toxicity of individual components, namely
84 concentration addition and response addition without (Backhaus, 2014; Altenburger et al., 2004) and with
85 (Altenburger et al. 2003) QSAR approaches.

86 Here, instead of prioritizing single substances, we take a more realistic and broader approach by evaluating
87 risks to aquatic organisms arising from the mixture of as many as possible known consumed pharmaceuticals in
88 Sweden. We assess the mixture and prioritize substances within the mixture.

89 With the current work we hope to give a valuable contribution to three areas of environmental concern
90 currently understudied: exposure, spatial and temporal variability and mixture toxicity of pharmaceuticals in
91 river water. The objectives of the current work were:

- To predict exposure to multiple top consumed pharmaceuticals in the seven major rivers in Sweden and in river basins in the area of Stockholm City.

- To predict how sources of variability, such as river discharge and water temperature, and uncertainty, such as retention in water treatment plants, impact exposure to the pharmaceuticals at different times and different river catchment locations.

- To evaluate the ecotoxicological impacts of the mixture of pharmaceuticals using bioavailable concentrations predicted by the STREAM-EU model.

2. Material and Methods

2.1. Study Description

Concentrations in water and ecotoxicological effects of mixtures of human pharmaceuticals in aquatic organisms were predicted for the Stockholm City area (population 1.5 million) and for the seven major rivers in Sweden: Torne River (basin population 45293, average discharge: 370 m^3/s, river length: 522 km), Kalix River (basin population 30314, average discharge: 290 m^3/s, river length: 461 km), Lule River (basin population 18589, average discharge: 515 m^3/s, river length: 461 km), Ume River (basin population 73488, average discharge: 450 m^3/s, river length: 470 km), Ångerman River (basin population 52102, average discharge: 485 m^3/s, river length: 460 km), Indal River (basin population 119811, average discharge: 460 m^3/s, river length: 430 km) and Dal River (basin population 266447, average discharge: 379 m^3/s, river length: 520 km).

54 top consumed human pharmaceuticals in Sweden in 2011 according to Socialstyrelsen (2015) were investigated. Table S1 (Supplementary Material) lists the 54 substances for which predicted environmental

concentrations (PECs) were calculated, their correspondent anatomical therapeutic chemical (ATC) category and medians for the predicted concentrations in each catchment studied.

2.2. Exposure modelling

PECs of the pharmaceuticals were calculated with the temporally and spatially explicit STREAM-EU model (Lindim et al., 2016a) using a dedicated module for ionizing substances described in Lindim et al. (2017). STREAM-EU is a fugacity-based model that predicts transient state concentrations in river basins. STREAM-EU used as spatial grid the subbasins of the Swedish rivers' and subbasins in adjacent territories in Finland and Norway belonging to the basins studied (the average subbasin area in the grid was 28 km^2). The simulations were performed with a daily time step.

The input data for the simulations consisted of: environmental data (hydrology, pH, air and water temperatures) as well as emissions and physico-chemical properties of the substances studied. Daily hydrological data from the pan-European hydrology model E-Hype (Donnelly et al., 2013) and temperature data for the period studied were provided by the *Swedish Meteorological and Hydrological Institute (SMHI*). Spatially distributed emissions were calculated using Swedish statistical data for consumption of pharmaceuticals (Socialstyrelsen, 2015), as well as wastewater treatment retentions and human excretion rates employing the rational detailed in the Supplementary Material and data presented in Lindim et al. (2016b). Substances were assumed to be discharged in the water in the same subbasin where they were consumed. Physico-chemical properties for the drugs were obtained with ACD/Percepta (ACD/Labs, 2015) (pK_a, pK_b); ChemProp (UFZ, 2016; Schüürmann et al., 2007), KOWWIN v.1.68 model (EPI Suite, 2016) (Log K_{ow}) and CATALOGIC (Dimitrov et al., 2011a; Dimitrov et al., 2011b) was used for the degradation rates of the substances. Values for two main fate behavior determinants, Kow and half-life, are presented in Figure S3). The use of information on pH, temperature, ionization, degradation and partition in the model enables the

prediction of the bioavailable concentration (dissolved fraction) of the drugs to be further used in the risk assessment.

Annual medians of the predicted concentrations for the 54 drugs studied were calculated using model daily results for twenty equidistant locations along each river. For the Stockholm City area, annual medians were calculated using daily concentration results for the catchments in the area (Figure S1). Up to 16 spatial points per catchment were used depending on the catchment size.

2.3. Ecotoxicological effects prediction

Ecotoxicological impact prediction was based on laboratory ecotoxicity data derived for a number of different test species. The collected ecotoxicity data originate from a wide variety of publicly available data sources. However, the data were scrutinized for plausibility according to a process described by De Zwart (2002). The procedure followed is detailed in section 2 of the Supplementary Material.

The dataset for the 54 Swedish pharmaceuticals comprised the results for 2151 conducted ecotoxicity tests of which 1166 acute and 985 (sub)chronic on a total of 157 different taxa. Ecotoxicological pressure was predicted separately based on acute EC50 and chronic NOEC exceedances where data on acute EC50 values or chronic NOEC values is used for Species Sensitivity Distribution (SSD) construction. If insufficient acute EC50 or chronic NOEC values are available but other toxicity endpoints are, these data were extrapolated to acute EC50 and chronic NOEC values using empirical derived extrapolation values as presented in Table 1 (De Zwart, 2002; Duboudin et al. 2004, Brock et al. 2008). Those extrapolations are not to be considered similar to the application of an acute/chronic ratio (ACR), as the current extrapolation operates on the SSD-models, based on read-across data patterns. The correct interpretation of this extrapolation is a parallel shift in an SSD, which is far more robust than an ACR.

Table 1 - Ecotoxicity endpoint extrapolation scheme by a factorial step “From/To”.

From \ To	Order of extrapolation attempts to Acute EC50	Acute EC50 extrapolation factor	Order of extrapolation attempts to Chronic NOEC	Chronic NOEC extrapolation factor
Acute EC50	0	Multiply by 1	3	Multiply by 1/10
Acute NOEC	1	Multiply by 3	2	Multiply by 1/3
Chronic EC50	2	Multiply by 3	1	Multiply by 1/3
Chronic NOEC	3	Multiply by 10	0	Multiply by 1

A hybrid model was then applied for evaluating the mixture toxic pressure. This so called "mixed model" (De Zwart & Posthuma, 2005) uses a two-stage process based on log-normal SSD modelling (Posthuma et al., 2002). In the first stage, concentration additivity (CA) is assumed for substances with the same mode of action (MoA) and the Potentially Affected Fraction of species (msPAF) is calculated using the cumulative density function of the log-normal distribution by Taylor series approximation, as for instance represented by the MSExcel function

$msPAF_{CA}$ = NORM.DIST(log($\sum(c_i/HC50_i)$), mean = 0, σ_I, cumulative = TRUE) was used. Where c_i is the environmental concentration of substance i of specific MOA, $HC50_i$ is the mid point concentration of the SSD and σ_I is the slopeof the SSD.

In the second stage, the effect contributions for groups of chemicals with different modes of action are accounted for by response additivity (RA) as

$msPAF_{RA} = 1 - \prod_1^n (1 - msPAF_{CA})$, where n is the number of groups of different MOA.

The mixture toxic pressure evaluation derived from acute EC_{50} values, is primarily selected because it repeatedly demonstrated to yield results that most closely resemble impacts that can be observed in the field in terms of biodiversity loss (e.g. De Zwart et al., 2006; De Zwart et al., 2009; Posthuma and De Zwart, 2012).

Additionally, the mixture toxic pressure estimations based on chronic NOEC exceedances is performed in order to more closely adhere to currently advised procedures as laid down in the WFD and REACH Technical Guidance documents (e.g. EC, 2011). The predicted impact is presented as the mixture toxic pressure, expressed as the percentual multi-substance Potentially Affected Fraction of species (msPAF), which for the acute approach can be considered equal to the predicted percentual loss of biodiversity. From a European Union WFD policy point of view for individual chemicals, concentrations potentially affecting less than 5% of exposed taxa (HC5 – hazardous concentration for 5% of Taxa) are underlying the derivation of maximum acceptable concentrations (Lepper, 2005). For the combined action of chemicals in a local mixture, we also adopted the 5% level as acceptable.

3. Results and discussion

3.1 Predicted concentrations in Swedish waters

Depending on the river, 7 to 15 substances had predicted median annual concentrations higher than 0.1 ng/l (Figure 1, Table S1). Substances with concentrations above 0.1 ng/l in at least one of the rivers belong to the group: Metformin, Paracetamol, Ibuprofen, Furosemide, Naproxen, Ketoprofen, Omeprazole, Hydrochlorothiazide, Diclofenac, Gabapentin, Penicillin G, Hydroxycarbamide, Cetirizine, Piperacillin, Oxazepam, Ciprofloxacin, Carbamazepine and Tramadol. Of these only Metformin, Paracetamol, Furosemide and Ibuprofen surpassed 0.1 ng/l in all the seven rivers. Metformin, Paracetamol and Ibuprofen were the drugs with the highest predicted medians in all waterbodies (Figure 1 top, Table S1). Further drugs with high predicted values (4^{th}-10^{th} highest) differed from waterbody to waterbody likely reflecting the local patterns of consumption.

On average the lowest median concentrations for the 54 pharmaceuticals investigated were found for the Lule River. For a given substance, the highest median concentration in rivers was found in the majority of cases in

199 the Dal River, and for a few cases in the Torne River or in the Indal River (Figure 1, Table S1). Although the
200 Torne River basin is one of the least populous of the seven river basins, the highest predicted median
201 concentration for Paracetamol was for the Torne River. The Torne River, the northernmost river studied, has
202 marked freeze and thaw periods that cause dramatic flow changes (Helama et al., 2013) and may impact
203 dilution strongly.

204 Metformin, Paracetamol and Ibuprofen, in decreasing order, are the drugs with the highest predicted median
205 concentrations in all the seven rivers. The Metformin annual median concentration reached its maximum in the
206 Indal River with 91 ng/l and had its lowest value in the Lule River with 0.69 ng/l. These three substances also
207 top the consumption lists in the majority of the country, with amounts consumed in the range of tens to
208 hundreds of ton/y and typically with consumptions that are at least one order of magnitude higher than any of
209 the other studied chemicals (Socialstyrelsen, 2015; Lindim et al., 2016b).

210 17 drugs were found to have predicted median concentrations < 1 pg/l in all the seven rivers: 17-alpha-
211 ethinylestradiol, Alprazolam, Beta-estradiol, Chloramphenicol, Clonazepam, Clotrimazole, Dexamethasone,
212 Finasteride, Ifosfamide, Ketoconazole, Lorazepam, Paroxetine, Pindolol, Progesterone, Propanolol,
213 Roxithromycin and Terbutaline (Table S1).

214 The most represented anatomical therapeutic chemical (ATC) categories in substances with predicted
215 concentrations >= 0.1 ng/L were anti-inflammatory medicines followed by drugs for acid disorders. For some
216 rivers, analgesics (Indal River, Torne River) and antibacterials (Indal River, Torne River, Dal River, Kalix River)
217 also had more than one drug with concentration >= 0.1 ng/L.

218 For the Stockholm City area, 8 substances had median concentrations >10 ng/L (Metformin (477 ng/L),
219 Acetaminophen (159 ng/L), Ibuprofen (50 ng/L), Furosemide (43 ng/L), Ketoconazole (13 ng/L), Naproxen
220 (12 ng/L), Pindolol (11 ng/L)), and 16 were below the ng/L range (Figure 1, Table S1). Median concentrations in
221 the Stockholm City area were 5-50 times higher than in the rivers studied. For Stockholm, median predicted

222 concentrations at the catchments' exit point were previously reported in Lindim et al. (2017). Concentrations at
223 the catchments' exit points were 3-15 times higher than the median concentrations in the whole catchment
224 presented here.

225

226

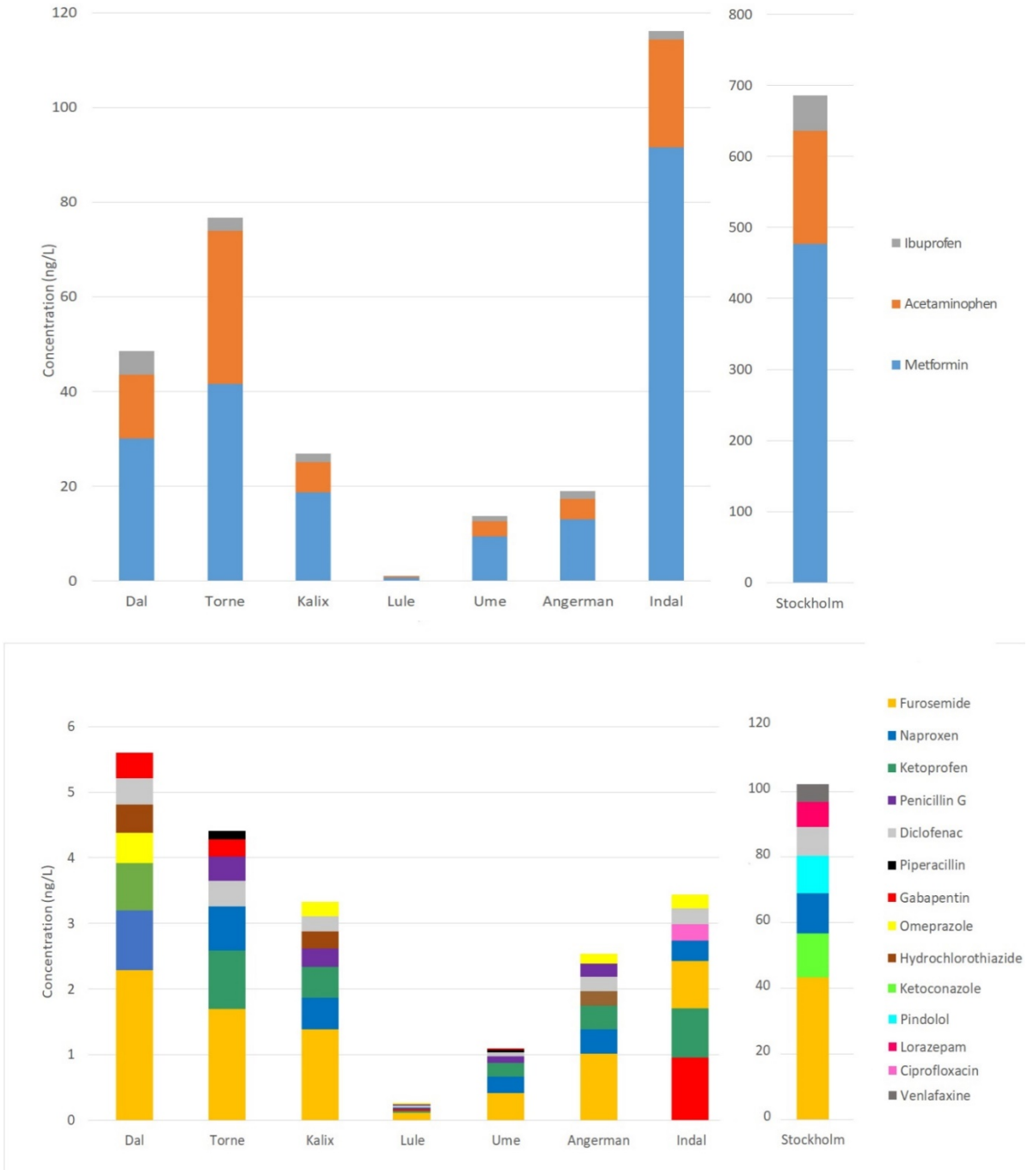

Figure 1: STREAM-EU predicted median annual concentrations for 2011 in Swedish rivers and Stockholm. Concentrations in decreasing order from bottom to top of columns. Top: Substances with the 1st-3rd highest predicted concentration. Bottom: Substances with the 4th-10th highest predicted concentration.

3.2 Uncertainty, variability and accuracy in the predicted exposure

Boxplots for the predicted concentrations of the drugs for which mixture toxicity was evaluated (Figure 2 for Stockholm and one of the rivers and Figure S2 with remaining rivers) help understand how sources of variability, such as river flow and water temperature, and sources of uncertainty, such as retention in WWTPs, affected the concentrations during 2011. Log_{10} scale plots were used to improve readability but some trends are not visible on the logarithmic scale, namely skewness. The Angerman River (Figure S2) and Ume River plots (Figure 2) show, for multiple substances, a positive skew (median closer to Q1 (25^{th} percentile) than Q3 (75^{th} percentile)) and upper heavy tails (outliers predominantly above the box), meaning the majority of the concentration values are in the lower range. The Angerman River had the highest number of positively skewed results of all rivers.

The spread of the data (from minimum to maximum) for each drug shows the annual variability. If extreme values are excluded, annual variability is given by the interquartile range (span of the box). The larger interquartile span was found for the Torne River (2-3 orders of magnitude for most substances). The majority of this variability is most likely attributable to river discharge variations. Flow rates in the Torne River in 2011 ranged from 150 to 1950 m^3/s, a much wider flow rate interval than in the other rivers studied. The Kalix River and Stockholm City area show small and very similar spans for all the substances (about 1 order of magnitude, less in the case of Stockholm), while the Ångerman River has interquartile ranges smaller than that for about half of the drugs and near 1.5 orders of magnitude for the other half. The remaining rivers show a box span of 1-1.5 orders of magnitude for all substances. Compared to the other rivers, the Indal River had the lowest annual variability for Acetaminophen, Metformin, Testosterone and Propanolol.

For all rivers only up to 5 drugs (Metformin, Furosemide, Acetaminophen, Ibuprofen and Naproxen) had their whole interquartile range lying in the ng/L range, the remaining drugs were in the pg/L range. In the Lule River, only Metformin and Acetaminophen had their interquartile range in the ng/L range. In the Ume, Ångerman and

Kalix rivers, Metformin, Furosemide, Acetaminophen and Ibuprofen had their interquartile range in the ng/L range. In the Indal, Dal, and Torne rivers all 5 drugs had their interquartile range in the ng/L range. For Stockholm surface waters, the interquartile range laid above 10 ng/L only for Metformin, Furosemide, Acetaminophen and Ibuprofen.

Periodic monitoring of pharmaceuticals in these waterbodies is not undertaken and measurements in the surface waters are not available. However, screening of urban effluents discharging to the Lule, Ume and Dal rivers was undertaken by the Swedish Environmental Protection Agency (Fick et al., 2011; Andersson et al., 2007) and those measurements were used to compare with our predictions. A river dilution factor of 500 for the discharged effluents was considered. The study of Keller et al. (2014) suggests that dilution factors for down-the-drain chemicals in Swedish rivers are in fact > 500. The measured values are represented by black dots in Figures. 2 and S2. Good model agreement with monitored values, understood as the monitored values lying within the minima-maxima interval of predictions, was found for the pharmaceuticals measured in the Lule River. In the Dal River, Carbamazepine is underpredicted while the predicted Metformin concentrations agrees with measurements. For the Torne River, the Oxazepam concentration is underpredicted and the estimated concentration of Tramadol agrees with measurements; while in the Angerman River both these substances are underpredicted. For the Ume River, model results agree with measurements for one quarter of the substances measured. For the others, the model underpredicts the concentrations. In general, the model tends to underpredict the concentrations in the rivers. However, for the Stockholm City area, more than 60% of the model results agree with the measurements and no trend of under-prediction is visible. Other authors surveying emerging contaminants in European rivers, found surface water concentrations for the same drugs to be within the pg/L-ng/L range, similar to our predictions (Kasprzyk-Hordern et al., 2008; Loos et al., 2010); da Silva et al., 2011; Vulliet et al., 2011; Carmona et al., 2014). The existence of variations in concentration of several orders of magnitude within a catchment over time have been observed by multiple authors surveying

European waterbodies (Lindholm-Lehto et al., 2016; Padhye et al., 2014; Mastroianni et al., 2016) and attributed mostly to dilution and emissions changes.

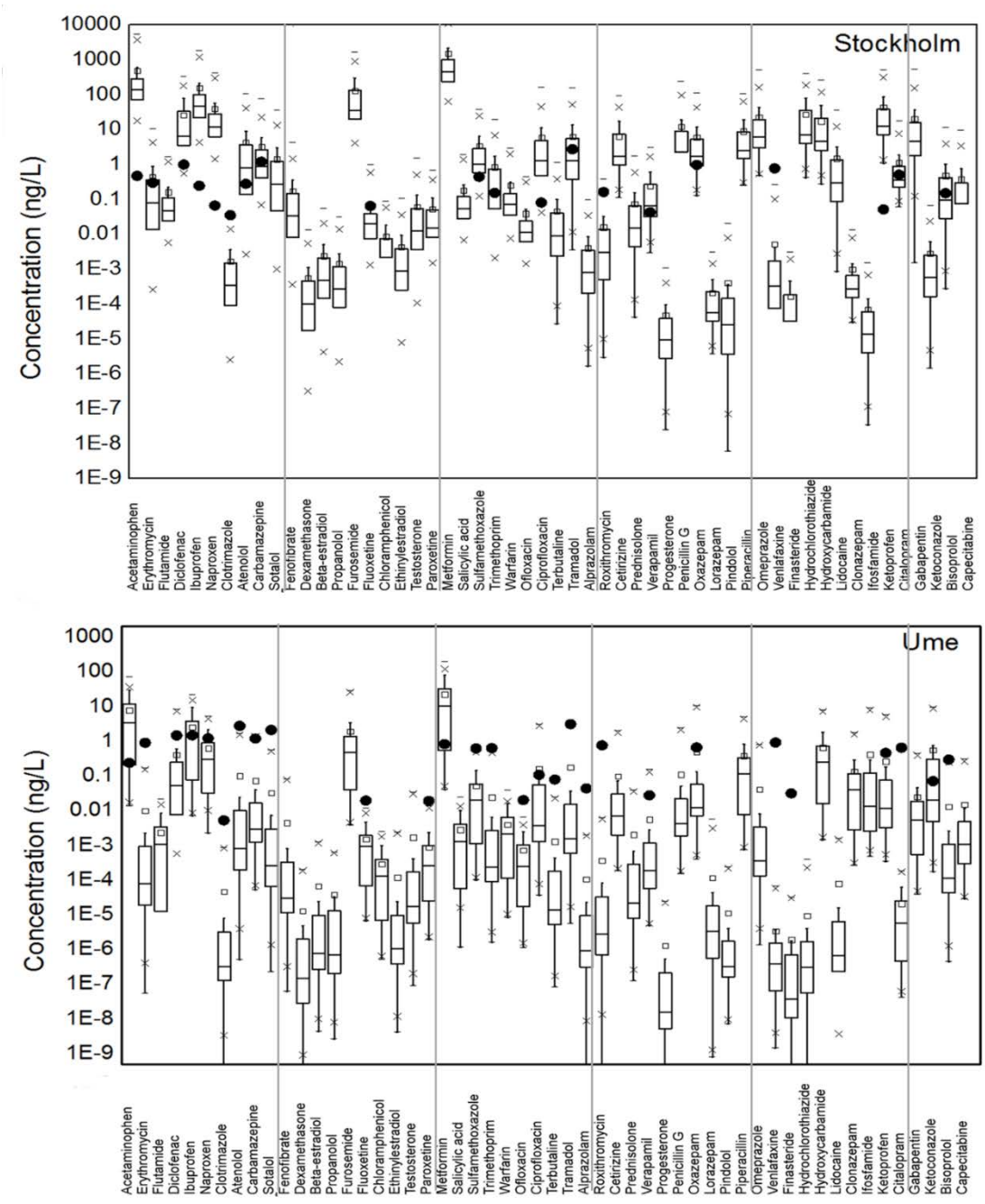

Figure 2: **Boxplots:** STREAM-EU predicted concentrations for 2011 in one of the Swedish rivers and Stockholm on a $\log_{10}$ scale. Boxes- median, Q1 and Q3. Open squares- mean. Xs- 1%, 99%. Dashes - minimum and maximum. Whiskers- outliers. Daily results for all river subbasins were used. **Black dots**: measurements from monitoring.

3.3. Predicted impacts of the local mixture of pharmaceuticals

As can be concluded from the evaluation of acute toxic pressure in Table 2, there are only 3 out of 8 waterbodies (Stockholm, Lule River, Torne River) that locally exceed at one or more of the multiple stations evaluated the aHC5 level of the pharmaceutical mixture toxicity. The highest overall toxic pressures exceeding 1% are restricted to 45 of 114 stations in total. For the evaluation of chronic toxic pressure, in 7 out of 8 waterbodies the cHC5 is exceeded, while the 1% level is exceeded at 73 out of 114 stations. As demonstrated in Table 3, the acute exceedances are mainly attributable to the predicted concentrations of Furosemide in Stockholm, Lule River and Torne River. Restricted to the Stockholm watersheds, Tramadol and Ibuprofen are predicted to cause an additional minimal impact on biodiversity. For the chronic toxic pressure, Table 3 shows that an additional 5 other pharmaceuticals (paracetamol, diclofenac, ethinylestradiol, erythromycin and ciprofloxacin) together in numbers multiplied by average intensity take an approximate 11% share in shaping the overall chronic mixture toxic pressure.

Table 2 -Acute and chronic toxic pressure summarized for the pharmaceutical mixtures predicted for the different waterbodies.

Waterbody	Number of Stations	Minimum acute toxic pressure	Average acute toxic	Maximum acute toxic pressure	Minimum chronic toxic	Average chronic toxic	Maximum chronic toxic pressure

			pressure		pressure	pressure	
Stockholm	27	0.0%	3.7%	**15.6%**	1.5%	11.0%	**38.9%**
Lule River	13	0.0%	0.8%	**7.4%**	0.0%	2.2%	**19.1%**
Torne River	11	0.0%	1.0%	**6.5%**	0.1%	3.3%	**17.6%**
Ångerman River	14	0.1%	0.9%	3.9%	0.4%	2.8%	**10.2%**
Indal River	16	0.0%	0.6%	2.0%	0.1%	1.8%	**5.6%**
Ume River	14	0.0%	0.4%	2.0%	0.1%	1.4%	**6.3%**
Dal River	11	0.0%	0.8%	1.9%	0.2%	2.9%	**6.7%**
Kalix River	8	0.0%	0.4%	1.4%	0.0%	1.7%	4.8%
Overall	114	0.0%	1.4%	15.6%	0.0%	4.3%	38.9%

Table 3 - The contribution of the top 5 of the 54 pharmaceuticals to the predicted toxic pressure of all local mixtures modelled. The remaining pharmaceuticals do not significantly contribute to overall toxic pressure.

	Acute EC50 exceedances				Chronic NOEC exceedances			
Chemical	Count of Top 5 chemicals with minimum toxic pressure contribution ≥ 0.1%	Minimum toxic pressure	Average toxic pressure	Maximum toxic pressure	Count of Top 5 chemicals with minimum toxic pressure contribution ≥ 0.1%	Minimum toxic pressure	Average toxic pressure	Maximum toxic pressure
Furosemide	92	0.1%	1.6%	12.4%	101	0.1%	4.2%	26.1%
Paracetamol	-	-	-	-	41	0.1%	1.1%	10.7%
Tramadol	21	0.1%	0.5%	3.4%	15	0.1%	0.7%	3.4%
Ibuprofen	4	0.1%	0.1%	0.2%	9	0.1%	0.9%	2.8%
Diclofenac	-	-	-	-	8	0.1%	0.6%	1.5%
Ethinylestradiol	-	-	-	-	3	0.3%	0.3%	0.3%
Erythromycin	-	-	-	-	1	1.5%	1.5%	1.5%
Ciprofloxacin	-	-	-	-	1	0.2%	0.2%	0.2%

Overall	117 of 570 (5 x 114)	0.1%	0.7%	12.4%	179 of 570 (5 x 114)	0.1%	1.2%	26.1%

Conclusions

Despite the diversity and in some cases high quantities of pharmaceuticals prescribed and consumed in Sweden, high concentrations (>10 ng/L) of pharmaceuticals in Swedish surface waters are only predicted for a few substances. Our results indicate that, in 2011, less than 10 substances out of the 54 top consumed drugs studied here were present in inland surface waters at concentrations > 10 ng/L with those peaks occurring mostly in the more densely populated area of the capital city, Stockholm. Within a given river catchment and during a one-year span, spatial and temporal variability and uncertainty sources were found to be responsible for considerable water concentration variations: 1-2 orders of magnitude, reaching a maximum of 3 orders of magnitude in one river with marked seasonal variations in hydrology.

According to our predictions, the acute risk of the mixture of the 54 drugs investigated is predominantly caused by only three substances: Furosemide, Tramadol and Ibuprofen. A further 5 pharmaceuticals (Paracetamol, Diclofenac, Ethinylestradiol, Erythromycin and Ciprofloxacin) were found to be associated with chronic risks accounting for a 11% share in shaping the overall chronic mixture toxic pressure. The same trend, that a few key substances within a mixture of organic contaminants are the main risk drivers, has been observed by other authors in mixture risk studies (Backhaus and Karlsson, 2014, Munz et al., 2017; Watanabe et al., 2016). Overall, acute toxic pressures in the Swedish catchments studied exceeded 1% in 45 of the locations analyzed (out of 114 locations). For chronic toxic pressure, in 7 out of 8 waterbodies the cHC5 exceeded the 1% level at 73 out of 114 stations.

In view of our findings, it is suggested that a reinforcement of monitoring and control efforts for Tramadol, Ibuprofen, Furosemide, Paracetamol, Diclofenac, Ethinylestradiol, Erythromycin and Ciprofloxacin would be a

beneficial measure. From our assessment, predicted current levels of pharmaceuticals in surface waters in Sweden pose potential risks to aquatic species in a low percentage of locations (7% of the locations analyzed for acute and 27% for chronic toxicity). However, there is sufficient evidence of risks in some areas that control measured may be necessary. For example, in areas with a high human population density, the concentration levels of only a single selected pharmaceutical (Furosemide) are such that biodiversity will significantly be reduced beyond the acceptability criterion of 5%. Our modelled impact predictions were verified against field ecological survey data where available. However, for several substances and locations, measurements do not exist. More monitoring efforts are desirable to diagnose the current situation in watersheds and validate modelled impact predictions.

Even if the one of the pharmaceuticals predicted to occur with the highest concentrations in most locations (Metformin) did not significantly contribute to overall toxicity, the occurrence of local high concentrations (Larsson, 2014) and the existence of drugs with reported effects at very low concentrations (Fong et al., 2014) are factors that may lead to significant aquatic impacts.

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Supplementary data

Supplementary Material related to this article can be found at https://

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