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Occurrence and fate of organic micropollutants (OMPs) in Lake Mälaren

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Abstract

The main objective of this study is to investigate the occurrence and fate of organic micropollutants (OMPs) in surface water in Lake Mälaren over one year, including their seasonal variations, correlations between compounds, spatial and vertical distribution. The water samples were enriched with solid phase extraction (SPE) and subsequently analyzed by ultra-high pressure liquid chromatography tandem mass spectrometry (UPLC-MS/MS). The applied multi-residue method, consisting of OMPs with a wide range of physico-chemical properties was earlier optimized and then assessed regarding its performance. From 122 tested target compounds, 74 obtained a good relative recovery (60-145%) and 50 were detected at least once above limit of quantification (LOQ), which ranged from 0.010 and 10 ng/L. The highest detected concentration was found for valproic acid (2600 ng/L) and lamotrigine (140 ng/L). The locations Ekoln and Västeråsfjärden were identified to be most affected by OMPs pollution. Seasonal patterns were observed for numerous OMPs and 7 compounds occurred without seasonal fluctuations. Only a few vertical distribution patterns and concentration gradients were observed, for instance, the deepest sampling depth (30m) from Ekoln showed considerable higher concentrations than the upper sampling depths in February. A strong positive correlation was found for carbamazepine and lamotrigine, but also for other OMPs. Two industrial chemicals, tolyltriazole and tris(2-butoxylethyl)phosphate showed very good analytical performance parameters and were detected frequently and it is recommended to incorporate these compounds more regularly in future analysis. No correlations between water chemistry were observed. To the best of our knowledge, this study is the first one to report the occurrence and distribution of OMPs representing such wide physico-chemical properties, including industrial chemicals, in a Swedish lake.

Keywords: multi-residue method, UPLC-MS/MS, SPE, occurrence, organic micropollutants, pharmaceuticals, Lake Mälaren, surface water, seasonality

Popular science summary

It's a matter of common knowledge, that most of our surface water resources are not as clean as they should be. Organic micropollutants (OMP) constitute a group of substances which are more and more of emerging concern due to their ubiquity in the environment and their potential toxicological hazard. Usually the concentrations of these compounds are very low ranging from ng/L to μg/L, which can be also expressed as parts per trillion (ppt) and parts per billion (ppb), respectively. For purposes of clarity one ppm is for example one single black sheep among one billion sheep. The unique properties of OMPs can lead to negative effects for aquatic organisms, plants and humans in even such small concentrations. In general, OMP encompass many different kinds of substances such as pharmaceuticals, personal care products, pesticides, perfluoroalkyl substances (PFASs), parabens and industrial chemicals. Usually the primary source for those substances to enter the water are effluents of wastewater treatment plants, which are simply not able to remove these kinds of substances effectively. The information about the occurrence of substances in a specific surface water body is important to understand the behavior of these substances, potential hotspots where most of them can be found and to identify priorities for future actions. The subject of this study was Lake Mälaren, which is the third biggest lake in Sweden and the major drinking water source in the Stockholm area. Water samples from eleven different sampling locations and eight different sampling months (from April '17 to April '18) were analyzed regarding 50 different OMPs that are widely used in large amounts and are known for possible negative effects in the environment.

All detected concentrations were below estimated acute toxic concerns, however not much is known about long-term subtle negative effects and effects when substances are interacting with each other. Some OMPs were found regularly to almost constant concentration levels during the entire year, while most of the OMPs show seasonal fluctuations which can be traced back to different usage rates (e.g. antidepressants, are a group of pharmaceuticals which are consumed more often in the winter time than during summer) and different elimination rates of OMPs at the wastewater treatment plan during the year. The sampling locations Ekoln and Västeråsfjärden are most polluted which is due to the close proximity to densely populated areas and the outlet of a wastewater treatment plant. In February the highest concentrations were found at the bottom of the lake at Ekoln (30 m sampling depth), which assumingly causes a higher risk of exposure for those fish which stay there during winter time. To the best of our knowledge, some industrial chemicals were never analyzed before in Lake Mälaren and surprisingly, two of them (tolyltriazole and tris(2-butoxylethyl)phosphate) showed very similar patterns of occurrence compared to, for example, the two pharmaceuticals carbamazepine and lamotrigine,

which are frequently analyzed and detected in the water. Knowing this, helps to assess the risk that these two industrial chemicals pose. The findings of this study contribute to a better understanding of the behavior of OMPs in surface water and provide a sound basis for further research.

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Abbreviations

ARF	Average Response Factor
APPI	Atmospheric Pressure Photoionization
BAM	Dichlorobenzamide
BCF	Bioconcentration Factor
C	Concentration
CEC	Critical Environmental Concentrations
DEET	Dietyltoluamide
DWP	Drinking Water Plant
EP	Emerging Pollutant
EQS	Environmental Quality Standards
ESI	Electrospray Ionization
EU	European Union
GAC	Granulated Activated Carbon
GF/F	Glass Microfiber Filters
H-ESI	Heated Electrospray Ionization
IC	Industrial Chemical
IS	Internal Standard
K_{ow}	Water Partition Coefficient
LOQ	Limit of Quantification
LC	Liquid Chromatography
MQ	Milli-Q Water
MS	Mass Spectrometry
MST	Matrix Matching Standard
NSAID	Non-Steroidal Anti-Inflammatory Drug
OMPs	Organic Micropollutants
OTC	Over-The-Counter
PC	Principle Component
PCA	Principle Component Analysis
PCP	Personal Care Product

PFASs Perfluoroalkyl Substances
pKa Acid Dissociation Constant
PLS Partial Least Square
PP Polypropylene
RC Regenerated Cellulose
SMHI the Swedish Meteorological and Hydrological Institute
SPE Solid Phase Extraction
SRM Selected-Reaction Monitoring
TAED Tetraacetylethylenediamine
UPLC-MS/MS ultra-high pressure liquid chromatography tandem mass spectrometry
WWTP Wastewater Treatment Plants

1 Introduction

1.1 Background

Organic micropollutants (OMPs) – also often referred as emerging pollutants (EP) – are a group of compounds that encompass pharmaceuticals, industrial chemicals (IC), personal care products (PCP), pesticides, parabens, perfluoroalkyl substances (PFASs) and others (Luo *et al.*, 2014). OMPs are to a high extent of anthropogenic origin, however can occur naturally as well. They can be detected in various environmental matrixes in trace concentrations ranging from few ng/L to several μg/L, namely in water, sediments, soil and biota (Nikolaou *et al.*, 2007). Furthermore, their fate and transport are complex and dependent on numerous factors, such as production, consumption/usage, disposal, transport, removal, transformation, resistance etc.

In general, emerging contaminants comprises three categories of compounds: they were just recently developed and therefore newly introduced into the environment or they were just recently detected although they are already present in the environment for some unknown time or they were only just recently identified as being potentially hazardous for the environment and/or humans (Houtman, 2010). The common feature shared by these compounds is their ubiquitous nature and the absence of guidelines and standards which are adopted to regulate their discharge into the aquatic environment (Houtman, 2010; Luo *et al.*, 2014). Regulations only exist in a compromised level: The European Union (EU) "watchlist", a EU-wide monitoring mechanism that addresses 10 substances/groups of substances and environmental quality standards (EQS) that exist only for a very limited number of compounds (Barbosa *et al.*, 2016). From a national perspective, the Swedish regulatory framework merely touches upon pesticides and PFAS's in drinking water (Tröger *et al.*, 2018). The fact, that the majority of about 3000 different substances, used in already only human medication in the EU, are not regulated and usually have a tendency to be environmental persistent and biological active gives rise to considerable

toxicological concern (Fent *et al.*, 2006). Adverse effects that are frequently associated with the occurrence of OMP's in the aquatic environment are the antibiotic resistance of microorganisms, acute or chronic toxicity, negative effects to non-target organisms, uncertainties regarding transformation products and metabolites and endocrine disrupting effects (Daughton & Ternes, 1999; Pérez-Fernández *et al.*, 2017).

Extensive studies targeting OMPs in surface water, in particular, lake basins, are limited. This is also the case for Lake Mälaren, Sweden's third biggest lake which is also an important natural drinking water resource, where long-term regular monitoring programs exist (Fölster *et al.*, 2014), but comprehensive data about OMPs are not available.

The sheer amount of OMP, their multi-facetted behaviors and complex correlations of environmental factors underline the challenge to depict fate and transport of OMP's in surface water. In spite of numerous analytical advances, analysis of trace compounds in environmental matrices are still challenging regarding its reliability, simplicity, duration, sensitivity and selectivity (Fedorova *et al.*, 2014).

This study aims to provide a comprehensive data set from a one-year sampling period at different locations and sampling depths for Lake Mälaren and moreover to contribute to the ongoing assessment of the possible environmental hazards of OMPs.

The main objectives of this study are:

- To optimize a multi-residue method, based on a single solid-phase-extraction (SPE) protocol followed by UPLC-MS/MS for the analysis of OMPs in surface water
- To investigate the occurrence of 50 OMPs in Lake Mälaren over one year.
- To investigate seasonal changes, spatial and vertical distributions of OMP concentrations in Lake Mälaren over one year.
- To study correlations between compounds and water chemistry of Lake Mälaren.

1.1.1 Occurrence of OMPs in the aquatic environment

A comprehensive understanding of the spatial and temporal occurrence of OMPs is essential to identify compounds that require greater attention. By incorporating compound and environmental matrix specific properties, conclusions regarding a compound's behavior in the environment can be drawn and will therefore facilitate and contribute to future decision-making for defining quality standards and regulations. Exposure and effects of OMPs can only then accurately be evaluated if profound knowledge about fate and transport is acquired (Andreozzi *et al.*, 2003). Car-

bamazepine, diclofenac, ibuprofen and caffeine are some of the most frequently detected compounds in surface waters (Luo *et al.*, 2014). Bezafibrate, metoprolol, iopromide, tramadol, erythromycin, azithromycin and clarithromycin are additional compounds usually being associated with a ubiquitous presence in surface water (Fent *et al.*, 2006; Ebele *et al.*, 2017; Yang *et al.*, 2017).

1.1.2 Sources, pathways and removal efficiency

There are different ways for OMP's to enter the environment; in general, one can differentiate between point and diffuse sources. Point sources are single locations that are clearly distinguishable from other pollution sources, whereas diffuse sources are rather elusive and are characteristic for broad geographical scales (Lapworth *et al.*, 2012). Examples for this are on the one side industrial effluents, hospital effluents, wastewater and sewage treatment plants, waste disposal sites, septic tanks and on the other side storm-water/urban runoffs, agricultural runoffs due to application of sewage sludge, leakages from sewer systems (Lapworth *et al.*, 2012; Li, 2014). The major identified pathway of introducing OMPs into the aquatic environment is the effluent of wastewater treatment plants (WWTP) consisting of processed influents from domestic, municipal and/or industrial systems (Daughton & Ternes, 1999; Choi *et al.*, 2008; Loos *et al.*, 2013). While the final effluent is discharged into surface waters, the remaining residual sludge is either disposed at landfills, which can for instance lead to percolation into groundwater, or used as fertilizer and applied to agricultural lands, where run-offs into water bodies are not unlikely (Daughton & Ternes, 1999; Ebele *et al.*, 2017). Some pharmaceuticals and personal care products (PCPs) may be released directly into aquatic bodies via improper disposal of unused medication or recreational activities such as bathing or swimming (Daughton & Ternes, 1999; Yang *et al.*, 2017).

Usually, conventional WWTPs are not designed for the purpose of removing OMPs, which is why OMPs are often still present in the effluent (Zorita *et al.*, 2009). Whether and how much a compound is removed does not only depend on the design of a treatment plant but also on the physico-chemical properties and the frequency of introduction of the compounds – some compounds may not be degraded at all or only very slow (Yang *et al.*, 2017).

Differences within the single steps of water treatment and their respective mechanisms – primary, secondary and tertiary – are apparent. Several studies investigated this and suggest that removal efficiency is insufficient for primary treatment, whereas secondary treatment is already much more effective and tertiary treatment the most promising option (Altmann *et al.*, 2014; Luo *et al.*, 2014; Falås *et al.*, 2016). An example of tertiary treatment is the incorporation of granulated activated carbon (GAC) filters or ozonation into the operating. When GAC filters are used –

as it is the case in the drinking water plant (DWP) at Lake Görväln – regular regeneration or replacement are important to ensure continuous high levels of removal of OMPs (Tröger *et al.*, 2018). Luo et al. ascertained wide compound-specific variations in the OMPs removal efficiency for WWTPs ranging from 12.5% to 100% (Luo *et al.*, 2014). Despite additional treatment, some compounds might still occur in drinking water in usually low concentrations, well below acute toxicity levels (Luo *et al.*, 2014; Tröger *et al.*, 2018).

1.1.3 Natural attenuation process

Once entered the aquatic environment, the concentration of OMPs is expected to decrease with increasing distance to the point of discharge, due to dilution and natural attenuation mechanisms (Vieno *et al.*, 2005; Daneshvar *et al.*, 2010b). Here, sorption and biodegradation are essential processes. However, also photodegradation is a key factor for natural attenuation. The rate of photodegradation relies on the strength of solar irradiation and on the presence of photosensitizer acting substances to enable photodegradation in the first place (Fent *et al.*, 2006). Although natural attenuation mechanisms contribute to a steady decrease of OMP concentrations, spatial distribution and detection in big water compartments, such as Lake Mälaren, is not detained.

1.2 Limitations of the study

Some OMPs are undergoing transformation through wastewater treatment or human extraction so that there are eventually modified and unchanged OMPs discharged (Azzouz & Ballesteros, 2013). Modified OMPs, so-called transformation products might pose an even higher risk to the environment and humans than the parent compounds. To date, knowledge about occurrence and toxicology of transformation products is limited. The present study does not focus on these transformation products of OMPs.

Due to the vast amount of target analytes, not every single compound will be addressed specifically and compared with concentrations presented in the literature. In the course of this thesis, some compounds of particular interest are discussed more deeply.

2 Materials and Methods

2.1 Chemicals and consumables

For chemical analysis, ultrapure water was generated by a Milli-Q (MQ) Advantage Ultrapure Water purification system and filtered through a 0.22 μm Millipak Express membrane and an LC-Pak polishing unit (Merk Millipore, Billercia, MA). Methanol, acetonitrile, ammonium acetate, formic acid, ammonia and ethyl acetate of high analytical grade were acquired from Sigma-Aldrich (Sweden).

All analytical standards used for analysis were of high purity grade (>95%). Native standards (n=122) originate from Sigma-Aldrich (Sweden). Isotopically labeled standards (IS) (n=26) for the target compounds were obtained from Wellington Laboratories (Canada), Teknolab AB (Kungsbacka, Sweden), Sigma-Aldrich and Toronto Research Chemicals (Toronto, Canada). Detailed information about internal and native standards can be found elsewhere (Rostvall *et al.*, 2018).

Several consumables were used in the present study, mainly for sample preparation. For SPE empty polypropylene (PP) tubes (6 mL) and sorbent materials Sepra ZT (Strata-X), Sepra ZT-WCX (Strata-X-CW) and ZT-WAX (Strata-X-AW) were acquired from Phenomenex (Torrance, USA). The sorbent material Isolute ENV+ and the frits (20 μm, 6 mL) were obtained from Biotage (Ystrad Mynach, UK). The samples were filtered using a glass microfibre filter (grade GF/F, Whatman, thickness 0.42 mm, pore size 0.7 μm) and regenerated cellulose syringe filters (RC) of 15 mm diameter and 0.2 μm pore size purchased from Millipore (Cork, Ireland) and Phenomenoex(Torrance, CA, USA), respectively, were used.

2.2 Selected compounds

In total 122 compounds were evaluated in the present study, consisting of 80 pharmaceuticals, 19 industrial chemicals, 7 personal care products, 3 pesticides, 3 vitamins, 3 parabens, 2 artificial sweeteners, 2 stimulants, 1 contrast medium, 1 opioid and 1 isoflavone. The pharmaceuticals cover several different therapeutic groups, such as analgesics, anesthetics, antibiotics, anticancer, antidepressants, antidiabetics, antidiarrhoeal, antifungals, antihistamines, antihypertensives, antilipemic agents, antimalarials, antipsychotic, antisecretory agent, beta blockers, diuretics, nonsteroidal anti-inflammatory drugs (NSAID) and sedatives.

The multiresidual approach of this study was based on a method developed in the Department for Aquatic Sciences and Assessment SLU, which focused on an array of OMP's that were chosen due to their high annual consumption and wide scope of application in the private sector and their continuing concern about their possible adverse effect on humans and aquatic organisms.

This target screening method was optimized by testing 35 additional compounds on a triple-stage quadrupole mass spectrometer MS/MS TSQ QUANTIVA (Thermo Fisher Scientific). A compound was incorporated in the method if the instrument was able to ionize the compound and its fragments could therefore be determined in order to quantify and qualify the compound. This is essential to avoid false positive identification of compounds (Krauss *et al.*, 2010). Additionally, the chromatographical column had to be able to separate the target compounds from endogenous substances with similar retention times and the LOQ shouldn't be too high. Out of the 35 tested compounds, 21 were added to the final analytical method.

2.3 Study site and sample collection.

Mälaren Lake is the third biggest lake in Sweden. It is the major supply for drinking water production in the Stockholm area and at the same time a receiving water body for several wastewater treatment plants (Swedish EPA, 2017). The lake is enclosed by Stockholm to the east, Uppsala to the north and Västerås to the west. The Mälaren area is considered as one of the fastest economically expanding regions in Sweden and at the same time, Stockholm has the

Figure 1. Sampling on the 11th of November 2017. Skarkolmen Uppsala.

greatest increase in population increase in Europe (11% in the next five years) (WssTP, 2013).

The lake's surface area is 1140 km², maximum depth is about 64 m and the water residence time is 2.8 years (Wallin *et al.*, 2000; Daneshvar *et al.*, 2010a). The surrounding area is characterized by 57% forest area, 20% agricultural area and 11% water bodies (Sonesten *et al.*, 2013). The lake basin has a branched structure which entails various bays of different shapes and depths (Willén, 2001; Moore *et al.*, 2008). This allows to divide the lake into different basins and to regard it separately. There are 12 incoming rivers to Mälaren: Arbogaån, Hedströmmen, Köpingsån, Kolbäcksån, Eskilstunaån, Svartån, Sagån, Råckstaån, Örsundaån, Fyrisån, Märstaån and Oxundaån (from west to east) (Sonesten *et al.*, 2013). The map (figure 2) gives a good overview of the described sampling site.

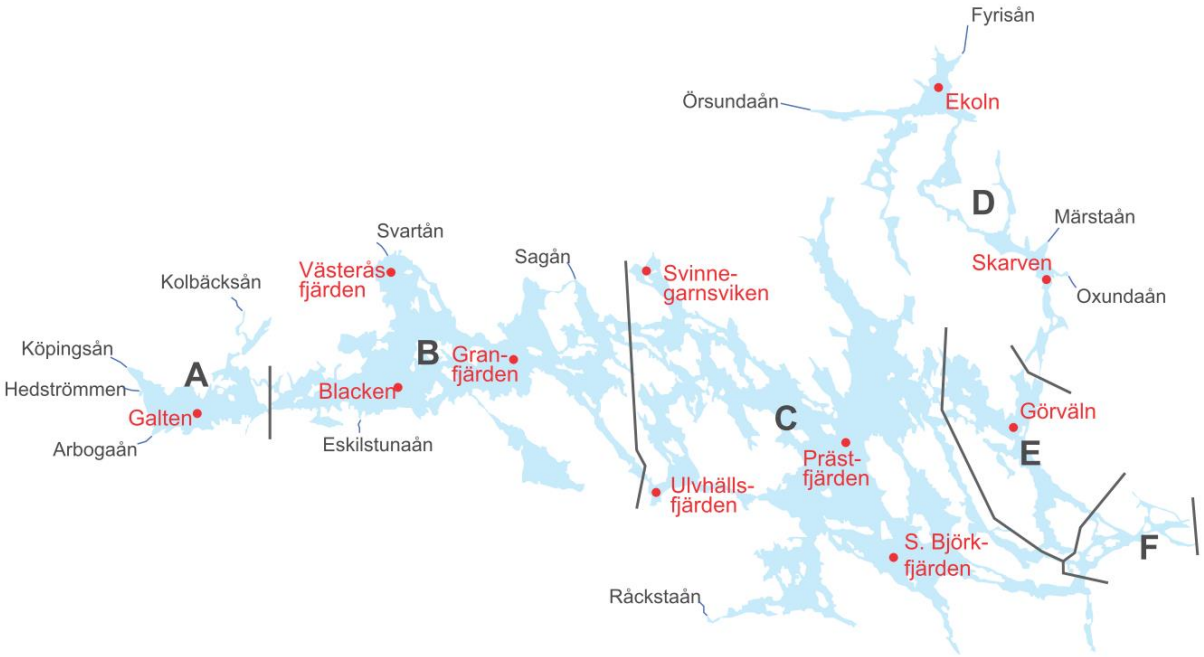

Figure 2. Map of Mälaren showing the sampling sites, incoming streams and the theoretical division of Lake Mälaren in six basins (A-F) (Sonesten *et al.*, 2013).

Eight different sampling events were conducted in the course of this study, starting in February 2017 and followed by April, May, July, August, September, November and April 2018. In total, 11 sampling points were part of the study: Galten, Blacken, Västeråsfjärden, Granfjärden, Svinnegarnsviken, Ulvhällsfjärden, Prästfjärden, S. Björkfjärden, Ekoln, Skarven and Görväln. However, the sampling sites varied slightly during the sampling period, and only 5 locations were consistently collected throughout most of the period: Ekoln, Galten, Görväln, Skarven and Västeråsfjärden. Usually, surface water (0.5m) were collected for the different locations,

with the exception of Ekoln, Görväln and in one occasion Prästfjärden, which were sampled for three different depths (0.5 m, 15 m, 30 m or 40 m). The appendix table A4 contains a detailed list of the exact sampling points of this study.

2.4 Sample preparation

Water samples were taken as grab samples in 1 L PP-bottles during the period from February 2017 to April 2018. Sampling bottles were rinsed three times before being filled. In total, 84 samples were analyzed. All samples were stored at 8°C at the Department for Aquatic Sciences and Assessment at SLU. Detailed information about the sampling sites, dates and location can be found in table A4 in the in appendix.

Figure 3. Set-up of filtering unit.

For the SPE analysis, 500 mL of the aliquots were used. Before extraction, all samples including blanks were vacuum filtered to remove suspended solids and avoid subsequent clogging during SPE. The glass microfiber filter used (grade GF/F, Whatman, thickness 0.42 mm, pore size 0.7 μm) were burned at 400°C for four hours before use. By thoroughly shaking the samples before the filtration it was ensured to obtain homogenized samples. The filtration unit was cleaned with MQ water and methanol between different samples. The instrumental setup of the filtering unit is shown in Figure 2.

As the extracted samples will be used for a following study focusing on non-target screening, the extraction materials chosen for the present study needed to be compatible with the subsequent method and support it. The combined results of the present target-based study and the nontarget analysis allow a holistic environmental risk assessment (Gago-Ferrero *et al.*, 2015a). Due to this reason, SPE was conducted with home-made cartridges following the method developed by Gago-Ferrero et al. (2015a; b). For the purpose of covering a broad range of compounds and enabling their enrichment, four different powder materials were selected and mixed together (200 mg Strata-X, 150 mg Isolute ENV+, 100 mg Strata-X-AW and 100 mg Strata-X-CV) (Gago-Ferrero *et al.*, 2015b). An illustration of the composition of a cartridge can be found in figure A2 in the appendix.

The samples were spiked with the IS mix (50 ng/ per sample aliquot before SPE).

In the first step of SPE extraction, cartridges were conditioned (by gravity) in two steps by adding 6 mL of methanol and 6 mL of MQ water into the reservoirs. Reservoirs got loaded and the flow rate was adjusted to roughly one drop per second by means of vacuum. Another 6 mL of MQ was added after all the aliquot ran through and the cartridges were dried under vacuum for 20 min.

The eluate is collected in plastic tubes after adding 4 mL of methanol/ethyl acetate (1:1) containing 2 % ammonia directly into the cartridge, followed by 2 mL of methanol/ethyl acetate (1:1) containing 1.7 % formic acid. This step was done under gravity.

To decrease the volume of the extract, nitrogen stream is applied until a volume of approximately 1 mL is reached, then transferred to an amber glass vial, rinsed 3 times with methanol and evaporated again to exact 500 μL. Analytes are vortexed and 500 μL of MQ water is added before analysis.

The set-up of the SPE extraction including manifold, adapters, stop-cocks, reservoirs and vacuum outlet is shown in figure 3.

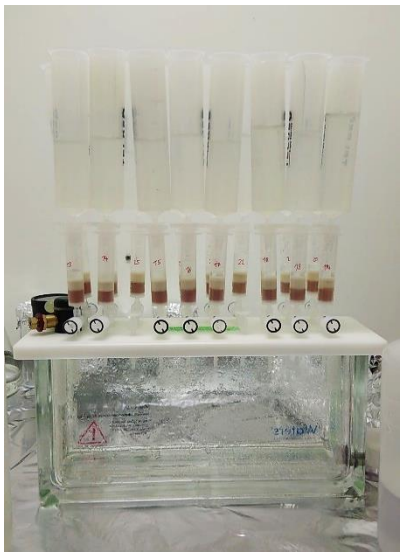

Figure 4. Set-up of SPE, showing the cartridges, loaded reservoirs, valves, stock-cocks and manifold.

2.5 Instrumental analysis

The need to analyze complex sample matrixes with unknown interferences, such as environmental samples, is widely met with coupling a separation technique with an identification and quantification method, represented by chromatography and mass spectrometer (MS).

For liquid chromatography (LC), the two key elements for the separation of components in the sample are a liquid mobile phase in which the analytes are diluted, and a stationary phase represented by the column (Skoog *et al.*, 2017). The physical-chemical properties of a compound determine its characteristic retention time, which is needed to identify it – the polarity of a compound plays a pivotal role in this process. The choice of column considerably affects the resolution and run time in LC.

Before the analysis in the mass spectrometer, the compounds need to be ionized. Electrospray ionization (ESI) is a rather soft liquid-phase ion source which has a

very high sensitivity to the concentration of a compound and works in an appropriate way in combination with LC (Hoffmann & Stroobant, 2007).

A commonly used method for target analysis is the triple quadrupole mass spectrometer, which however exhibits restrictions for suspect and non-target screening (Krauss *et al.*, 2010). The operating principle can be described in a three-step process involving two stages of mass analysis (MS/MS). Firstly, a mass spectrometer filters a precursor ion, which is then dissociated into fragments within the collision cell and lastly the resulting product spectrum is analyzed by the second mass spectrometer (Hoffmann & Stroobant, 2007).

The samples were analyzed by a DIONEX UltiMate 3000 ultra-high pressure liquid chromatography (UPLC) system (Thermo Scientific, Waltham, MA, USA) coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ QUANTIVA, Thermo SCIENTIFIC, Waltham, MA, USA). An Acquity UPLC BEH-C18 column (Waters, 100 mm × 2.1 i.d., 1.7 μm particle size from Waters Corporation, Manchester, UK) was used as an analytical column. Injection volume was 10 μL for all samples. A heated electrospray ionization (H-ESI) was used to ionize the target compounds. The spray voltage was set to static: positive ion (V) 3500. Nitrogen (purity >99.999%) was used as a sheath gas (50 arbitrary units), auxiliary gas (15 arbitrary units) and sweep gas (2 arbitrary units). The vaporizer was heated to 400°C and the capillary to 325°C. Two selected reaction monitoring (SRM) transitions were monitored for all analytes. The mobile phase consisted of MQ with 5 mM ammonium acetate and acetonitrile. The flow rate was 0.5 mL/min and run time was 15 min having switched positive and negative electrospray ionization modes.

The above-mentioned ionization conditions were set as tuning conditions for the SRM of individual compounds. The tuning was performed with an infusion of 1 μg/mL solution of each analyte into the stream of the mobile phase (300 mL/min of MQ water + 5 mM ammonium acetate/acetonitrile, 50/50). The tube lens voltage and collision energy of the two most abundant transitions were optimized.

The chromatography data acquisition mode was performed in a positive and negative mode using selected-reaction monitoring. Xcalibur software (Thermo Fisher Scientific, San Jose, CA, USA) software was used for optimizing the instrument methods and running of samples. The obtained data were evaluated using TraceFinderTM 3.3. software (Thermo Fisher).

2.6 Method performance

The performance of the method was assessed with regard to its linearity, LOQs, relative recovery, precision, blanks and matrix effect.

For testing the linearity of the method, a ten-point calibration curve in the concentration range from 0.01 ng/L to 250 ng/L was created. For each separate analysis, the calibration curve was measured twice, at the beginning and at the end of the sequence to check instrumental stability. The linearity of the calibration curve was validated by calculating the coefficient of determination R^2.

Instrumental LOQ's were calculated as one half of the lowest calibration point in the calibration curve where relative standard deviation of average response factor (ARF) was < 30% (in some cases one or two points at low concentration levels had to be removed). LOQs for each analyte in each sample were calculated by using the peak area of the lowest calibration point in the calibration curve. Average, minimum and maximum values of LOQ of the particular analytes can be found in table A1 in appendix.

The relative recovery, also known as trueness, verifies the performance of the extraction method (SPE, UPLC-MS/MS). This is done by spiking a known concentration of target analytes into the water samples (100 ng/sample) and correlate it with the detected concentration after extraction and analysis – so-called fortified samples.

The precision of the method is evaluated by the repeatability of the study. For this purpose, duplicates were conducted for every tenth sample. The values allow the comparison of the analysis within a batch of samples and between different batches. The repeatability is calculated by the ratio of standard deviation of the duplicates and the average detected concentration of the compounds times 100. Optimal repeatability rates are lower that 30%.

Quantification of the target compounds is done by using an internal standard (IS) calibration model. An optimized quantification of the analytes was established by combining four calibration curves and hence, to smooth possible outliers.

As the mass and retention time of a compound is relevant for the detection by UPLC-MS/MS, the optimal approach would be to use an isotopically labeled form for each of the target compounds, as it is stated in the Commission Decision 2002/657/EC (European Commission, 2002). For target compounds that could not be matched with a specifically designed IS due to restricted commercial availability, a surrogate IS needed to be selected. This was the case in particular for the newly tuned compounds. The chosen IS should reflect the physical-chemical properties, retention time and categorial grouping of the compound as much as possible. This step is also essential to obtain acceptable recovery rates for the compounds.

A mix of endogenous substances, such as proteins, lipids, minerals, salts and others can considerably affect the extraction and analysis. This phenomenon is commonly termed matrix effect. The resulting effect of ion suppression or enhancement were taken into consideration by matrix matching standards (MST). As the matrix effect can differ with the different compositions of the samples, the MST's were

chosen in such way that the most frequent locations Ekoln, Görväln, Skarven, Galten and Västeråsfjärden were covered and could be therefore assigned to the respective sample. For Ekoln and Görväln MST values for the different depths were determined and were incorporated as an average value in the calculation of real concentrations of the samples. Those samples that are not directly presented by a corresponding MST from the respective location, the real concentrations were calculated by using the MST with the highest matrix effect.

Matrix-matched standards were prepared from water samples spiked with ISs at concentration levels of 50 ng per sample and native compounds at concentration levels of 100 ng per sample after extraction. The peak area/IS ratio determined in non-spiked samples was subtracted from the peak area/IS ratio in matrix-matched standards to achieve the matrix-affected response factor. Additionally, matrix effects were calculated and are presented in table A2 in the appendix. Negative values are associated with ion suppression whereas positive values are associated with ion enhancement.

To exclude any concerns of contamination and evaluate possible memory effects, each batch of analysis was conducted with two blanks, MQ water and tap water, which were filtered, extracted, eluted and analyzed in the exact same way as the samples. PP-bottles and SPE reservoirs were rinsed three times with methanol; adapters, stop-cocks from the SPE and needles from the evaporation step were ultrasonicated twice for 15 min. All analytical work was conducted while wearing gloves.

Method performance parameters (R^2, repeatability; relative recovery) are shown in table 1 in paragraph 3.1.

2.7 Statistical analysis

The statistical program JMP from SAS institute was used for data analysis, graphical processing and statistical tests, notably principle component analysis (PCA) and partial least square (PLS) analysis. In addition, the spreadsheet program Microsoft Excel was used to calculate concentrations and data analysis. For maximum, median and average values, only concentrations >LOQ were used.

3 Results and Discussion

3.1 Method performance

In the present study, 122 compounds were evaluated in the course of SPE and UPLC-MS/MS. In spite of prior tuning, throughout the analysis it became apparent, that 11 compounds were not able to be analyzed in a qualitative and quantitative way. These 11 substances consist of 6 ICs, 4 pharmaceuticals and one PCP. Reasons for omission became mostly clear during acquiring the data via the software TraceFinder. No clearly detected peaks, no sufficient chromatographic separation, a lack of ionization of the compound to determine a qualitative and quantitative fragment or high variability in the results, no linear response of the calibration curves were the main reasons for excluding those compounds. Due to their vast diversity, knowledge about industrial chemicals, their behavior and analytical protocols for their determination in environmental samples is limited or lacking completely – as it is the case of sebacic acid, tetraethylene glycol, dibutyl thiourea, tetraacetylethylenediamine (TAED), mono-n-butylphosphoric acid and 4-dodecylbenzenesulfonic Acid. Three of the omitted compounds are part of the EU-Watchlist: the two macrolide antibiotics azithromycin and erythromycin and the UV-filter 2-ethylhexyl-methoxycinnamate. The difficulties to analyze these compounds are well known in the literature. Instead of the chosen UPLC-MS/MS set-up of the present study, variations in the sample preparation, liquid phase, ion source, column etc. will achieve considerable different results (Pérez-Fernández *et al.*, 2017). For instance, using atmospheric pressure photoionization (APPI) instead of H-ESI as an ion source will yield much better outcomes for some compounds (Lindberg *et al.*, 2014).

For 74 OMPs of the remaining 111 OMPs the method was suitable by obtaining a relative recovery within the range of 60% to 145%, thus leading to the exclusion of 23 pharmaceuticals (including clarithromycin, the third macrolide antibiotic on

the EU-Watchlist), 6 ICs, 4 PCPs, 3 vitamins and 2 artificial sweeteners due to unacceptably low recovery rates and therefore restrictions in their quantification. For 22 OMPs the recovery rate was under 60% with ricinoleic acid having the lowest recovery rate of 3%, for 13 OMPs the recovery rate was above 145% with oleic acid having the highest recovery rate of 624%, and 3 times no recovery rate was obtained as the LOQs were too high. 15 additional compounds are within the range of 40% to 160%. The bad recovery rates of the 23 OMPs imply that using the described method is not appropriate and different methods, more targeted towards their specific analysis requirements, are needed.

As the target analytes of the present study are quite heterogeneous and cover a wide range of physico-chemical properties, finding conditions that attain acceptable chromatographic behaviors to adequately quantify the compounds is a complicated matter (Grabic *et al.*, 2012). For instance, different mobile phases can improve the chromatographic performance regarding reduced peak tailings and better resolutions for some compounds considerably – for some compounds the effect may, however, entail the complete opposite (Baker & Kasprzyk-Hordern, 2011). Whatever condition is chosen, it is an issue that constitutes a compromise for the analytes in terms of sensitivity and selectivity but ultimately seeks a good overall performance (Huntscha *et al.*, 2012). The choice of sorbent material for SPE is essential to attain good recovery rates (Baker & Kasprzyk-Hordern, 2011; Pérez-Fernández *et al.*, 2017). Not only were the powder sorbents used in the present study originally chosen for a non-target analysis, but also do home-made cartridges entail a certain uncertainty as a 100% homogeneity of the cartridges cannot be guaranteed. Investigating factors like the applied temperature during the evaporation step, vials, sample volumes, filters being used, are important to consider to achieve optimized recovery rates (Baker & Kasprzyk-Hordern, 2011). SPE related issues are partially discussed in Gago-Ferrero *et al.* (2015a; b) For future analysis a method adaptation is recommended, in particular regarding the choice of cartridges for SPE extraction.

Individual LOQs for each compound in each sample are summarized in average, minimum and maximum values and are presented in table A1 in the appendix for only the 50 OMPs which were detected at least once above the LOQ and not removed for some other reason (see paragraph 3.2.1). The same applies to repeatability and linearity. Those compounds which attained good recovery rates, however were not detected above LOQ are listed in table A3 in the appendix including recovery rates and linearity.

The range for the $LOQs_{average}$ for the 50 OMPs reaches from 0.010 to 5.0 ng/L (median 0.090 ng/L), for $LOQs_{min}$ from 0.0070 to 3.9 ng/L (median 0.062 ng/L) and for $LOQs_{max}$ from 0.020 to 10 ng/L (median 0.26 ng/L). For four compounds LOQs > 5.0 ng/L were occasionally calculated: acetaminophen ($LOQ_{average}$ = 5.0 ng/L),

ibuprofen ($LOQ_{average}$ = 5.0 ng/L), valproic acid ($LOQ_{average}$ = 3.6 ng/L) and 3-(4-methylbenzylidene)camphor ($LOQ_{average}$ = 3.3 ng/L).

The instrumental analysis of the present study shows good linearity for the majority of compounds ($R^2 > 0.980$), with the exception of atenolol ($R^2 = 0.961$) and irbesartan ($R^2 = 0.975$).

Sample duplicates with high frequencies of detection are the most suitable ones to show the repeatability of the used method. For this reason, only duplicates from Ekoln, Västeråsfjärden, Blacken and fortified samples are presented in table 1. Looking at the fortified samples, only one analyte exceeded the 30%, namely lidocaine (55%). Lidocaine, however, showed good repeatability rates for the other duplicates. Besides that, 88% of the duplicates show a good precision (<30%) of the SPE analysis.

Matrix effects are presented in table A2 in the appendix and show a good comparability of the different sampling points. High ion suppression or enhancement of an analyte in one of the sampling sites is usually reflected in the other sampling sites as well. No evident deviation for any of the matrix matching samples was observed, so that assigned MSTs for the calculated concentrations are approved. Seemingly arbitrary behaviors arise for: atenolol, bicalutamide, clozapine, irbesartan, amitriptyline, valproic acid and venlafaxine. In most cases, the deviating matrix effect stems from Västeråsfjärden, or occasionally from Ekoln. Greater polluted water in conjunction with the proximity to a large city likely contains more matrix compounds that might explain the alteration in detected concentrations of analytes.

Some studies suggest correlations between polarity and molecular weight of the compounds with matrix effects (Cappiello *et al.*, 2010). However, no evident correlations could be found. Considerable high matrix effects were obtained for daidzein (range -170% to 349%), di-(2-ethylhexyl)phosphoric acid (range -101% to 122%) and lamotrigine (range -246% to 280%, Görväln 2018: 21%). For venlafaxine, there is an outlier value (437%) for MST Ekoln, although all the matrix effects of the other sampling points range from -8% to 41%.

17 industrial chemicals were tested in the course of this study. Although several IC were priorly tuned on the method and some of them even incorporated into the method, it became apparent that the method is rather unfitting due to largely not acceptable recovery rates and high variability in the results. Only 7 IC had a good recovery and from those 4 IC were detected above the LOQs. ICs were not part of the original developed analytical method. To my best knowledge, for some compounds an analytical protocol for their determination in environmental samples is not yet known.

Table 1. *Physico-chemical properties, relative recovery, coefficient of determination R², repeatability of duplicates and frequency of detection of positive analytes. In total 84 samples were analyzed. (pKa: acid dissociation constant; log Kow: water partition coefficient)*

								Repeatability				
Compound	Category	Type	Monoisotopic mass (Da)	pKa	log Kow	Relative Recovery	R^2	Ekoln (0.5m)	Ekoln (15m)	Blacken	Fortified Samples	Frequency of Detection
Atenolol	Pharmaceutical	Beta blocker	266.2	9.6 [a]	0.16	99%	0.9613	n.d.	5%	1%	4%	46%
Sotalol	Pharmaceutical	Beta blocker	272.1	8.3 [a]	0.37	114%	0.9962	n.d.	141%	n.d.	4%	8%
Nicotine	Stimulant		162.1	3.2 [a]	1.0	104%	0.9994	1%	2%	n.d.	1%	23%
Metoprolol	Pharmaceutical	Beta blocker	267.1	9.7 [b]	1.7	94%	0.9965	0%	2%	3%	12%	88%
Atorvastatin	Pharmaceutical	Antilipemic drug	558.2	4.3 [b]	6.4	99%	0.9969	n.d.	n.d.	n.d.	5%	18%
Carbamazepine	Pharmaceutical	Antiepileptic	236.0	4.2 [a]	2.3	99%	0.9903	1%	2%	8%	10%	99%
Cetirizine	Pharmaceutical	Antihistamine	388.9	2.7 [b]	1.7	73%	0.9895	23%	17%	1%	31%	87%
Citalopram	Pharmaceutical	Antidepressant	324.1	9.4 [a]	3.7	62%	0.9994	3%	9%	53%	6%	63%
Mirtazapine	Pharmaceutical	Antidepressant	265.1	7.1 [a]	3.0	73%	0.9985	16%	8%	n.d.	2%	50%
Oxazepam	Pharmaceutical	Sedative	286.0	1.7 [a]	3.3	83%	0.9961	3%	2%	10%	4%	88%
Pyrimethamine	Pharmaceutical	Antimalarial	248.1	7.3 [a]	2.7	83%	0.9901	n.d.	n.d.	n.d.	3%	6%
Lamotrigine	Pharmaceutical	Antiepileptic	255.0	5.7 [a]	0.99	120%	0.9884	3%	2%	10%	29%	100%
DEET	Pesticide	Insect repellent	191.1	-	2.3	94%	0.9980	1%	1%	4%	5%	100%
Bezafibrate	Pharmaceutical	Antilipemic drug	361.1	3.6 [a]	4.3	88%	0.9961	n.d.	n.d.	n.d.	4%	20%
Sulisobenzone	PCP	UV filter	308.0	-2.4 [b]	0.37	83%	0.9971	9%	42%	n.d.	5%	62%
Dibutyl phosphate	Industrial Chemical	Lubricant	210.2	0.88 [b]	2.3	104%	0.9982	n.d.	n.d.	86%	7%	52%
Tolyltriazole	Industrial Chemical	Corrosion inhibitor	133.2	8.4 [a]	1.7	114%	0.9997	1%	5%	6%	9%	100%
Ifosfamide	Pharmaceutical	Anticancer	260.0	-	0.86	88%	0.9917	2%	49%	n.d.	1%	24%
Bicalutamide	Pharmaceutical	Anticancer	430.4	13	2.3	130%	0.9983	2%	2%	2%	1%	100%

Compound	Category	Type	Monoisotopic mass (Da)	pKa	log Kow	Relative Recovery	R^2	Repeatability				Frequency of Detection
								Ekoln (0.5m)	Ekoln (15m)	Blacken	Fortified Samples	
Bisoprolol	Pharmaceutical	Antihypertensive	325.4	9.3 [b]	1.8	99%	0.9975	5%	2%	1%	4%	76%
Clozapine	Pharmaceutical	Antipsychotic	326.1	3.6 [a]	3.4	78%	0.9880	12%	n.d.	n.d.	2%	19%
Diazepam	Pharmaceutical	Sedative	284.0	3.3 [a]	2.7	88%	0.9835	29%	28%	23%	3%	37%
Fexofenadine	Pharmaceutical	Antihistamine	501.7	8.8 [b]	2.8	83%	0.9918	7%	1%	2%	6%	86%
Caffeine	Stimulant		194.1	10 [a]	-0.07	99%	0.9985	3%	9%	4%	1%	100%
Tramadol	Pharmaceutical	Analgesic	263.1	9.4 [a]	3.0	109%	0.9954	6%	3%	7%	4%	82%
Valsartan	Pharmaceutical	Antihypertensive	435.2	3.8 [b]	3.7	109%	0.9982	n.d.	n.d.	n.d.	7%	18%
Codeine	Pharmaceutical	Opiate	299.1	8.2 [a]	1.3	78%	0.9979	n.d.	n.d.	n.d.	1%	10%
Oxycodone	Opioid		315.1	8.9 [a]	0.66	78%	0.9981	15%	8%	n.d.	13%	25%
2,2'-Dimorpholinyldiethylether	Industrial Chemical	Process regulator	244.2	-	-1.3	83%	0.9995	19%	n.d.	n.d.	8%	19%
Diclofenac	Pharmaceutical	NSAID	295.0	4.2 [a]	4.0	88%	0.9972	n.d.	24%	n.d.	10%	37%
Ethylparaben	Paraben	Preservative	166.0	8.3 [a]	2.5	109%	1.0000	n.d.	n.d.	n.d.	6%	11%
Propylparaben	Paraben	Preservative	180.0	8.4 [a]	3.0	94%	0.9990	n.d.	n.d.	n.d.	0%	42%
Methylparaben	Paraben	Preservative	152.0	8.4 [a]	2.0	104%	1.0000	n.d.	n.d.	n.d.	1%	33%
Furosemide	Pharmaceutical	Diuretic	330.0	4.3 [b]	2.3	88%	1.0000	n.d.	n.d.	n.d.	1%	21%
Diltiazem	Pharmaceutical	Antihypertensive	414.1	7.7 [a]	2.8	88%	0.9976	n.d.	n.d.	n.d.	1%	10%
Ibuprofen	Pharmaceutical	NSAID	206.1	4.4 [a]	3.8	78%	0.9979	n.d.	n.d.	n.d.	7%	2%
Irbesartan	Pharmaceutical	Antihypertensive	428.2	3.5 [b]	5.3	94%	0.9753	2%	1%	1%	1%	62%
Propranolol	Pharmaceutical	Beta blocker	259.1	9.5 [a]	2.6	125%	0.9986	33%	16%	2%	1%	52%
Lidocaine	Pharmaceutical	Anesthetic	234.1	8.0 [a]	1.7	135%	0.9979	0%	1%	0%	55%	85%
Losartan	Pharmaceutical	Antihypertensive	422.1	4.1 [a]	4.0	94%	0.9891	0%	2%	6%	2%	62%
Omeprazole	Pharmaceutical	Antisecretory Agent	345.1	4.8 [b]	3.4	94%	0.9959	n.d.	n.d.	n.d.	11%	7%

Compound	Category	Type	Monoisotopic mass (Da)	pKa	log Kow	Relative Recovery	R^2	Repeatability				Frequency of Detection
								Ekoln (0.5m)	Ekoln (15m)	Blacken	Fortified Samples	
Acetaminophen	Pharmaceutical	Analgesic	151.0	9.4 [a]	0.46	94%	0.9939	n.d.	n.d.	n.d.	14%	1%
Amitriptyline	Pharmaceutical	Antidepressant	277.1	9.4 [a]	5.0	109%	0.9966	n.d.	n.d.	n.d.	6%	14%
Valproic acid	Pharmaceutical	Antiepileptic	144.1	4.6 [a]	3.0	114%	0.9992	n.d.	n.d.	141%	13%	43%
Venlafaxine	Pharmaceutical	Antidepressant	277.2	9.3 [b]	3.3	83%	0.9992	11%	16%	n.d.	2%	71%
Daidzein	Isoflavones		254.1	-	2.6	94%	0.9642	n.d.	n.d.	n.d.	2%	8%
Di-(2-ethylhexyl)phosphoric acid	Industrial Chemical	Solvent Extraction	322.2	-	6.1	104%	0.9959	n.d.	n.d.	2%	10%	18%
Tris(2-butoxylethyl) phosphate	Industrial Chemical	Flame retardants	398.5	-	3.8	94%	0.9997	18%	4%	n.d.	0%	76%
3-(4-Methylbenzylidene)camphor	PCP	UV filter	254.2	-	5.9	62%	0.9995	n.d.	n.d.	n.d.	27%	4%
Fluoxetine	Pharmaceutical	Antidepressant	309.1	10 [b]	4.7	114%	0.9880	n.d.	n.d.	n.d.	7%	1%

[a] experimental pKa, [b] theoretical pKa

3.2 Occurrence of OMPs

3.2.1 OMP concentrations

Out of the 74 OMPs with good relative recovery, 58 compounds were detected at least once above the limit of quantification.

Laurilsulfate was removed despite a good recovery rate. It was detected only once in one of the duplicates which results in an unacceptable repeatability value of 141%. Despite of good repeatability in the fortified samples, the high variability of the concentrations of samples, the repeatability and LOQs (variance 119%) led to the decision to remove the compound.

This also applies for the plasticizer Tributyl citrate acetate in a similar way. Low relative recovery (62%), unacceptable repeatability and high variability in concentrations led to its omission.

Antibiotics and antifungals had to be removed as well. Six pharmaceuticals belong to this group: metronidazole, metronidazole-OH, sulfamethoxazole, trimethoprim, clindamycin and climbazole. The compounds were omitted due to stability issues of internal and native standards. As it is suggested in literature (Ort *et al.*, 2010), freshly prepared standard mixed are crucial to obtain reliable results. Unfortunately, this was not assured.

Comprehensive monitoring studies focusing on OMPs in surface water are rare, especially with regard to lake basins. As river water is usually more directly affected by WWTPs effluents and dilution differs in terms of magnitude, a comparison of the obtain concentrations of the present thesis with other studies is impeded.

Five analytes were found in all sampling points: DEET, lamotrigine, bicalutamide, tolyltriazole and caffeine. Very high frequencies of detection (>80%) above LOQs were also obtained for carbamazepine (99%), metoprolol (88%), oxazepam (88%), cetirizine (87%), fexofenadine (86%), lidocaine (85%) and tramadol (82%). The highest detected concentrations (> 100 ng/L) were found for valproic acid and lamotrigine. Figure 4 illustrates the 20 compounds found with the highest concentrations, their median concentration and frequency of detections. Due to the long sampling period, some compounds have considerable fluctuating concentrations,

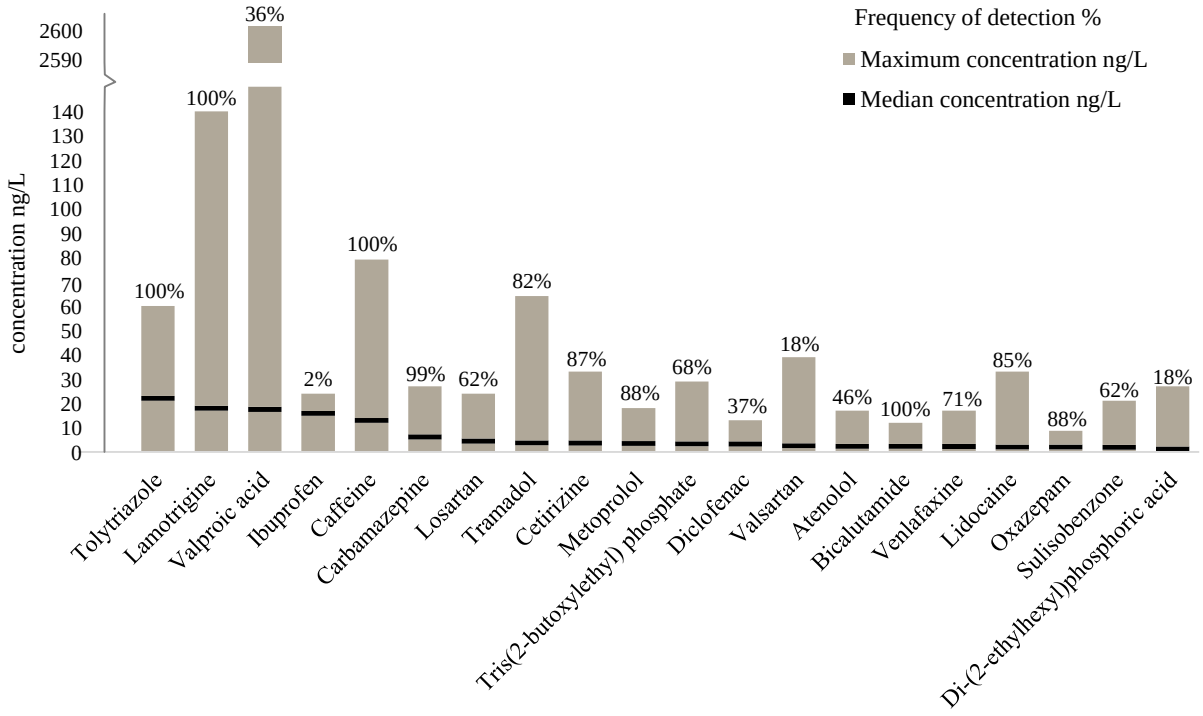

Figure 5. Top 20 highest detected OMPs throughout the entire sampling period of one year. The figure shows the maximum detected concentration, the medium concentration and the frequency of detection of the specific compound. In total 84 samples were analyzed.

with occasional high concentrations. To place less weight on these very high concentrations, median instead of average concentrations were chosen to be displayed. In general, the median is less affected by outliers and has advantages in particular when the distribution of a data is not symmetrical.

Carbamazepine, valproic acid and lamotrigine are the most frequently prescribed antiepileptics, accounting for 72% of initiating monotherapies in Sweden; with an increasing trend to lamotrigine (Bolin *et al.*, 2017). Since the physico-chemical properties of lamotrigine and carbamazepine are very similar, both antiepileptics, their behavior and occurrence usually go hand in hand (see paragraph 3.3). Numerous studies evince the low elimination rates of carbamazepine in WWTP (Li, 2014; Ebele *et al.*, 2017). Neither sorption, biodegradation nor photodegradation seems to achieve good removal outcomes (Fent *et al.*, 2006). Maximum (27 ng/L and 140 ng/L) and median (6.2 ng/L and 18 ng/L) detected concentrations for carbamazepine and lamotrigine, respectively, are within usually expected ranges. A sampling event in Lake Mälaren conducted by Daneshvar *et al*. (2010a) detected higher concentrations by roughly 8 orders of magnitude for carbamazepine (Daneshvar *et al.*, 2010a).

Valproic acid is the compound found with the highest concentrations ranging from 2.1 ng/L to 2600 ng/L with the median concentration 17.5 ng/L. Information about biodegradation and removal efficiency are inconsistent. According to the website TOXNET, bioconcentration in aquatic organisms is unlikely due to a bioconcentration factor (BCF) of 3 (TOXNET), whereas at the same time valproic acid was observed to change social interactions between zebrafishes (Zimmermann *et al.*, 2015), however, the Stockholm County Council determines the environmental risk of valproic acid as insignificant but also states the uncertainty of the assessment due to lack of data (Stockholm County Council, 2014). No clear conclusion regarding the toxicological effect of valproic acid in Lake Mälaren can be drawn.

The ubiquitous nature of caffeine is not surprising, as it is widely known that caffeine is simply found everywhere; its concentration can even reach up to a few μg/L (Sousa *et al.*, 2018). In that perspective, the highest detected concentration of 79 ng/L and median concentration of 13 ng/L are acceptable.

Similar holds true for the insect repellent DEET (diethyltoluamide) which is quite usually found in high frequencies in surface water (Sandstrom *et al.*, 2005). Maximum (8.3 ng/L) and median concentrations (1.95 ng/L) are low.

According to Daneshvar *et al*., metoprolol is "the most sold beta-blocker in Uppsala", and annual sales are more than twice as much as the beta-blocker atenolol (Daneshvar *et al.*, 2010a). Maximum concentration is 18 ng/L, median concentration 5.23 ng/L. These results are well comparable to the concentrations found by Daneshvar *et al*. (2010a) in Lake Mälaren; also regarding maximum and median concentrations found for atenolol, which are just slightly lower. The reason for this seems to be differences in removal efficiencies of WWTPs and excretion ratios of parent compound or metabolites (Daneshvar *et al.*, 2010a).

Tramadol is an analgesic drug used for moderate to severe pain relieve (WHO, 2014). It is mainly present in soluble form as volatilization and sorption are expected to be low (Rúa-Gómez & Püttmann, 2012). Maximum detected concentration found was 64 ng/L and median concentration 3.8 ng/L, which is acceptable when comparing it to detected concentrations in river water in UK which exceeded single μg/L (Baker & Kasprzyk-Hordern, 2011). Tramadol is occasionally termed as a mild-opioid, similar to codeine (Olsson *et al.*, 2017). It's potential for dependency is considered low (WHO, 2014), however, growing abuse rates among young adults are of rising concern (Olsson *et al.*, 2017). Just recently in January 2018, a local Swedish newspaper reported the confiscation of great amounts of tramadol in Uppsala and that smuggling of tramadol increased strongly (Lindqvist, 2018). This indicates that Lake Mälaren might be affected by increasing tramadol consumption rates and the compound should be part of future monitoring programs.

Tolyltriazole is a corrosion inhibitor frequently used in dishwasher detergents and in vehicle/aircraft antifreezing products; it belongs to the group of benzotriazole

and is associated with high solubility in water, low biodegradability as well as low sorption abilities (Giger *et al.*, 2006). Maximum detected concentration is 60 ng/L (Ekoln 30 m, Feb ‘17) and median concentration is 22 ng/L. This is below the concentration found in Swiss lakes, with ranges up to a few μg/L, however, its high frequency of detection is well in agreement with studies investigating river water (Giger *et al.*, 2006; Wang *et al.*, 2016). Nearby located airports – Arlanda airport is situated to the east of Lake Mälaren – may considerably contribute to the occurrence in surface water (Giger *et al.*, 2006). The high and frequent detected concentrations in surface water raise the question about its presence in drinking water. This was confirmed by Janne et al. and Wang et al. (2011; 2016).

Bicalutamide is next to ifosfamide one of the antineoplastic drugs detected in Lake Mälaren. Methotrexate was not detected. Bicalutamide is an antiandrogen used for 79% of prostate cancer treatment in Sweden and said to be difficult to biodegrade (Besse *et al.*, 2012; Grundmark *et al.*, 2012) which explains the continuous detection in all the sampling points. A maximum concentration of 12 ng/L and median concentration of 2.3 ng/L is tolerable and seems not to raise high toxicological concerns (Besse *et al.*, 2012; Santos *et al.*, 2017).

For 34 of 51 compounds, maximum detected concentrations were compared with predicted critical environmental concentrations (CEC) calculated by Fick *et al.* (2010). CECs facilitate a quick and simplified approach to evaluate the potential of individual compounds to cause adverse pharmacological effects at certain water concentrations. This methodology is based on the correlation of plasma concentration in exposed fish with human therapeutic plasma concentrations (Fick *et al.*, 2010). All maximum concentrations were well below the CECs. However, no CEC values were available for some of the most frequent and highest detected compounds, for instance, DEET, nicotine, sulisobenzone, tolyltriazole, valproic acid, the three parabens and for the other industrial chemicals.

None of the detected concentrations represent an acute risk for humans or fauna according to current states of knowledge. However, high insecurities regarding chronic toxicity, adverse effects on non-target organisms and synergistic effects still remain and should not be disregarded.

Additional information for the 50 OMPs regarding CAS number, molecular formula, charge and hydrophobicity is shown in table A5 in the appendix.

3.2.2 Spatial distribution

In total 11 different sampling locations distributed around Lake Mälaren were part of the study: Ekoln, Skarven, Görväln, Västeråsfjärden, Blacken, Prästfjärden, Svinnegarnsviken, Granfjärden, Ulvhällsfjärden and Södra Björkfjären. Only 5 lo-

cations, including different sampling depths for two of the locations, were consistently collected throughout most of the period: Ekoln (0.5 m, 15 m, 30 m), Görväln (0.5 m, 15 m, 40 m), Västeråsfjärden (0.5 m), Galten (0.5 m), Skarven (0.5 m).

For a better understanding of the results, it is important to point out, that there are considerable differences between the sampling locations regarding the residence time of the water, incoming flow rates, surrounding land use, volume and depth.

Depending on the residence time, some basins are more prone to higher concentrations of pollutants than others, due to limited self-cleaning abilities and different background levels of substances (Sonesten *et al.*, 2013). These self-cleaning abilities are somewhat at the same time basin dependent natural attenuation mechanisms. In the course of this, the volume and depth of a basin are relevant factors since the extent of larger bottom areas interacting with the surface water, the extent of wind and waves having an impact and the process of sedimentation do affect biodegradation, sorption and photodegradation (Wallin *et al.*, 2000).

For various purposes, Mälaren is divided into 6 theoretical basins (see figure 2). The westernmost and smallest basin Galten in terms of volume receives about 46% of the incoming water and has therefore the shortest residence time together with the easternmost basin, which is where Mälaren and its outlet is linked with the Baltic sea (theoretical turnover rate is between 0.5 – 1 month) (Sonesten *et al.*, 2013). Västeråsfjärden, Blacken and Granfjärden form together the second biggest basin in terms of volume and have a theoretical water turnover rate of roughly 7 months. The biggest basin is represented by Svinnegarnsviken, Ulvhällsfjärden, Prästfjärden and S. Björkfjärden and is characteristic for the longest residence time with 1.8 years. Ekoln and Skarven form the most northern basin with a residence time of 1.2 years, which leaves the last basin Görväln with a residence time of roughly 5 months (Wallin *et al.*, 2000).

There are two main flow directions of the water in Mälaren: one coming from the west moving to the east and the other coming from the north and continuing to the south. The ultimate mixing of those masses occurs at Görväln (Wallin *et al.*, 2000).

The sampling sites Västeråsfjärden and Ekoln are most closely located to big cities and are therefore subject to rather direct pollution. In contrast, Görväln, Galten and Skarven are rather remote areas. The water for the drinking water plant is withdrawn at Görväln, which is approximately 50 km away from Ekoln.

Only two sampling months, namely September ’17 and April ’18, covered all 11 different sampling locations that were part of the study, the spatial distribution of OMPs in the entirety of Mälaren was addressed in only these two months. In general, differences between locations were shown in different concentration levels and different absolute numbers of OMPs that were detected of the total 50 analyzed OMPs at a specific location.

Västeråsfjärden is the sampling location where the highest sum concentration and most of the OMPs were detected, followed by Ekoln and Svinnegarnsviken (see table 2). Densely populated areas usually have greater adverse impacts to surrounding water bodies due to an elevated usage of pharmaceuticals/chemicals (Luo *et al.*, 2014). This, together with the fact that Ekoln and Västeråsfjärden are affected by incoming rivers carrying WWTP effluent water, can explain the findings.

Table 2. *Differences of sampling locations regarding sum of concentrations and the absolute number of OMPs detected above LOQ of total 50 OMPs. All values constitute average values from the two sampling months September '17 and April '18.*

Location	Sum OMP (ng/L) and standard deviation	Absolute number of OMPs detected > LOQ (n=50)
Västeråsfjärden	234 (±27)	33
Ekoln	161 (±66)	30
Svinnegarnsviken	141 (±14)	28
Skarven	134 (±4.8)	24
Ulvhällsfjärden	90 (±4.7)	21
Blacken	83 (±3.1)	25
Galten	79 (±8.0)	23
Görväln	79 (±8.3)	21
Granfjärden	76 (±3.5)	22
Prästfjärden	53 (±10)	15
S. Björkfjärden	48 (±8.1)	18

S. Björkfjärden and Prästfjärden are at the bottom of the list (see table 2), showing that these are the location with the lowest sum concentrations and the least number of OMPs being detected. The latter is situated most centrally in the lake basin so that effects of typical point sources are negligible. Similar holds true for S. Björkfjärden.

It needs to be stressed out that these observations ignore seasonal trends and compound specific behaviors. The compositions of OMPs are very different for each location. Furthermore, for this interpretation only two sampling events for each location were included. Further sampling is needed. However, when looking at the five sampling locations which were continuously sampled (Västeråsfjärden, Ekoln, Skarven, Gärväln, Galten) for the entire sampling period, the same trend could be observed with Västeråsfjärden and Ekoln being the most polluted sites.

With Ekoln being the northernmost part of Lake Mälaren, it can be expected that the OMP concentration is diluted while continuing more south. Indeed, this trend can be observed: sum OMP concentrations decreased by a factor of 0.83 at Skarven

and by a factor of 0.49 at Görväln compared to Ekoln. These numbers merely indicate the trend of dilution; they are not universally valid and don't allow derivations for separate OMP observations or different sampling months.

Furthermore, water mass movement and mixing activities seem to affect the concentrations at sampling locations as well. Lamotrigine and carbamazepine are two highly correlating compounds (see paragraph 3.3). In Ekoln and Västeråsfjärden a clear linear relationship between those two compounds can be observed (see figure A1 in the appendix). This pattern is still shown for Skarven, however, not anymore for Görväln. The mixing of the north-south and west-east stream hamper the original observed prevailing pattern of linearity. The bigger the distance from discharging point sources, the more difficult to observe these patterns and trends since the effect of water chemistry, water movement and natural attenuation mechanisms gets stronger and becomes very complex.

3.2.3 Seasonal variations

Samples were collected in eight different months (February, April, May, July, August, September and November in 2017 and April in 2018). The seasons were classified based on water temperature (figure 6).

Unfortunately, water temperature data for November was missing. Since there was a sharp temperature drop compared to September – first snow events occurred

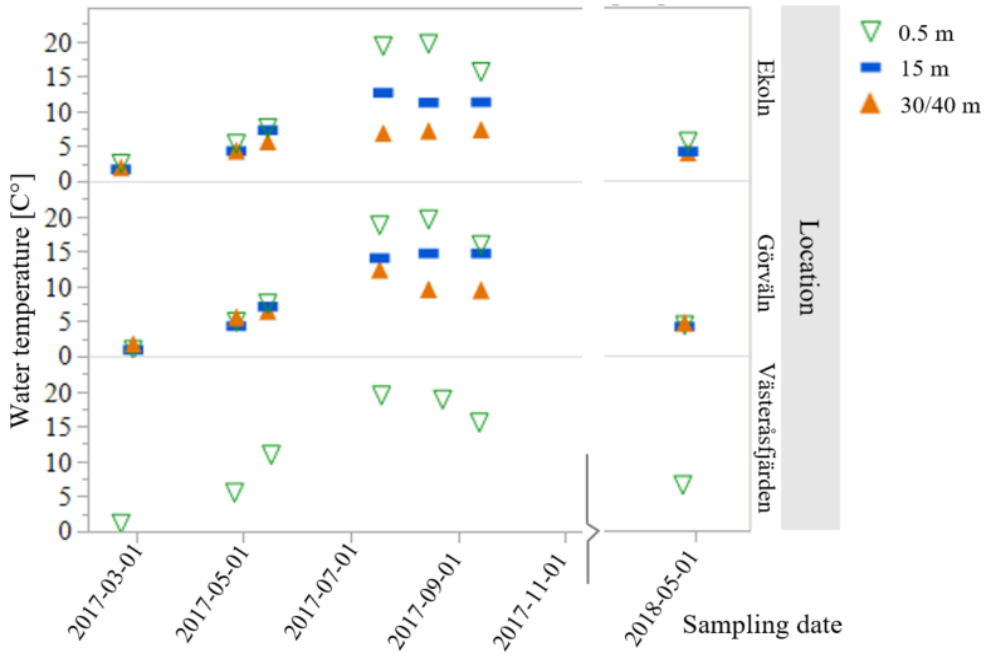

Figure 6. Vertical distribution of water temperature for different locations throughout the sampling period

as shown in the picture (figure 1) from the sampling day – the November sampling is classified as late-autumn/winter event. Ultimately, there are three periods represented: late autumn-winter (November, February), spring (April 2x, May) and summer-early autumn (July, August and September). For convenience only, these periods will be simply addressed as winter, spring and summer.

Differences between the seasons are apparent by, amongst others, concentrations and detection frequencies of a sepcific OMP during a specific season. The latter is termed here as seasonal detection frequency. When a seasonal detection frequency of an OMP is higher than the total detection frequency of that OMP throughout the entire sampling period, it implies that the compound was found more frequently in that very season than in the other seasons. Both approaches to assess seasonality are incorporated in the figures presented on the next pages, showing for winter, spring and summer the top 20 OMPs with the highest detected concentrations (figure 7, 8 and 9). By comparing those three seasonal top 20 highest compound figures, it is recognizable that there are 14 reoccurring compounds: bicalutamide, caffeine, carbamazepine, cetirizine, lamotrigine, lidocaine, losartan, metoprolol, sulisobenzone,

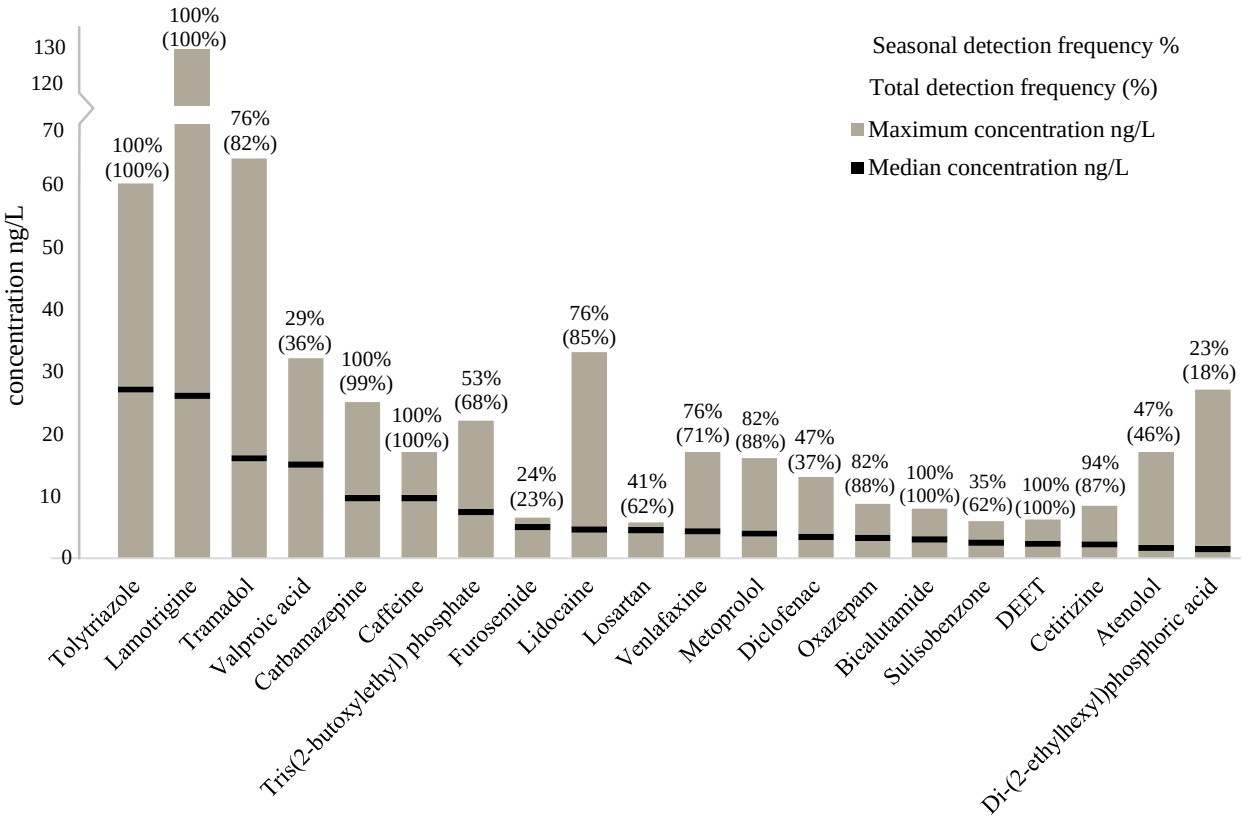

Figure 7. Top 20 highest detected OMPs during **winter** sampling events. The figure illustrates the highest detected concentration and median concentration in winter. Seasonal detection frequency indicates how often a specific compound was detected in the winter months and total frequency of detection is associated to the entire sampling period. (*n*=17)

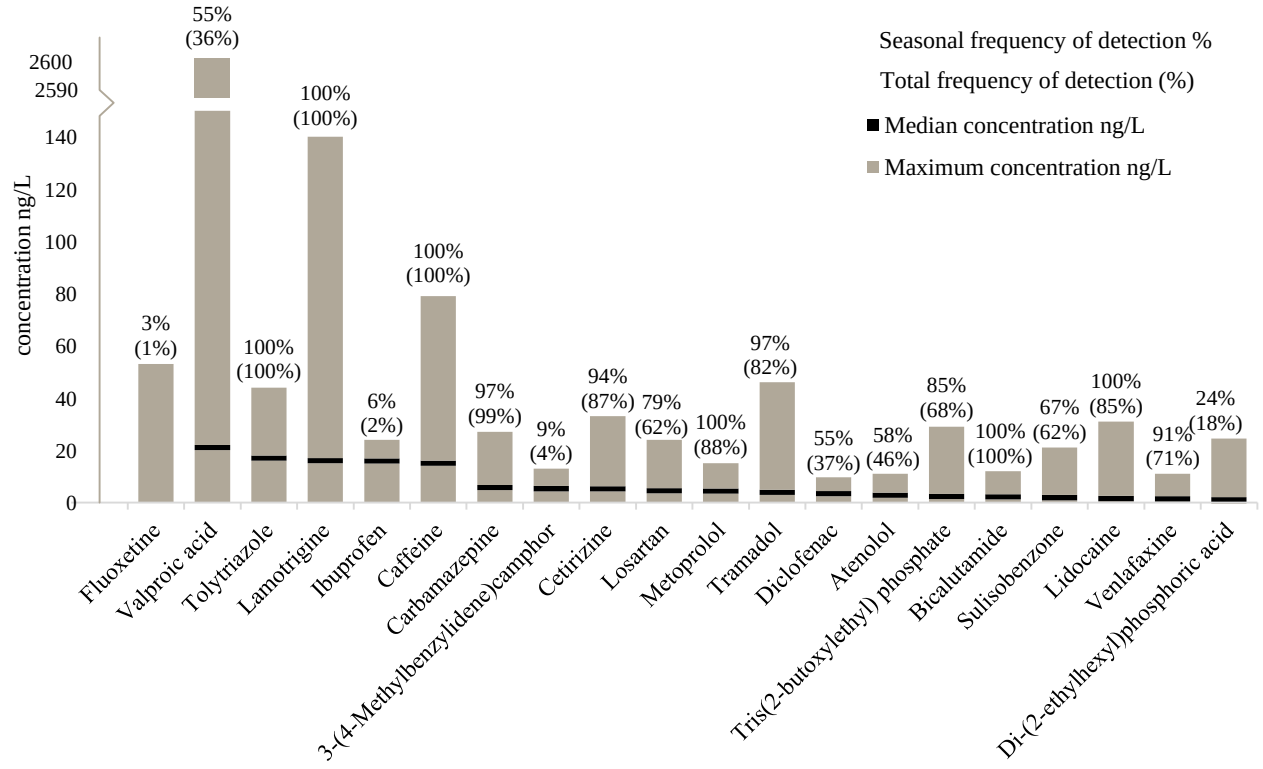

Figure 8. Top 20 highest detected OMPs during **spring** sampling events. The figure illustrates the highest detected concentration and median concentration in spring. Seasonal detection frequency indicates how often a specific compound was detected in the spring months and total frequency of detection is associated to the entire sampling period. (*n*=33)

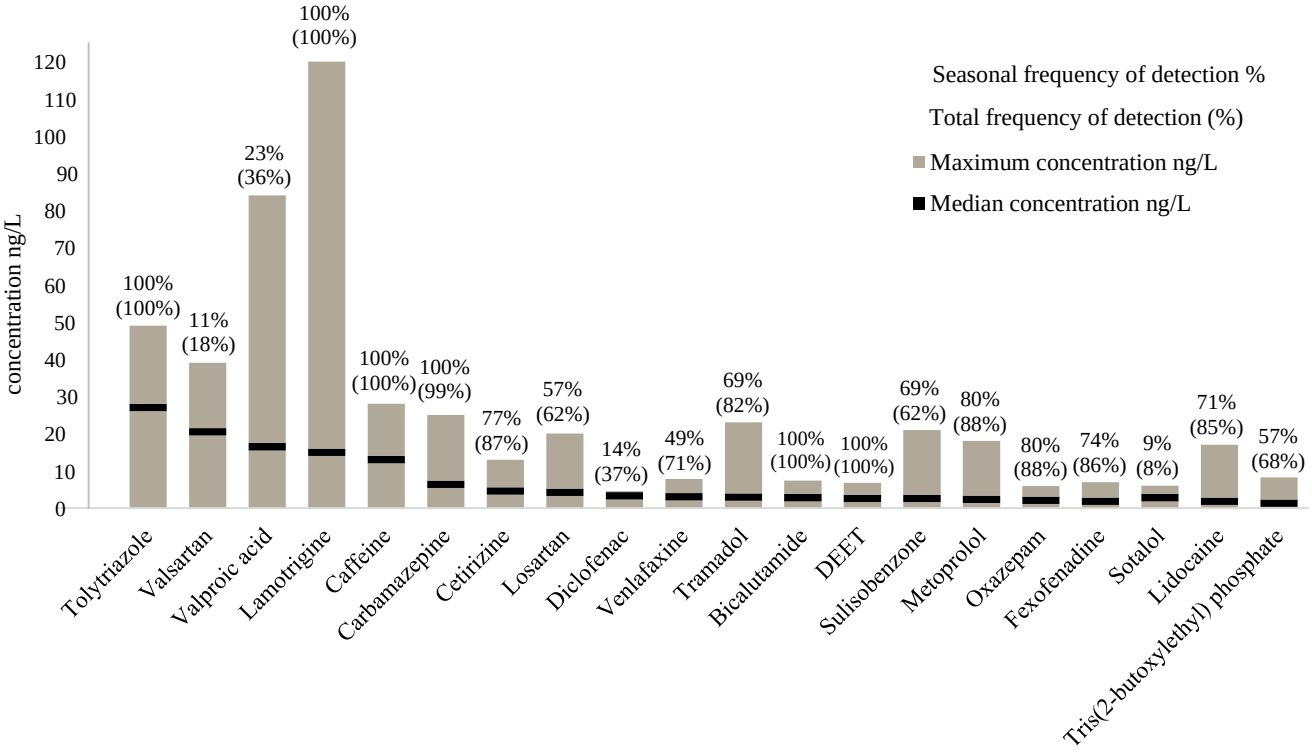

Figure 9. Top 20 highest detected OMPs during **summer** sampling events. The figure illustrates the highest detected concentration and median concentration in summer. Seasonal detection frequency indicates how often a specific compound was detected in the summer months and total frequency of detection is associated to the entire sampling period. (*n*=35)

tolyltriazole, tramadol, tris(2-butoxylethyl)phosphate, valproic acid and venlafaxine These are the compounds that were present with the highest concentration throughout the entire year. This does however not automatically imply that there are no fluctuations within the concentration. The detected concentration is simply just always higher than the rest of the 50 compounds. These compounds should certainly be taken into account for future OMP monitoring programs in Lake Mälaren.

Seven compounds show no considerable annual fluctuations and therefore no seasonal patterns in detection levels: bicalutamide, carbamazepine, DEET, lamotrigine, metoprolol, oxazepam and tolyltriazole. These seven compounds were identified with a quite similar approach as the determination of the performance parameter repeatability by considering the standard deviation of the seasonal average concentration for a respective compound. The specific criteria used to identify these compounds is described in appendix 2.

When looking at the different concentration levels of a compound for the different seasons, it could be observed that usually higher concentrations of an OMP were found in the spring sampling months, followed by the winter season. In addition, a specific compound was in general more frequently detected in spring and winter than in the summer months. A similar trend could be observed when looking at the number of compounds that were detected at a specific season: all of the 50 compounds were found in spring, while a few compounds were not detected at all in winter or summer.

Some considerable differences are shown for single target analytes and pointed out in the following. Nicotine was detected for 51% of the sampling points in the summer time but for 0% and 3% in winter and spring time, respectively. Atorvastatin, an antilipidemic agent, was detected for 36% in the spring samples but only to 6 % in both winter and summer. Pyrimethamine, an antimalarial, was detected in almost a third of the winter samples (24%), and only once during the spring months, which is also the total highest concentration of 0.070 ng/L. Valsartan, an antihypertensive drug, was detected in roughly one third of the spring samples (33%) and only in 11% in the summer ones, and still, the concentrations detected in summer were that high, so that it has the second highest median concentration value of 21 ng/L, as illustrated in figure 9. Methylparaben was detected in 65% of the winter sampling months, whereas spring and summer months account for 30% and 20%, respectively. Lidocaine, a local anesthetic,was detected in all spring samples and 76% during winter sampling events and 71% during summer. Although diclofenac, a NSAID, was found in 55% of the spring samples, the highest concentration of 13 ng/L and also the only time within the top 20 occurred during winter sampling events (detection frequency 47%). Diclofenac was detected in only 14% during summer time. Fluoxetine, an antidepressant, was detected only once in spring

throughout the entire sampling period. In fact, the concentration was even quite high: 53 ng/L.

The highest detected concentration of an OMP for each season together with calculated median concentrations and seasonal detection frequencies can be found in table A6 in the appendix.

For some compounds, reasonable explanations can be found. For instance, the highest concentration found for cetirizine, an antihistamine, was found in spring time with 33 ng/L and the lowest maximum concentration of the three seasons was found in winter time with 8.4 ng/L. Cetirizine is widely used to treat allergy symptoms caused by hay fever so that its peak usage is usually in springtime when plant pollens are most intense (Kosonen & Kronberg, 2009). However, in contrast, for fexofenadine, the second antihistamine analyzed in the course of the present study, the highest concentration was detected in summer time with 6.9 ng/L, followed by spring with the highest detected concentration of 5.3 ng/L and 3.6 ng/L in the winter time (see figure 10). Both compounds are over-the-counter (OTC) drugs, however,

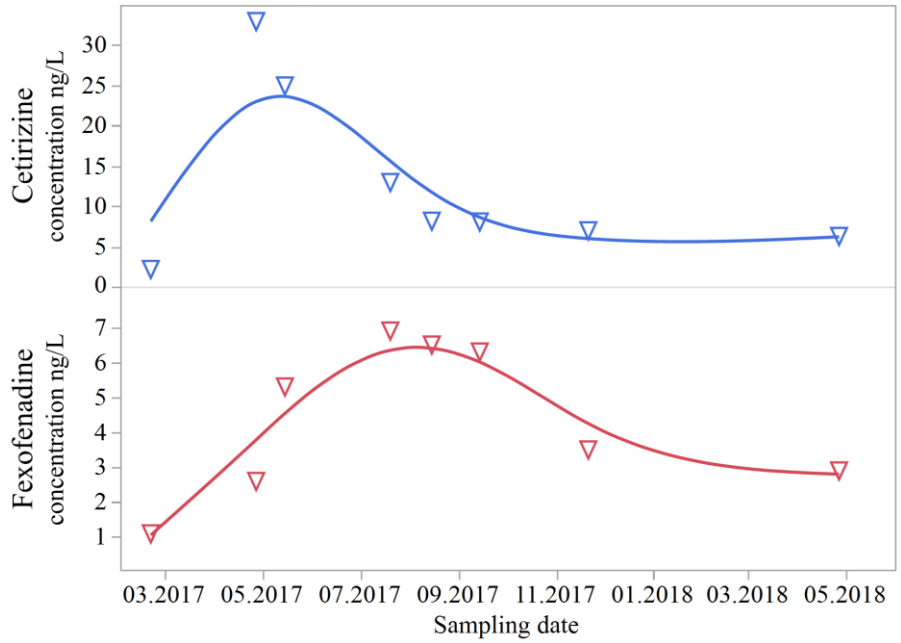

Figure 10. Seasonal trend of detected concentrations for the two antihistamines cetirizine and fexofenadine.

an antihistamine reviewing paper states that cetirizine is contained in 60% of antihistamine medication, whereas fexofenadine comprises merely 4% (Kosonen & Kronberg, 2009). Biodegradation rates are low and it is suggested that cetirizine is excreted to 100% in unmetabolized form and biodegradation is very limited (de

Graaff *et al.*, 2011). Variances of the concentrations between seasons are for cetirizine much higher than for fexofenadine. Therefore, it is assumed that the concentrations obtained for fexofenadine are derived to a higher extent from constant background levels than cetirizine.

Literature agrees with the overall low concentration trend of OMPs in the summer time (Vieno *et al.*, 2005; Daneshvar *et al.*, 2010a; b). Higher solar radiation, no ice covers and higher temperatures are factors responsible for increasing natural attenuation rates. Additionally, in winter lower removal efficiencies from WWTPs were reported in Vieno *et al.*, (2005) due to the temperature dependent biodegradation process, which eventually caused higher OMP discharges into receiving water. However, Fernández *et al.*, (2014), concluded that seasonal removal efficiencies of WWTPs are very much compound dependent. A counteracting factor for this observation is generic increased precipitation during winter and therefore dilution of analytes (Azzouz & Ballesteros, 2013). A closed ice cover will lead to a time lag of this effect, though. Swedish springs are still quite cold, water temperatures as shown in figure 6 are just starting to increase and solar radiation intensity did not reach its peak, yet. Additionally, accumulated concentrations during the winter months might explain the high occurrence patterns of OMPs during the spring time.

April is the only month that was sampled twice, once in 2017 and once in 2018. This allows direct comparison. 7 times a compound was detected at one of the April sampling events while it was not detected in the other year. Excluding those 7 cases, higher maximum concentrations were detected to 55% in April ’17 and 45% in April ’18. A bigger gap between the years can be observed while looking at median concentrations. Here, April ’17 obtained considerable higher median values than April ’18 (84% vs. 16%). Looking at the frequencies of detection a shift in favor of April ’18 is apparent, where compounds were detected more frequently to 81% of the total sampling points. The main reason for lower concentrations in April ’18 is due to the dilution mechanism. Precipitation in summer and winter 16/17 was scarce so that concentrations assumedly accumulated during winter months. In fall ’17 there were, however, some heavy rainfall events, which ultimately led to a sudden dilution effect. Furthermore, winter 17/18 was endowed with an abundance of snow, whose thaw caused further dilution (weather information was derived from open data by the Swedish Meteorological and Hydrological Institute (SMHI)).

It is important to point out that data points for the winter season were limited. It is recommended to continue with further even more frequent sampling events during the winter time to support the above made hypothesis.

3.2.4 Vertical distribution in the water column

Lake Mälaren is unique by its diverse basin characteristics, one varying factor being the depth. As an entirety, Lake Mälaren has a mean depth of 12.7m and 20% of the lake area is shallow (<3m) (Sonesten *et al.*, 2013). In the course of this study, two of the deepest lake basins, Ekoln and Görväln, were taken and analyzed from different levels (0.5 m, 15 m, 30/40 m). Maximum depth for Ekoln is 50 m and for the Görväln basin 63 m (Sonesten *et al.*, 2013). The maximum depth from the specific sampling point at these two basins is not known.

Throughout the season different mixing states at the lake occur. Temperature determines water density, which ultimately affects the stratification of lakes. However, the major driver for heat exchange is wind (Kirillin & Shatwell, 2016). As it is seen in figure 6, there is a clear temperature gradient in the months July, August and September between the different water sampling depths. In contrast, April and May show little variations which imply well mixed water layers. For the month with the coldest water temperatures, February, no large temperature gradient is seen. However, one has to consider, that Swedish lakes are usually still covered by ice at that time, so that external effects, such as solar radiation, precipitation and wind are mostly negligible due to major isolation.

Although samples from different depths were collected from Görväln and Ekoln, only samples from Ekoln were considered for assessing concentration gradients, as the compounds are more frequently detected (see paragraph 3.2.2.) and the dilution effect is in general lower as in Görväln due to a higher direct impact of the incoming river Fyrisån, which carries the effluent from a WWTP.

When looking at the vertical distribution of concentration levels in the water column for some sampling months no considerable fluctuations of OMP concentrations were observed. This was the case for both April sampling events (2017 and 2018) and November. High variations of OMP concentrations occurred in February and May, moderate variations in July and August and low variations in September. This observation does not entirely agree with the measured temperature gradient patterns for the different months (see figure 6) but in general explains well typical stratification processes in surface water.

Clear patterns regarding the vertical distribution of OMP concentrations in the water column were only found for the sampling months February and May. In February, sum OMP concentration of the deepest water column (30m) was by a factor of 1.9 and about 1.8 times higher than the sum OMP concentration of the sample depth 0.5 m and 15 m, respectively (ΣOMP concentration in ng/L: 231 (0.5 m); 249 (15 m); 441 (30 m)). In May, the highest sum OMP concentration occurred at the 0.5 m water level, which was about 1.5 times and 1.9 times higher than the sum

OMP concentration of the sample depths 15 m and 30 m, respectively (ΣOMP concentration in ng/L: 499 (0.5 m); 269 (15 m); 330 (30 m)). Hence, there is not a steady increasing or decreasing concentration gradient in May as it was the case for February. No clear trends were observed for any of the other sampling months.

The calculated orders of magnitude for the months February and May need to be treated very carefully as these numbers are strongly generalised and don't consider compound specific fluctuations.

In winter time, the water is usually much denser, and in case of ice coverage, water from inflowing streams will sink and not mix with upper levels, as it was observed in Lake Tegel in Germany (Schimmelpfennig *et al.*, 2016). This might be the reason for Lake Mälaren as well. Clearly much higher concentrations were detected in the deepest water level in February. Considering that most fish usually stay in the theoretical warmer bottom level, there might potentially be an increased risk of exposure of fishes by OMPs in the winter.

The major reason that no concentration gradients could be observed for the April months and November are probably the well mixed layers during that time. In warmer months incoming flows tend to stay in the surface water level, which might be the reason for the gradient patterns in May, however it doesn't explain why no clear gradient patterns were observed for the other summer months. August and September seem to be transition months, although water temperature between the depths still vary. This leads to the assumption that temperature gradients are not the only driver for vertical occurrence patterns of OMPs.

No statistical test was conducted, so it is not known if the findings of vertical distribution are significant. However, the results were well comparable to those at Lake Tegel in Germany. Further research regarding environmental fluid dynamics and more frequent sampling events are needed to draw clear conclusions.

3.3 Correlations between OMPs

The numerous OMPs being used and ultimately released into the environment calls for the identification of correlating compounds to facilitate monitoring programs, fate and transport models. Keeping in mind that constantly newly designed chemicals are introduced to the market with no discharge regulation or environmental quality standards being set-up, knowledge about correlations would allow to respond more quickly and address these substances more effectively. However, this is easier said than done. Simply having two OMPs belonging to the same therapeutic group or having similar physical-chemical properties, for instance, doesn't automatically imply similar behavior.

A principle component analysis (PCA) was performed in the present study to find some relationships between the analyzed compounds. PCA is a useful tool that aims to find underlying/latent variables which would otherwise be very difficult to see. The considered values for PCA form independent linear clusters that cover the variance of the data the best. These combinations are summed up in so-called principle components. The first and second principle component (PC) are the ones explaining the data the best.

To reduce the complexity of the study, sample points from different depths beside surface water (0.5m) were excluded and only compounds with a frequency of detection (>50%) were chosen for the PCA.

The first two PCs account for 70% of the variation in the data, broken down in 55% for PC1 and 15% for PC2. To describe 85% of the data four PC's are needed. The loading plot (figure 11 B) illustrates the correlations between the original variables and the first two PCs. The figure shows that all variables correlate positively

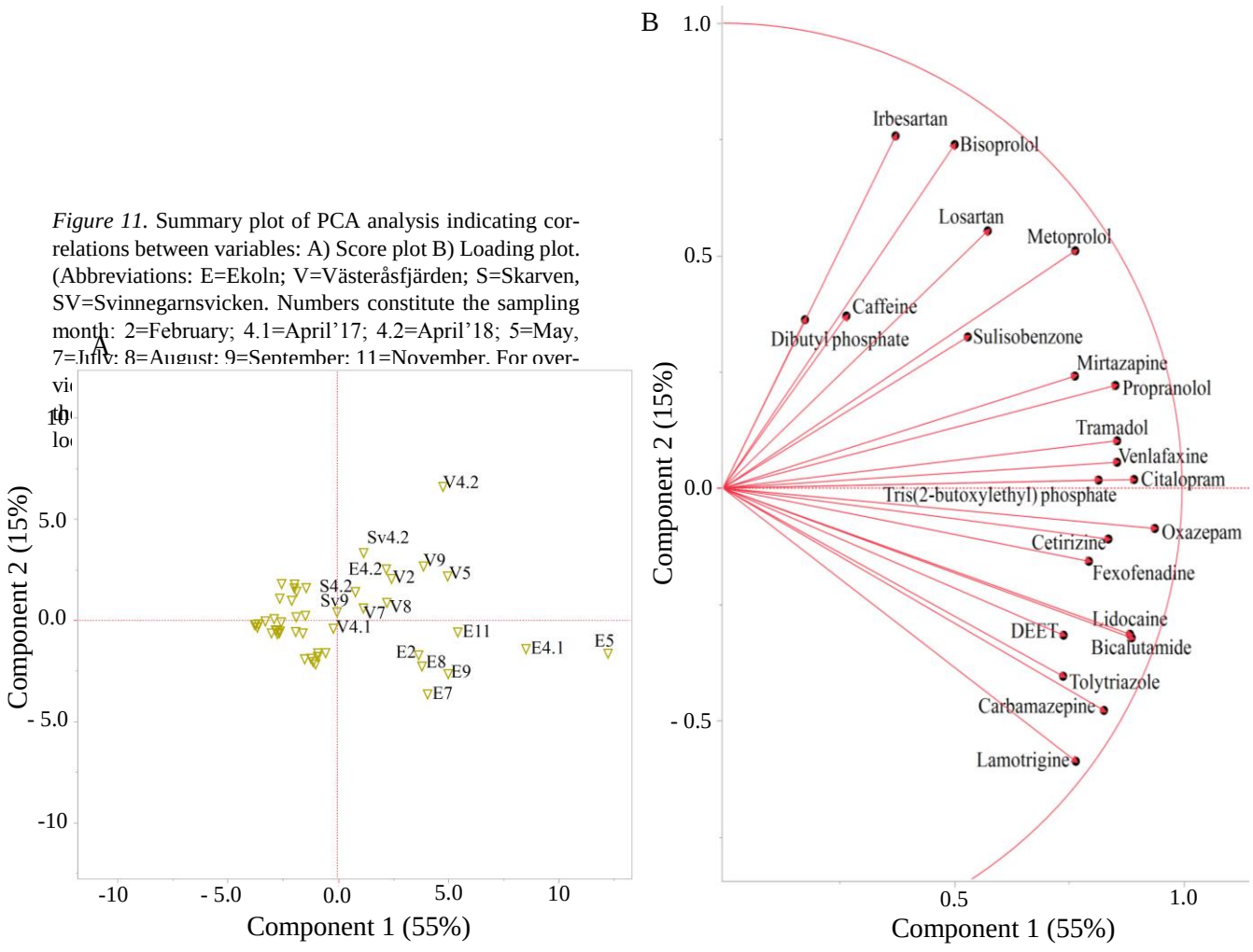

Figure 11. Summary plot of PCA analysis indicating correlations between variables: A) Score plot B) Loading plot. (Abbreviations: E=Ekoln; V=Västeråsfjärden; S=Skarven, SV=Svinnegarnsvicken. Numbers constitute the sampling month: 2=February; 4.1=April'17; 4.2=April'18; 5=May, 7=July; 8=August; 9=September; 11=November. For over-

to the first PC as they are directed to the right within the PC1 dimension (x-axis). The distribution within the PC2 dimension is more spread out, showing positive and negative correlations. The strong positive correlation of the OMPs with PC1 is driven by the samples from Ekoln and Västeråsfjärden as shown in the score plot.

Some of the compounds previously identified to occur to consistent levels during the year are located closely together (carbamazepine, lamotrigine, tolyltriazole, DEET and bicalutamide). The original established criteria (Appendix 2) to assort these OMPs was just not met by fexofenadine and lidocaine; the two compounds positioned directly next to the others. This arises the question at which point a compound can be classified as consistent and what are the specific criteria to do so. To my current knowledge, no valid official criteria do exist. The same applies to the evaluation of seasonality.

So what are possible underlying variable for these correlation patterns? Certainly, the persistency and removal efficiency of the OMPs relating thereto, play an essential role. For OMPs to occur in such a big water compartments as Lake Mälaren, high persistence to removal mechanism is basically a prerequisite in the first place. Provided, that the effluent of the WWTP is the primary pathway of OMPs to enter the aquatic environment. Caffeine is a compound which is generally removed well in WWTPs, which puts it somehow in an oppositional position to, for instance, carbamazepine. No acceptable correlation was found for caffeine. The possibility that contamination might be an issue cannot be excluded.

In general, adjacent compounds indicate a correlation between those very compounds. However, one cannot simply jump to conclusions, as multiple interactions between the variables will cause shifts. Therefore, partial least square (PLS) analysis was performed to explore correlations between two compounds. In table 3 only the highest found significant correlations between two compounds are presented.

Strong correlations are shown between the same group of consistent occurring compounds, with lamotrigine and carbamazepine being able to explain 91% of the variation of the other. Antiepileptics, beta blockers, antihypertensives and antidepressants seem to correlate best with those compounds from the same therapeutic group. However, there are some crossovers. For instance, even though cetirizine and fexofenadine do significantly correlate with each other (41%), another compound seem to explain the respective variation even better. Metoprolol the compound which was also assorted to that very group, does not correlate with any of those compounds significantly, which is also shown in the loading plot. In contrast, tolyltriazole an industrial compound does very well correlate with carbamazepine, lamotrigine, oxazepam and DEET. Tramadol and tris(2-butoxyethyl)phosphate, two seemingly complete different compounds (an analgesic and flame retardant), are able to explain 81% of each other's variation. This is very surprising. No pKa value for the flame retardant was found, the chemical structures are very different and the

K_{ow} value is 3.01 for tramadol and 3.75 tris(2-butoxyethyl)phosphate, indicating moderate and high hydrophobicity; so no apparent link between the compounds can be found. Further investigation is needed to understand this correlation.

Table 3. *Correlations between compounds according to PLS analysis by statistical program JMP. Only the best possible statistical significant correlation for each OMP is presented. Reciprocal best correlations between OMPs are marked with **

Correlating OMPs		Variation explained in percent
Lamotrigine	Carbamazepine	91% (*)
Venlafaxine	Mirtazepine	83% (*)
Bicalutamide	Carbamazepine	82%
Tramadol	Tris(2-butoxyethyl)phosphate	81% (*)
Tolyltriazole	Carbamazepine	80%
Citalopram	Venlafaxine	80%
Lidocaine	Bicalutamide	78%
Oxazepam	Carbamazepine	74%
Lorsartan	Sulisobenzone	74% (*)
Fexofenadine	Carbamazepine	67%
Metoprolol	Propranolol	67% (*)
DEET	Carbamazepine	66%
Cetirizine	Oxazepam	65%
Bisoprolol	Irbesatan	46% (*)
Caffeine	Losartan	20%
Dibutyl phosphate	none	-

The two industrial chemicals tolyltriazole and tris(2-butoxyethyl)phosphate are not even nearly as well documented as carbamazepine and other ubiquitous termed OMPs regarding their occurrence, toxicity and degradation potential. Having such strong correlation patterns with carbamazepine and tramadol, respectively, might already give some better insight into the fate and transport of these compounds. The fact, that both industrial compounds were successfully quantified in the multi-residue method of this study is a novelty. Continuing consideration and investigation in future analysis is recommended.

It needs to be pointed out, that such observed correlations have to be treated very carefully, though. Too much is still not known about the behavior of OMPs to elucidate every angle and every variable of seemingly correlating compounds. Performing this analysis in an entirely different matrix, such as wastewater, sediments or drinking water will probably lead to a different outcome. Different underlying variables will account for different principle components.

3.4 Correlations between OMPs and water chemistry of Lake Mälaren

Due to the complexity of environmental samples, several water chemistry parameters were incorporated into the PCA in an attempt to find a better principle component. This included data about Chlorophyll-a content, water temperature, total phosphor, silicium content, oxygen content, absorbents, turbidity and visible depth. The data was provided by the Department of Aquatic Science and Assessment, Geochemistry Section, SLU which was obtained as part of routine monitoring programs at Mälaren.

Contrary to the assumption that this approach will allow explaining the behavior of the analyzed OMPs to a better degree, no correlations were observed. In fact, the best component combination explained even much less. No data for this outcome is presented here.

4 Conclusion and outlook

The study aimed to comprehensively investigate the current OMPs pollution status of Lake Mälaren during a one year study. The profound data interpretation considered several aspects such as spatial and vertical distribution, seasonal variations and correlations between OMPs. It was shown that the occurrence of OMPs in surface water are highly dependent on numerous factors; proximity to point sources, dilution factor, lake basin characteristics, to name but a few. This study contributed therefore to a better understanding of fate and transport of OMPs in large water bodies. Several aspects of this study support findings of ongoing research projects and should provide new impetus for further research. OMP exposure hotspots in Lake Mälaren are clearly located where WWTP effluents are mixed with the receiving water body. In total 122 compounds were evaluated in the present study, consisting of 80 pharmaceuticals, 19 industrial chemicals, 7 personal care products, 3 pesticides, 3 vitamins, 3 parabens, 2 artificial sweeteners, 2 stimulants, 1 contrast medium, 1 opioid and 1 isoflavone.

Although dilution and natural attenuation effects are considerably degrading concentrations of OMPs once they are introduced to the aquatic environment, this study was still able to detect 50 OMPs above LOQs by the means of a simple, reliable, fast and sensitive method using UPLC-MS/MS and SPE. Concentrations were below acute toxicity levels. However, the regularity of detections of most target analytes during the one year sampling period poses the question of long-term toxicity risks for aquatic organisms, where adverse effects are insidious and irreversible once they are manifested. Besides that, combined effects when OMPs are interacting with each, commonly termed as synergistic or cocktail effect, are additionally important to consider but very difficult to assess. The presented data is no exemption in this regard showing varied composition profiles of OMPs for the sampling points in terms of concentration levels and simultaneously detected compounds.

Regular follow-up sampling events, especially with more frequent winter sampling are needed for an improved view of occurrence and seasonality of OMPs in

Lake Mälaren and in order to support the findings of this study. Furthermore, ongoing optimizations of analytical methods to incorporate additional OMPs such as industrial chemicals with good performance parameters are needed to facilitate further investigations. Although no specific patterns for detected concentrations regarding selected water chemistry data were found, flow models, mixing models or extensive studies addressing the relationship of OMP occurrence with lake-specific mechanisms (e.g. wind-driven circulation, stratification, removal efficiencies, natural attenuation mechanisms, residence times of lake basins etc.) will help to find patterns and to draw significant conclusions. There is much potential for future research and this study hopes to provide a basis to do so.

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Appendix 1

Table A1. *Average, maximum and minimum LOQ's from positive compounds*

OMP	Average	MAX	MIN
Atenolol	0.089	0.29	0.061
Sotalol	0.15	0.56	0.11
Nicotine	0.062	0.22	0.041
Metoprolol	0.083	0.27	0.046
Atorvastatin	0.19	0.4	0.1
Carbamazepine	0.032	0.066	0.02
Cetirizine	0.035	0.07	0.028
Citalopram	0.01	0.02	0.0076
Mirtazapine	0.025	0.051	0.019
Oxazepam	0.033	0.067	0.025
Pyrimethamine	0.018	0.036	0.014
Lamotrigine	0.29	0.58	0.23
DEET	0.093	0.2	0.076
Bezafibrate	0.28	0.45	0.23
Sulisobenzone	0.3	0.49	0.25
Dibutyl phosphate	0.22	0.36	0.18
Tolyltriazole	0.98	1.6	0.81
Ifosfamide	0.075	0.12	0.062
Bicalutamide	0.023	0.048	0.012
Bisoprolol	0.012	0.024	0.0066
Clozapine	0.022	0.041	0.017
Diazepam	0.023	0.044	0.018
Fexofenadine	0.02	0.038	0.016
Caffeine	0.8	1.6	0.65
Tramadol	0.07	0.12	0.05
Valsartan	0.69	1.2	0.5
Codeine	0.081	0.14	0.059
Oxycodone	0.085	0.15	0.061
2,2'-Dimorpholinyldiethyl-ether	0.069	0.12	0.05
Diclofenac	2	3	1.6
Ethylparaben	0.19	0.3	0.11
Propylparaben	0.062	0.09	0.046
Methylparaben	0.31	0.47	0.23
Furosemide	1.2	1.8	0.95
Diltiazem	0.065	0.15	0.029

Ibuprofen	5	7.4	3.9
Irbesartan	0.011	0.024	0.0089
Propranolol	0.025	0.061	0.012
Lidocaine	0.034	0.13	0.018
Losartan	0.16	0.29	0.13
Omeprazole	0.029	0.054	0.018
Acetaminophen	5	10	3.4
Amitriptyline	0.067	1.2	0.023
Valproic acid	3.5	5.1	0.79
Venlafaxine	0.25	0.54	0.18
Daidzein	0.49	1	0.37
Di-(2-ethylhexyl)phosphoric acid	0.12	0.24	0.1
Tris(2-butoxylethyl) phosphate	0.13	0.27	0.11
3-(4-Methylbenzylidene)camphor	3.3	6.8	2.1
Fluoxetine	1.4	4	0.77

Table A2. *Matrix effect of positive compounds. Negative values imply suppression, positive values enhancement.*

OMP	Görväln	Ekoln	Skarven	Galten	Västeråsfj.	Görväln 2018
Atenolol	-14%	0%	5%	-2%	-63%	0%
Sotalol	-6%	-12%	0%	8%	12%	5%
Nicotine	31%	40%	50%	47%	29%	39%
Metoprolol	22%	30%	40%	40%	26%	32%
Atorvastatin	-13%	-12%	-8%	-6%	7%	-1%
Carbamazepine	-45%	-48%	-48%	-39%	-58%	-31%
Cetirizine	-60%	-63%	-68%	-62%	-73%	-13%
Citalopram	2%	2%	1%	4%	2%	-6%
Mirtazapine	-4%	-3%	-3%	0%	-8%	-5%
Oxazepam	-26%	-27%	-30%	-23%	-25%	-16%
Pyrimethamine	-21%	-22%	-22%	-20%	-14%	-18%
Lamotrigine	-107%	-120%	-122%	-101%	-161%	-119%
DEET	-11%	-7%	-12%	-12%	-7%	-18%
Bezafibrate	-13%	-11%	-12%	-9%	-17%	10%
Sulisobenzone	31%	27%	34%	31%	25%	34%
Dibutyl phosphate	-3%	-5%	2%	-4%	-7%	-3%
Tolyltriazole	-4%	-12%	2%	-14%	-2%	1%
Ifosfamide	-18%	-21%	-18%	-15%	-15%	-5%
Bicalutamide	-2%	0%	2%	5%	38%	13%
Bisoprolol	5%	7%	7%	10%	34%	0%
Clozapine	0%	-1%	-2%	5%	21%	-41%

Diazepam	-19%	-15%	-18%	-13%	-8%	-11%
Fexofenadine	-2%	-2%	-3%	1%	20%	11%
Caffeine	-7%	-11%	-3%	-5%	4%	4%
Tramadol	-33%	-30%	-26%	-28%	-3%	-98%
Valsartan	-19%	-17%	-19%	-8%	1%	-25%
Codeine	-24%	-16%	-15%	-15%	-11%	8%
Oxycodone	-30%	-21%	-23%	-16%	2%	-3%
2,2'-Dimorpholinyldi-ethyl-ether	-43%	-40%	-43%	-42%	-10%	-19%
Diclofenac	-30%	-39%	-22%	-27%	-28%	13%
Ethylparaben	-52%	-52%	-45%	-47%	-35%	-16%
Propylparaben	-11%	-13%	-10%	-10%	-7%	-19%
Methylparaben	-52%	-54%	-53%	-63%	-60%	-54%
Furosemide	-10%	-12%	-14%	-11%	-9%	4%
Diltiazem	-22%	-20%	-25%	-16%	-11%	-12%
Ibuprofen	-22%	-22%	-30%	-21%	-31%	-31%
Irbesartan	-14%	-16%	-14%	-23%	5%	0%
Propranolol	22%	21%	29%	18%	45%	39%
Lidocaine	-23%	-117%	-25%	-22%	-18%	-22%
Losartan	-9%	-7%	-7%	-7%	-2%	-12%
Omeprazole	27%	29%	29%	30%	47%	19%
Acetaminophen	48%	52%	51%	54%	57%	33%
Amitriptyline	-6%	-5%	-3%	-9%	20%	0%
Valproic acid	-3%	3%	14%	11%	-2%	-38%
Venlafaxine	-20%	437%	-21%	-41%	-17%	-8%
Daidzein	-270%	-276%	-283%	-281%	-349%	-170%
Di-(2-ethylhexyl)phos-phoric acid	-280%	-251%	-246%	-263%	-275%	21%
Tris(2-butoxylethyl) phosphate	-4%	-2%	3%	-5%	6%	14%
3-(4-Methylbenzyli-dene)camphor	16%	14%	15%	10%	15%	-7%
Fluoxetine	-3%	1%	1%	2%	6%	9%

Table A3. *Relative recovery rate and linearity (R^2) of compounds with good relative recovery (60%-145%) that were not detected above LOQ or excluded.*

OMP	Category	Type	Relative Recovery	R^2
Albuterol	Pharmaceutical	Beta blocker	73%	0.9732
Terbutaline	Pharmaceutical	Beta blocker	94%	0.9919
BAM	Pesticide	Pesticide	109%	1

Chlorzoxazone	Pharmaceutical	Muscle Relaxant	125%	0.9996
Climbazole	Pharmaceutical	Antifungal	94%	0.9844
Clindamycin	Pharmaceutical	Antibiotic	94%	0.9989
Iopromide	Contrast medium	Contrast medium	104%	0.9972
Memantine	Pharmaceutical	Alzheimer	73%	0.9965
Aceclofenac	Pharmaceutical	NSAID	88%	0.9967
Meclofenamic acid	Pharmaceutical	NSAID	109%	0.9978
Laurilsulfate	Industrial chemical		83%	0.9988
Thiabendazole	Pesticide		78%	0.9848
Methotrexate	Pharmaceutical	Anticancer	99%	0.9958
4-Chloro-3-methylphenol	Pharmaceutical	Antiseptic	83%	0.994
Ramipril	Pharmaceutical	Antihypertensive	104%	0.999
Metronidazole	Pharmaceutical	Antibiotic	99%	0.9832
Metronidazole-OH	Pharmaceutical	Antibiotic, metabolite	94%	0.9963
Sulfamethoxazole	Pharmaceutical	Antibiotic	114%	0.9804
Trimethoprim	Pharmaceutical	Antibiotic	88%	0.9854
Sertraline	Pharmaceutical	Antidepressant	88%	0.9991
Carazolol	Pharmaceutical	Beta blocker	68%	0.9989
Tributyl citrate acetate	Industrial chemical		62%	1

Table A4. *Precise sampling information showing labels, location, depth and sampling date*

Location	Depth [m]	Date
Görväln	0.5	2.27.2017
Görväln	15	2.27.2017
Görväln	40	2.27.2017
Ekoln	0.5	2.20.2017
Ekoln	15	2.20.2017
Ekoln	30	2.20.2017
Skarven	0.5	2.22.2017
Galten	0.5	2.14.2017
Väster-åsfjärden	0.5	2.20.2017
Görväln	0.5	4.27.2017
Görväln	15	4.27.2017
Görväln	40	4.27.2017
Ekoln	0.5	4.27.2017
Ekoln	15	4.27.2017
Ekoln	30	4.27.2017
Skarven	0.5	4.27.2017
Väster-åsfjärden	0.5	4.26.2017
Galten	0.5	4.26.2017
Görväln	0.5	5.15.2017
Görväln	15	5.15.2017
Görväln	40	5.15.2017
Ekoln	0.5	5.15.2017
Ekoln	15	5.15.2017
Ekoln	30	5.15.2017
Skarven	0.5	5.15.2017
Galten	0.5	5.18.2017
Väster-åsfjärden	0.5	5.17.2017
Görväln	0.5	7.18.2017
Görväln	15	7.18.2017
Görväln	40	7.18.2017

Location	Depth [m]	Date
Ekoln	0.5	7.20.2017
Ekoln	15	7.20.2017
Ekoln	30	7.20.2017
Skarven	0.5	7.20.2017
Galten	0.5	7.19.2017
Väster-åsfjärden	0.5	7.19.2017
Görväln	0.5	8.15.2017
Görväln	15	8.15.2017
Görväln	40	8.15.2017
Ekoln	0.5	8.15.2017
Ekoln	15	8.15.2017
Ekoln	30	8.15.2017
Skarven	0.5	8.15.2017
Galten	0.5	8.23.2017
Västeråsfj,	0.5	8.23.2017
Görväln	0.5	9.14.2017
Görväln	15	9.14.2017
Görväln	40	9.14.2017
Ekoln	0.5	9.14.2017
Ekoln	15	9.14.2017
Ekoln	30	9.14.2017
Prästfjärden	0.5	9.13.2017
Prästfjärden	15	9.13.2017
Prästfjärden	40	9.13.2017
Skarven	0.5	9.14.2017
Svinne-garnsviken	0.5	9.13.2017
Södra Björk-fjärden	0.5	9.12.2017
Ulvhällsfjärden	0.5	9.12.2017

Location	Depth [m]	Date
Galten	0.5	9.13.2017
Blacken	0.5	9.13.2017
Väster-åsfjärden	0.5	9.13.2017
Granfj. Djurgårds U.	0.5	9.12.2017
Görväln	0.5	11.21.2017
Görväln	15	11.21.2017
Görväln	40	11.21.2017
Ekoln	0.5	11.21.2017
Ekoln	15	11.21.2017
Ekoln	30	11.21.2017
Skarven	0.5	11.21.2017
Skarven	0.5	4.25.2018
Görväln	0.5	4.25.2018
Görväln	15	4.25.2018
Görväln	40	4.25.2018
Södra Björk-fjärden	0.5	4.24.2018
Prästfjärden	0.5	4.24.2018
Ekoln	0.5	4.27.2018
Ekoln	15	4.27.2018
Ekoln	30	4.27.2018
Svinne-garnsviken	0.5	4.24.2018
Ulvhällsfjärden	0.5	4.24.2018
Granfj. Djurgårds U.	0.5	4.24.2018
Galten	0.5	4.24.2018
Blacken	0.5	4.24.2018
Väster-åsfjärden	0.5	4.24.2018

Table A5. *Additional information about compounds showing CAS-number, molecular formula, charge and hydrophobicity. Charge and hydrophobicity were derived from pKa and K_{ow}, respectively. Charge: 0=neutral, 1=anionic, 2=cationic)*

OMP	CAS number	Molecular formula	Charge	Hydrophobicity
Atenolol	29122-68-7	C14H22N2O3	2	low
Sotalol	3930-20-9	C12H20N2O3S	2	low
Nicotine	54-11,5	C10H14N2	1	low
Metoprolol	51384-51-1	C15H25NO3	2	low
Atorvastatin	134523-00-5	C33H35FN2O5	1	high

Carbamazepine	298-46-4	C15H12N2O	1	moderate
Cetirizine	83881-51-0	C21H25ClN2O3	1	low
Citalopram	59729-33-8	C20H21FN2O	2	high
Mirtazapine	85650-52-8	C17H19N3	2	moderate
Oxazepam	604-75-1	C15H11ClN2O2	1	moderate
Pyrimethamine	58-14-0	C12H13ClN4	2	moderate
Lamotrigine	84057-84-1	C9H7Cl2N5	1	low
DEET	134-62-3	C12H17NO	-	moderate
Bezafibrate	41859-67-0	C19H20ClNO4	1	high
Sulisobenzone	4065-45-6	C14H12O6S	1	low
Dibutyl phosphate	107-66-4	C8H19PO4	1	moderate
Tolytriazole	29878-31-7	C7H7N3	2	low
Ifosfamide	3778-73-2	C7H15Cl2N2O2P	0	low
Bicalutamide	90357-06-5	C18H14F4N2O4S	0	moderate
Bisoprolol	104344-23-2	C18H31NO4	2	low
Clozapine	5786-21-0	C18H19ClN4	1	moderate
Diazepam	439-14-5	C16H13ClN2O	1	moderate
Fexofenadine	153439-40-8	C32H39NO4	2	moderate
Caffeine	58-08,02	C8H10N4O2	0	low
Tramadol	27203-92-5	C16H25NO2	2	moderate
Valsartan	137862-53-4	C24H29N5O3	1	high
Codeine	76-57-3	C18H21NO3	2	low
Oxycodone	76-42-6	C18H21NO4	2	low
2,2'-Dimorpholinyldi-ethyl-ether	6425-39-4	C12H24N2O3	-	low
Diclofenac	15307-86-5	C14H11Cl2NO2	1	high
Ethylparaben	120-47-8	C9H10O3	2	moderate
Propylparaben	94-13-3	C10H12O3	2	moderate
Methylparaben	99-76-3	C8H8O3	2	low
Furosemide	54-31-9	C12H11ClN2O5S	1	moderate
Diltiazem	42399-41-7	C22H26N2O4S	2	moderate
Ibuprofen	15687-27-1	C13H18O2	1	high
Irbesartan	138402-11-6	C25H28N6O	1	high
Propranolol	525-66-6	C16H21NO2	2	moderate
Lidocaine	137-58-6	C14H22N2O	2	low
Losartan	114798-26-4	C22H23ClN6O	1	high
Omeprazole	73590-58-6	C17H19N3O3S	1	moderate
Acetaminophen	103-90-2	C8H9NO2	2	low

Amitriptyline	50-48-6	C20H23N	2	high
Valproic acid	99-66-1	C8H16O2	1	moderate
Venlafaxine	93413-69-5	C17H27NO2	2	moderate
Daidzein	486-66-8	C15H10O4	-	moderate
Di-(2-ethylhexyl)phosphoric acid	298-07-7	C16H35O4P	-	high
Tris(2-butoxylethyl) phosphate	78-51-3	C18H39O7P	-	high
3-(4-Methylbenzylidene)camphor		C18H22O	-	high
Fluoxetine	54910-89-3	C17H18F3NO	0	high

*Table A6. Seasonal maximum and median concentrations [ng/L] and seasonal frequency of detection for the positive compounds (the higher value within the seasons is marked in **bold**)*

Season	Winter	Spring	Summer	Winter	Spring	Summer	Winter	Spring	Summer
OMP	Seasonal maximum concentrations [ng/L]			Seasonal median concentrations [ng/L]			Seasonal frequencies of detection		
Atenolol	**17**	11	3.9	1.65	**2.8**	1.45	47%	**58%**	34%
Sotalol	4.3	2.4	**5**	**3.15**	1.64	1.8	**12%**	6%	9%
Nicotine	n.d.	2.3	**2.4**	-	**2.3**	0.545	0%	3%	**51%**
Metoprolol	16	15	**18**	3.95	**4.4**	2.35	82%	**100%**	80%
Atorvastatin	0.4	0.97	**1.3**	0.4	0.24	**0.81**	6%	**36%**	6%
Carbamazepine	25	**27**	25	**9.6**	5.7	6.4	**100%**	97%	100%
Cetirizine	8.4	**33**	13	2.2	**5.2**	4.6	**94%**	**94%**	77%
Citalopram	**5.4**	2.6	1.4	**0.935**	0.49	0.5	59%	**70%**	57%
Mirtazapine	**3**	1.2	0.62	**0.63**	0.3	0.295	53%	**64%**	34%
Oxazepam	**8.7**	8.6	5.9	**3.25**	1.6	2.05	82%	**100%**	80%
Pyrimethamine	0.038	**0.07**	n.d.	0.03	**0.**07	-	**24%**	3%	0%
Lamotrigine	130	**140**	120	**26**	16	15	100%	100%	100%
DEET	6.2	**8.3**	6.8	2.3	1.4	**2.6**	100%	100%	100%
Bezafibrate	0.98	**2**	0.49	**0.725**	0.565	0.36	12%	**36%**	9%
Sulisobenzone	5.9	**21**	21	2.48	1.85	**2.6**	35%	67%	**69%**
Dibutyl phosphate	5.1	**5.8**	1.2	**0.96**	0.715	0.81	**71%**	67%	31%
Tolyltriazole	**60**	44	49	27	17	**27**	100%	100%	100%
Ifosfamide	**0.41**	0.33	0.25	**0.205**	0.13	0.175	24%	**30%**	17%
Bicalutamide	7.9	**12**	7.4	**3**	2.2	2.8	100%	100%	100%
Bisoprolol	0.91	**2.5**	1.3	0.27	**0.39**	0.22	76%	**88%**	66%
Clozapine	**0.37**	0.34	0.044	**0.125**	0.084	0.042	24%	**30%**	6%
Diazepam	**0.11**	0.075	0.08	**0.062**	0.043	0.053	29%	27%	**49%**
Fexofenadine	3.6	5.3	**6.9**	0.785	0.84	**1.85**	82%	**10**0%	74%
Caffeine	17	**79**	28	9.6	**15**	13	100%	100%	100%
Tramadol	**64**	46	23	**16**	3.9	2.95	76%	**97%**	69%
Valsartan	n.d.	6.1	**39**	-	2.4	**20.5**	0%	**33%**	11%
Codeine	n.d.	**1.5**	n.d.	-	**1.05**	-	0%	**24%**	0%
Oxycodone	0.7	**1.1**	0.58	0.2	**0.64**	0.345	18%	18%	**34%**
2,2'-Dimorpholinyldi-ethyl-ether	**2.7**	1.5	1.4	0.32	**0.9**	0.38	**24%**	18%	17%
Diclofenac	**13**	9.6	3.9	**3.4**	3.35	3	47%	**55%**	14%
Ethylparaben	0.86	**8.6**	0.55	0.86	**3.95**	0.55	6%	**18%**	3%
Propylparaben	0.6	**1.2**	0.5	0.175	**0.19**	0.145	**47%**	42%	40%
Methylparaben	2.2	**8.2**	2.6	0.83	**3.05**	1.1	**65%**	30%	20%
Furosemide	**6.5**	6	4.5	**5**	3.25	3.55	24%	**36%**	11%
Diltiazem	0.071	**0.11**	n.d.	**0.071**	0.056	**-**	6%	**21%**	0%

Ibuprofen	n.d.	**24**	n.d.	-	**15.85**	**-**	0%	**6%**	0%
Irbesartan	1	**1.2**	0.85	0.37	**0.43**	0.27	41%	**79%**	54%
Propranolol	**0.46**	0.43	0.42	**0.27**	0.15	0.19	47%	**64%**	43%
Lidocaine	**33**	31	17	**4.6**	1.5	1.8	76%	**100%**	71%
Losartan	5.7	**24**	20	**4.5**	4.5	4.2	41%	**79%**	57%
Omeprazole	**0.13**	0.093	0.046	**0.13**	0.071	0.0455	6%	**9%**	6%
Acetaminophen	n.d.	**4.6**	n.d.	**-**	**4.6**	**-**	0%	**3%**	0%
Amitriptyline	0.18	**0.37**	0.22	**0.18**	0.13	0.093	6%	**24%**	9%
Valproic acid	32	**2600**	84	15	**21**	16.5	29%	**55%**	23%
Venlafaxine	**17**	11	7.8	**4.3**	1.35	3	76%	**91%**	49%
Daidzein	n.d.	**3.4**	2.1	-	**2.05**	1.7	0%	**12%**	9%
Di-(2-ethylhexyl)phos-phoric acid	**27**	24	2.3	**1.455**	0.505	0.415	**24%**	**24%**	11%
Tris(2-butoxylethyl) phosphate	22	**29**	8.2	**7.4**	2.25	1.305	53%	**85%**	57%
3-(4-Methylbenzyli-dene)camphor	n.d.	**13**	n.d.	-	**5.3**	-	0%	**9%**	0%
Fluoxetine	n.d.	**53**	n.d.	-	-	-	0%	**3%**	0%

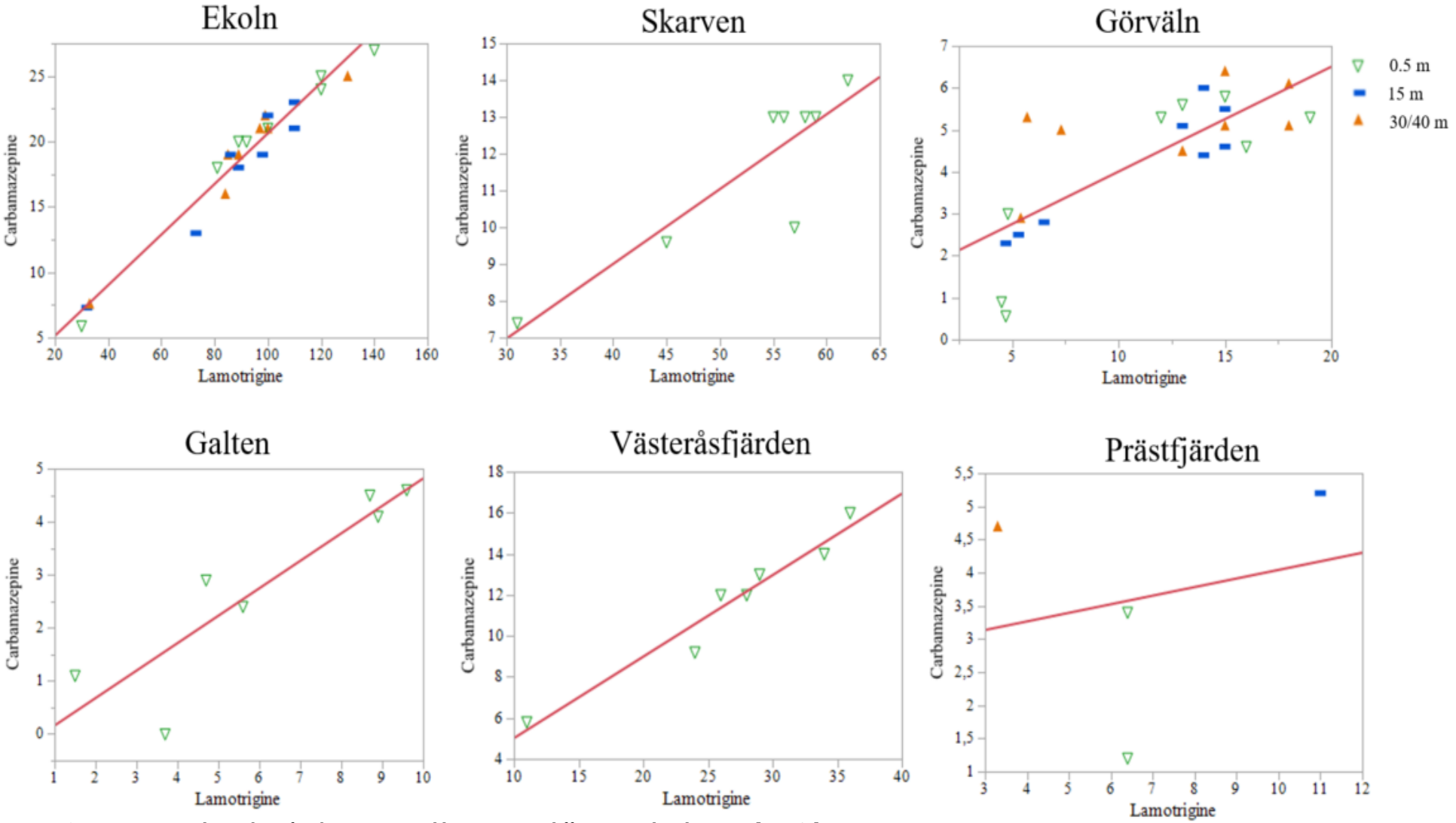

Figure 12. Linear relationship of carbamazepine and lamotrigine at different sampling locations [in ng/L]

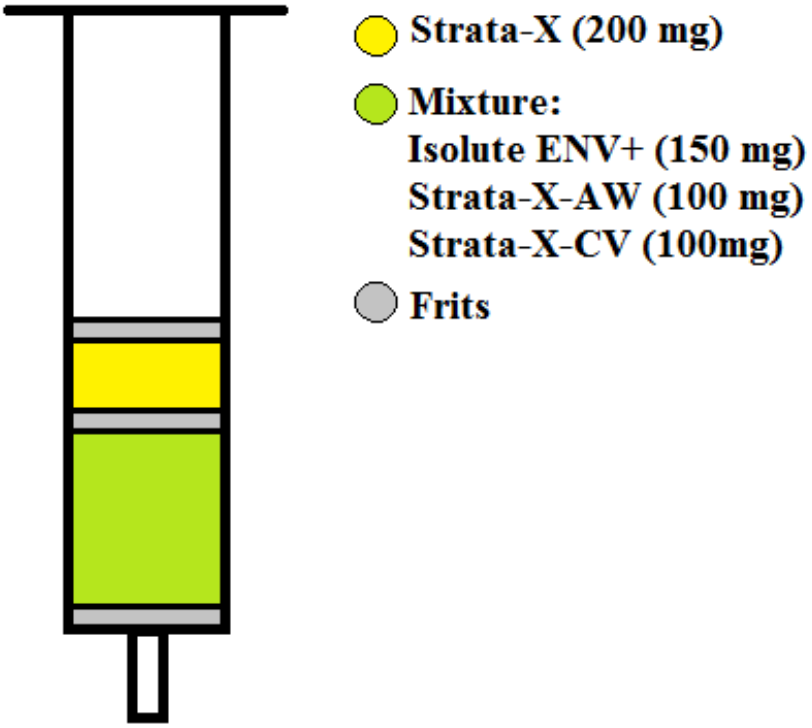

Figure A2. Home-made cartridges for SPE, showing the different composition of the sorbent materials. Developed by Gago-Ferrero et al. (2015b).

Appendix 2

Criteria for the determination of OMPs without major seasonal fluctuations of the detected concentrations

The following equation was used to mathematically identify OMPs without major seasonal fluctuations:

$$\text{OMP fluctuation: } \frac{SD\ (\bar{x}(WinterC);\ \bar{x}(SpringC);\ \bar{x}(SummerC))}{\bar{x}\ (\bar{x}(WinterC);\ \bar{x}(SpringC);\ \bar{x}(SummerC))} \times 100\ < 15\%$$

SD = standard deviation
$\bar{x}$ = mean
C = concentration

The basic idea behind this equation is to identify those compounds where the fluctuations between seasonal average concentrations (for winter, spring and summer) are limited. This approach is similar to the determination of the performance parameter 'repeatability' where duplicates of a sample are used to assess the repeatability of an analytical procedure. Usually, a good repeatability is reached when the calculated value is below 30%. For the purpose of identifying the described compounds, however, it was decided to use more stringent criteria where the calculated value needed to be below 15%. Furthermore, only little variations between highest and median concentrations for each season and seasonal detection frequencies were accepted.

Average seasonal concentrations instead of median concentrations were used, as a symmetrical distribution of the data is a crucial condition for the consistent regular occurrence of a compound. Therefore, high concentrations were given greater importance.