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Exploring the Behaviour of Emerging Contaminants in the Water Cycle using the Capabilities of High Resolution Mass Spectrometry

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Abstract: To characterize a broad range of organic contaminants and their transformation products (TPs) as well as their loads, input pathways and fate in the water cycle, the Department of Environmental Chemistry (Uchem) at Eawag applies and develops high-performance liquid chromatography (LC) methods combined with high-resolution tandem mass spectrometry (HRMS/MS). In this article, the background and state-of-the-art of LC-HRMS/MS for detection of i) known targets, ii) suspected compounds like TPs, and iii) unknown emerging compounds are introduced briefly. Examples for each approach are taken from recent research projects conducted within the department. These include the detection of trace organic contaminants and their TPs in wastewater, pesticides and their TPs in surface water, identification of new TPs in laboratory degradation studies and ozonation experiments and finally the screening for unknown compounds in the catchment of the river Rhine.

Keywords: Emerging contaminants · High-resolution mass spectrometry · Non-target screening · Transformation products · Water cycle

State-of-the-Art in Comprehensive Water Quality Analysis

The coupling of liquid chromatography (LC) with mass spectrometry (MS) using electrospray or atmospheric pressure chemical ionization has recently become increasingly popular as it enables the detection of a wider range of compounds including polar and highly hydrophilic compounds. LC-MS techniques are especially of interest for many compounds found in water matrices that are not easily amenable to GC-based methods without derivatisation. Consequently, in recent decades a myriad of household, agricultural and industrial chemicals including pharmaceuticals, pesticides, surfactants, plasticizers and steroid hormones have been detected by research institutes and authorities actively monitoring wastewater, surface waters and groundwater.[1] More recently, high-resolution acquisition has become more accessible to research institutes and authorities with the development of the Orbitrap analyser (Thermo Scientific) and significant improvements to Time-of-Flight (ToF) technologies.[2] This makes it possible to perform target and non-target screening with one LC-HRMS full scan acquisition. The post-processing of these data can be divided into three major categories (see Fig. 1) as defined by Krauss *et al.*:[2b] i) *target analysis* using reference standards, ii) *suspect screening* using prior information but no reference standards to look for 'suspected substances' and iii)

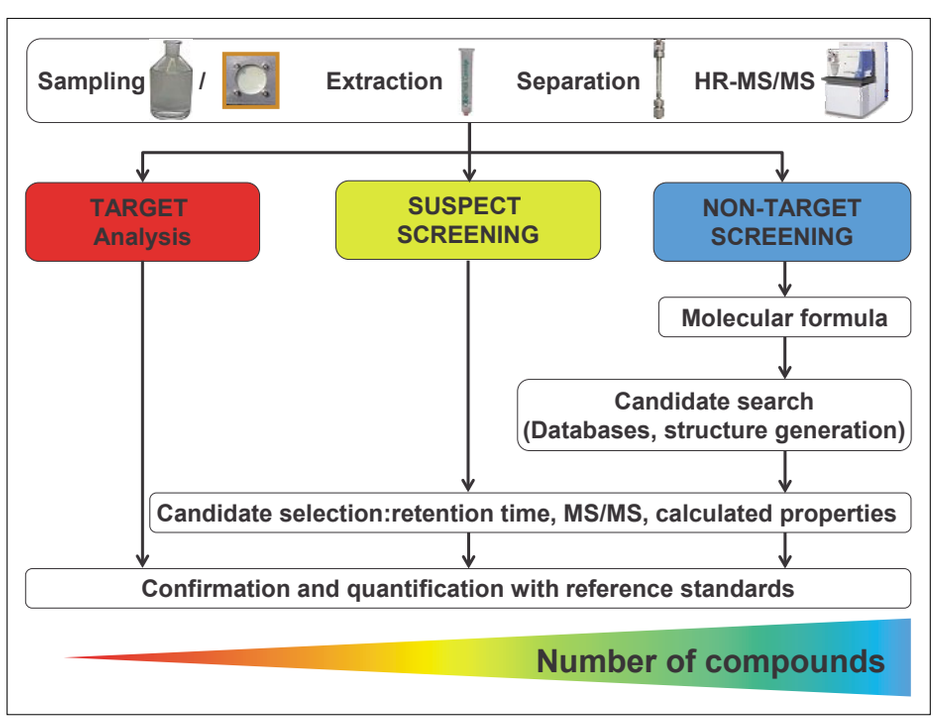

Fig. 1. Workflows for (i) quantitative target analysis with reference standards, (ii) suspects screening without reference standards, and (iii) non-target screening of unknowns in environmental samples by using LC-high resolution tandem mass spectrometry.

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non-target screening, where no prior information or reference standards are available in advance.

Reference standards and ideally the corresponding isotope-labelled internal standards should be available in order to perform a comprehensive *target analysis*. The reference standards are used to determine the concentrations in the sample, match the measured retention times and the fragmentation patterns (MS/MS). Internal standards assist in determining the sample-specific response and increase the quantification accuracy. With the increasing numbers of known contaminants, a complete target analysis covering all substances is becoming unachievable as this would require the purchase of thousands of standards.

As not all substances are known to be present *a priori*, target analysis can be complemented with *suspect screening* methods to tentatively identify other potentially relevant compounds.[3] To perform *suspect screening* with LC-HRMS(/MS), an exact mass can be calculated from the molecular formula of compounds 'suspected' to be present in the sample. The chromatogram is then searched for the corresponding precursor ions, isotopic patterns and even fragmentation information. While the exact mass screening is quite fast, the gathering of the additional evidence to confirm the identity of the suspected compound (see Fig. 1) remains time-consuming. In contrast to GC-MS methods, with comprehensive spectral libraries available, databases for LC-MS/MS are still small and less comparable due to the greater variation in fragmentation behaviour compared with Electron Impact Ionization-MS.[4]

The most difficult case is *non-target screening*, where no *a priori* information is available about many peaks detected in the samples. It is often difficult to unambiguously identify the structure corresponding to non-target peaks; not even the molecular formula is always clear. High accuracy, high resolution data complemented with high accuracy MS/MS information improves the chances to determine a unique molecular formula, especially using the additional isotope signals ^{34}S, ^{15}N and ^{18}O available on very high resolution instruments.[5] A clear molecular formula reduces the number of candidates retrieved from compound databases such as ChemSpider and PubChem, which is often the first step to identify potential structural candidates in non-target screening. The identification of 'unknown unknowns', *i.e.* compounds not present in compound databases, requires extensive manual interpretation or structure generation, increasing the time commitment for identification further.

Another advantage of comprehensive full scan acquisition is that the highly resolved full-scan data can also be used to identify further substances retrospectively. For instance, chemicals newly considered to be relevant to water quality can be extracted from earlier datasets in order to reconstruct historical water pollution patterns.

Department of Environmental Chemistry at Eawag (Uchem)

The primary goals of the Department of Environmental Chemistry at Eawag are to achieve a mechanistic understanding of the fate of anthropogenic organic (micro-)pollutants in the water cycle and of the resulting exposure of the aquatic environment, as well as to derive mitigation measures to improve water quality based on these insights. More precise aims are to:

i) determine the spatial and temporal exposure of water bodies to a broad range of chemical pollutants and their transformation products (TPs), and to derive models to predict these patterns,

ii) study the different fate processes that determine the behaviour, mass fluxes and effects of contaminants in the environment, with an emphasis on biological transformation,

iii) develop, evaluate and improve practical tools for reducing pollution such as chemical risk assessment methods, water management and mitigation measures at the source as well as end-of-pipe.

Uchem utilizes a combination of field, laboratory, and modelling studies to achieve these goals. Field studies start with the selection of appropriate catchments or experimental sites across Switzerland or beyond using high-resolution GIS land use analysis, consumption pattern and exposure modelling amongst other methods, often in collaboration with cantonal or federal authorities. A suitable sampling concept to address different input pathways, including active and/or passive sampling,[6] is then developed in the next step. Advanced analytical techniques for target, suspect and non-target screening are used to analyse liquid and solid environmental samples such as surface water, wastewater and sediment. Specific fate processes are studied in more detail in laboratory experiments under defined conditions. Biological processes are an important focus and are investigated at different interfaces between biota and chemicals. Prevalent transformation processes and stable TPs formed in activated sludge are studied and related to the metabolic potential of the sludge consortia using molecular biology-based characterization techniques, aiming thus to improve the model-based prediction of biotransformation products and rates.[7] The bioavailability of pollutants to bacteria and invertebrates, as well as the resulting internal doses and transformations are studied using toxicokinetic experiments.[8] Transformation pathways of aquatic contaminants are also elucidated on the basis of their stable isotope fractionation.[9] Together with the engineers at Eawag, the fate of contaminants during advanced wastewater and drinking water treatment such as sorption to activated carbon and ozonation is characterized with regard to the elimination of micropollutants and the formation of TPs and by-products.[10]

To address these research questions, Uchem applies and develops LC-HRMS/MS methods for the detection of i) known targets, ii) suspected and iii) unknown compounds. In the following, illustrative examples from recent research projects conducted in the Department of Environmental Chemistry at Eawag are presented, which show the great contributions of HRMS/MS to laboratory and field studies.

Target, Suspect and Non-Target Screening of Swiss Wastewater Effluents

Effluents from municipal wastewater treatment contain thousands of substances that are in daily use in industry and households and are thus a major source of chemical contamination for surface waters. The characterization of polar contaminants in wastewater effluents is still very limited, but ever-increasing with high-resolution mass spectrometry opening new avenues.

Effluent samples after conventional treatment were collected from ten different municipal wastewater treatment plants (WWTPs) in Switzerland during dry weather in February 2010 with the aim to determine the 'typical' composition entering Swiss surface waters.[5] 0.25 L of each 24 hour flow-proportional composite sample were enriched using a mixed-bed multi-layer solid-phase extraction cartridge comprising Oasis HLB, Isolute ENV+, Strata-X-AW and Strata-X-CW (details in ref. [11]) after the addition of over 100 isotope-labelled internal standards. HPLC separation of the extracts was performed on a XBridge C18 column using an acidic methanol/water gradient. Full scan MS detection with data-dependent MS/MS acquisition was performed after electrospray ionization (ESI) in the positive and negative mode with an LTQ Orbitrap XL or Q-Exactive (resolution R >60,000 at m/z 400, for m/z = 115 to 1000) from Thermo Fisher Scientific (San Jose, USA).

Target compounds were selected according to the sample type and their expected occurrence in Swiss waters,[12] including pharmaceuticals, illicit drugs, industrial chemicals, polyfluoroalkyl sub-

stances (PFASs), food additives, corrosion inhibitors, personal care products (PCPs), biocides, pesticides, as well as TPs of several substance classes. In total, 364 target compounds were investigated, including 91 TPs. The highest observed concentrations (in the µg/L range) were associated with corrosion inhibitors, artificial sweeteners and pharmaceuticals, as shown in Fig. 2. These results were comparable with concentrations reported within an EU-wide survey of 18 countries.[13] TPs were also shown to be extremely relevant: six TPs of corrosion inhibitors and pharmaceuticals were amongst the top 20 highest concentration target compounds.[5]

Further investigations using software developed at Uchem (enviMass, the R packages nontarget, and RMassBank – see *http://www.eawag.ch/forschung/uchem/software)*, revealed that only 1.2% (on average) of the detected peaks from the ten samples could be assigned to target compounds. Furthermore, an intensity-based prioritization showed that only four targets were amongst the top 30 most intense peaks in the negative mode (acesulfame, cyclamate, diclofenac, saccharin), and two in the top 30 from positive mode (DEET and 4-acetamidoantipyrine). Assessment of the high-resolution isotope patterns revealed a dominance of sulfur-containing compounds in ESI negative measurements and an extensive suspect screening was performed using surfactants and their TPs. Several homologous series were detected (*e.g.* linear alkylbenzyl sulfonates, sulfophenyl alkyl mono- and di-carboxylic acids, alkyl tetralin sulfonates and their carboxylic acids as well as alkyl ethoxy sulfates).[5] One of the remaining peaks for non-target identification was also successfully identified and confirmed as 1,3-benzothiazole-2-sulfonate, known to be an oxidation product of a vulcanization accelerator.

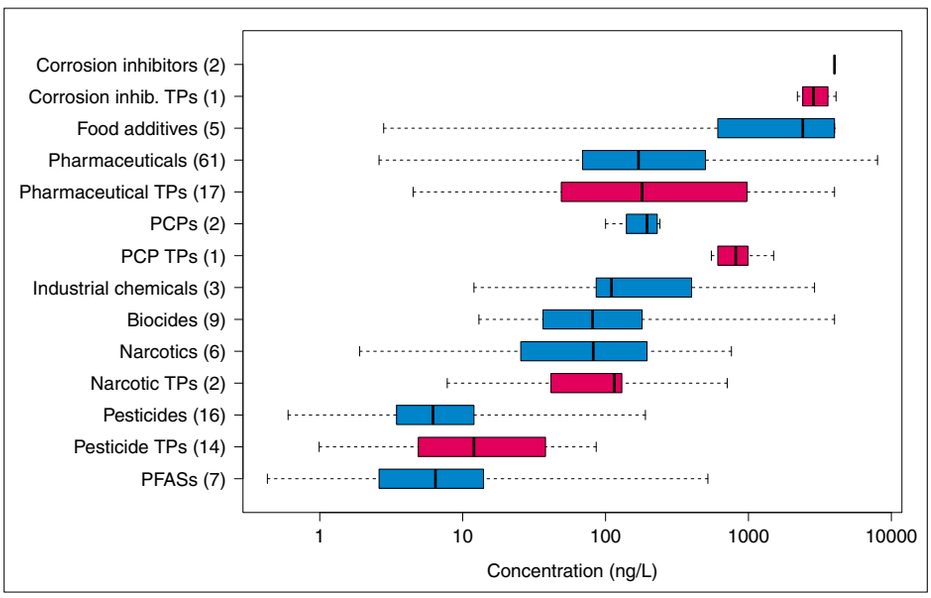


Fig. 2. Concentration box-plots for target compound classes over ten wastewater treatment plant effluent samples. Whiskers extend to the data extremes. TPs = transformation products (red bars); PCP = personal care products; PFCs = perfluorinated compounds. In brackets the number of compounds included in each substance class is given.

Target and Suspect Screening of Pesticides in Swiss Surface Water

Pesticide use is heavily dependent on local conditions (*e.g.* land use, application behaviour, climate), and thus the exposure to surface waters is highly spatially and temporally variable.[14] Ideally, all pesticides that could potentially occur in the environment should be measured to form a comprehensive picture of the surface contamination. However, analytical restrictions have prevented this so far and monitoring programs have instead focused on selected pesticides (mainly herbicides and legacy insecticides). Screening methods based on LC-HRMS/MS address these limitations and enable a fast and efficient screening for nearly all registered, synthetic organic pesticides in Swiss surface waters, without the need to purchase all reference standards. To demonstrate this, 45 bi-weekly composite samples were taken from five locations in Switzerland (see Fig. 3) between March and July 2012 to obtain a more comprehensive picture of pesticide exposure in Switzerland. In total, 249 compounds including plant protection products and biocides plus 134 major TPs were investigated across all five medium-sized catchments, chosen to represent a variety of crops.[15]

Reference standards were purchased for 45 fungicides and insecticides that were considered highly likely to be found in Swiss surface waters on the basis of sales information and substance properties such as hydrophobicity and degradation in soil and water.[16] These standards were used to optimize and validate a LC-HRMS/MS target screening method using a similar method to that described above on the

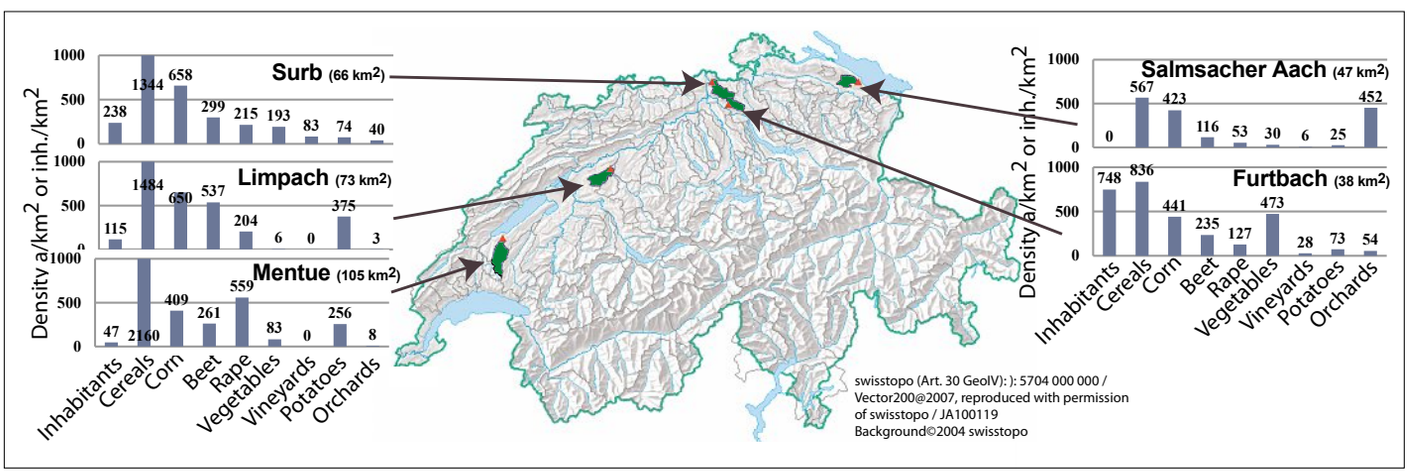


Fig. 3. Study sites with land use information of the five catchments in Switzerland. The number in brackets represent the catchment size. Green: catchment area, red: sampling point, a = 10 x 10 m; inh = inhabitants.

QExactive instrument. These 45 substances were then also used as artificial suspects to optimize and evaluate a suspect screening approach using the exact mass of each substance as the only input parameter *a priori*.[3] The software ExactFinder V. 2.0 (Thermo Fisher Scientific Corporation) was used to pick all peaks with a mass accuracy <5 ppm in the chromatogram. Automatic filter criteria including blank subtraction, peak area, peak shape, signal to noise ratio and isotope pattern were optimized to reduce the false positives without losing too many target compounds. With the optimized automatic procedure, 70% of all peaks from the target screening were detected, while 95% of the missing peaks (false negatives) were in the low intensity range. This demonstrates that a slightly higher limit of quantitation (LOQ) compared to manually evaluated target analysis cannot be avoided. A full suspect screening was then applied to the remaining substances for which no reference standard was available *a priori* (real suspects), using the optimized method. In the end, 25 of these 158 suspects were definitely confirmed by purchased reference standards. As an example, a TP of the neonicotinoide imidacloprid, listed in the Footprint database[16] was detected in surface water for the first time (Fig. 4).[3] For several further TPs reference standards were not available, and thus the measured MS/MS spectra were compared with predicted spectra using software such as MetFrag[17] and MassFrontier (HighChem Ltd., Thermo Fisher Scientific Corporation).

In total 54 herbicides, 31 fungicides, 17 insecticides, 2 compounds only registered as biocides and 40 transformation products were detected in all surface water samples.[15] Between 30 and 50 parent compounds were detected in each two-week composite sample. Although the measured concentrations for single compounds were mostly low, the total pesticide concentration was above 1000 ng/L in 78% of samples. Furthermore, 23 herbicides, 5 fungicides, 2 biocides and 1 insecticide were present in concentrations above 100 ng/L, the current legal water quality requirement in Switzerland.[18] The chronic environmental quality standards, which were derived by the Ecotox Centre of the Eawag/EPFL (*http://www.oekotoxzentrum.ch/index_EN*) in line with the Technical Guidance Document of the Water Framework Directive of the European Union, were exceeded for 19 single substances. Using a mixture toxicity approach based on concentration addition, exceedances occurred over the whole measurement period in all rivers.[15]

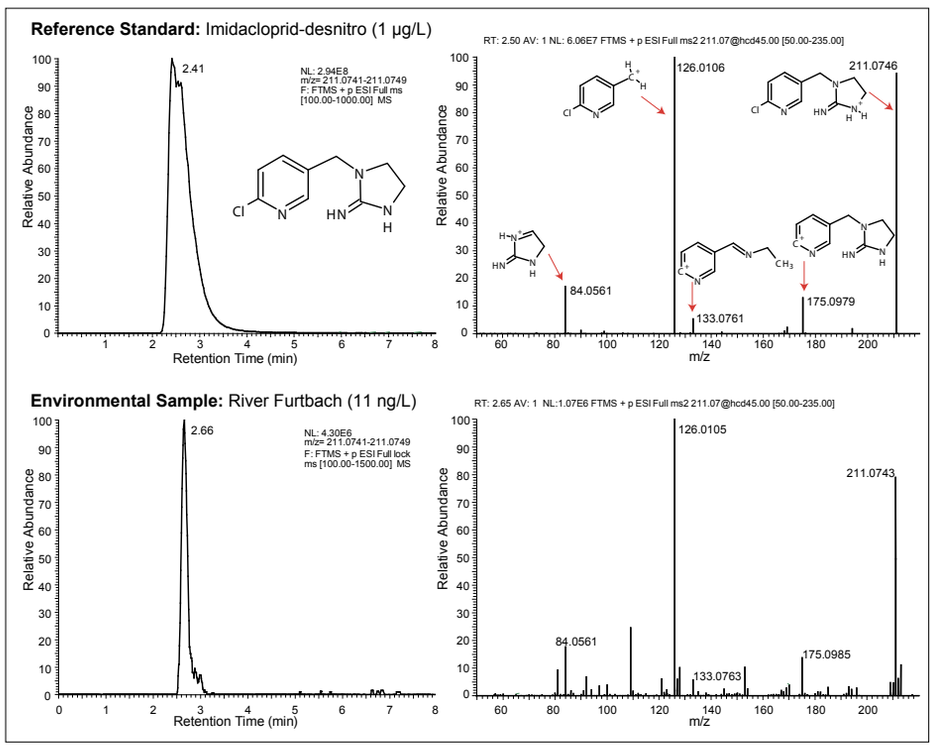


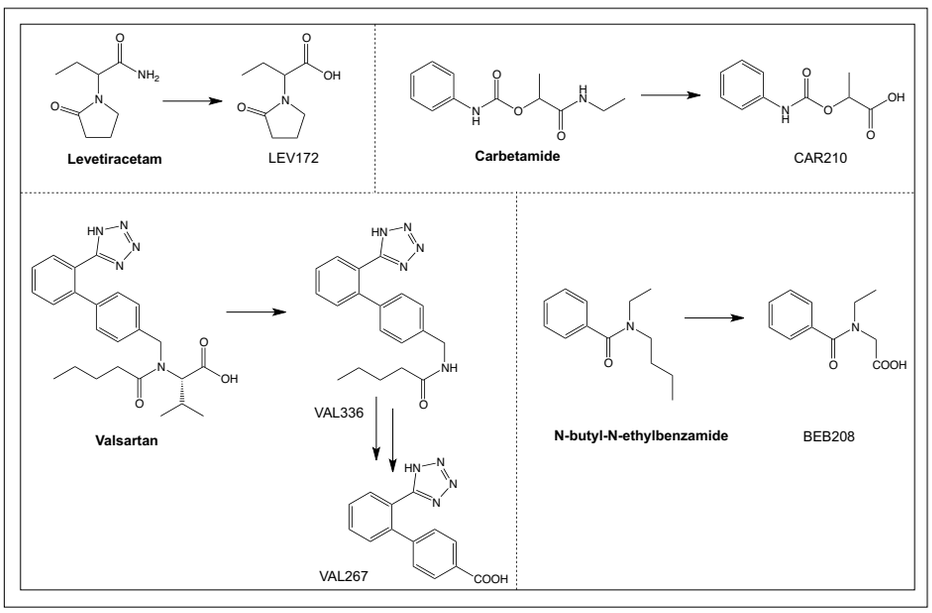
Fig. 4: Mass spectrum of the transformation product imidacloprid-desnitro detected in a surface water sample (bottom) during the suspect screening approach and later confirmed by a reference standard (top).

Identifying Microbial Transformation Products in Laboratory Studies using Suspect and Non-target Screening

Knowledge of possible transformation processes can be used to assist the search for transformation products in environmental samples *via* suspect screening approaches. In addition to expert knowledge, transformation pathway prediction systems like the 'Eawag Biocatalysis/Biodegradation database and prediction system' (Eawag-BBD/PPS, *http://eawag-bbd.ethz.ch*), hosted by Uchem, are frequently used to support suspect screening (*e.g.* refs [7,19]). The accuracy of pathway prediction heavily depends on the availability of a sufficiently broad and consistent database of biotransformation pathways measured in environmentally relevant systems to train the prediction system. To improve these databases, we perform detailed laboratory studies of biotransformation processes in activated sludge for contaminants with prevalent functional groups in wastewater such as amines and amides. Both suspect and non-target approaches are used for transformation product identification.[9a,20] Four examples of initial transformation reactions for amides in activated sludge are given in Scheme 1. On the basis of data from 30 amides, it became apparent that primary and secondary amides were preferably hydrolysed initially, while tertiary amides were preferably dealkylated oxidatively unless other, more easily oxidisable moieties such as unbranched alkyl chains or benzyl groups were present in the molecule.[7] Accordingly, the overly general amide rules in the Eawag-BBD/PPS were adapted to increase the specificity in accordance with these findings.

Investigating Ozonation Processes using Suspect and Non-Target Screening

While the prediction of oxidative processes using a similar prediction system as the Eawag-BBD/PPS does not yet exist, the development of such a system is an objective of a collaborative project with the Department of Water Resources and Drinking Water at Eawag. The oxidation of drinking and wastewater for disinfection purposes has a long tradition, but the benefits of using oxidation for micropollutant removal during wastewater treatment have only been demonstrated recently.[21] Besides activated carbon treatment, ozonation is the most promising technology to enhance the treatment capacity in WWTPs for the increased removal of micropollutants and enable compliance with recent changes to the Swiss Water Protection Ordinance.[22] Ozone is a selective oxidant that is particularly reactive toward functional groups with high electron densities, as present in many micropollutants. TPs that are identified during laboratory investigations are subsequently monitored in pilot and full-scale drinking and wastewater water treatment processes.

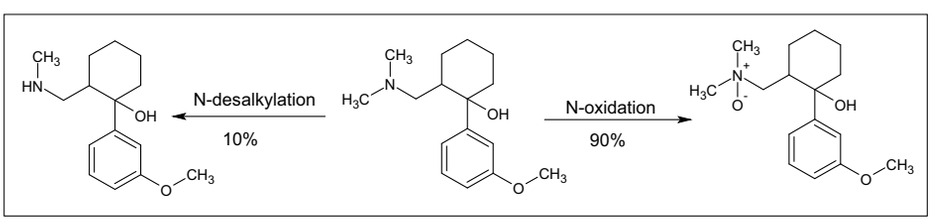


Scheme 1. Exemplary initial biotransformation pathways of primary (levetiracetam), secondary (carbetamide) and tertiary amides (valsartan, N-butyl-N-ethylbenzamide) elucidated with LC-HR-MS/MS-based suspect and non-target screening for transformation products.

As an example, bench-scale ozonation experiments performed on 100 µM micropollutant stock solutions with varying micropollutant:ozone molar ratios between 2:1 to 1:10 in the presence of a radical scavenger (t-butanol) and a phosphate buffer[23] were analysed directly by LC-HRMS without any sample preparation. The formation of TPs was determined using a differential analysis between treated samples (spiked/ozonated) and control samples (spiked/not ozonated and unspiked/ozonated), while the structures of the TPs were elucidated *via* MS/MS spectral interpretation and confirmed with reference standards where available. Experiments confirmed for example the initial transformation of the analgesic agent tramadol into two TPs, as already reported in literature.[24] Tramadol reacted quickly with ozone to form predominantly N-oxide- and N-desmethyl-tramadol with conversion yields up to 90% and 10% of initial tramadol, respectively (Scheme 2). These TPs were oxidized further in presence of a large excess of ozone. N-oxide-tramadol was also detected in ozonated surface water collected from a pilot-scale treatment plant up to a yield of 10% from the parent compound.[25]

Non-Target Screening in the Rhine Catchment

Lake Constance is one of the largest lakes in Europe with a catchment area of 11 500 km^2 and a population of about 1.6 million people. The main tributary of Lake Constance is the river Rhine, comprising 60% of the total inflow. As the lake water is used as a drinking water resource for 4.5 million people, water quality analysis is an important issue. LC-HRMS/MS is perfectly suited for the sensitive screening of known and unknown compounds in lake water.[26] Non-target screening was performed in 2008 with lake water samples at different depths to detect previously unknown site-specific compounds. Following SPE enrichment and HPLC-ESI-HRMS/MS analysis (see above), 4200 peaks were detected in the extracted ion chromatograms from the positive mode measurements, following blank subtraction. This corresponded to roughly 3500 unique compounds on the basis of the isotope and adduct information available in the measurements. Of the 600 peaks with an intensity above 100,000 units, 34 were assigned to target analytes present at the low ng/L level such as pharmaceuticals, biocides and pesticides. Peaks with the distinctive chlorine isotope patterns were investigated further and molecular formulas were calculated for these peaks considering the seven Golden Rules.[27] For the compound with the formula $C_9H_7Cl_2N_5$, a database search in SciFinder (ACS, accessed 2009) revealed 39 structures. Seven of these were excluded based on implausible retention times and the remaining 32 structures were sorted according to the number of references in SciFinder. Almost 2000 references were found for lamotrigine and the MS/MS fragments measured in experiments could be explained using MassFrontier. A reference standard confirmed the identity of lamotrigine and allowed the quantification to only a few ng/L in lake water. Lamotrigine is a widely used anticonvulsant drug, which was detected subsequently in the US at significant concentrations in wastewater and surface water.[28] Now included as a target analyte, lamotrigine was quantified in water samples from monitoring stations at the river Rhine in 2011. The increasing load along the river Rhine up to 40 kg per week at the estuary is depicted in Fig. 5, illustrating the widespread use and persistence of lamotrigine in the aquatic environment.



Scheme 2. Reaction pathway of tramadol during ozonation in presence of a hydroxyl radical scavenger.[24]

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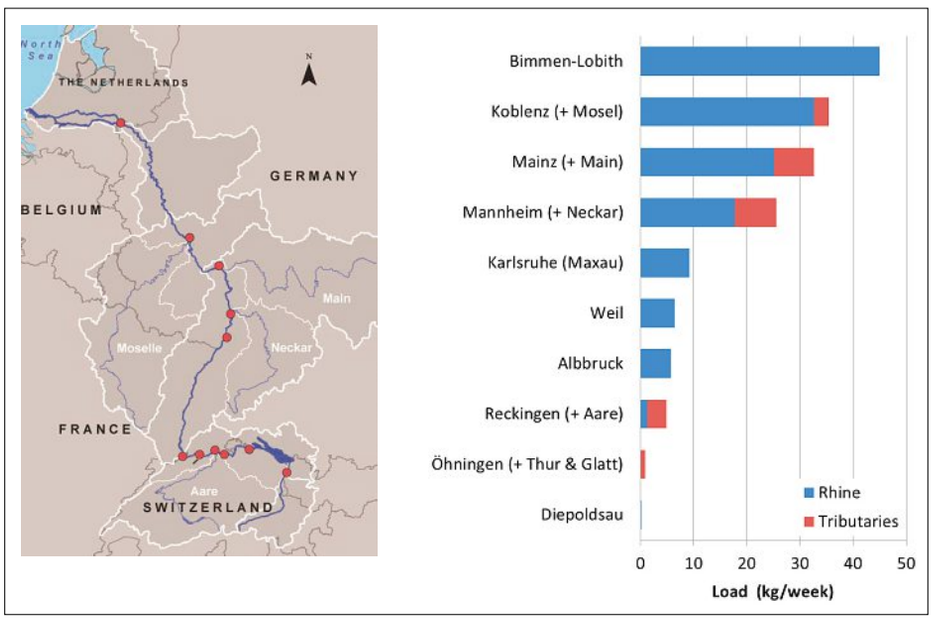

Fig. 5. Cumulative weekly load of lamotrigine along the river Rhine, from monitoring samples along the river in the Switzerland, Germany and the Netherlands.

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