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Review

Anthropogenic Trace Compounds (ATCs) in aquatic habitats — Research needs on sources, fate, detection and toxicity to ensure timely elimination strategies and risk management

Sabine U. Gerbersdorf [a,*], Carla Cimatoribus [b,f], Holger Class [a], Karl-H. Engesser [b], Steffen Helbich [b], Henner Hollert [c,d,e], Claudia Lange [b], Martin Kranert [b], Jörg Metzger [b,f], Wolfgang Nowak [a], Thomas-Benjamin Seiler [c], Kristin Steger [a], Heidrun Steinmetz [b], Silke Wieprecht [a]

[a] Institute for Modelling Hydraulic and Environmental Systems, University of Stuttgart, Pfaffenwaldring 61, 70569 Stuttgart, Germany
[b] Institute for Sanitary Engineering, Water Quality and Solid Waste Management, University of Stuttgart, Bandtäle 2, 70569 Stuttgart, Germany
[c] Department of Ecosystem Analysis, Institute for Environmental Research, RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany
[d] State Key Laboratory of Pollution Control and Resource Reuse, School of the Environment, Nanjing University, China
[e] College of Environmental Science and Engineering and State Key Laboratory of Pollution Control and Resource Reuse, Tongji University, 1239 Siping Road, Shanghai, China
[f] University of Applied Sciences Esslingen, Kanalstrasse 3, 73728 Esslingen, Germany

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ABSTRACT

Anthropogenic Trace Compounds (ATCs) that continuously grow in numbers and concentrations are an emerging issue for water quality in both natural and technical environments. The complex web of exposure pathways as well as the variety in the chemical structure and potency of ATCs represents immense challenges for future research and policy initiatives. This review summarizes current trends and identifies knowledge gaps in innovative, effective monitoring and management strategies while addressing the research questions concerning ATC occurrence, fate, detection and toxicity.

We highlight the progressing sensitivity of chemical analytics and the challenges in harmonization of sampling protocols and methods, as well as the need for ATC indicator substances to enable cross-national valid monitoring routine. Secondly, the status quo in ecotoxicology is described to advocate for a better implementation of long-term tests, to address toxicity on community and environmental as well as on human-health levels, and to adapt various test levels and endpoints. Moreover, we discuss potential sources of ATCs and the current removal efficiency of wastewater treatment plants (WWTPs) to indicate the most effective places and elimination strategies. Knowledge gaps in transport and/or detainment of ATCs through their passage in surface waters and groundwaters are further emphasized in relation to their physico-chemical properties, abiotic conditions and biological interactions in order to highlight fundamental research needs. Finally, we demonstrate the importance and remaining challenges of an appropriate ATC risk assessment since this will greatly assist in identifying the most urgent calls for action, in selecting the most promising measures, and in evaluating the success of implemented management strategies.

Contents

1. Introduction on Anthropogenic Trace Compounds (ATCs) . . . 86
 1.1. Good water quality is linked to intact aquatic systems . . . 86
 1.2. Micropollutants: low concentrations, high alert . . . 86
 1.3. From precaution to legal enforcement . . . 86
 1.4. Protection through knowledge: where are we? . . . 87
2. What are the pre-requisites for successful management directives based on innovative measuring, monitoring and modelling strategies? . 87
 2.1. Why should we care about managing ATCs in the first place? . . . 87
 2.2. Measuring and monitoring must become far-sighted and standardized routine . . . 87
 2.3. Modelling and management needs fundamental small-scale research . . . 88

* Corresponding author.
E-mail address: sabine.gerbersdorf@iws.uni-stuttgart.de (S.U. Gerbersdorf).

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3. Do we need an all-inclusive chemical analysis of ATCs or can we do more with less? . . . 88
3.1. Progress and limitations in instrumental analysis . . . 88
3.2. The importance of appropriate sampling designs . . . 89
3.3. The innovative way towards indicator substances . . . 90
4. Are the acute and long-term effects of ATCs related to concentration, cumulative or synergistic effects and mode of actions? . . . 91
4.1. Biomonitoring: highest sensitivity at lowest concentrations . . . 92
4.2. Bioanalysis: quantifying toxic effects for improved health risk assessment and management . . . 92
4.3. The complexity of various test systems from cell-based tools to environmentally valid endpoints . . . 92
4.4. Complementary techniques: the right strategy pinpoints the culprit . . . 93
5. Are WWTPs the main pathway of ATC emission from urban areas or are there other exposure paths to consider? . . . 94
5.1. Passage of ATCs through the WWTP . . . 94
5.2. Often neglected but important: stormwater runoff and combined sewer overflow . . . 95
5.3. Recycling of organic solid waste and biosolids — a win–lose situation . . . 96
6. Elimination of ATCs from water systems: is there a way towards more sustainable approaches at full-scale? . . . 96
6.1. How to determine the best treatment for ATC removal? . . . 96
6.2. Is biodegradation the ultimate solution for elimination? . . . 97
6.3. What should be done next on elimination and legislative levels? . . . 98
7. Behaviour and fate of ATCs in the environment: gone for good or primed for comeback? . . . 99
7.1. Hydrophobic ATCs and cohesive sediment dynamics . . . 99
7.2. The subsurface passage . . . 99
7.3. The role of the microbial EPS matrix . . . 100
8. Risk management: how to assess and control the true risks of ATCs given all these research challenges? . . . 100
8.1. What is required for a sound risk assessment? . . . 100
8.2. Solid teamplay wins the day . . . 101
8.3. Risk management requires a global system perspective . . . 101
9. Conclusions . . . 101
Acknowledgements . . . 102
References . . . 102

1. Introduction on Anthropogenic Trace Compounds (ATCs)

1.1. Good water quality is linked to intact aquatic systems

The access to clean water is of ever increasing significance, and therefore water has been designated as the "new gold of the 21st century" (UN resolution 64/292, 2010). There is now a consensus that the sustainable long-term supply of high-quality water is inevitably linked to the ecosystem health of aquatic and adjacent habitats by their provision of essential ecosystem services such as waste decomposition, nutrient sequestration, purification and detoxification of soils, sediment and water. In contrast to this, the presently abundant exploitation of water resources and the ongoing pollution of aquatic systems deteriorate vital aquatic resources in terms of water quantity and quality as well as ecosystem functionality.

1.2. Micropollutants: low concentrations, high alert

Up to now, more than 89 million chemical compounds have been registered at the CAS (Chemical Abstract Service, 2014. https://www.cas.org.). The number of anthropogenic substances in waters grows daily due to newly introduced products, and this threatening situation becomes increasingly clear due to improved analytics. Of growing concern are the "emerging contaminants" or micropollutants, such as pharmaceuticals and personal care products (PPCPs) as well as steroid hormones, surfactants, industrial chemicals and pesticides (Luo et al., 2014; Schwarzenbach et al., 2010). These micropollutants, hereinafter referred to as Anthropogenic Trace Compounds or ATCs, usually occur in the ppt to ppb (parts-per-trillion/billion) range. Such trace concentrations along with the large numbers and types of ATCs represent a challenge for both detection and elimination strategies (Loos et al., 2010). Previous research (e.g., by Benner et al., 2013) documents that we have to expect an increasing accumulation of ATCs in aquatic systems: There is a continuous re-supply from diffusive entry paths (e.g., application of pesticides, agricultural use of sewage sludge or wastewater irrigation) and point sources (e.g., release from production sites, incomplete elimination by wastewater treatment plants (WWTPs), discharge of sewer overflows and outlets, leakage from landfills). For instance, natural and synthetic hormones such as 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) have been determined in the effluents of German WWTPs in concentrations up to 21 ng/L and 62 ng/L, respectively (BUND, 2001), that are well above the limits of the environmental quality standards (EQSs) given by the European Commission (2011). Diclofenac as one of the most commonly detected pharmaceuticals is continuously released into surface waters by WWTP effluents to accumulate to concentration levels up to 50 μg/L (Höger et al., 2005). To further complicate the situation, ATCs possess various modes of action according to their designed purposes that result in a multitude of toxicity potencies, even at the lowest concentration levels (e.g., Orias and Perrodin, 2013; Sumpter and Johnson, 2005 for pharmaceuticals and endocrine disrupting substances, respectively). For the abovementioned examples, E2 and EE2 have been shown to induce hormonal activity in the brown trout (*Salmo trutta*) at concentrations as low as 10 ng/L and 0.3 ng/L, respectively; while diclofenac concentrations between 0.5 and 50 mg/L resulted in significantly decreased haematocrit values and histopathological changes in gills, kidneys and liver of this salmonid fish (BUND, 2001; Höger et al., 2005). Last but not least, there are also first hints that most ATCs induce effects that completely differ from their intended effectiveness (Waring and Harris, 2005); e.g., the industrial chemicals bisphenol A, nonylphenols and some phthalates have shown strong oestrogenic effects on aquatic organisms (Kasprzyk-Hordern et al., 2009).

1.3. From precaution to legal enforcement

While obviously hazardous substances can eventually be banned (e.g., Stockholm Convention 2001 on Persistent Organic Pollutants POPs), such a course of action is still hampered by the rudimentary eco- and toxicological assessments that are currently available for micropollutants. Nevertheless, the high probability of cumulative as well as sub-acute and chronic effects by this large cocktail of ATCs (e.g., Schwarzenbach et al., 2006) calls for regulation and protection measures on the basis of the "precautionary principle" (Houtman, 2010; Raffensperger and deFur, 1999). The precautionary principle states that scientific uncertainty about a future risk (here of ATCs) should encourage policy makers to take stronger prevention measures today. This principle is already implemented in some legal systems such as the European law (e.g., EU-Water Framework Directive WFD 2000/60/EC); for instance single micropollutants are listed as "priority substances", and recently pharmaceuticals as well as steroid hormones have been implemented on the related watch list (Directive 2013/39/EU, European Parliament and The Council, 2013). Another example concerns the regulation of ATCs in drinking water using safety threshold values based on the German health-related indicator value concept developed by the German Federal Environment Agency (UBA; Grummt et al., 2013). However, such environmental or drinking water quality standards for ATCs are limited to certain regions or countries, and the situation is even worse on the emission side, where discharge guidelines and standards do not exist for most ATCs (Allan et al., 2006; Luo et al., 2014). To accomplish timely regulation and legal enforcement of ATC levels in the environment, further research on chemical detection and biological responses is indispensable to better understand the exposure routes and the fate of ATCs within aquatic systems.

1.4. Protection through knowledge: where are we?

Due to the growing awareness of possible adverse effects of ATCs in waters, the research activities and funding has increased significantly in recent years. Available reviews on micropollutants in aquatic systems focus on certain ATC categories (e.g., pharmaceuticals, Sumpter and Johnson, 2005), validate analytical techniques (e.g., Comerton et al., 2009), assess ecotoxicological questions (e.g., Maurer-Jones et al., 2013), address specific elimination strategies (e.g., Benner et al., 2013) or concentrate on specific water systems such as groundwaters (e.g., Lapworth et al., 2012). Rarely is the ATC topic presented in a more comprehensive manner; for instance by crossing disciplinary boundaries in uncovering significant trends and developments for certain ATC categories (e.g., Richardson and Ternes, 2014) as well as tackling their potential effects on human health (e.g., Schwarzenbach et al., 2010) or by following occurrence and removal of selected ATCs from source to sink (Luo et al., 2014). To the best of our knowledge, there has been no attempt so far to give a broader picture of ATCs in aquatic habitats. This is a huge task involving various compartments (in natural and technical systems), covering various scales (from macro- to microscale) and addressing numerous questions from fundamental to applied research that originate from the engineering as well as the natural science disciplines. In tackling this broader view, we refer to a core fraction of the available literature for each aspect. With this approach, the present paper aims to briefly cover the status quo and to disclose remaining challenges and knowledge gaps concerning ATC occurrence, fate, detection and toxicity, thus contributing to a more holistic approach and to the development of innovative research designs on ATCs in aquatic systems. Specifically, we raise the following questions:

* What are the pre-requisites for successful management directives based on innovative measuring, monitoring and modelling strategies? (Section 2)
* Do we need an all-inclusive chemical analysis of ATCs or can we do more with less? (Section 3)
* Are the acute and long-term effects of ATCs related to concentration, cumulative or synergistic effects and mode of actions? (Section 4)
* Are WWTPs the main pathway of ATC emission from urban areas or are there other exposure paths to consider? (Section 5)
* Elimination of ATCs from water systems: is there a way towards more sustainable approaches at full-scale? (Section 6)
* Behaviour and fate of ATCs in the environment: gone for good or primed for comeback? (Section 7)
* Risk management: how to assess and control the true risks of ATCs given all these research challenges? (Section 8)

These questions are addressed, one by one, in the following sections.

2. What are the pre-requisites for successful management directives based on innovative measuring, monitoring and modelling strategies?

The drive to define and implement effective but also costly measuring, monitoring and modelling efforts requires first of all the understanding that ATCs pose a considerable threat to aquatic habitats and drinking water; this is motivated in Section 2.1. Section 2.2 will provide arguments why sampling practise and analytical methods should be implemented with a long-term, far-sighted perspective and standardized on an international basis. In Section 2.3, we will emphazise the need for fundamental research on process understanding since abiotic and biotic interactions on the microscale will determine the environmental fate of ATCs, and where and how to best eliminate them; this knowledge is the basis for modelling and for derivation to sound management directives.

2.1. Why should we care about managing ATCs in the first place?

At first glance, the trace concentrations in which ATCs occur in waters seem to represent a luxury problem of industrial nations when compared to the world-wide water quality issues such as salinization, toxic algae blooms, hygienic factors or other human-health related contaminations by nitrate or arsenic (e.g., Berg et al., 2007; Heisler et al., 2008; Kaushal et al., 2005). However, there are several reasons as to why ATCs must be taken seriously. Firstly, ATCs such as pharmaceuticals and pesticides have been specifically designed to act biologically with high potency, thus profound effects on wildlife can even occur in the low nanogram per litre range (Sumpter and Johnson, 2005). Consequently, the potency of ATCs is a key risk factor for human and wildlife exposure as well as ecosystem functionality. Moreover, we have little information about chronic impacts which might be much more severe than acute effects (Lange et al., 2001). Thirdly, possible reactions of organisms to a multitude of stressors occurring simultaneously are also uncharted territory. It is therefore vital to limit further pressures on aquatic systems many of which are already heavily burdened by anthropogenic activities, even without ATCs. Besides natural waters, technical systems such as urban systems have rather short and intense water cycles. Consequently, urban systems are prone to increasing ATC pollution but, at the same time, greatly depend on a well-functioning biocoenosis for ATC degradation in technical elimination processes (such as adsorption in activated sludge within WWTPs). Regardless of being natural or technical, aquatic systems have only a certain resilience against external forces before the system switches from a desired to an unwanted ecological status (Scheffer and Carpenter, 2003). After the perturbation of the habitat to an unwanted status, it is extremely difficult to re-establish the original status.

Given these reasons, acting on the precautionary principle is the preferred alternative, in particular for ATCs.

2.2. Measuring and monitoring must become far-sighted and standardized routine

Our modern life style confronts us continuously with new and potentially persistent contaminants that are increasingly released around the globe (Kummerer, 2010). So far, politics and water management tend to concentrate on imminent problems caused by a few substances of high public and scientific concern. Examples for these acute, apparent cases in the past are the eutrophication and collapse of waters due to high loadings of nitrogen and phosphate in the 1970s or the piles of foams on water surfaces due to non-biodegradable tensides in the 1950/60s (Correll, 1998; Schindler, 2006). The same line of action applies to ATCs; micropollutants received attention during acute events caused by accidental spills from the chemical industry such as the dioxin release in Seveso (Italy) in 1976 (Consonni et al., 2008; Reggiani, 1978) and, 10 years later, the Sandoz spill into the Upper Rhine River near Basel, Switzerland (Giger, 2009).

Instead of this short-sighted mode of action, monitoring must be implemented on a far-sighted long-term basis. Consequently, a change in monitoring practise is indispensable in order to get a comprehensive overview of the sources, transport and behaviour of ATCs in the environment as well as of their temporary or permanent sinks. This would also enable us to better distinguish between daily scenarios and extreme events. However, vast amounts of money and human ressources would be needed for this huge task. Therefore, alternative strategies are required that investigate the so-called indicator substances instead of the whole ATC cocktail. Another major shortcoming of current monitoring programs concerns ATC measurements done in different parts of the world or countries that are hardly comparable. Part of the reason is that associated environmental conditions are often not documented, the studies lack adequate sampling modes and moreover, mostly retain their own traditional laboratory protocols (Coquery et al., 2005; Ort et al., 2010). These issues on indicator substances and standardized sampling design as well as analytical procedures will be further explored in Section 3.

2.3. Modelling and management needs fundamental small-scale research

In order to manage micropollutants, it has to be decided (a) which ATCs have to be eliminated to what extent, (b) where in the water cycle this would be most efficient and (c) which technical means should be applied to be successful and sustainable. All of these aspects require a sound knowledge of ATC abundance, properties, fate and impact in the environment, which is essentially determined by two closely related features — the sources and the physico-chemical characteristics of ATCs. The introductory paths of ATCs are clearly linked to their origin and purposes. ATC purposes or mode of actions depend on and determine their physico-chemical properties that in turn impact their bioavailability, behaviour and persistence in the environment.

The research on biological responses to ATC exposure is the key to achieving regulatory limits on the basis of potential and proven toxicity. Section 4 will deepen this topic by highlighting the need for new test systems aimed at demonstrating long-term effects of ATCs on single organisms and community level as well as balancing the various test levels and end-points (from gene to population) better. The question on “where best to eliminate” and how to achieve the best rate of removal can only be answered through knowledge of the various sources of ATCs; Section 5 will deal with this issue. Briefly, ATCs can enter the aquatic system during manufacturing processes (production level), after their application at locations that relate to their designated use (usage level) and during incomplete removal efforts (disposal level). Nevertheless, identification of sources is just the first step; in order to deal with the ATC load we need to develop and implement appropriate and targeted water treatment techniques that also work at full-scale, which is explored in Section 6. Targeted elimination routines as well as the choice of overall elimination strategies will be dictated by ATC design, designated use and mode of action. However, the long-term goal should be more sustainable in finding new ways to reduce, substitute or avoid hazardous ATCs during their production (Malaj et al., 2014).

Substitution policies or elimination strategies to avoid the entry of ATCs into the environment is certainly a top priority. However, due to various diffuse and uncontrollable entry paths, ATCs continue to accumulate in the aquatic habitat. Hence, one needs to understand their environmental fate and impact better to develop and fine-tune appropriate management options. Again, the structure and the individual functional groups of the ATCs determine not only their binding features, their bioaccumulation and toxic potential but also their transport and fate. While some are polar and water-soluble, others preferentially bind to particles. At first sight, dissolved, polar ATCs are more likely to occur in groundwaters although the processes governing subsurface passage (sorption, degradation, dilution) can largely decrease ATC concentrations (Luo et al., 2014; Teijon et al., 2010). Non-polar ATCs couple their fate closely to fine sediments in rivers and lakes; these fine sediments are heavily colonized by microbial communities that may additionally bind and degrade ATCs (Gerbersdorf et al., 2008, 2011). The topic of sediment-bound ATCs and their possible impact on biofilm communities that fulfil important ecosystem services, one of them being biostabilization of fine sediments, is further discussed in Section 7.

Future research will have to address ATC characteristics and the small-scale processes that lead to their sorption and degradation. Deeper knowledge on the micro-scale is vital to understand ATCs' behaviour in surface waters, within the subsurface and in technical systems. Such an improved process understanding of the physico-chemical–biological interactions that determine ATCs' whereabouts is essential for mathematical/numerical models of water quality, hydraulics and sediment transport. Advanced predictive models along with risk assessment (presented in Section 8) are an important basis for urgently needed decision support because they can help to analyse and compare the possible benefits of competing management options. These tools could indicate the most effective survey, restoration and conservation strategies for our aquatic habitats and derive the most promising actions to improve ATC elimination rates within WWTPs.

3. Do we need an all-inclusive chemical analysis of ATCs or can we do more with less?

ATCs pose a tremendous challenge for chemical analytics, in terms of comprehensive detection and sensitivity of the methods applied (Section 3.1) as well as in the reliability of the data gained due to uncertainties in sampling protocols and boundary conditions (Section 3.2). Moreover, ATC analysis is associated with high costs of instruments, consumables and human resources; consequently there is now a paradigm shift towards the routine detection of the so-called indicator substances (Section 3.3).

3.1. Progress and limitations in instrumental analysis

The major subject of papers on ATCs concerns methodological issues in chemical analysis and there are numerous reviews that report on various approaches and instruments (Richardson and Ternes, 2014). Briefly, in recent years, the analytical trend is the application of high-resolution mass spectrometry (HRMS) coupled to gas or liquid chromatography (GC/LC) (Comerton et al., 2009; Richardson and Ternes, 2014). With recent instrumental development, time-of-flight (TOF) mass spectrometers are capable of full-scan mass spectra for all analytes without a loss in sensitivity; this allows derivation of empirical formulas and chemical structures of targeted as well as non-targeted analytes of a polar, non-volatile nature (Richardson and Ternes, 2011, 2014). However, broader screening under increasing resolution of analytes is only part of the challenge; the association of ATCs with complex water matrices hampers the establishment of one standardized method for the analysis of all micropollutants in environmental waters (Comerton et al., 2009). In that respect, GC/MS, which is mainly applied for non-polar and volatilizable compounds, has the advantage of being less prone to matrix interferences (Reddersen and Heberer, 2003). Yet, atmospheric pressure photoionization (APPI) has been increasingly applied due to its improved ionization for non-polar compounds (Richardson and Ternes, 2014). The newest trend is to avoid complicated and time-consuming sample preparation such as solid phase extraction (SPE) or other preconcentration steps by injecting complex water samples directly onto an LC column (aqueous injection-LC/MS, Richardson and Ternes, 2014).

Despite the welcomed increase in sensitivity, the analytical costs remain or even multiply; this makes a comprehensive screening of all ATCs far too expensive. As a consequence, most studies deliver either few data points of low temporal (e.g., only 5% of about 4000 sites investigated for ATCs in Europe were monitored every year) and spatial (e.g., fewer investigations in South Europe and the Baltic States as compared to Northern Europe) resolution or investigate selected compounds only, and mostly a combination of these restrictions applies (Malaj et al., 2014). On top of that, inter-laboratory trials revealed huge differences in accuracy and traceability of the results. Therefore, besides higher instrumental sensitivity, internationally standardized analytical methods and new certified reference material that resembles natural waters are needed (Coquery et al., 2005).

3.2. The importance of appropriate sampling designs

With enhanced sensitivity of the chemical analyses, it becomes increasingly important to reflect on sampling strategies as they can represent a major source of inaccuracy (Ort et al., 2010). A survey of 87 articles on PPCPs revealed that 99% explain their analytical methods while, in contrast, only 11% of the analysed articles describe sampling protocols (Ort et al., 2010). This scientific perception concerning sampling strategies is symptomatic and unfortunate. Proper sampling is important for both the quality of the environmental data gained and their comparability to other studies, locations or times in order to derive large-scale conclusions and assessments. To start with, the right time and frequency of sampling is in particular decisive for ATCs that show high and compound-specific dynamics on the daily or seasonal scale. WWTPs face this challenge of daily strong fluctuations in continuously incoming ATCs (Fig. 1 shown for three pharmaceuticals and one urban pesticide) along with the episodic appearance of other ATC classes (e.g., pesticides, insect repellents) (taken from Steinmetz and Kuch, 2013). Neglecting these short- and long-term variations in ATC occurrence precludes understanding of dynamic processes in the environment and may even lead to wrong conclusions in terms of elimination success within WWTPs. The latter is illustrated in Fig. 2 (taken from Steinmetz and Kuch, 2013) where the 48 hour-variations in tris-(2-chlorethyl)-phosphate (TCEP) concentrations in the influent and effluent indicate two aspects: first of all, determination of elimination success or failure depends strongly on the time of sampling and, secondly, the pre-treatment of the samples (here filtered versus unfiltered) might severely impact the absolute and relative concentration patterns of substances tending to sorb onto particles. In this context, "diffusive gradients in thin films" (DGT) is an interesting approach for minimizing the effects of fluctuations during sampling (Davison and Zhang, 2012). DGT can provide information on solute concentrations and dynamics in sediments, soils and water. So far, however, systematic investigations have focussed mainly on trace metals.

Besides the crucial pre-treatment steps, sampling preservation to suppress biological action or avoid chemical oxidation is a similarly important aspect: pH changes due to acidification, for example, might induce a shift in phase distribution (e.g., for diclofenac Steinmetz and Kuch, 2013). Furthermore, the choice of sampling equipment used for sampling, transport and storage is decisive in order to avoid both, sorption of lipophilic ATCs and leakage processes of material components such as softener (Hillebrand et al., 2013; Mompelat et al., 2013; Ort et al., 2010).

One of the most important but often neglected issue concerns the documentation of metadata associated with the sampling to identify and trace all sources of possible variations (Hanke et al., 2007). Consequently, conditions such as pH values, conductivity, temperature, suspended particulate matter or chemical and biological oxygen demand should be recorded on a routine basis (Hanke et al., 2007). The same applies to flow variations due to meteorological conditions, water consumption or type and conditions of sewer; thus ideally, normalized loads should be reported (Ort et al., 2010). Without this metadata, it is hardly possible to compare the data within one location and between different lakes, river basins or WWTPs. With some constraints, harmonized sampling guidelines and validated methods have been developed for monitoring campaigns e.g., in Europe through CEN/TC230 and ISO/TC147, which address most of the above named issues (Coquery et al., 2005). However, less than 5% of the 87 reviewed studies on PPCPs considered internationally acknowledged sampling designs (Ort et al., 2010). Additionally, proficiency testing schemes or external quality control is missing entirely (Coquery et al., 2005; Hanke et al., 2007). This is a major obstacle to more reliable and comparable ATC detection, to complement specific case studies with large-scale analyses and successfully implement internationally valid and comparable laws (Allan et al., 2006; Malaj et al., 2014).

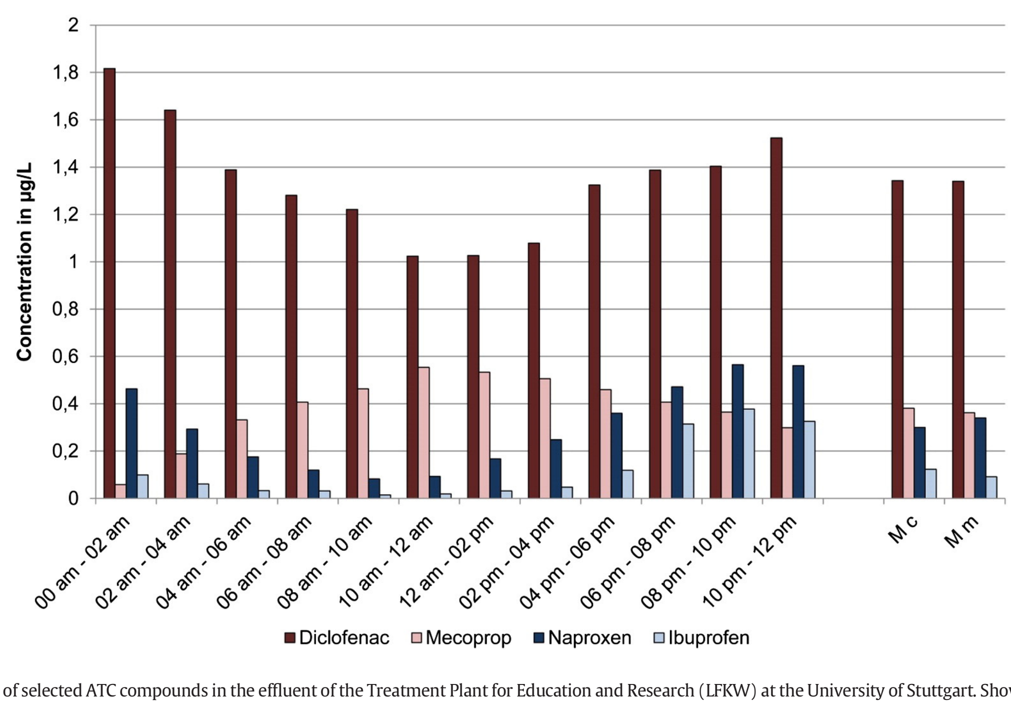

Fig. 1. Daily fluctuations of selected ATC compounds in the effluent of the Treatment Plant for Education and Research (LFKW) at the University of Stuttgart. Shown are the concentrations of three pharmaceuticals and one urban pesticide over 24 h at dry weather discharge. The samples were taken as 2 h-composite samples and analysed using GC/MS. The calculated (M c) and measured (M m) mean values are indicated on the right side. The measured mean values were obtained by analysing the 24 h-composite sample.
Graph from Steinmetz and Kuch, 2013 and complemented with mean values by Claudia Lange.

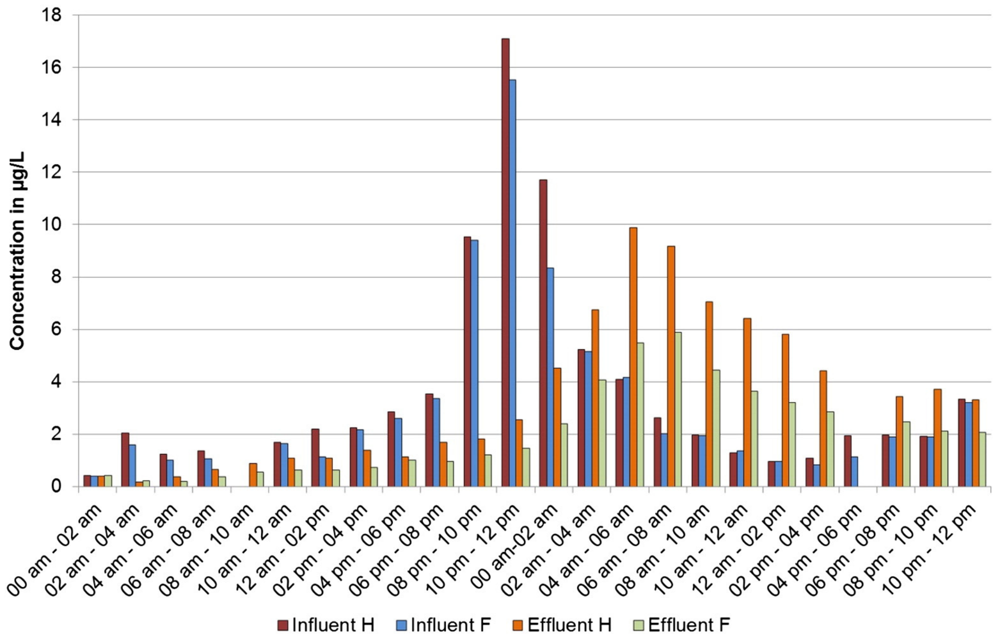

Fig. 2. Diurnal variations of the flame retardant tris-(2-chlorethyl)-phosphate (TCEP) in the influent and the effluent of the Treatment Plant for Education and Research (LFKW) of the University of Stuttgart. Shown are the concentrations over 48 h. The samples were taken as 2 h-composite samples and either measured directly (homogenized, H) or filtered (F). Graph from Steinmetz and Kuch, 2013.

3.3. The innovative way towards indicator substances

As much as it is indispensable to reduce data uncertainties by ideally unified sampling and analytic strategies, it is virtually impossible to address *all* of the more than 100,000 compounds within the daily used ATC cocktail at all times and locations (Schwarzenbach et al., 2006). Instead, targeted combinations of surveillance (providing baseline data), operational (additional data for water bodies at risk) and investigative (assessing causes of failure, process understanding) monitoring strategies are needed (Allan et al., 2006). This, however, requires the selection of indicator ATCs; thus it has been suggested to prioritize and target those substances that pose the greatest risk to human health (Benner et al., 2013; Schwarzenbach et al., 2010). This approach is problematic because it is difficult to categorize ATCs according to their toxicity (e.g., Goetz et al., 2010) based on too little ecotoxicological data available to validate "predicted no-effect concentrations" (PNECs) of single substances, let alone ATC cocktails. Other attempts at ATC prioritization focus on certain product classes (e.g., pharmaceuticals, Besse and Garric, 2008) or exposure pathways (e.g., stormwater runoff/combined sewer overflow and WWTPs, respectively, Birch et al., 2011; Reemtsma et al., 2006). This mode of selection highlights only a fraction of the ATC cocktail or ATC sources and needs constant updating because, almost daily, new ATCs enter the market while others have been phased out (e.g., lindane, DDT European Parliament 2004). Consequently, rather slow legal enforcement (e.g., the European Union took about 12 years to develop their water framework directive) is mostly overtaken by ATC market discontinuities. This has led to a paradigm shift away from the detection of single compounds towards the identification of reference substances. In this regard, it seems promising to screen selective compounds according to their physico-chemical properties as has been done for the atmospherically transported and globally distributed POPs (e.g., Brown and Wania, 2008). The work of Goetz et al. (2010) as well as Jekel et al. (2013) is based on the same idea to prioritize aquatic ATCs by their phase distribution, persistence and input dynamics. Goetz et al. (2010) distinguished seven exposure categories and presented potentially water-relevant micropollutants for Switzerland according to three factors: (1) their presence in surface waters, (2) the availability of data on annual consumption and (3) analytical methods for detection. While the approach of Goetz et al. (2010) focuses mainly on water-soluble ATCs and targets micropollutants typical to the Swiss situation, we propose to broaden this approach for non-polar and ubiquitously occurring substances. The latter is particularly important when considering the whole water cycle instead of merely individual compartments (e.g., surface waters) or individual systems (e.g., WWTPs).

Based on our own extensive monitoring data sets, intensive literature survey and well-known physico-chemical properties, we propose to categorize ATCs in 4 classes: A) water-soluble, effectively biodegradable, (B) particle-bound, effective elimination by solids removal, (C) particle-bound, effectively biodegradable and (D) water-soluble, non-biodegradable (Fig. 3, Table 1). ATCs in each of these four classes have an important indicative role; for instance reference ATCs from categories (A) and (C) can indicate problems from direct wastewater discharge (e.g., by storm surge from sewer overflow) or insufficient elimination within WWTPs (e.g., by disturbed processes with low biological activity, short retention times). The absence of indicator ATCs from (B) in surface waters infer that the solids separation in WWTPs is working well, while increasing concentrations could imply diffusive entry by erosion of agricultural land or surface runoff. If ATCs of type (B) enter the environment, they might bind to fine sediments to be transported over large distances in aquatic systems until they finally deposit and accumulate; thus having huge implications on sediment and habitat quality. Substances that fall into category (D) are not eliminated by WWTPs without an additional treatment step for ATC removal and as such, pose a great risk to the aquatic surface and subsurface waters. Most research efforts focus on type (D) substances, reflected in prohibition lists and papers. Fig. 3 and Table 1 indicates potentially suitable reference ATCs from all four classes (e.g., caffeine, carbamazepine, triclosan) that are relevant in terms of their concentrations, easy to detect with common methods in sufficient accuracy and where a sound data basis should be available. Selection of these appropriate ATCs for innovative monitoring campaigns would indicate elimination success or failure, identify hot spots of contaminations and verify protection measures; both in technical and natural systems. Although routine detection of these indicator substances does not primarily aim to judge on the bioavailability or toxicity aspect of the scenarios discussed

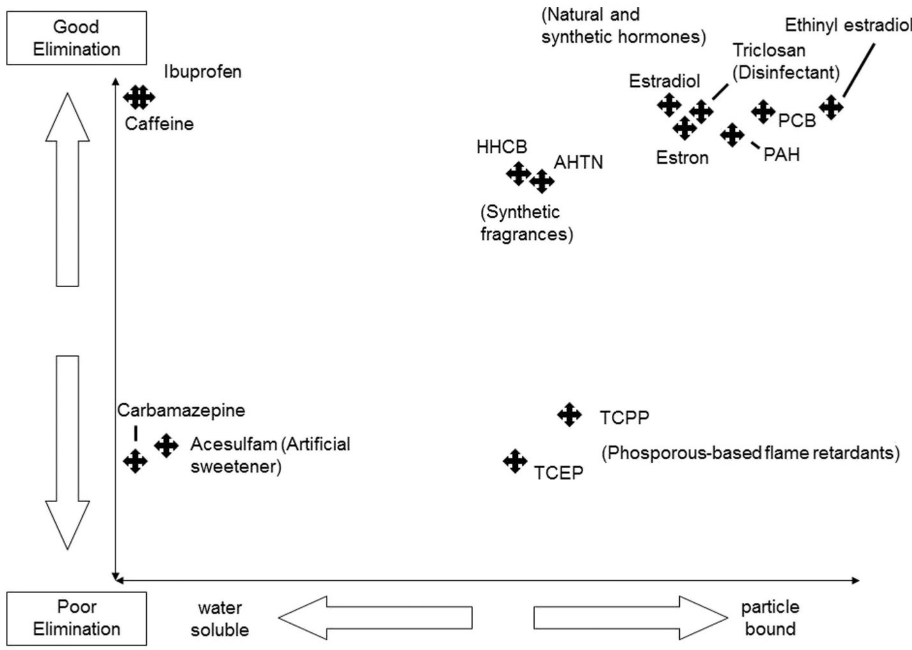

Fig. 3. Elimination behaviour of selected micropollutants in municipal wastewater treatment process.

above, it would be highly desirable to link this scheme to environmental risk assessment (ERAs) of ATCs in the near future.

4. Are the acute and long-term effects of ATCs related to concentration, cumulative or synergistic effects and mode of actions?

To answer this question, biomonitoring approaches give a highly sensitive indication of ATC presence and ecotoxicological effects and thus have a great potential as early warning systems, although some issues remain to be addressed such as cross-sensitivity or background noises (Section 4.1). Whereas biomonitoring measures biomarkers and effects using field-exposed biota, bioanalytics use experimental in vitro or in vivo setups to determine the hazardous potential of ATCs under controlled exposure conditions. As a consequence, bioanalysis can not only detect but also quantify toxic effects at various concentrations of ATCs (Section 4.2). To unravel the mechanisms behind a certain toxic effect caused by ATC exposure, present research aims at developing biomarkers for different organisation levels ranging from (sub)cellular target sites to adverse effects on whole organisms. When looking at the impact on populations and communities, intra- and interspecies relations need to be considered too (Section 4.3). The big challenge is the long-term exposure of the ecosystem to a complex cocktail of ATCs; in this context, passive sampling and passive dosing is increasingly used to better mimic natural uptake routes and exposure conditions, respectively. Finally, to combine biotesting with chemical identification in one sample is an additionally promising Line of Evidence (Section 4.4).

Table 1
ATC classes, respective indicator substances and their ability for indication of different emission sources.

ATC class	Indicator substances		Assessment of	Indication for		
	Substance class	Single substances	Advanced wastewater treatment	Treated municipal wastewater	Untreated municipal wastewater	Surface runoff (e.g., traffic or agriculture)
A: water-soluble, effectively biodegradable	Food ingredients	Caffeine	−	−	+	−
	Pharmaceuticals	Ibuprofen	−	−	+	−
	Industrial chemicals	TAED	−	−	+	−
B: particle-bound, effective elimination by solids removal	Personal care products	Triclosan	−	−	+	−
		Synthetic musks: HHCB, AHTN, HHCB-lactone	−	(+)	+	−
	Industrial chemicals	Flame retardants: TCEP, TCPP	−	−	+	−
	Others	PAH	−	−	(+)	+
C: particle-bound, effectively biodegradable	Steroids	Cholestane, cholestanole	−	−	+	+
D: water-soluble, non-biodegradable	Pharmaceuticals	Diclofenac	+	+	−	−
		Carbamazepine	+	+	−	−
		Metoprolol	+	+	−	−
		Sulfamethoxazole	+	+	−	−
		Lidocaine	+	+	−	−
	Industrial chemicals	Benzotriazole	+	+	(+)	−
	Urban pesticides	Mecoprop	+	(+)	−	+
	Personal care products	DEET	+	+	−	−

DEET: insect repellent N,N′-diethyltoluamide; HHCB: synth. fragrance galaxolide; AHTN: synth. fragrance tonalide; TCEP: phosphorous flame retardant tris-(2-chloroethyl)-phosphate; TAED: tetraacetyldiethylenediamine (bleach activator in washing agents); HHCB-lactone: degradation product of HHCB; TCPP: phosphorous flame retardant tris-(chloropropyl)-phosphate.

4.1. Biomonitoring: highest sensitivity at lowest concentrations

Despite progress in the sensitivity of chemical analysis, some ATCs occur well below the analytical limits of most currently used routine methods (Loos et al., 2010; Richardson and Ternes, 2014). More importantly, the presence of detectable ATCs gives no information on their bioavailability and toxic potential. Consequently, there is a need for highly sensitive on-site warning systems that are effect-based but still robust, easy-to-use, capable of high sample throughput and automatable. Effect-based monitoring approaches possess great potential as early warning systems due to their quick metabolic reactions and ability to integrate over the entire toxic potency. The general idea is that an organism or even a subcellular bioanalytical system exposed to certain molecules (or groups of molecules) responds with a detectable signal. These reactions might either indicate acute celltoxic, mutagenic, genotoxic, immunotoxic or teratogenic effects or a combination hereof. In this context, ATCs with the potential to alter biology and behaviour of organisms are of special interest. For instance, endocrine disruptors exhibit a detrimental impact on reproduction through interfering with the hormonal system. Neurotoxins are capable of altering feeding, reproduction and survival success, thus having consequences for the fitness of whole populations. While these toxic effects are quantified in bioanalysis (Section 4.2) and modes of actions are revealed by biomarkers (Section 4.3), biological screening approaches generally give only a simple yes/no answer. Nevertheless, as a first step, this provides valuable and relatively fast information on ATC occurrence.

Bacteria have long been preferred in these biomonitoring systems due to their rapid response, their relatively easy genetic manipulation and the low maintenance costs. However, adapting laboratory-based bioanalytical systems to a setup with online measurements represents a huge challenge that involves (1) coping with the cross-sensitivity to other molecules relevant in natural or technical systems (e.g., humic acids), (2) enhancing the biological signals above background noises, and (3) successfully immobilizing the organisms to avoid washing-out effects. Nevertheless, there has been progress; for instance a real-time toxicity test based on the fluorescence of a modified bacterial strain has been proven to be successful for detecting phenol, toluene and benzene as well as several heavy metals in wastewater (Cho et al., 2004). Besides tests on respirometry, active and passive luminescence, nitrification or enzyme inhibition, the bioluminescence assays with *Vibrio fischeri* or *Photorhabdus luminescens* are the most widely used and prominent bacterial assays (Girotti et al., 2008).

However, to better account for sub-lethal ATC concentrations and cover a broader spectrum of possible biological responses, there is nowadays a trend to extend effect-based tools for riverine monitoring to higher eukaryotic organisms. This is for instance pursued by the NORMAN network of reference laboratories, research centres and related organisations to monitor emerging environmental substances. Online monitoring systems using image processing-based analysis of the swimming behaviour of daphnids (Lechelt et al., 2000; Ren et al., 2007) are receiving wide attention. Recent studies with *Polystichum setiferum* (plant assay) and embryos of *Danio rerio* (fish assay) revealed their potential as sensitive alarm systems through alterations in fertility, sex ratios, growth, behaviour and changes in DNA at low, environmentally relevant concentrations (67–500 ng/L) of pharmaceuticals (Esteban et al., 2013). The high sensitivity of such biological test systems is linked to the higher number of possible target sites for pollutants in more complex organisms. Furthermore, in terms of human-health related questions, higher organisms may react more similarly to toxic substances than protozoa or bacteria. Thus, tests with higher organisms help to describe the relevance of ATC-related environmental issues to the broader public and policy-members.

Other promising approaches involve biospectroscopy methods applying FTIR (Fourier transform infrared spectroscopy), ATR (Attenuated total reflection)–FTIR, Raman spectroscopy, NIRS (Near-infrared spectroscopy), or MALDI (Matrix-assisted laser desorption/ionization)–FTIR. With these non-invasive techniques, damages can be detected on (sub)cellular level through alterations in the spectral biochemical fingerprints; the latter represent the architectural structures of a tissue, cell or biomolecule (Martin et al., 2010; Obinaju and Martin, 2013). Biospectroscopy is a robust and cost-effective technique that allows high-throughput capabilities and has been successfully applied for investigating effects of, e.g., PBDEs (Barber et al., 2006), PCBs (Llabjani et al., 2010) and OCPs (Ukpebor et al., 2011). It also has been proven to be applicable to rather unusual matrices such as bird feathers (Llabjani et al., 2012).

4.2. Bioanalysis: quantifying toxic effects for improved health risk assessment and management

The primary purpose of biomonitoring is to detect potentially harmful pollutants in the environment. Bioanalysis using in vitro assays goes one step further to expose single species to ATCs at various concentrations in the laboratory and to reveal the biological response of the monitored biota. This allows derivation of specific effect concentrations, such as the lowest concentration causing a statistically significant effect (lowest observed effect concentration LOEC), the highest concentration causing no effect (no observed effect concentration NOEC) or a fixed effect-level concentration as calculated from a regression of the experimental data (e.g., concentration causing 50% of the observed effect EC50). This evaluation allows the establishment of EQS values that should not be exceeded by actual ATC concentrations in order to maintain the health of the water body; this is called "compliance checking" (Coquery et al., 2005; Goetz et al., 2010).

As for biomonitoring, the high sensitivity of bioanalytical tests is a key advantage: for instance, they are increasingly being used to evaluate the efficiency of tertiary water treatment steps for removal of natural and synthetic hormones, because they can be applied even for ATC concentrations below current chemical analysis capabilites. For example, a successfully reduced oestrogenicity was reported for hospital effluents (Esteban et al., 2013; Maletz et al., 2013). A prominent example for environmental compliance checking at lowest concentrations concerns 17-alpha-ethinylestradiol (EE2) and the natural hormone 17-beta-estradiol (E2). Both substances influence the sexual function and differentiation in aquatic organisms at very low concentrations, and both occur below the analytical limits of quantification of most routine chemical methods (Loos et al., 2010). Because of their dose-dependent effects demonstrated by the feminization of fathead minnow (*Pimephales promelas*) males and the resulting near extinction of this species due to impacted reproduction (Caldwell et al., 2008; Kidd et al., 2007), these two substances are now listed as priority substances with EQSs of 35 pg/L for EE2 and 0.4 ng/L for E2, respectively (European Commission, 2011). These bioanalytical investigations using whole organisms exposed to the complex environmental sample most accurately represent the (bio)availability and the current risk due to ATC contamination on site.

4.3. The complexity of various test systems from cell-based tools to environmentally valid endpoints

While whole-organism approaches are generally time and labour-intensive with a low sample throughput rate, miniaturised test systems offer a rapid screening with statistically necessary replication for large spatial scale studies. They use specific cell lines or small organisms (e.g., embryos of *D. rerio*) that cover a range of major ecotoxicological endpoints such as mutagenicity/genotoxicity, endocrine disruption or dioxin-like activity (e.g., Eichbaum et al., 2014; Keiter et al., 2006; Reifferscheid et al., 2008). Most assays are conducted in microtiter plates, and determination of the biomarker is realized via adsorption and/or fluorescence/luminescence measurement by means of a multiwell microplate reader.

Recently, the use of such sensitive small-scale effect-based tools (i.e., simple in vitro oestrogen-receptor transactivation assays) for the screening of oestrogenic activity for EQS compliance monitoring was recommended by the technical report on Aquatic Effect Based Monitoring Tools of the European Commission to overcome the detection problems in chemical analytics (Wernersson et al., 2014). For instance, the Yeast Estrogen Screen assay (Routledge and Sumpter, 1996 adapted to; Schultis and Metzger, 2004), the commercial ER CALUX® (Estrogen Receptor-mediated Chemically Activated Luciferace gene expression; Van der Linden et al., 2008), and the non-commercial T47D-Kbluc assay (Wilson et al., 2004) are three widely used oestrogen receptor transactivation assays that represent suitable tools for monitoring oestrogenic activity (Hecker and Hollert, 2011; Kase et al., 2009).

If these biological miniature-test systems give rise to alarm, one can verify effects on whole organisms through in vitro approaches in the laboratory. Whole organisms' approaches have long been an indispensable part of the standardized program in monitoring water quality: best known is the trilogy test series on algae (*Lemna minor*), small crustaceans (*Daphnia magna*) and fish (*Leuciscus idus*) (OECD iLibrary ISSN 2074–5761). However, with this limited selection of tests, the various modes of action of a given pollutant are unaccounted for (Fent et al., 2006). The same substances might cause hugely different effects depending on the organisms (Escher and Hermens, 2002; Posthuma et al., 2001). Moreover, the same substance might also induce a variety of effects as shown by the study of Waring and Harris (2005) who reported effects of endocrine disruptors that extended beyond altering reproduction to immune function, behaviour and memory. This clearly illustrates the complexity of the subject and the challenges ahead to assess the environmental risk of ATCs.

The challenge for future studies therefore lies in the identification of the differences in toxicity in different phyla and to establish species sensitivity distribution curves. To get a more comprehensive idea of ecotoxicological effects, test systems need to cope with low concentrations to judge possible impairment of communities in terms of their functionality and diversity. In this context, biomarkers (measurable metabolic products to indicate pollution exposure) in whole organisms can be used to reveal the underlying modes of action (Brinkmann et al., 2013; Hudjetz et al., 2013).

Altogether, proven harm on single organisms in the laboratory is just the first step towards environmental relevance: one needs to verify the tested effects in the natural surroundings. However, this is complicated due to three issues: (1) various intra- and interspecies relations, (2) the complex cocktail of ATCs experienced by the single organisms and (3) chronic effects that are too long-termed to be visible in short-term laboratory tests. For tackling the issue (1) of intra- and interspecies relations, there are new test approaches based on structural changes in the species composition, for instance within biofilms (e.g., PICT — pollution induced community tolerance studies, Rotter et al., 2011). These approaches account for effects on population and community levels and need more consideration in the future. Since toxicological effects of ATCs will impact the sub-cellular target sites up to shifts on the population level, it is important to develop a test battery that can sufficiently mirror the most vital levels of complexity. The second issue (2) on the huge variety of ATCs in the aquatic environment has been addressed in recent years by studies that investigated the combination effects of e.g., pharmaceuticals (Cleuvers, 2003; Pomati et al., 2008), metabolites (Wetterauer et al., 2012) or pesticides (Relyea and Hoverman, 2006; Rodney et al., 2013) on aquatic organisms. Beyond single molecule classes, the organisms are exposed to larger numbers of ATCs with varying physico-chemical features and toxicity, as well as combined effects on aquatic life and human health; especially over longer exposure times. The latter constitutes a general problem in ecotoxicology: whether miniature system or whole organism approaches, all test systems aim for immediate impairments up to lethal effects. Consequently, we have nowadays substantial evidence on acute toxicity but little information available on chronic effects (Cleuvers, 2003; Lawrence et al., 2009; Pomati et al., 2008; Ricart et al., 2010). Finally (3) we know that many aquatic organisms are continuously exposed to low levels of ATCs over long periods, and hence the evaluation of chronic toxicity by effect-based tools is one of the next urgent challenges in ecotoxicological testing. Research should thus focus on obtaining data from long-term effects, e.g., the selection or stabilisation of antibiotic resistance carriers (bacteria or genetic elements) that impose a possible threat to human health. For both acute and chronic effects we might have strong indication regarding impact at the community and environmental level (e.g., Kidd et al., 2007). Nevertheless, further research is required to give detailed evidence of the adverse effects of ATCs on whole ecosystems, especially when considering synergistic, additive or antagonistic effects in mixtures of ATCs and other chemical compounds in the environment.

4.4. Complementary techniques: the right strategy pinpoints the culprit

Besides the complex issue of choosing the right test to address the appropriate levels and phases of toxicity, the correct choice and application of test material is equally important for a comprehensive toxicity assessment. Physico-chemical properties of ATCs largely determine their bioavailability and hence their toxicity to aquatic life and human health. Consequently, for a reliable risk assessment of ATCs, samples should represent the fractions of contaminants that actually enter the organisms and lead to effects at their target sites. An increasingly important approach to accomplish this is passive sampling using material that mimics substance uptake by aquatic organisms (for an overview cf. Mayer et al., 2003; Vrana et al., 2005). There are different sampler types available to cover a broad range of substance groups (e.g., hydrophilic, hydrophobic). In parallel, the rough separation of ATCs from the complex environmental matrix reduces complexity and facilitates comprehensive bioanalytical analysis of the sample extract. In the next step, one has to consider how and where to dose the sample extract in a defined test system. For instance, materials used in microtiter plates strongly absorb certain ATCs, thus reducing their availability to the test cells or organisms. Furthermore, uncontrolled exposure conditions might result in metabolization, volatilization, photodegradation or other undesired chemical reactions. In order to attain stable exposure concentrations, passive dosing is increasingly used (Seiler et al., 2014; Smith et al., 2010). Here, the freely dissolved concentration of the test substance is controlled during its exposure by partitioning from a reservoir loaded in a biocompatible polymer (Mayer et al., 1999). Future developments need to find ways for a more rapid setup of passive dosing experiments to eventually provide high-throughput capabilities.

When it comes to the question of the specific cause of an observed effect, however, comprehensive determination of the vast number of chemicals typically present in an environmental sample is not possible with current available technology. Moreover, without a priori knowledge of the chemicals existing in the sample, one does not know what to look for. In this context, an approach supplementing chemical analysis with bioanalytical techniques and effect-directed analysis (EDA) has been developed in the last decade. It is based on a combination of fractionation procedures to separate different groups of chemicals, biotesting that pinpoints the active fractions, and subsequent chemical analyses to identify single substances causing the observed effects (Brack, 2003; Hecker and Hollert, 2009). Selection of the appropriate analytical techniques should be guided by the physico-chemical characteristics of ATCs in the specific fractions. EDA studies have already successfully identified unknown chemical stressors and led to new knowledge about the fate and effect of various environmental pollutants (Brack et al., 1999, 2007). Such knowledge has proven valuable to find the source of the contaminants or decide on remedial actions (Higley et al., 2012). Hence, EDA was recently suggested as an additional Line of Evidence in Weight-of-evidence studies (Hecker and Hollert, 2009).

To conclude, whether it is about (online) biomonitoring or small-scale in vitro assays (bioanalytics) in the laboratory, the complexity of environmental samples and ATC composition as well as the variety of potential organisms/targets and possible effects are posing the biggest challenge in ecotoxicological research. Fig. 4 illustrates this complexity on the ecosystem level that again comprises an unknown number of different ATCs as a mixture that can affect the organisms, the different levels of organismal complexity ranging from cellular organisms and targets on a cellular level to complex whole organisms, as well as the variety of different species. Online-biomonitoring and bioanalytics both reduce the original complexity of the ecosystem level when investigating ATCs since they only represent a small part of the entire complexity. Biomonitoring aims at populations but selects one or few species from the entire biodiversity, and bioanalytics further reduce the ecosystem to the individual level. The toxicity of the complete ATC mixture is reduced to the bioavailable part through biomonitoring, whereas testing whole extracts in bioanalytics reveals the toxic potential of the extractable fractions. Organisms are simplified as (sub)cellular targets when applying cell-based tools; biomonitoring systems still focus on the entire organism. Either approach can have weaker or stronger meaning for the different properties of an ecosystem and the immediacy of ATC effects. Therefore, the choice of the test system determines the significance of the acquired data for a particular study aim. For example, when using cell-based bioanalytical tools, data might reveal effects at a cellular level and show the mode of action but with relevance for the individual only. Furthermore, the approach will deliver rapid results on acute effects, however nothing can be said about possible phenomenological adverse outcomes and effects on population levels in the long-run. On the other hand, biomonitoring might provide no information on how a certain effect on the population level can be explained. Results therefore have to be interpreted cautiously to assess the environmental relevance of ATC exposure. If necessary, effect-directed analysis (EDA) can be applied for substance identification and structure elucidation.

5. Are WWTPs the main pathway of ATC emission from urban areas or are there other exposure paths to consider?

WWTPs are not specifically designed to remove ATCs and thus, their elimination is at best erratic. Since certain ATC classes are linked with their exposure paths, PPCPs have been most associated with WWTP discharge of ATCs into receiving waters (Section 5.1). Besides these obvious “down the drain” compounds, very different ATCs such as urban pesticides or polycyclic aromatic hydrocarbons (PAHs) from surface runoff or sewer basins overflow might also reach WWTPs, but there is an equal risk of direct emissions into the environment (Section 5.2). Moreover, the increasing recycling of biosolids from WWTPs constitutes another important pathway of ATCs to the environment (Section 5.3).

5.1. Passage of ATCs through the WWTP

Although ATCs might enter the aquatic environment by diffuse sources (e.g., pesticides on agricultural land), it seems evident that most ATC release is due to their utilization in households, institutional, commercial or industrial sectors, thereby generating domestic and industrial wastewater streams, respectively, that reach WWTPs (Fig. 5). Conventional wastewater treatment employs mechanical, chemical and biological processes to precipitate and degrade wastewater constituents like organic carbon, nitrogen and phosphorus and to separate solid fractions (sludge). While these procedures are supposed to provide an environmentally safe effluent stream in order to protect the receiving environment, the traditional treatment steps are not designed to remove ATCs (Bolong et al., 2009). Numerous studies address the passage of selected ATCs through WWTPs by investigating their concentrations in the influents and effluents (reviewed by Luo et al., 2014) and two major findings seem to be most relevant.

Firstly, the elimination of ATCs varied greatly, from 0% (e.g., fire retardant TCEP, Loos et al., 2013) up to 100% (e.g., pharmaceutical acetaminophen, Behera et al., 2011); as previously indicated in Section 3.3. Thus, although not specifically addressed in current WWTPs, ATCs are

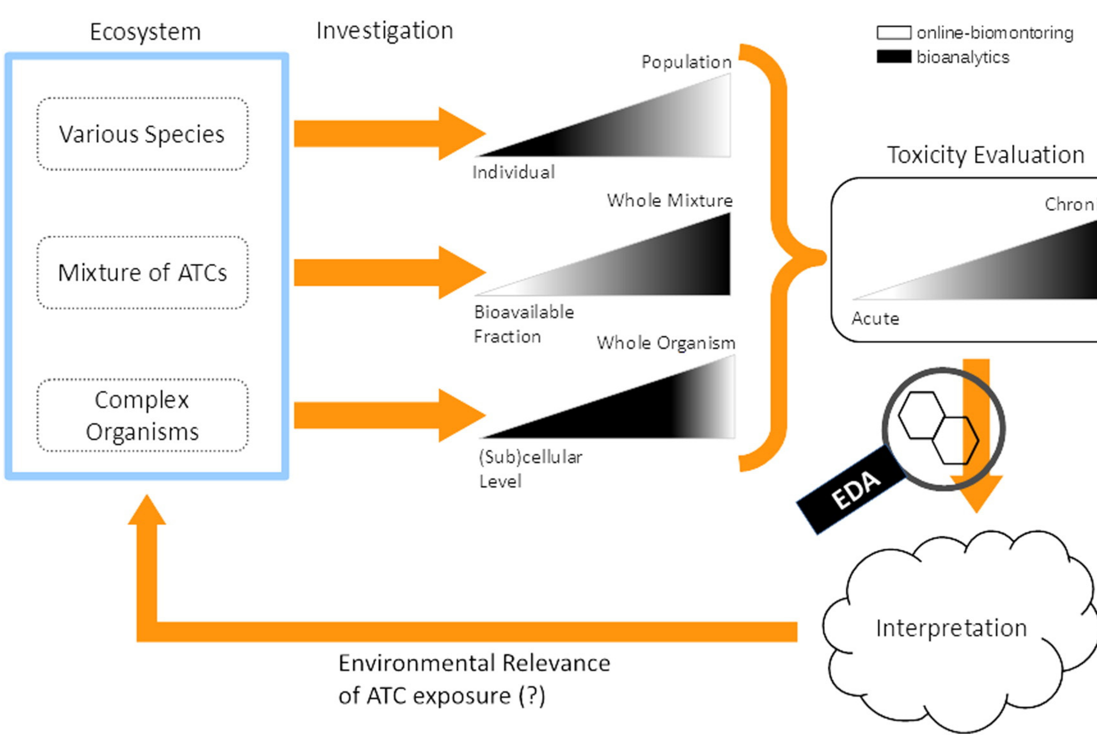

Fig. 4. The complexity of ecotoxicological investigation and evaluation of ATC exposure. Gradients roughly depict relation of the respective property to either online-biomonitoring or bioanalytics. Refer to the text for detailed explanation.
Graph by Thomas-Benjamin Seiler.

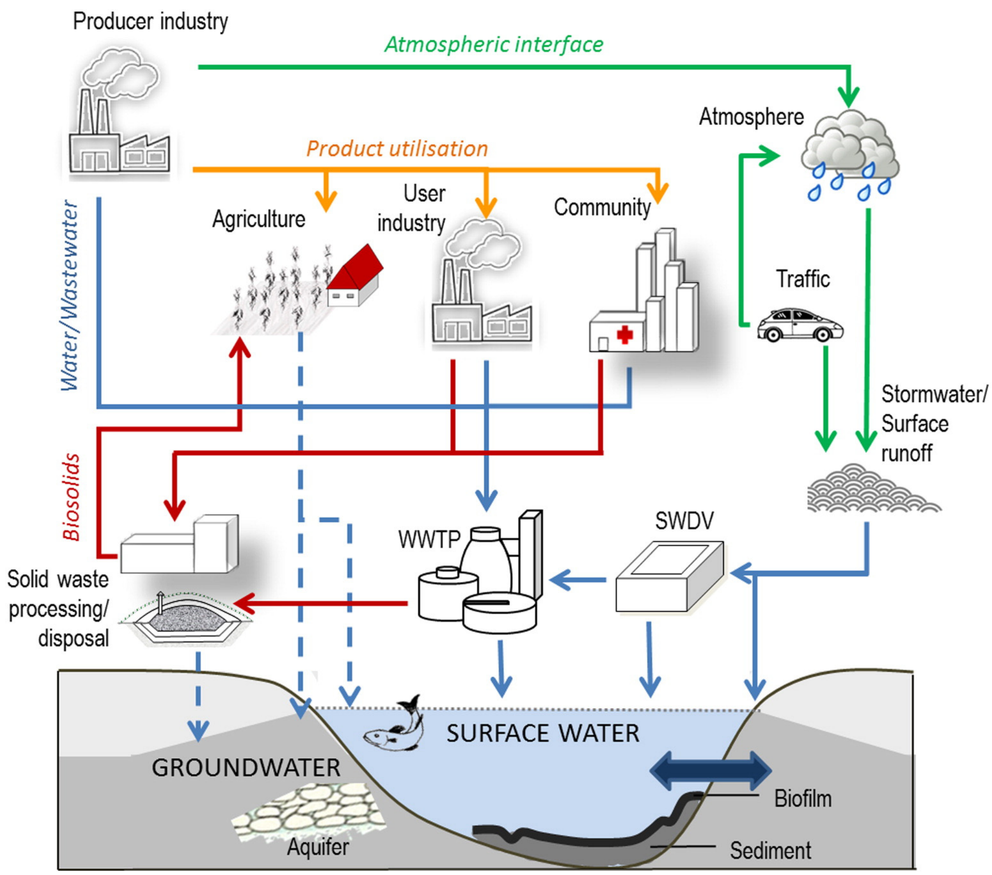

Fig. 5. Exposure pathways of ATCs into the aquatic environment (WWTP: Wastewater treatment Plant; SWDV: Stormwater Detention Vault). Note: the term biosolids represents here both, the use of WWTP sludge (strict sense of the word biosolids) and biowaste (organic waste from compost or digestate) for fertilizing fields.
Graph by Demet Antakyali (Grontmij GmbH).

potentially removable during treatment if they are highly degradable (e.g., anti-inflammatory ibuprofen) or if they associate with the segregated particles (e.g., disinfectant triclosan). However, the removal of some ATCs in these categories is erratic and inefficient and many ATCs will be released into and accumulate in the aquatic environment (Malaj et al., 2014; Schwarzenbach et al., 2006).

Secondly, the overview of Luo et al. (2014) confirmed that the majority of ATCs investigated in wastewater streams belongs to the PPCPs grouping; all of which are "down the drain" compounds. Various studies established a clear link between the production amounts, the usage pattern and the occurrence of PPCPs in WWTPs (Choi et al., 2008; Kasprzyk-Hordern et al., 2009). In identifying WWTPs as the main pathway of these ATCs to the environment, PPCPs became a major focus of studies on ATC removal potential by conventional treatments (e.g., Behera et al., 2011; Gracia-Lor et al., 2012). Nevertheless, there are other classes of ATCs that find their way to WWTPs, for instance industrial chemicals such as the plasticizer bisphenol A. Such industrial chemicals are released into wastewater streams on the manufacturing level (here: during the production of plastics or resins) and, later on, after usage in households (e.g., Kasprzyk-Hordern et al., 2009).

It seems useful to distinguish ATCs into product classes with targeted features since their utilization purpose strongly determines whether they end up in WWTPs. Consequently, this type of classification is implemented in laws and regulations (e.g., Medicinal Products Act/The Drug Law, Federal Law Gazette 2011 or REACH Registration, Evaluation, Authorization and Restriction of Chemicals, Regulation EC No 1907/2006). However, much more important is the actual behaviour of each ATC substance, which varies significantly within one product class and depends on their physico-chemical properties that determine elimination, possible transport and environmental impact (see also Section 3.3.).

5.2. Often neglected but important: stormwater runoff and combined sewer overflow

As mentioned above, WWTPs are a continuous conduit of ATCs discharged with the sewage from households and industry. However, during rain events, WWTPs connected to a combined sewer system face not only PPCPs or industrial chemicals but also other ATC classes: incoming pesticides such as mecoprop which are generally used in "weed-and-feed"-type lawn fertilizer, on facades or in roof greening as well as organo-phosphorous compounds, PAHs and benzothiazoles from e.g., tire abrasion and road wear (Koeleman et al., 1999; Singer et al., 2010). This rather distinct entry of ATCs from surface runoff poses a huge challenge for conventional treatment. Although these ATCs from surface runoff can be partially eliminated within the WWTP, all overall it leads to a greater variety of ATCs discharged into the receiving waters by WWTPs' effluents.

The bigger problem concerns heavy rainfalls that induce the overflow of filled sewer basins (Luo et al., 2014, Fig. 5). In this case, ATCs from surface runoff as well as from sanitary and industrial sewage are directly discharged into the receiving water bodies. This direct emission of untreated contaminated water into the aquatic environment is highly undesirable. ATCs in surface runoff from streets or building/roofs are then accompanied by airborne pollutants from traffic and industrial emissions that are washed out by rainfall from the atmosphere (Singer et al., 2010); most of them being in the upper ecotoxicological range (e.g., Malaj et al., 2014). Along with the washout of pesticides from agricultural activities (e.g., Wittmer et al., 2010), the aquatic habitat might face a sudden exposure to various ATC substances at once, with unknown synergistic, additive or antagonistic effects.

5.3. Recycling of organic solid waste and biosolids — a win–lose situation

The problem of diffusive ATC entry has been enhanced due to the ambitions to recycle solid waste (generated by any type of treated/digested organic material) and biosolids (originating from the sludge of WWTPs) (Fig. 5). For nutrient recovery, in particular for geogenic phosphorous, it makes sense to re-use biosolids on fields or irrigate agricultural land with wastewater. Moreover, compost or digestate from separately collected biowaste is used as a substitute of mineral fertilizer and to improve soils by e.g., providing organic substances (humus) and increasing field capacity. In addition, European and national laws on renewable energy aim to reduce organic substances disposed in landfills, while at the same time, the biogas production from organic waste is promoted. Consequently, recycling of organic solid waste from municipal or agricultural sources has been drastically increased in recent years. Simultaneously, the quality and quantity of the organic residuals, in particular regarding ATCs, changed. For instance, the use of animal manure as co-fermentation substrate in anaerobic digestion increases the antibiotic and hormone concentration in the digestate (Amlinger et al., 2004; Duran-Alvarez et al., 2014). More work is needed to ensure the quality of organic fertilizers in terms of re-usability concerning ATC contents. Aerobic or anaerobic treatment of municipal biowaste and biosolids produces composted or fermented residuals which may not only contain important nutrients and minerals, but also ATCs from pesticides, plastic additives, solvents, and food stabilizers (Amlinger et al., 2004; EU, 2004; McGowin et al., 2001). Hence, the reuse of biosolids (sewage sludge and secondary fertilizers) on farmland, nowadays a common procedure in Europe, has raised safety concerns regarding possible contamination by ATCs (Petousi et al., 2014; Sadej and Namiotko, 2010). Several studies have revealed considerable concentrations of PAHs, biphenyls, dioxins, furans, pesticides, phthalates, tensides and PCBs (polychlorinated biphenyls) in compost and liquid digestate from biowaste treatment (Braendli et al., 2007; Christian-Bickelhaupt et al., 2008; McGowin et al., 2001; Pereira and Kuch, 2005; Sadej and Namiotko, 2010). A study of the Swiss Environmental Office has shown that concentrations vary depending on the type of treatment (aerobic/anaerobic) and the process conditions (thermophilic/mesophilic) (Kupper et al., 2008). For instance, some of these ATCs (e.g., PAHs, PCBs, PBDE (polybrominated diphenyl ethers), DEHP (diethylhexyl phthalate)) have been reduced in biowaste during aerobic and anaerobic processes with dependence on the process temperature (Staeb, 2011).

Although ATCs are introduced by this biowaste and biosolid recycling, there is also another aspect: the accumulation of organic matter within the soil increases the sorption rates for ATCs and, thus, might facilitate the filter and degradation capacity of the soil (Duran-Alvarez et al., 2014). In this respect, recent research on bioremediation of PAH-contaminated soil emphasizes the role of humic substances in facilitating desorption of PAHs and their degradability (Sayara, 2010). Nevertheless, there are many knowledge gaps concerning the impact of biowaste and biosolids pre-treatment on ATC occurrence and fate in agricultural soils. Evaluating the effects of treatment conditions on the concentration, persistence and behaviour of organic micropollutants would help policy makers define the best procedures to ensure safe and sustainable recycling of nutrients.

In summary, recycling of biowaste and biosolids introduces those ATCs that were persistent to elimination strategies during solid waste and wastewater treatment into the environment. Thus, whether directly (by effluent discharge) or indirectly (via sewer basin overflow or through recycling of biowaste and biosolids), WWTPs constitute the main pathway of ATCs into the environment (Fig. 5).

6. Elimination of ATCs from water systems: is there a way towards more sustainable approaches at full-scale?

The implementation of innovative technologies for specific ATC removal at full-scale requires answers to crucial questions from fundamental and applied science. Two of the most promising approaches, ozonation and activated carbon filtration, are discussed briefly to visualize the complex interactions between ATC types, boundary conditions and dosage that determine removal efficiency (Section 6.1). Bioaugmentation seems to be another promising approach if the right microbial consortia can be found to cope with the rather low and fluctuating ATC concentrations (Section 6.2). Multistage processes may be the best way forward, but nevertheless, avoidance of ATCs during production and consumption should be the top priority (Section 6.3).

6.1. How to determine the best treatment for ATC removal?

Efficient elimination of ATCs depends on both the chosen position for elimination along the ATC release-and-transport pathway that determines the ATC load and composition and on the chosen elimination technique that is based on the physico-chemical properties of the targeted ATCs. In terms of location, elimination could be conducted either directly at production (point of source), within the treatment plants for solid waste, wastewater and drinking water or at the point of consumption (e.g., through water-tap filters). The elimination point should be economically viable and based on occurrence as well as feasibility. For example, the main load of pharmaceuticals is discharged by household wastewater, not by wastewater from medical facilities (Heberer and Feldmann, 2005). In terms of feasibility, one can choose between, e.g., highly concentrated wastewaters at decentralized locations versus larger mixture of chemicals in lower concentrations at public treatment systems. At present, most efforts have concentrated on elimination techniques at conventional WWTPs (see Section 5.), and we will briefly present the two most promising approaches that are both implemented at pilot-scale and full-scale in Germany. About 10 WWTPs use the named techniques in the German state of Baden-Württemberg (http://www.koms-bw.de) and in Switzerland (http://www.bafu.admin.ch/).

Among the group of oxidative methods, ozonation is a widely discussed option due to its efficiency for ATC removal. In contrast to other oxidants such as hydrogen peroxide, ozone is highly selective in its reactions and has a strong affinity to electron-rich organic functional groups; still it has been shown to produce various toxic and persistent oxidation products (Benner et al., 2013; Benner and Ternes, 2009a, 2009b; Kruithof and Masschelein, 1999). Removal efficiency by ozone towards ATCs is low and highly dose-dependent for some substances. The doses normally applied in WWTPs for general reduction of bacterial counts are not sufficient for complete ATC removal (Benner et al., 2013). Nevertheless, some ATCs might be eliminated to a large extent at low doses (e.g., diclofenac, carbamazepine), while others such as atrazine and iopromide need a higher dose of ozone (Abegglen and Siegrist, 2012). However, higher doses might increase the risk of undesired by-products. Thus, the optimization of ozone doses to remove a wide spectrum of ATCs is a challenge.

The same applies to adsorptive technologies such as the application of activated carbon. Metzger et al. (2012) reported varying removal of 70 ATCs within one municipal WWTP dependent on the activated carbon dosage (Fig. 6). At powdered activated carbon (PAC) doses of 10 mg/L and 20 mg/L, around 25% and 45%, respectively, of the 70 investigated ATCs were reduced with an efficiency of more than 80% (Metzger et al., 2012). Furthermore, the removal efficiency by activated carbon varies as well with the ATC type; Fig. 6 clearly indicates higher elimination of pharmaceuticals as opposed to industrial chemicals at higher PAC dosages. Hence, to judge the additional treatment steps, the choice of the considered ATCs plays an important role and is not

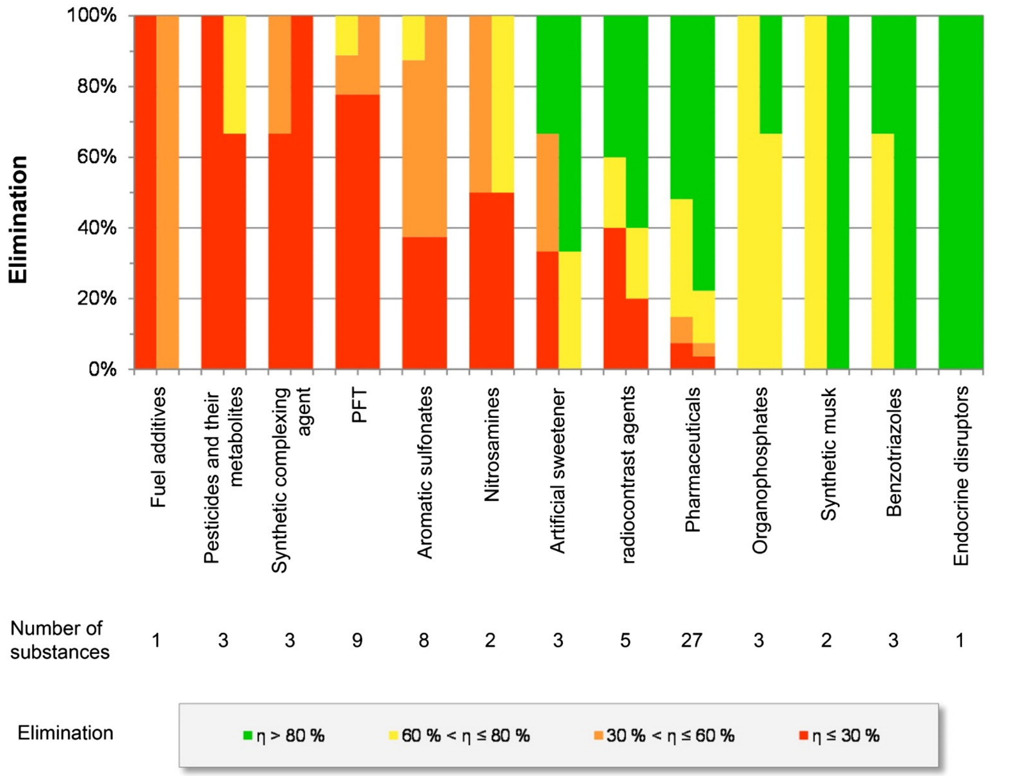

Fig. 6. Elimination of different ATCs by adsorption with PAC at a municipal WWTP; left bars with 10 mg PAC/L, right bars with 20 mg PAC/L. Modified after Metzger et al., 2012.

straightforward for the removal of all ATCs. In addition to the issues on doses and ATC type, the removal efficiency of ATCs by activated carbon strongly depends on the highly variable concentration and type of organic "background" in wastewaters (matrix effects). On the plus side, activated carbon not only targets the semi-polar to polar substances that are not removed by flocculation (e.g., Ternes et al., 2002) but also retains many transformation products resulting from biological or chemical degradation (Benner et al., 2013; Boehler et al., 2012). The high efficiency of activated carbon in ATC removal from wastewater (implemented after the biological treatment and final sedimentation) has been demonstrated repeatedly in the laboratory but rarely conducted at full-scale (e.g., Boehler et al., 2012; Snyder et al., 2007). Nevertheless, there are several issues remaining, ranging from fundamental research questions (e.g., impact of boundary conditions like pH and redox potential on the sorption processes, sorption and desorption of ATCs with very diverse chemical characteristics and different concentrations within complex matrices) to applied issues (e.g., selection of carbon with ideal physico-chemical properties, subsequent detection and separation of activated carbon) to the successful implementation on full technical scale (e.g., cost-effective dosing, contact time, control strategies).

6.2. Is biodegradation the ultimate solution for elimination?

In order to sidestep the additional usage of chemicals (e.g., ozone, flocculants) and to avoid a secondary source of waste (e.g., activated carbon), it is worth evaluating the potential of microorganisms in ATC elimination for future implementation in water and wastewater treatment. This so called "bio-augmentation" approach needs, first of all, successful identification and isolation of single species or microbial consortia that are able to target ATCs. If microbes mineralize ATCs, they might either directly grow on this substrate (metabolic approach) or convert ATCs in co-metabolic reactions that often lead to transformation products (Benner et al., 2013). In both cases, the microbes need substrates, and these substrates have to exceed a certain threshold in available concentration (Fig. 7). The energetic profit from mineralization must be higher than the metabolic "costs", such as for enzyme synthesis, active transport or defence reactions versus harmful substances (metabolic burden). So far, little is known about microbial metabolism at low concentrations (i.e., in the ng/L range). Therefore it is difficult to predict whether degradation of ATCs will actually happen, especially when there are other, more easily degradable substrates available that may even act as catabolic repressors. Boethling and Alexander (1979a), Boethling and Alexander (1979b) as well as Seto and Alexander (1985) successfully demonstrated degradation of very low glucose concentrations (ng carbon/L). However, it is yet to be examined if these results are transferrable to complex molecules like ATCs; especially when they are the sole source of carbon and energy (which may be valid e.g., for ATCs in drinking water). While the enzymes for glycolysis are expressed constitutively, almost all peripheral degradation pathways have to be firstly induced by the substrate; thus, the microbes have to be exposed to a sufficient amount of the potential substrate. In the natural environment, however, ATCs occur in low and fluctuating concentrations. Despite dilution and concentration effects in the wastewater effluent due to rainfall or human activity peaks, the situation in the WWTPs is slightly more favourable in terms of ATC concentrations. Additionally, high concentrations of analogous organic substances would allow co-metabolism that would make complete degradation of ATCs in WWTPs more likely. Nevertheless, the simple equation "the higher the concentration the more probable and efficient the microbial elimination" might not apply in every case. In hospitals, for instance, the usage of antibiotics and disinfectants raises the toxicity for the microbes in the effluent that could prevent any degradation activity (Kummerer, 2001).

Another issue concerns the pre-transformation of ATCs before they arrive at the WWTP. Ibuprofen, for instance, is metabolized during passage through the human body by detoxifying cytochrome P450 oxidases, resulting in 2- and 3-hydroxy-ibuprofen (Hamman

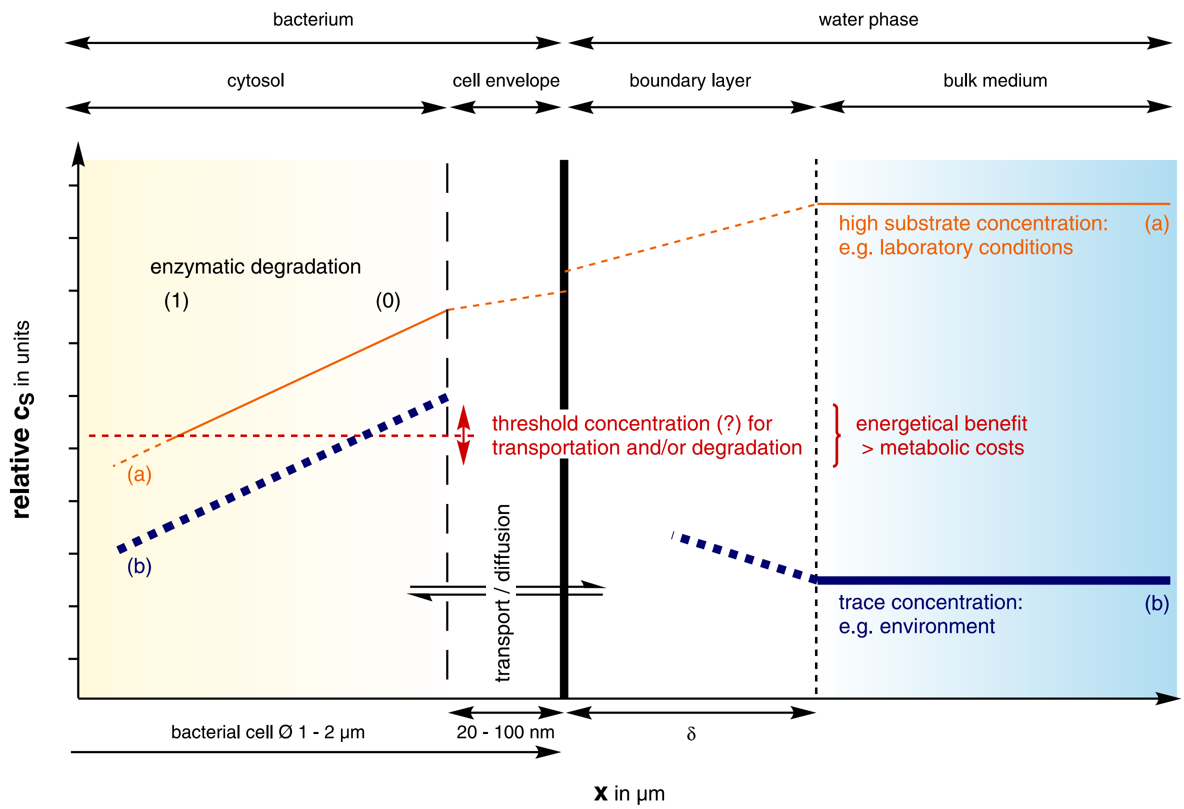

Fig. 7. Mass transfer model for bacteria adapted from the two-film theory. Substrates with concentrations in the range of g/L (a) and those in trace level (b) concentrations (6 to 9 orders of magnitude lower) get into the cell by different means of transportation. Certain, but yet not quantified threshold levels have to be met in order to trigger enzymatic degradation (following zero- (0) and first-order (1) kinetics).
Graph by Steffen Helbich.

et al., 1997). Complete bacterial degradation differs significantly from this transformation reaction. First, the acid side chain is removed, and then the ring gets cleaved via the *meta*-pathway (Murdoch and Hay, 2005). Unfortunately, the human transformation process renders the molecule unusable for bacteria, thus decreasing the potentially degradable amount arriving in WWTPs and simultaneously accumulating yet another ATC in the water body. Another example where the formation of secondary products often leads to persistent and harmful compounds can be shown for triclosan. The molecule gets cleaved enzymatically, resulting in a 2,4-dichlorophenol moiety (Kim et al., 2011; Lee and Chu, 2013). This compound has a strong inhibitory effect on the bacterial metabolism at or above a concentration of 0.1 mM (Liu and Chapman, 1984; Pieper et al., 1989), is toxic (LD_{50} 47 mg/kg oral in rats; LD_{50} 790 mg/kg dermal exposure in mammals) and can easily be absorbed via the human skin (NTIS Vol. OTS 0534822). It can further be dimerised to polychlorinated dibenzodioxins (PCDDs) by biological (Oberg et al., 1990) and chemical (Zoller and Ballschmiter, 1986) means.

Among all the stated fields of research (enrichment, isolation, concentration thresholds, metabolic products and by-products), there is one final challenge to tackle: the economic technical implementation. While it is feasible that adapted individual species can be obtained to degrade certain ATCs, it is highly unlikely to find a "superbug" or mixed culture with the ability to degrade all ATCs simultaneously. Among others, the biomass has to be retained on a suitable bed to prevent wash-out and, moreover, competitors that might outgrow the desired consortium have to be kept at low abundances. Here, the immobilization of specialised biofilm on membrane reactors as an after-treatment tool in WWTPs seems to be promising as a relatively easy-to-operate and low-energy consuming solution that can be developed for specific applications.

6.3. What should be done next on elimination and legislative levels?

Each of the approaches presented above need a deeper understanding on the basic physical, chemical and biological interactions with ATCs since these processes are far from being understood. Moreover, there are many problems to consider due to the constantly varying conditions in operational parameters, wastewater flow, and in ATC concentrations. While these highly fluctuating boundary conditions will have a varying impact on ATC removal depending on the chosen techniques, a thorough knowledge is required to apply the most appropriate operation strategies. Altogether, there is currently no method available which sufficiently addresses the whole ATC cocktail; let alone in an economically viable and sustainable way. Multi-stage processes combining certain techniques may be the way forward to better address the increasing spectrum of ATCs. However, even perfect end-of-pipe strategies could not solve all problems since they are acting on a local basis. First attempts to gather larger data sets infer that ATC pollution is already a continental-scale problem and, as such, requires solutions on a larger scale (Allan et al., 2006; Malaj et al., 2014). In this regard, the highest priority should be given to the reduction or avoidance of ATCs during the production process (e.g., green chemistry) and in consumerism (e.g., education, innovative take-back systems) (Malaj et al., 2014; Schwarzenbach et al., 2006). This direction needs more than just encouragement; thus it will be necessary to ban those ATCs that are harmful and accumulating in the environment by legislative enforcement, with the exception of life-saving pharmaceuticals. Holistic initiatives such as the European Water Framework Directive or regulations such as REACH (Registration, Evaluation, Authorization and Restriction of Chemicals, regulation EC No 1907/2006) are a good start to promote necessary research on analytics and ecotoxicology which is the basis for regulatory instruments.

7. Behaviour and fate of ATCs in the environment: gone for good or primed for comeback?

Whether from incomplete removal in WTTP effluents or by diffuse sources, after their entry into the natural aquatic environment, there is little known about the further transport and fate of ATCs in surface and subsurface waters (Sections 7.1 and 7.2). In contrast to inorganic ATCs (e.g., heavy metals) that are not subject to degradation but exhibit different behaviour under varying redox regimes, organic ATCs experience a wide range of environmental partitioning and transformation reactions via chemically induced or microbiologically mediated processes (Schwarzenbach et al., 2010). Thereby, ATC fate is triggered first of all by their physico-chemical characteristics such as water-solubility and degradability to impact sorption capacity and persistence, respectively (see also Section 3). However, the microbially produced matrix of extracellular polymeric substances (EPS) plays a crucial role in ATC binding, transformation and degradation too (Section 7.3).

7.1. Hydrophobic ATCs and cohesive sediment dynamics

The non-polar ATCs show a high affinity to particulate matter and thus represent the fraction that can be removed from the wastewater stream in WWTPs by solids separation (e.g., triclosan, see Sections 3.3. and 5.1.). Once in the natural environment, hydrophobic ATCs might bind to particles and, thus, couple their fate closely to the Erosion, Transport, Deposition, and Consolidation (short ETDC) cycle of cohesive sediments. In fluvial systems, these bound ATCs are transported downstream along with the sediment load where they temporarily deposit on river banks, in floodplains, reservoirs, lakes, wetlands, deltas and harbours. These polluted sediments are of great ecological and economic concern since they might impact benthic habitat quality. Further, they can be remobilized during certain events such as dredging or flooding to then act as a secondary source of pollution (Gerbersdorf et al., 2011; Woelz et al., 2009). The importance of contaminated sediments for sediment management and water quality in river basins has finally been recognized (EU WFD, SEDNET 2004). Nevertheless, as with the macropollutants in the past, the "out of sight, out of mind" strategy seems to be presently repeated in ATC research where the focus clearly lies on polar compounds (e.g., Goetz et al., 2010). And yet, some of these non-polar ATCs associated with sediments have been designed to act biologically such as triclosan (Dann and Hontela, 2011). These types of ATCs might strongly affect benthic life and, in particular, biofilms that form the basis of all higher life and provide important ecosystem services (e.g., self-purification, carbon transfer, Gerbersdorf et al., 2011).

One important ecosystem function of biofilms is biostabilization: the microbes secrete extracellular polymeric substances (EPS) that virtually glue sediment particles together to increase their resistance to hydrodynamic forces (Paterson, 1989). This, in turn, delays the possible resuspension of sediments into the water body where potentially associated ATCs become bioavailable again; either in their original form or possibly as even more harmful transformation products (Dann and Hontela, 2011). There is first evidence that this stabilizing capacity of natural biofilm is significantly impaired by exposure even to single ATCs; and effects of ATC cocktails are expected to worsen the situation (Lubarsky et al., 2012). Hence, the ongoing emissions of ATCs could induce a negative feedback mechanism: formerly immobilized pollutants such as metals, organic pollutants and radionucleotides (Woelz et al., 2009, SEDNET 2004) might be more easily released by resuspension events to then further impact biofilm functions and higher aquatic life (Brinkmann et al., 2013; Dann and Hontela, 2011). Biofilms growing around sediment particles also modulate post-entrainment flocculation since they change the characteristics (size, density and settling velocity) of the eroded material which influences subsequent transport and deposition (Droppo, 2004; Gerbersdorf et al., 2008; Paterson et al., 2000). Although biofilm growth significantly affects sediment movement and has thus attracted numerous research activities, the precise binding mechanisms need to be unravelled and the highly variable (temporarily and spatially) biological–sedimentological interactions must be better understood (Gerbersdorf and Wieprecht, 2015). In terms of ATCs, the constantly alternating environmental conditions experienced during the ETDC cycle (e.g., high oxygen versus anoxia, changes in pH values and organic background) influence the chemical transformations and microbial biodegradation that determine the fate of non-polar ATCs. It is no coincidence that the highest metabolic activities happen at interfaces with strong physico-chemical gradients ("intermediate disturbance theory") such as the sediment–water boundary or within eroded flocs that both promote cascade-like degradation and co-metabolism (Gerbersdorf et al., 2004; Wotton, 2004). Hence, a sound knowledge and precise prediction of sediment dynamics is the first step towards understanding the fate and dynamics of particle-associated ATCs both in the natural environment and in technical systems (sewers, storm water overflow discharge).

7.2. The subsurface passage

Polar, non-degradable ATCs, on the other hand, might travel almost unhindered through surface waters and most of their attenuation in the aqueous phase is due to dilution within the river or sewer (Gomez et al., 2012). Although generally the infiltration of contaminants into the subsurface is limited due to flow course, travel time, sorption and degradation processes, polar ATCs with a low partition coefficient (such as trimethoprim) tend to remain in the dissolved phase and are thus more likely to reach and affect groundwater resources (Dougherty et al., 2010; Teijon et al., 2010). Nevertheless, the presence of a soil/sediment matrix can substantially complicate the relevant transport mechanisms of advection and diffusion as well as dispersion. Moreover, reaction processes such as ionic interactions, sorption and desorption are highly influenced by the properties of the matrix. This is particularly valid if these reactions are controlled by small-scale mixing and mass transfer mechanisms that depend strongly on pore-scale geometries and small-scale matrix heterogeneities (Ghanbarian et al., 2013).

There are many examples of the complex and unique mechanisms at work in subsurface conditions. First, non-polar ATCs that sorb strongly onto particles are subject to still poorly understood colloid and particle transport in porous media (Bedrikovetsky et al., 2011; Leon-Morales et al., 2004). Second, the soil and the hyporheic zone can exhibit strong geochemical gradients that are drivers for different types of reactions than in well-mixed surface waters (e.g., Lawrence et al., 2013). Third, the chemistry and large specific surface of clay and silt minerals in the subsurface resembles the complexity of fine sediments mentioned above (e.g., Sposito et al., 1999). Fourth, reaction kinetics found in well-mixed systems such as open waters may differ substantially from the kinetics that apply in the subsurface which is typically a diffusion-limited type of reactor (e.g., Luo et al., 2014). Fifth, the release of polymeric substances by microorganisms can have significant consequences for the porosity and permeability of soils, sediments and the hyporheic zone (e.g., Gerbersdorf and Wieprecht, 2015). Thereby, EPS permeates the void space and bridges soil and sediment particles (Fig. 8) to influence the percolation of ATCs, but information on this is scarce. Such local changes in permeability induce further fluctuations in the flow velocity (Sharp et al., 2005), which likely affects the transport of ATCs. There is an extremely complex interaction between organic material, biofilms, pore space, pore fluids, and the contained chemical species that is only poorly understood (Tang et al., 2013). Therefore, to develop predictive approaches concerning the fate and behaviour of ATCs in the subsurface would require a quantitative description that is currently unavailable. What aggravates the poor predictability of transport and fate of ATCs in the subsurface is that the mere porous media characteristics are difficult to assess in practical terms, given the limited observability and spatial heterogeneity of the subsurface (Gerlach and Cunningham, 2011). This provides a further source of uncertainty.

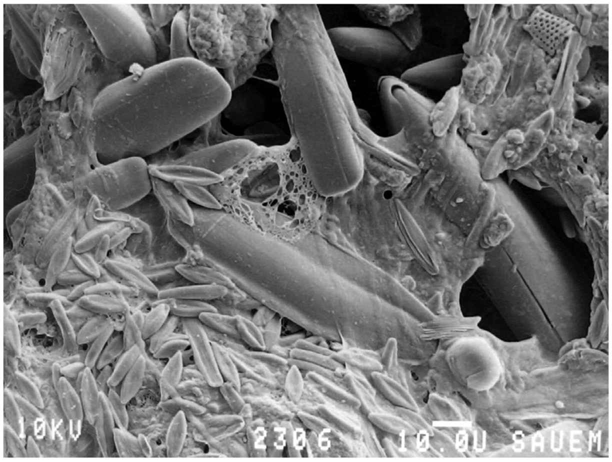

Fig. 8. EPS embedded microorganism within a biofilm: diatoms of various sizes that secrete polymeric substances to bind to each other and to sediment particles, thus enhancing sediment stability and impacting the whereabouts of non-polar ATCs.
Low Temperature Scanning Microscopy LTSM image from the SERG laboratory of Prof. D.M. Paterson, image by I. Davidson, EU Marie Curie RTN project KEYBIOEFFECT.

Regarding the development of numerical models for simulating ATC transport in the subsurface, there are two components to be considered and, eventually, combined. First, modelling fluid flow through porous media is well established, even for multiple fluid phase (Helmig, 1997), but there are remaining challenges in describing these processes at larger scales — especially for variably water-saturated soils. Second, the interaction of ATCs with the porous matrix and possibly with organic matter (sorption, reaction, biofilms) has a high demand for fundamental research to obtain reliable quantitative models. And third, these models need to be combined since they strongly interact.

To conclude, modelling the fate and behaviour of ATCs in the subsurface poses large challenges, because flow and transport paths belowground together with the resulting degree of dispersion and mixing, travel or residence times in subsurface compartments with various biogeochemical regimes, are subject to immense uncertainty. This uncertainty stems from the combination of irregular velocity fields due to material heterogeneity and the poor observability of the subsurface.

7.3. The role of the microbial EPS matrix

Considering purely physical interactions with the mineral fraction of soils and sediments, only a negligible part of non-polar ATCs could be bound (Schwarzman and Wilson, 2009). However, fine sediments constitute of a large fraction of organic matter of allochthonous and autochthonous origin that exhibit a great sorption capacity to non- or semipolar ATCs. The organic matrix is usually a mixture of refractory components such as humic acids from plant degradation or freshly produced material secreted by macrofauna and microorganisms. Microbially produced EPS containing sugars, proteins, DNA, lipids and all combinations hereof, have received considerable research attention (More et al., 2014). Like humic acids, this EPS matrix offers numerous binding sites due to various functional groups and substituents and thus, hydrophobic pollutants can be directly adsorbed or immobilized here, possibly rendering ATCs innocuous (Pal and Paul, 2008). Furthermore, EPS covers the microbial cells and might thus mediate ATCs passage into the cells. This mediation could have both negative (inducing acute or chronic exposure effects) and positive (establishing the contact to potential degraders) impacts (Flemming and Wingender, 2001; Wuertz et al., 2000) (Fig. 8). The interactions of the EPS matrix with ATCs and their physico-chemical features will determine whether they are bound in the outer surrounding of the cells (glycocalyx, sheet) or whether they are able to cross cell membranes (Schwarzenbach et al., 2010; Spaeth et al., 1998). The binding location may have consequences for ATCs sorption, transformation and degradation, but the possible importance of the EPS matrix for ATC removal has not yet been fully recognized.

8. Risk management: how to assess and control the true risks of ATCs given all these research challenges?

Risk assessment aims to judge the probability of a negative impact to occur and the degree of the detriment as well as to develop and evaluate implemented risk mitigation strategies (ISO_31000, 2009). In terms of ATCs, risk assessment is thus closely dependent on the progress of other disciplines such as chemistry, ecotoxicology, microbiology or engineering science and on better knowledge of avoidance as well as elimination strategies.

8.1. What is required for a sound risk assessment?

Risk is generally defined as a possible detriment to some (protection) good or system, with an associated uncertainty about the likelihood to occur and the degree of detriment (Aven and Renn, 2009). In this regard, ATCs qualify very well for comprehensive risk assessment and management according to the precautionary principle (Raffensperger and Tickner, 1999) (see also Section 1) because:

- Many of them have a proven or suspected potential for negative impact.
- They have unknown or varying types of negative consequences.
- There is uncertainty in whether (or to which degree) the impacts will occur.
- It is often unknown in what parts of the environment, engineered systems or organisms/humans they will occur, accumulate or cause harm.

Consequently, ATCs can be considered as an imminent source of risk for human and ecosystem health; hence risk assessment and management becomes an immediate and ongoing obligation.

Risk assessment has become an internationally standardized procedure (ISO_31000, 2009) as illustrated in Fig. 9. First significant steps in risk management include the risk analysis phase with the definition of objectives, targets and all possible hazards for these targets as well as all possible pathways how the hazards can impact the targets (Fig. 9).

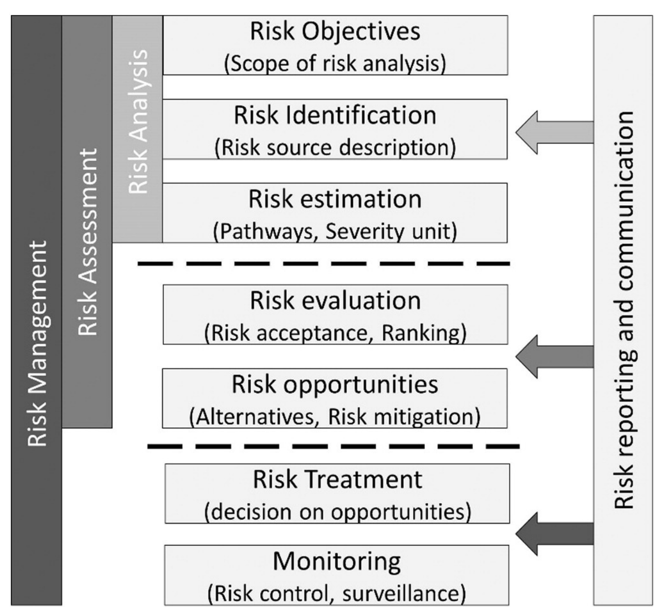

Fig. 9. Risk management framework.
Modified after ISO_31000 (2009).

For ATCs, however, there is practically no state-of-the-art environmental risk assessment and management on a catchment-scale or environmental level. Large-scale assessments would require a sound knowledge that depends strongly on all of the research challenges addressed in this review: it would need sophisticated monitoring schemes (Section 2), improved chemical analysis (Section 3) and ecotoxicological assessments (Section 4) as well as advanced models to predict the fate and transport of ATCs within the environment (Section 7). The previous sections have revealed clearly that the current knowledge is inadequate to allow definitive catchment-scale risk assessment and management schemes. Thus, advances in risk analysis are conditioned on simultaneous progress in chemical and ecotoxicological classification and all the other fundamental research that helps to better understand ATC behaviour in surface and subsurface waters.

In a second phase, risk analysis moves into risk assessment by evaluating the risk against given standards, guidelines, or by ranking different risks against each other. Possible risk mitigation strategies are identified, which in our case would require better availability and understanding of avoidance and or elimination strategies (Sections 5 and 6). To complete the risk management cycle, the third phase chooses and implements mitigation strategies and confirms their success by adequate monitoring (Sections 2, 3, 4). Therefore, we need smart sampling strategies and sophisticated analytical methods to determine ATC occurrence and toxicity in sufficient temporal, spatial and compound-specific resolution. In this context, the new concept of measuring distinct ATCs that characterise certain fractions of physico-chemical behaviour (Section 3.3) is vital since it will cover presently unknown or unnoticed ATCs. The available data are used to revisit the risk management procedure in ever-repeating cycles. The entire process has to be flanked by calculating the assessed versus the acceptable risk in communication with involved stakeholders and the public in order to achieve necessary actions and constraints.

8.2. Solid teamplay wins the day

Altogether, this indicates that risk assessment, risk management and modelling are vital elements in addressing the issues on ATC occurrence, fate and hazardous potential. However, this is only achievable through multidisciplinary approaches: Monitoring, measuring and modelling, elimination/substitution strategies, and regulatory instruments are all involved in risk management, and many (if not all) environmental compartments have to be considered as sources, pathways or targets. A very specific and urgent need for interdisciplinary ATC risk management arises immediately in the first phase during the definition of targets and units in which to quantify or estimate the risks. Several authors have shown that there is no universal risk metric, and each stakeholder has its own priorities (e.g., human-toxicological, biotoxicological, ecological, economical, technical) (Enzenhoefer, 2013; MacGillivray et al., 2006). Each different risk metric will lead to different and possibly conflicting courses of action in order to minimize the respective risk metric (de Barros et al., 2012; Tapiero, 2013). Therefore, the choice of risk metrics is not only crucial for subsequent decisions, but also complex to communicate and reconcile. Under ambiguous objectives, it is advised to analyse several risk metrics in order to learn whether they are in fact competing or not, and to unravel the mutual trade-off in focusing on one or the other risk metric. This leads to multi-objective decision methods (Torres et al., 2012). For ATCs, there are numerous ways to measure the severity of possible impacts. Consequently, chemical analyses, human toxicology, biotoxicology, environmental impact assessments as well as economical and technical considerations need to be included in ATC risk management.

Recalling that the definition of risk involves probability, and that decision support systems require models, two more interdisciplinary aspects come into play: The uncertainties associated with ATC-related risks are manifold and occur on different levels. Modelling statistical parameter inference and stochastic-numerical simulation tools are typically essential for quantifying uncertainty in predictions of future risk levels. Additionally, there is scenario uncertainty that originates from unknown boundary conditions triggered by future changes in land use, population density, political situations and risk perception. Scenario uncertainty can only be addressed with instruments of the social sciences.

8.3. Risk management requires a global system perspective

It has been argued by many authors that risk assessment must be performed on an aggregated and cumulative level (US_EPA, 2007). This intends to account for the simultaneous occurrence of different (possibly interacting) contaminant doses, and how they accumulate their responses in the affected systems over time. Basically, this requires invoking the so-called source–pathway–receptor concept (US_EPA, 2007), often also interlinked with the so-called multi-barrier concept (CCME, 2004). The source–pathway–receptor concept considers all pathways and uptake routes available from any individual hazard to the subject of protection. Some of these pathways will appear as sequences of sub-systems to be crossed, and each of these sub-systems may pose a barrier to the further propagation of risk and hence needs to be understood.

For the case of ATCs, these thoughts directly lead to a global systems perspective. One has to identify, assess, monitor, model and predict all possible *sources* of release. Also, one has to monitor, model and predict their fate and transport in all possible *pathways* through the entire aquatic habitats (soil passage, groundwater, surface waters, sanitary engineering systems, bioaccumulation, food chain, and so forth). Finally, one has to monitor, model and predict the impacts at all possible *receptors* (water quality, toxicity to ecosystems or humans, impact on engineered systems and so forth), and how these impacts interact. Thus, it is indeed important to consider the complete picture of natural and technical systems in order to perform risk assessment. Furthermore, in tackling the global systems perspective, various disciplines have to cooperate; for instance the possible pathways require experts in hydrology, hydrogeology, morphology, soil science, atmospheric sciences, geochemistry, and porous medium sciences while the receptors invoke human toxicology, ecotoxicology, ecology, microbiology and process management. The involved monitoring aspects across all these pathway segments call for (bio-) chemical analysis, and for (geo-) statistical data interpretation.

9. Conclusions

The continuous load to aquatic systems by ATCs has led to numerous activities in research, application and legislation, whether based on ecotoxicological evidence or acting on the precautionary principle. Up to now, most resulting publications have a certain perspective (e.g., from the chemical analytic point of view) and focus on one group of substances (e.g., endocrine disrupting compounds) or one specific environment (e.g., wastewater treatment plants). This review illustrates the need for a multi-disciplinary effort that addresses crucial questions on ATC occurrence, fate, detection, toxicity, elimination and risk assessment from source to sink. Thereby we consider the human impact on ATC entry and distribution as well as the potential impairment of the environment and human health by ATCs. With the broader view on both natural and technical aquatic systems, covering different scales and involving fundamental as well as applied science, we aim to contribute to a timely, innovative and holistic research design for ATCs in aquatic systems.

In order to get a comprehensive picture on ATCs' occurrence and fate, our review acknowledges briefly the essential improvements in the sensitivity of chemical analysis. Equally important are sophisticated monitoring campaigns that are based on internationally validated sampling guidelines (e.g., representative locations, frequency and type of sampling) and methods for analysis and data evaluation. In proper monitoring and analysis, the boundary conditions, interactions between compartments as well as periodic or episodic variations have to be considered for a better large-scale comparability of ATC data. To meet the challenges by the daily growing numbers and complexity of ATCs, we postulate a future focus on indicator substances that represent chemical classes with similar physico-chemical properties and, thus, similar characteristics of solubility and persistence. Appropriately chosen indicators can describe specific introductory pathways as well as transport behaviour and final sinks for certain ATC classes. In this context, a paradigm shift is required in such that the indicators should not be chosen by their toxicity.

Nevertheless, knowledge on toxicity is vitally important since this is the basis to reduce or substitute ATCs by legal enforcement, identify locations in urgent need of action and verify the successful implementation of prevention or elimination strategies. Despite much progress in both bioanalytics and biomonitoring, new test systems have to evolve and to be harmonized to better assess on various toxicity levels (from gene to whole organism, from bacteria to vertebrates, from community to environment). The big challenge ahead is to comprehensively investigate a highly complex system of intra- and interrelations using laboratory – and thus simplified – approaches, and still understand what the findings mean on an environmental level. We also highlight the urgent need to extrapolate from well-known acute toxicity to long-term effects on environmental and human health.

Our review further concerns the exposure paths of ATCs and identifies the WWTPs as a main pathway, whether directly or indirectly, while emphasizing the problems associated with surface runoff, sewer basin overflow as well as the recycling of biowaste and biosolids. Briefly, the status quo and challenges for current physical, chemical and biological ATC elimination techniques are presented. While new technologies such as ozonation or activated carbon seem to be quite effective in ATC removal, the interactions between ATC type, boundary conditions and dosage are not entirely understood although they largely determine removal success. Bioaugmentation seems to be a promising alternative for investing additional research; however, finding the right microbial consortia to degrade substances in low and fluctuating concentrations still poses a challenge, from laboratory level up to technical implementation. The benefit of these locally acting end-of-pipe strategies is then opposed to what should be the top priority for larger-scale solutions: avoidance strategies.

ATCs are released into the environment where they can accumulate, as previous research has shown. Despite this fact, there is surprisingly little information on the fate of ATCs in natural habitats. Particle-associated ATCs might couple their fate closely to the dynamic of fine sediments that, in turn, is very much influenced by (micro-) biological activity. New findings on the complex interrelation between microbial secreted EPS and cohesive sediment stability are presented that also point to the crucial role of biofilm for sorption and degradation of non-polar ATCs. This might even apply for polar ATCs that, after travelling unhindered through the water body, can eventually enter the subsurface (e.g., soils, the hyporheic zone and groundwater) where small-scale pore geometry encased by organic material might substantially complicate transport and attenuation processes. Altogether, this illustrates the essential role of biofilms in ATCs fate by changing sediment stability and sediment entrainment (a phenomenon called biostabilization), subsurface porosity and permeability as well as sorption and degradation capacity of sedimentary compartments.

Last but not least, the necessary steps and the importance of a comprehensive risk assessment for ATCs are demonstrated in order to assist the “source to tap” approach in implementation and evaluation of regulative policies and management directives. Finding new ways towards a holistic research design for ATCs is essential, especially when regarding the future challenges in water allocation and water quality in terms of demographic (9 billion humans in 2050, longer life-spans) and global changes (weather extremes, unprecedented variance in the precipitation regime) as well as ongoing globalization (intensified and unsustainable use of water resources) (IPCC, 2012).

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