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Pharmaceutical residues and other emerging substances in the effluent of sewage treatment plants

Review on concentrations, quantification, behaviour, and removal options

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Preface

The removal of pharmaceutical residues and other emerging substances from the effluent of sewage treatment plants is critical for the protection of water quality and thus an important contribution to a sustainable society in balance with nature. The topic is gaining increasing interest and many organizations are involved in research, development and building up our knowledge. At this stage of knowledge development, it is important to recognize the complexity of the behaviour of emerging substances in sewage treatment plants and thus also in the assessment of efficiency and applicability of removal techniques. Several aspects such as target definition, sampling, sample handling and analysis, result evaluation as well as total costs and environmental impact of a technology need to be assessed in a holistic approach to provide practical advice on choice of technologies and to set realistic expectations.

The collection of guidelines in this report, including all the different aspects mentioned above, is intended to increase the general awareness and knowledge at all levels in relevant organizations such as legislation authorities and sewage treatment plants and to support decision making and implementation of new technologies.

This state-of-the-art compilation comprises different aspects that have been identified as important when dealing with priority and emerging substances, from their quantification, definition of removal targets, treatments technologies and systems, to environmental impacts. The aim of the report is also to provide a hands-on guide for STPs, authorities, and other organizations already engaged or intending to work with the removal of pharmaceutical residues and other emerging substances from the effluent of sewage treatment plants.

To provide a complete review, various national and international experts and scientific reviewers from various organizations and related projects have been involved.

The report and other activities within the project "*Systems for the purification of Pharmaceutical residues and other emerging substances"* are partly funded by the Swedish Agency for Marine and Water Management after a proposal by the Swedish Government. The Swedish Water & Wastewater Association (SWWA) was assigned to be responsible for the related call.

List of abbreviations

DDD	Defined daily doses
EQS	Environmental quality standard
FR	Flame retardant
GAC	Granular activated carbon
LCA	Life cycle assessment
LCC	Life cycle cost
LOD	Limit of detection
LOEC	Lowest observed effect concentration
LOQ	Limit of quantification
MBR	Membrane Bioreactor
PAC	Powdered activated carbon
PE	Person equivalents
PEC	Predicted environmental concentration
PNEC	Predicted no effect concentration
SSA	Single substance approach
STP	Sewage treatment plant
WEA	Whole effluent assessment
WFD	EU Water framework directive

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Summary

Pharmaceutical residues and other emerging substances pass through modern sewage treatment plants (STPs) and end up in the receiving waters and sludge. In several studies, recipient concentrations have been detected with expected effects on aquatic organisms. Chemicals released via STPs may also enter the aquatic food-web and cause effects in higher organisms such as fish-eating birds or mammals including humans. Studies have also shown that antibiotics in the environment may contribute to the increase of antibiotic resistant genes in bacteria, which is a serious threat to our possibility to cure life-threatening diseases on the global scale. Current STP treatment technologies are usually not fit to remove microbial stable chemical pollutants and the evaluation of the removal efficiency of the STP systems applied today, is not complete. The evaluation of the removal efficiency of the substances in the STP systems is usually based on chemical analysis of the presence of certain substances in influent and effluent waters. However, there are difficulties associated with this approach, e.g. since some substances are metabolized into potentially more harmful substances which are not captured in the analysis unless they are actively sought for. Furthermore, some substances are formed in the STPs, resulting in higher levels in effluents than in influents. In addition, effluent concentrations may sometimes be lower than the analytical detection limits, yet still higher than or close to established risk concentrations emphasizing the need for developments of the analytical methods.

Several studies have been performed in recent years, evaluating the efficiency of different treatment technologies from various aspects. The aim of this review, which was conducted as part of the project *"Systems for the purification of Pharmaceutical residues and other emerging substances",* is to provide a solid knowledge base and to give recommendations on emerging substances, methods for quantification, potential treatment options and future developments, as well as to highlight knowledge gaps. The report focuses on *targeted effluent water quality,* including legislative status and quality assessment methods, d*etection and quantification of substances and their effects*, including sample treatment during sampling, preparation and storage, as well as analytical methods and methods for quantification of toxicity. Furthermore, the report covers a review on *emerging substances at STPs,* including previously measured levels and removal efficiencies, future trends and potential environmental impacts. Finally, the report also covers *technologies for the removal of emerging substances in STPs,* including upstream work, secondary and tertiary treatment technologies. As a result of this review, a number of recommendations are given on the different topics covered in the report, a selection of which is listed below.

Substance groups of particular interest for novel/improved treatment technologies at STPs (specific substances are listed in the report)

- Pharmaceuticals
- Plasticizers – phthalate esters
- Flame retardants
- Phenolic substances
- Per- and polyfluoroalkyl substances (PFAS)
- Microorganisms i.e. bacteria and viruses, in particular antibiotic resistant bacteria and their resistant genes

Detection and quantification of substances and their effect

- Follow the laboratory instructions and sampling protocols rigorously, to avoid contamination and undesired transformation of analytes.
- Ensure that the method limit of quantification (LOQ) is low enough compared to existing surface environmental quality standards and predicted no effect concentration (PNEC),
- All details surrounding sample pre-treatment, blank corrections, analytical methods and precision should be clearly documented.
- Adapt the design of eco-toxicity tests to the situation and elaborate in collaboration with the laboratory.

Effluent water quality

- Environmental Quality Standard annual average and maximum allowable concentration values (AA EQS and MAC EQS) or PNEC-values should be applied to assess the risk for effects on the aquatic ecosystem.
- Negligible or zero emissions should be targeted for very persistent, bio-accumulating and/or reproduction disturbing substances.
- Complementary whole effluent toxicity tests are recommended when presence of unknown substances is expected.

Technologies for the removal of emerging substances (combinations of treatment systems are highly relevant)

- Upstream activities to reduce influent levels are first priority, but have natural limitations, especially concerning pharmaceuticals. Sludge handling is also an important aspect. Prior to STP modifications, on-site tests to generate knowledge about site-specific STP conditions are necessary
- Secondary treatment options may become important, e.g.:
  - MBRs, combining enhanced degradation with separation.
- Tertiary treatment options including new technologies thereof, e.g.:
  - Activated carbon filtration, including activated carbon produced from biomass (i.e. BAC, MAC, ModAC)
  - Advanced oxidation with ozone

All removal solutions have to be assessed based on their cost as well as their environmental impact, in particular the complementary treatment systems such as the advanced oxidation with ozone or activated carbon systems. Ideally, the complete treatment processes including both main and secondary treatment should be assessed and compared to new removal technical solutions, potentially through application of Life Cycle (LCA, LCC) assessments, to facilitate the identification of the most significant items of a system and possible improvements.

Sammanfattning

Många läkemedelsrester och andra prioriterade föroreningar passerar igenom avloppsreningsverk (ARV) och hamnar i recipienten och slam, ibland i nivåer som kan påverka vattenlevande organismer. Kemikalier som släpps ut via avloppsreningsverk kan också anrikas i den akvatiska näringskedjan och orsaka effekter i högre organismer såsom fiskätande fåglar eller däggdjur inklusive människor. Studier har också visat att antibiotika som hamnar i miljön kan bidra till uppkomsten av antibiotikaresistenta gener i bakterier, vilket är ett allvarligt hot mot vår möjlighet att bota livshotande sjukdomar på den globala skalan. Eftersom nuvarande behandlingstekniker har utvecklats främst för att avlägsna partikulärt material samt kväve och fosfor är de inte alltid anpassade för att rena bort mikrobiellt stabila kemiska föroreningar. Utvärderingen av effektiviteten av olika behandlingstekniker för avlägsnande av sådana ämnen baseras vanligtvis på analyser av förekomst av ett ämne i inkommande och utgående vatten. Det finns dock problem med detta tillvägagångssätt eftersom vissa ämnen metaboliseras till potentiellt mer skadliga substanser som inte automatiskt fångas i analysen. Dessutom kan vissa ämnen bildas i reningsverken, vilket kan resultera i högre nivåer i utgående än i inkommande vatten. Dessutom kan de utgående koncentrationerna ibland vara lägre än detektionsgränserna, men trots det ändå vara högre än eller nära etablerade riskkoncentrationer.

Flera studier har utförts under de senaste åren, där effektiviteten i olika behandlingstekniker har utvärderats från olika aspekter. Syftet med denna översyn, som genomfördes som en del av projektet "*Systemförslag för rening av läkemedelsrester och andra prioriterade svårnedbrytbara ämnen"*, är att ge en gedigen kunskapsbas samt rekommendationer om prioriterade ämnen, metoder för kvantifiering, behandlingstekniker och utvecklingsbehov samt att belysa kunskapsluckor. Rapporten är särskilt inriktad på att sammanfatta kunskapen gällande *effluentens vattenkvalitet*, vilket inbegriper lagstiftning samt metoder för kvalitetsbedömning, *detektion och kvantifiering av föroreningar och deras effekter*, inklusive provbehandling under insamling, beredning och lagring, samt analysmetoder och metoder för kvantifiering av toxicitet. Vidare omfattar rapporten en översyn av *prioriterade föroreningar vid reningsverk*, inklusive tidigare uppmätta halter och reningseffektivitet, framtida trender och potentiella miljöeffekter. Slutligen, innefattar rapporten *tekniker för avlägsnande av prioriterade föroreningar i avloppsreningsverk*, inklusive uppströms arbete, sekundära och tertiära behandlingstekniker. Som ett resultat av denna översyn, ges ett antal rekommendationer avseende de olika områden som behandlas i rapporten, varav ett urval listas nedan:

Prioriterade föroreningar med särskilt behov av nya/förbättrade behandlingstekniker vid avloppsreningsverk (specifika föroreningar finns listade i rapporten)

- Läkemedel
- Mjukgörare - Ftalatestrar
- Flamskyddsmedel
- Fenolära ämnen
- Per- och polyfluoroalkyl ämnen (PFAS)

- Mikroorganismer, dvs bakterier och virus, i synnerhet antibiotikaresistenta bakterier och deras resistenta gener

Detektion och kvantifiering av föroreningar och deras effekter

- Laboratorieinstruktioner och provtagningsprotokoll måste följas noggrant för att undvika kontamination och oönskad omvandling av ämnen.
- Säkerställ att kvantifieringsgränsen (LOQ) för metoden är tillräckligt låg jämfört med miljökvalitetsnormer och PNEC, och att alla detaljer kring provbehandling, blankkorrigeringar, analysmetoder och kvalitetskontroll är tydligt dokumenterade.
- Utformningen av ekotoxicitetstester måste anpassas till situationen och bör utarbetas i samarbete med laboratoriet.

Koncentrationer i utgående vatten

- Miljökvalitetsnormer (AA-EQS och MAC-EQS) eller ”predicted no effect concentration” PNEC-värden bör tillämpas för att bedöma risken för effekter på det akvatiska ekosystemet.
- Försumbara eller nollutsläpp bör eftersträvas för mycket långlivade, bioackumulerande och/eller reproduktionsstörande ämnen.
- I de fall okända substanser förväntas förekomma, rekommenderas kompletterande toxicitetstester (s.k. ”whole effluent toxicity tests).

Tekniker för avlägsnande av prioriterade föroreningar (kombinationer av behandlingssystem är högst relevant)

- Uppströmsarbete för att minska inkommande mängder har störst prioritet, men har sina naturliga begränsningar, särskilt när det gäller läkemedel. Slamhantering är också en viktig aspekt, då många hydrofoba ämnen fördelas till slam. Före modifieringar i reningsprocesserna, krävs platsspecifika tester för att kartlägga de lokala förutsättningarna på det enskilda reningsverket.
- Sekundära behandlingsalternativ kan bli viktiga, t.ex
  - MBR, som kombinerar förbättrad nedbrytning med separation.
- Tertiära reningsalternativ inklusive vidareutveckling av t.ex.:
  - Filtrering med aktivt kol, inkl. aktivt kol från biomassa (dvs BAC, MAC, ModAC)
  - Oxidation med ozon

Alla tekniklösningar måste bedömas utifrån ett kostnads- samt miljöpåverkansperspektiv, i synnerhet de kompletterande behandlingssystemen såsom avancerad oxidation med ozon eller system med aktivt kol. Helst ska de kompletta befintliga behandlingsprocesserna inklusive både primär- och sekundär rening bedömas och jämföras med nya reningstekniska lösningar, eventuellt genom tillämpning av förenklad livscykelanalys (LCA) och livscykelkostnadsanalys (LCC), för att underlätta identifieringen av de viktigaste parametrarna i systemet och förbättringsmöjligheter.

1 Background

Pharmaceutical residues and other emerging substances discharged from our society to the environment can adversely affect aquatic ecosystems. Therefore, such discharged substances require an emission inventory including all relevant sources or pathways for these substances to allow investigation and implementation of adequate mitigation measures. For pharmaceutical residues and other emerging substances there are several points and diffuse sources of different importance such as hospitals, industries, private households etc. which should be targeted by source abatement if possible. However, as illustrated in the guidance document related to the Directive 2008/105/EC on Environmental Quality Standards in the Field of Water Policy (the EQS Directive), pathways are complicated, since transporting the mentioned pollutants from different sources to the aquatic environment may include direct discharges of wastewater, overflow discharge of untreated wastewater in sewer systems, and other direct emissions to recipients (EC 2012a). For pharmaceutical residues and other emerging substances, emissions from sewage treatment plants (STPs) are, however, the most significant source of load on the recipients. STPs collect the wastewater flows from many different sectors of our society and represent the final barrier before discharging these flows into the environment The substances end up in STPs where most of them are not completely degraded (Loos *et al.,* 2013; SEPA 2008). Specifically pharmaceuticals are designed to be effective at low concentrations in the body and to be stable against e.g. stomach acid and microbial degradation, and many pharmaceuticals are thus persistent to degradation also in the STP environment. As they pose a risk of irreversibly disturbing ecosystems in recipients (Gerrity and Snyder, 2011; Hollender *et al.,* 2009; Wahlberg *et al.*, 2010; Wert *et al.,* 2007), current STPs need to supplement their treatment processes with additional systems for reducing these types of emissions.

Sewage treatment plants (STPs) are built to separate suspended solids and to reduce degradable dissolved organic matter, nitrogen and phosphorus, but not for reduction of non-biodegradable dissolved compounds although these may be removed to some extent by e.g. adsorption. A recent compilation of available measurements of pharmaceutical residues in wastewater comprising all Swedish reports and surveys between 2001 and 2009 (Falås *et al.,* 2012a) shows that 70 different substances have been observed in the influent wastewater with median concentrations of a few ng/L to ~ 100 µg/l. The study also showed that there was enough data to compare the influent and effluent concentrations for a total of 62 substances. Several of the substances present in high concentrations in the influents, such as acetaminophen and ibuprofen, were removed to almost 100%, while others such as diclofenac remained largely unaltered. In general, the substances considered can be divided into quartiles. Approximately 25% of the substances are removed to a high degree and can certainly be removed by optimized treatment with existing technology. Around 25% of the substances are removed to a modest degree, often with varying degree of removal efficiency. These substances will require additional treatment to ensure sufficient reduction. Around 25% of the substances have no or only limited reduction in standard Swedish STPs and additional treatment is a necessity to remove such substances. Approximately 25% of the substances have an adverse reduction in the works, i.e. a

higher measurable concentration in the effluent after treatment than in the influent water to the STPs.

The EU Water framework Directive (WFD), in Sweden implemented in water management (Förordning 2004: 660), requires actions for a number of particularly dangerous substances that are emitted to the aquatic environment. Future defined environmental quality standards (EQS) might lead to additional requirements for discharges from STPs. In July 2013, the European Parliament decided, for the first time, to include three pharmaceuticals in a "watch list" of emerging pollutants that may be placed on the WFD priority list (Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy, European Parliament, 2013). Switzerland has already introduced requirements for additional treatment for the reduction of pharmaceutical residues in larger STPs.

The concentrations of certain pharmaceutical substances in Swedish surface waters are close to, and in some cases even above concentrations that may affect aquatic organisms (Brodin *et al.,* 2013; Fick *et al.* 2011) The concentration closest to the effect concentrations in Swedish recipients are endocrine disruptors, such as ethinyl estradiol and estriol, as well as some tranquilizers and antidepressants, such as oxazepam and fluoxetine. Another problem is the emission of antibiotics, such as quinolones, folic acid antagonists, sulfonamides and tetracyclines. Studies have shown that antibiotics at concentrations found in the environment may contribute to the appearance of antibiotic-resistant genes in bacteria (Gullberg *et al.,* 2011). The increase in antibiotic resistance is a serious threat to our ability to heal normal infection diseases (WHO 2014).

The evaluation of the efficiency of various STP treatment techniques is usually based on the concentrations of certain substances in the influents compared to the concentrations in the effluents. However, there are difficulties, because some substances, especially pharmaceuticals, are often present in their metabolized form in the influents, which will not be detected when performing analyses aimed at the original substance. New approaches such as non-target screenings using the DAIOS (Database-Assisted Identification of Organic Substances, www.daios-online.de/daios/) or STOFF-IDENT (RiSKWa 2015) tools can help to identify potential substances and their characteristics, but targeted analysis is needed for specific substances determinations. Analytical problems due to the complex matrix in influent wastewater can also contribute to difficulties in detection and quantification. STP processes involves the conversion of the substances, but they are often not degraded completely.

Various removal methods have been evaluated in several large projects, such as EU project POSEIDON and REMPHARMAWATER and the ongoing Swedish MistraPharma. Especially in Germany and Switzerland, advanced treatment technologies have been tested on a large scale (Abegglen and Siegrist, 2012; ARGE 2013). Also in Sweden, the most promising and new technologies have been tested in direct collaboration between STPs and research organisations (Baresel *et al.,* 2014; Ek *et al.,* 2013a; 2013b; 2014; Wahlberg *et al.,* 2010).

2 Introduction

As certain pharmaceutical residues and other emerging substances pass today´s STPs and reach water recipients, it becomes necessary to link existing and new knowledge with the aim of contributing to the implementation and further development of effective wastewater treatment. There are emerging substances that we might not now about yet. For some of the already identified substances there is not sufficient data to assess them from an environmental point of view, analytical methods for their quantification do not exist or are inadequate and degradation products from different removal techniques are not sufficiently investigated. Further, the problem of emerging substances in wastewater effluents has not been seriously debated until recently and these substances are mostly still unregulated. Many initiatives have been taken in recent years, both in Sweden and internationally, and with a growing knowledge base there is now a much larger willingness to implement removal of pharmaceutical residues and other emerging substances in the best possible way.

Much knowledge has already been gained during recent years when working with this problem. Researchers, institutions, technology providers and problem owners (STPs, chemical and pharmaceutical companies, legislative authorities, retailers, doctors and patients) can provide and link existing knowledge with insights of present limitations in our understanding. This includes which substances to prioritise, their quantification and technical means to remove or limit emissions of such substances. Therefore, this report as a compilation of that knowledge was initiated within the project "*Systems for the purification of pharmaceutical residues and other emerging substances*" conducted by IVL Swedish Environmental Research Institute, the Royal Institute of Technology (KTH) and the two STPs SYVAB Himmerfjärdsverket and Stockholm Vatten AB with financial support from the Swedish Agency for Marine and Water Management.

2.1 Objectives

The current project intends to provide STPs and legislation authorities with information about the most significant pharmaceutical residues and other emerging substances to target and to provide decision support for understanding and selecting effective treatment alternatives for the removal of these substances from a sustainability and system perspective. For this, also a better understanding of secondary aspects needs to be presented and discussed.

The aims are to provide a better understanding of the current knowledge base and to give recommendations on quantification methods, potential treatment options and future developments as well as to highlight knowledge gaps. This is accomplished by reviewing existing literature on the occurrence of pharmaceuticals and other organic environmental pollutants in effluents from STPs and by evaluating this occurrence in relation to existing risk limit values, or potential eco-toxicological effects. Reported reduction efficiencies and limitations of existing treatment technologies are provided. An in-depth review of upcoming promising wastewater treatment technologies concerning the substances under study is also provided.

2.2 Review strategy and limitations

This compilation of information has been made by a group of experts from different research fields. Results from both fundamental and applied research, experiences from national and international projects and collaborations, and other relevant sources have been utilized.

Regarding the review of emerging substances, the work is based on previous scientific literature that is not formally published including national and international surveys, statistic databases, legislation-related lists of emerging substances and the so-called Watch List of potential priority substances as well as on international experience, as the EU project POSEIDON and the German Framework RISKWA. Substances on the candidate list of substances of REACH were also considered. Further, many substances selected in previous studies as representatives for groups of substances, have been considered, as they already provide a certain amount of historical information.

The review focuses on the effluent of STPs in form of the treated wastewater discharged to the environment. As such, also all discussed items in this report focus on wastewater, e.g. sampling, emerging substances, removal targets, treatment technologies etc. Therefore, aspects such as for example overflow discharges of untreated wastewater in the sewer system, urban runoff or sludge handling are not discussed. Emissions of some of the discussed substances from these sources are, however, highly relevant especially considering sludge fertilizing as a common disposal alternative. Some of these aspects and their importance may be presented if closely connected to wastewater discussions but they are not inclusive and complete.

3 Targeted effluent water quality

In EU and Sweden specifically, the protection of the aquatic environment from pollution is implemented in several legislations and ordinances as well as in international agreements, and specific concern should be on reduction of substances included on regulated lists;

- Swedish ordinance (1998:899) about environmentally hazardous activities and health protection, section 5 in appendix
- Swedish ordinance (2004:660) implementation of the EU Water Framework Directive (WFD 2000/60/EEG)
- The list of priority substances within the Water Framework Directive, implemented by the Swedish Agency for Marine and Water Management regulation (HVMFS 2013:19 revised by HVMFS 2015:4) about specific pollutants, appendix 2 and appendix 5, classification and Environmental Quality Standards (EQS) regarding surface water, appendix 6.
- New priority substances and the watch list of substances with the purpose to improve the information basis for future identification of priority substances according to the EU directive 2013/39/EU (implemented in HVMFS 2015:4).
- The Stockholm Convention POPs-regulation (EG) nr 850/2004
- HELCOM Baltic Sea Action Plan, 11 substances pointed out of specific concern
- Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). *REACH* was developed to improve the protection of human health and the environment from the risks that can be posed by chemicals. Includes regulations of more than 10000 substances.
- Article 59(10) of the REACH Regulation EC no. 1907/2006. ECHAs Candidate List of substances of very high concern (SVHC) for Authorisation (http://echa.europa.eu/web/guest/candidate-list-table) which may cause severe, long-term effects on the ecosystems. Regards more than 160 substances January 2015.

Focus is generally on limiting emissions or concentrations of various substances to the aquatic environment and improving of the actual status of the recipient as such indirectly targeted. The sensitivity to various emissions varies among different recipients and quantitative effect assessments in recipients are difficult. Ensuring that discharges from STPs do not include any significant concentrations of the targeted substances is thus a pragmatic cautionary approach.

For the recently reviewed list of priority substances in directive 2013/39/EU (originally 33 priority substances, now a list of 45 substances) within the Water framework directive, Environmental Quality Standard values (EQS) have been defined. The EQS values represent a threshold value, the highest acceptable concentration in the aquatic environment for all water bodies. EQS are defined for water, biota and/or sediment and are either an annual average (AA EQS) or a maximum allowable concentration (MAC EQS). The EQS in the water bodies should have been achieved by December 2015. Acceptable exceptions for not reaching the EQS by 2015 are if there will be a gradually improved quality after 2015, or that it is economically or technically impossible to reach

and there will not be a degradation of status. The EQS should definitely be reached by 2027, and the only acceptable exception is if natural conditions make it impossible to reach by 2027. Latest information of classification of EQS for each water body in Sweden is available at www.viss.lansstyrelsen.se.

Further concern should be given to *specific pollutants* according to the WFD (2000/60/EEG), which present a significant risk to, or via, the aquatic environment on specific water bodies. The list of specific pollutants was suggested by the Swedish EPA (SEPA 2008) and a suggested updated list of substances has been on review from the Swedish Agency of Marine and Water Management during the 2014 (HVMFS 2013:19 revised by HVMFS 2015:4 appendix 2 and appendix 5). The specific pollutants list (now 26 substances/substance groups) regards the substances included on the 2013/39/EU watch list and other specific pollutants discharged in significant quantities to Swedish water bodies.

Within the WFD, *priority substances* are used in the *chemical status* classification to determine good chemical status/failing to achieve good chemical status, while the *specific pollutants* list of substances are used in the *ecological status* classification to determine status between high/good and good/moderate.

Regarding wastewater the REVAQ certification system, developed and operated by the Swedish Water & Wastewater Association, the Federation of Swedish Farmers (LRF), The Swedish Food Federation and Swedish food retailers federation, in close cooperation with the Swedish Environmental Protection Agency, should further be considered, as it is intended to reduce the load of dangerous substances on the STPs, support recycling of nutrients, and to mitigate risks during recycling. REVAQ pollution load preventions, is largely focused on upstream source reductions.

Concentrations of pharmaceutical residues and several other organic substances in wastewater effluents, however, are not regulated by current legislation. The main reason for this may be the relatively young debate and the absence of a good understanding and consensus on which substances that should be regulated at what concentrations. In August 2013, three pharmaceuticals, diclofenac (anti-inflammatory), 17-β-estradiol and 17-α-ethinylestradiol (both sex hormones) were added to the European Commission's watch list of priority substances. At the latest in September 2017, the Commission shall propose measures at EU and/or Member State level to manage those substances. In 2014 another seven substances or groups of substances were proposed and is now added to the watch list, among them 2-ethylhexyl 4-methoxycinnamate (a sunscreen agent), triphenyl phosphate, and the antibiotics erythromycin and clarithromycin (Carvalho *et al.,* 2014). The STPs will have to comply with existing and upcoming EQS in the near future.

The EQS values have been developed based on ecotoxicology tests and safety precautions regarding persistence and bioaccumulation. Thus, for some substances the EQS values are very low, which is a challenge for analytical laboratories since detection limits are now always sufficiently low in conventional analytical methods. . The Swedish Government has developed a national toxic-free strategy in which one of its seven priority areas is to reduce the environmental impact of persistent organic substances (SOU 2012). Thus, there are indications for a future regulation of

pharmaceutical residues and other organic substances. However, there are certainly good reasons to reduce emissions of organic substances to the aquatic environment even without regulations at place.

In addition, in wastewater reclamation, considered one of the most crucial techniques for increasing water availability, improving water resources management and minimising environmental pollution, standards and regulations are rare. The World Health Organization (WHO) focuses on the protection of public health in terms of bacterial contamination. National regulations may exist but mostly for irrigation reuse of wastewater (Dalahmeh and Baresel, 2014)

When it comes to quality of treated wastewater for release to recipients, the target should be to not decrease the environmental quality of the recipient and harm aquatic life. The precautionary principle, often referred to in pollution discussions, should be considered and applied when discussing emissions of pharmaceutical residues and other emerging substances. Theoretically, no release at all of priority substances might be optimal, but this is not realistic when resources necessary to achieve this are considered. A point with enough treatment to an acceptable cost in money and resources has to be found.

3.1 Assessments of removal targets

The efficiency of a STP to remove pharmaceuticals or other emerging substances are normally given as percentage removal from inlet to outlet. However, when it comes to possible-toxicological effects of the effluent, it is the residual concentration, or really the amount, that is important.

The concentrations of emerging substances in treated sewage are low, and very seldom give acute effects. The possible chronic effects are difficult to foresee for a single compound, and even more difficult for a mixture of partly unknown substances in the wastewater. A possible approach is to look at all *known* compounds separately and compare the concentration in the receiving waters (environmental concentrations, EC) to the Predicted No Effect Concentration (PNEC). This is the so-called Single-substance ecotoxicology effect test (see Section 5.5.1 for more information on PNEC and the EC/PNEC-factor). This is, however, a simplification, since not enough is known about how compounds in a mixture affect the toxic impact, and PNEC values are not known for many compounds. In addition, the concentrations in the effluent should be considered with respect to the dilution in the recipient and the concentration in the recipient and then compared to the PNEC values. The dilution factor varies over the year for every sewage plant. Both annual average as well as maximum concentrations should be considered according to the WFD to be comparable to available EQS.

An alternative may be the use of a selected number of substances as indicator substances for assessing both emissions and different treatment options and thus allow a good evaluation without the risk of losing essential information. These indicator substances or functional indicators as suggested by Jekel *et al.* (2015) can be based on recent screenings, studies, literature and other sources with comparable conditions. This report summaries a functional indicator substance list based on the reviews

compiled to guide to cost-efficient and relevant evaluations of removal efficiencies in the STPs (further reading in chapter 7, table 7.1).

As wastewater may contain substances for which results from toxicological tests are not available, or as it may contain unknown substances, whole effluent assessments (WEA) that measure the effects of STP effluent on the survival, growth and reproduction of organisms, are recommended to assess the effects of the effluent on the aquatic environment (see Section 5.5.3). In addition, assessment factors to account for test uncertainties are recommended.

For strongly bio-accumulating and persistent substances, there is no actual PNEC value (and such values would be misleading too), since a long time exposure to very low concentrations can still lead to harmful concentrations in biota. For these compounds, minimum emission is extra important.

The calculation of an environmental concentration (EC value) for each compound is of course dependent on a reliable quantification in the effluent. The concentrations are often below the limit of quantification, LOQ, partly due to a complex water matrix. With the suggested very low PNEC value 0.1 ng/L for ethinylestradiol and a dilution factor of 10 the effluent concentration should be 1 ng/L to get EC/PNEC = 1. Present chemical analysis methods are not good enough to quantify 1 ng/L. There are similar problems with other substances with low EQS, such as brominated diphenylethers and PFOS.

Another problem regards how to evaluate concentrations in effluents below LOQ and thus, how to evaluate removal efficiencies. A value < 10 ng/L, might be 8 ng/L or 1 ng/L. This is a problem irrespective if the treatment effect is reported as percent removal or as remaining concentration. In a table < 10 ng/L or > 95 % removal are obvious, but in a graph, LOQ/2 is often used. This is more or less well founded depending on the slope of the dose-response curve above LOQ.

Released amounts of different compounds are related to the volume of effluent water and normal concentrations after treatment. Considerably higher amounts may result from occasional problems in the STP. The greatest impact is probably for highly hydrophobic compounds that might follow temporary high losses of biomass from the system. It might be important to minimize the loss of suspended particles, whether it is bio-sludge or other organic or inorganic particles that can serve as carriers for hydrophobic material. If an acceptable understanding of the relationship of persistent organic substances and the particles distribution in the effluent would exist, a reduction of such particles could be used as an indirect quality parameter for the occurrence and removal of highly hydrophobic compounds by various treatment steps. However, it should be noted, that the more particles that are removed from the effluent, the larger the amount of adsorbed substances in the sludge, unless they are degraded.

4 Priority and emerging substances at sewage treatment plants

Although STPs are not primary sources of environmental releases of anthropogenic environmental pollutants, they provide a good opportunity to break the release chain and prevent chemicals from further distribution into the aquatic and terrestrial environment via effluent water and municipal sludge.

This section describes properties, use and fate as well as measured concentrations and expected environmental impact of selected priority and emerging substances at Swedish STPs, and includes active pharmaceutical ingredients and typical industrial and consumer chemicals used as e.g. plasticizers, flame-retardants and personal care products. The substances have been ordered according to common practice in the literature, mainly based on structure (e.g. phthalates, phenols) but sometimes based on function (e.g. flame retardants, pharmaceuticals). Measured effluent concentrations of pharmaceuticals and other priority and emerging substances in Swedish (and other) STPs are presented in this chapter, together with discussions on usage trends. Influent concentrations are also included where available. Since both influent and effluent concentrations are needed to assess removal efficiencies in STPs this is a limitation in the assessment. Each section is concluded by an outlook, whereby expected future trends or chemical shifts and needs for enhanced treatment technologies are discussed.

4.1 Pharmaceutical residues

Pharmaceuticals or active pharmaceutical ingredients (APIs) and their metabolites are excreted from the human bodies via urine and/or faeces. It has been shown that pharmaceuticals from different therapeutic groups e.g. antibiotics, analgesics, anticancer drugs, contraceptives and anti-depressant drugs have toxic effects in the environment (Vasquez *et al.,* 2014). According to Vasquez *et al.* (2014), the most frequently detected pharmaceuticals are analgesics, antibiotics, diuretics, beta-blockers, hormones, antidepressants, psychiatric and lipid regulators. A recent compilation of existing screenings of pharmaceuticals in Swedish STP effluent showed that about 25 % of all identified pharmaceutical substances are almost completely removed by traditional secondary treatment processes (Hörsing *et al.,* 2014). Another 25 % are significantly but not entirely removed. Removal of the remaining 50 % of these substances is assumed possible only by complementary removal methods.

APIs are categorized according to the so-called Anatomical Therapeutic Chemical (ATC) system, controlled by the World Health Organization, aimed to provide a systematic classification scheme that can be used for e.g. sales statistics. Individual active substances are organized into different ATC-groups, depending on the target organ and their mode of action. The usage of APIs is here presented as DDD/1000 inhabitants per day where DDD corresponds to the number of defined daily doses. Figure 4.1 shows the overall consumption of prescribed pharmaceuticals in Sweden between the years 2006 and 2014, based on the statistics database of the Swedish National Board of Health and Welfare. As evident, there has been a gradual increase in the pharmaceutical consumption, from 1360 DDD/1000 inhabitants per day in 2006 to

1500 DDD/1000 inhabitants per day in 2014, where pharmaceuticals for the cardiovascular system account for the majority of the increasing amounts.

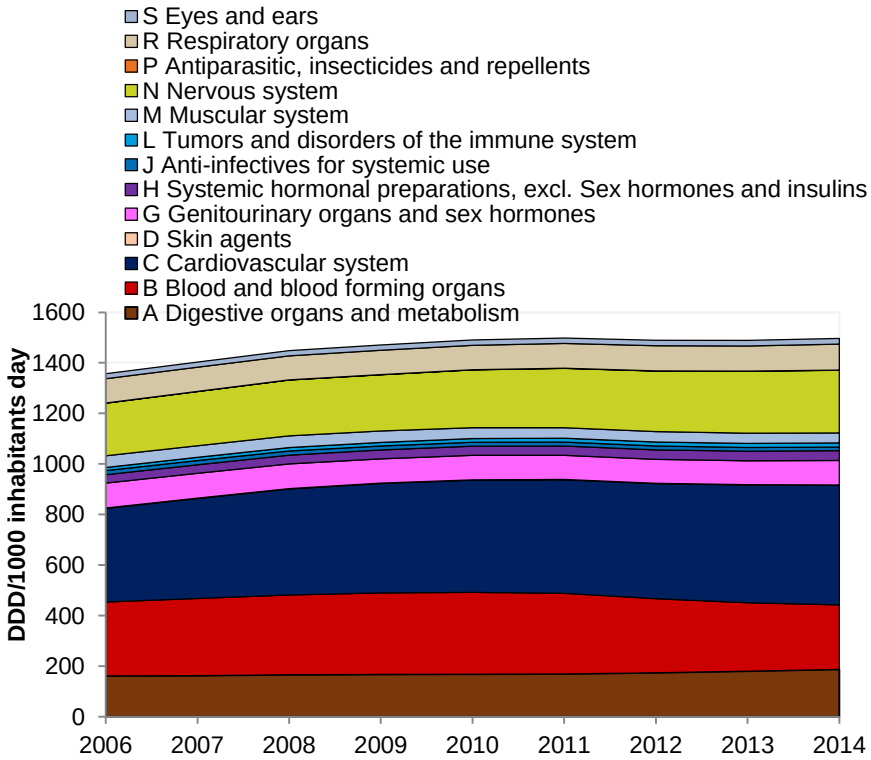


Figure 4.1. DDD (defined daily doses) of prescribed pharmaceuticals per 1000 inhabitants and day (Swedish National Board of Health and Welfare, 2015).

The ATC classification structure is useful to illustrate the overall use of prescribed drugs. On this overall level however, it does not reveal the consumption pattern of individual active ingredients. Neither does it illustrate the specific functions of the drugs. For example, antibiotics may be found under several different major categories since they are used to treat bacterial infections in many different types of organs. From an environmental perspective, it is important to know what the typical function is, since different types of pharmaceuticals may lead to different types of environmental effects, and may require different treatment technologies. Therefore, in the following subchapters, we have arranged individual active ingredients under different head categories, based on their main function where substances from different ATC-categories may be treated together.

4.1.1 Antibacterial and anti-inflammatory substances

Properties and use

Antibacterials include pharmaceutical categories such as antibiotics, antifungals, antimycobacterials, antivirals, immunoglobulins, vaccines, antiparasetics, insecticides and repellents and are categorized under different ATC-groups. They are used to treat different bacterial inflammations and fungous infections in different organs. These substances are generally water-soluble based on the Log K_{OW} and Log K_D-values where K_{OW} is generally below 5 (see Table 4.1). They include both acidic and base compounds reflected by their pKa-values, which range from 1.6 to 11. Antibiotics such as for example sulfamethoxazole can be transported as conservative ions and thus end up in groundwater as was shown by Barber *et al.* (2009).

The *anti-inflammatory* drugs cover a wide spectrum with respect to their physical-chemical properties, and include both bases and acids (Table 4.1). However, the LogK_D-values presented in Table 4.1 are low thus, they are expected to occur mainly in the water phase and not sorbed to sludge.

Table 4.1. Selected physical-chemical properties of antibacterial and anti-inflammatory pharmaceuticals.

Substance	Log K_D/ Log K_{ow}	pKa	Ref.
Antibacterial			
Azithromycin	- / 0.65	7.34	2
Ciprofloxacin	4.3 / 0.28	6.43, 8.49	1
Clarithromycine		8.99	3
Clindamycine		7.66	3
Doxycycline		4.5, 8.44, 9.3, 10.84	3
Erythromycin	- /3.06	8.88	1,2
Levofloxacin	- / -0.39	6.05, 8.22	1
Metronidazole		2.55	3
Norfloxacin		6.3, 8.38	3
Ofloxacin		6.05, 8.22	3
Oseltamivir		8.81	3
Roxithromycin		9.27	3
Sulfadiazine		6.52, 2	3
Sulfamethoxazole	2.4 / 0.89	1.69, 5.57	1
Terbutaline		11.1, 8.72, 10	3
Tetracycline	-/ -1.3	3.30, 7.68, 9.69, 11.02	1,2
Trimethoprim	2.3 / 0.91	7.12	1,2
Anti-inflammatory substances			
Acetaminophen	- / 0.46	9.38	1
Diclofenac	1.2 / 4.51	4.01 - 4.15	1,2
Ibuprofen	0.9 / 3.97	4.31 -4.91	1,2
Naproxen		4.69	3
Salicylic acid		3.03	3

* NOEC No Observed Effect Concentrations
# Compiled in Wikipharma http://www.wikipharma.org/welcome.asp
1-Yang *et al.,* 2011; 2-Bakheit *et al.,* 2014; 3-Manallack. 2009.

According to the Swedish National Board of Health and Welfare (Socialstyrelsen) the use of antibacterials for systemic use and penicillins, amounted to 15 DDD/1000 inhabitants per day in 2013, which was about 3 times lower than the use of prescribed anti-inflammatory drugs, which amounted to about 27 DDD/1000 inhabitants per day (Figure 4.2). In addition to the prescribed doses displayed in Figure 4.2, non-

prescribed pharmaceuticals (purchased in pharmacies and/or grocery stores) contribute substantially to the overall consumption of anti-inflammatory drugs. In Sweden, approximately 40 anti-inflammatory drugs (consisting of different combinations of nine APIs) can be purchased without a prescription (Swedish Medical Products Agency, 2011). In 2011-2013 the consumption of four of the most sold pharmaceuticals, namely ibuprofen, paracetamol, acetylsalicylacid and diclofenac amounted to average sales of 177, 125, 62 and 25 DDD/1000 inhabitants per day respectively (where paracetamol has increased slightly during these three years, i.e. *14 times higher* than the use of all prescribed antinflammatory drugs together. As evident in Figure 4.2, the use of antibacterial as well as anti-inflammatory substances has decreased somewhat over the last eight years.

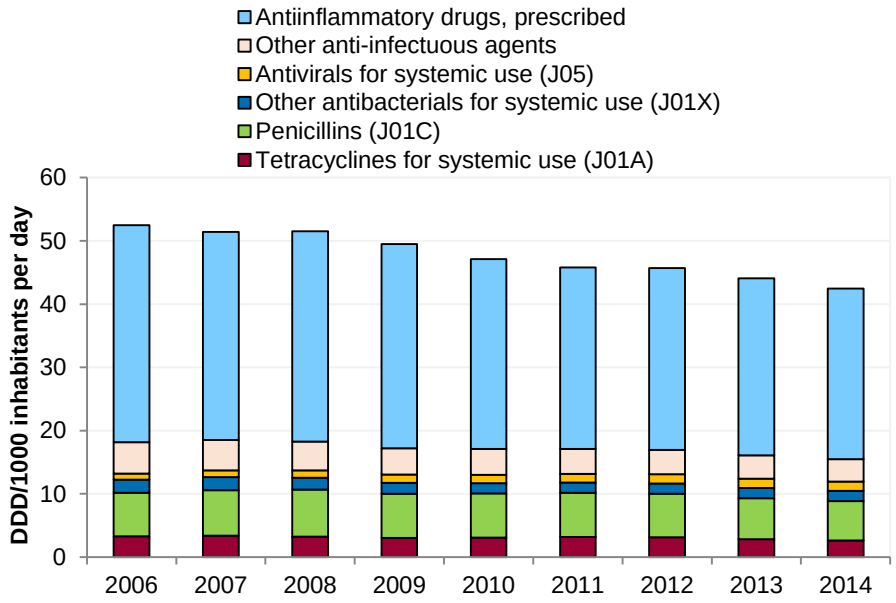


Figure 4.2. Prescription of antibacterials and antiinflammatory substances in Sweden between 2006 and 2014 (Swedish National Board of Health and Welfare, 2014).

Environmental impact

Due to the presence of antibacterials in the environment, concern has been raised regarding the formation of resistant bacterial genes in STPs as well as in the recipients. Furthermore, there is a concern that the concentrations discharged to the recipients sometimes approach effect levels (LOEC, see Table 4.2). A study performed at a Slovakian STP investigated resistance towards antibiotics, ampicillin, ciprofloxacin, gentamicin, tetracycline and chloramphenicol. It was concluded that bacterial resistance to some antibiotics was higher during wintertime and that the removal was insufficient for clarithromycin and azithromycin. In the wintertime, high concentrations of coliform bacteria resistant to ampicillin and gentamicin were found in the sludge. In the summer the number of bacteria with high-level resistance to all tested antibiotics increased in the sludge (Birošová *et al.,* 2014). It has also been shown that long-term exposure to low levels, sub-therapeutic concentrations, leads to increased antibiotic resistance in microbial populations (Gullberg *et al.,* 2011).

Concern about presence of anti-inflammatory pharmaceuticals in the environment initially arose when it was reported that vultures were endangered due to the presence of diclofenac in their food, i.e. dead cows (Oaks *et al.,* 2004). Recent research indicate that nonsteroidal anti-inflammatory drugs (NSAID) like diclofenac, ibuprofen and acetaminophen cause DNA damage with induced immunosuppression and genotoxicity in fish (Ribas *et al.,* 2014).

Fate and behaviour in sewage treatment plants

Antibacterials have been measured in STP influents, effluents as well as in recipients around the world. In Sweden, antibiotics are included in the national monitoring program since 2010, where highest concentrations have been reported for clindamycine, roxithromycin, erythromycin and clarithromycine (SEPA 2013a). Azithromycin, ciprofloxacin, norfloxacin, ofloxacin and tetracycline are detected at significantly lower concentrations (Table 4.2). As evident from the table, the concentrations found are often above the effect-levels, represented by the Lowest Observed Effect Concentration (LOEC). With the exception of clindamycine and erythromycin, concentrations in European effluents are on average higher than those concentrations found in Swedish STP effluents. In Sweden, the antibacterials ciprofloxacin and norfloxacin have further been detected in sludge (Haglund 2011). However, a slight decreasing trend of the concentration of norfloxacin in sludge from year 2004 to 2011 has been indicated, possibly due to a decrease in the prescriptions.

Reported mean concentrations of NSAID in STP effluents in Sweden range from ~30 to 900 ng/L. The highest concentration represents naproxen detected at 43 of 46 STPs (Falås *et al.,* 2012). The national environmental monitoring program include the anti-inflammatory drugs diclofenac, ibuprofen, ketoprofen, loperamide, naproxen and paracetamol, with concentrations ranging from below LOQ (10 ng/L) to 4 µg/L (Fick *et al.,* 2011). Globally, diclofenac and ibuprofen are frequently measured with concentrations reported from 10-1200 ng/L (Gracia-Lor *et al.,* 2012; Loos *et al.,* 2013; Luo *et al.,* 2014; Nam *et al.,* 2014; Patrolecco *et al.,* 2013). Concentration of mefenamic acid in Europe ranges from 2.5-390 ng/L (Luo *et al.,* 2014).

Outlook

The problem with resistant bacteria will most likely persist although the prescription of antibitocs has decreased somewhat, thus there will be a continued great need for efficient treatment technologies regarding antibacterials. In a review by Rizzo *et al.* (2013) it was summarized that despite research regarding inactivation of bacteria by applying advanced treatment technologies, e.g. adsorption, membranes, advanced oxidation including sand filtration, there is lack of knowledge on its effects on antibiotic resistance. Later research compared, e.g., chlorination with ozone and TiO2 photocatalysts. The evaluation of the effect on the DNA structure showed that chlorine did not affect the plasmid-DNA while ozone and the photocatalysis did. The higher the doses the more damage could be observed. Other treatments that have shown effect on antibiotic resistance are Fenton processes, photolytic and TiO2 photolytic (UVA-TiO2) treatment processes. The effect of disinfection were also summarized stating that some bacteria may survive chlorination and regrow at low chlorine doses. UV radiation for disinfection purposes damages DNA, however bacteria may recover replication mechanicms (Rizzo *et al.,* 2013).

Table 4.2. Measurements of antibacterials in Swedish STP-effluents (and other geographical locations in parenthesis) and lowest observed effect concentration (LOEC), or other ecotoxicological information.

Substance	Mean concentration (ng/L)	LOEC[#]	Ref.
Azithromycin	12.3 (130 - 505.5)		1,2,3
Ciprofloxacin	17.5 (211.2 - 630)	0.005-2.19 mg/L	1,2,3,4
Clarithromycine	114.2 (280 - 1213.5)	40 µg/L	1,2,3
Clindamycine	137.8 (55.5)	(IC_{50} >100 mg/L)	1,2
Difloxacin	(2.5)		1
Doxycycline	(5.3 – 9)	100-1000 µg/L	2,3
Enoxacin	(3.5)	2.88 µg/L	2
Enrofloxacin	(2.9)	15 mg/L	2
Erythromycin	182.7 (15)	1 µg/L	1,2,3
Levofloxacin	(41.75)	30 - 300 µg/L	2
Lomefloxacin	(2.2)	30 mg/L	2
Metronidazole	(28)	10-1000 mg/L	3
Norfloxacin	5.3 (20.6 - 150)	0.025-16000 µg/L	1,2,3,4
Ofloxacin	5 (400)	0.3- 25mg/L	1,3,4
Oseltamivir	(2.1)		2
Oseltamivir Carboxylate	(10.6)		2
Oxolinic Acid	(12)	NOEC* 10-380 µg/L	2
Oxytetracycline	(2)	0.9-100 mg/L	2
Penicillin V	(1)		2
Roxithromycin	130 (1.5 - 290)	40 µg/L	1,2,3
Sulfadiazine	(3.3)		2
Sulfadimethoxine	(3.7)		2
Sulfamerazine	(2.2)		2
Sulfamethazine	(2.5 - 114)	150 mg/L	2,5
Sulfamethizole	(2.4)		2
Sulfamethoxazole	(10 – 57)	10 µg/L -100 mg/L	2,5,6
Sulfamethoxypyridazine	(3.4)		2
Sulfamoxol	(2.7)		2
Sulfaphenazole	(1.8)		2
Sulfapyridine	(78.2)		2
Sulfaquinoxaline	(2.6)		2
Sulfathiazole	(2.9)		2
Sulfsalazine	(55.1)		2
Terbutaline	(1)		7
Tetracycline	23 (2.4 – 6.5))		1,2,3
Trimethoprim	(40 - 86.8)	0.29 µg/l - 100 mg/L	2,5

* NOEC No Observed Effect Concentrations
# Compiled in Wikipharma http://www.wikipharma.org/welcome.asp
1-Fick *et al.,* 2010; 2-Boehler *et al.,* 2012; 3-Verlicchi *et al.,* 2014;4- Haglund 2011; 5- Behera *et al.,* 2012; 6-Sun *et al.,* 2014a; 7-Loos *et al.,* 2013

Ibuprofen can be reduced by the existing biology in the STPs, ozone and activated carbon can also be applied. Chlorine dioxide, however, has no effect (Falås *et al.,* 2012a; Hey *et al.,* 2012a, 2012b; Hörsing *et al.,* 2014). The reduction of diclofenac can be increased by extended biological treatment (Falås *et al.,* 2012b) and further by applying ozone or chlorine dioxide (Hey *et al.,* 2012a, 2014; Hörsing *et al.,* 2014). Activated carbon, both in powder and granular form, have shown removal efficiencies of >96 % for diclofenac (Grover *et al.,* 2011; Hernández-Leal *et al.,* 2011; Hörsing *et al.,* 2014; Kovalova *et al.,* 2013; Yang *et al.,* 2011)

4.1.2 Drugs for the nervous system

Properties and use

Drugs intended for treatment of the nervous system include antidepressants, neuroleptics, ataractics/tranquilizers, hypnotics and sedatives, anesthetics, analgesics, antiepileptics, anti-Parkinson and psychoanaleptics. They are used for treatment of e.g. pain, depression, anxiety and Parkinsons disease. They include APIs, which are either bases or acids or a combination of both due to the existence or more than one functional group. The $LogK_D$ values presented in Table 4.3 for these APIs range from 0.1 to 4.2 implying that the main part of these APIs will be found in the water phase and only a minor part will be sorbed to sludge.

Table 4.3. Physical-chemical properties of some APIs for the nervous system.

Substance	Log K_D/ Log K_{ow}	pKa	Ref.
Antidepressants			
Amitriptyline	3.4/ -		3
Bupropion	2.1/ -		3
Citalopram	2.3/ -	9.57	2,3
Clomipramine	3.8/ -	9.46	2,3
Duloxetine	3.4/ -		3
Fluoxetine	3.7/ -	9,62	2,3
Maprotiline	3.7/ -		3
Mianserin	3.0/ -	8.25, 2.69	3
Mirtazapine		8.1, 2.25	2
Nefazodone	3.9/ -		3
Paroxetine	3.9/ -	10.32	2,3
Sertraline	4.2/ -	9.47	2,3
Venlafaxine	2	9.26	2,3
Neuroleptica, ataractics, hypnotics and sedatives			
Alprazolam		1.92	2
Chlorpromazine		9.21	2
Flunitrazepam		1,71	2
Flupentixol		8.1, 3.9	2
Fluphenazine	3.4/ -	8.3	2,3
Haldoperidol	2.8/ -		3
Hydroxyzine		10.8	2
Levomepromazine	3.0/ -	10.94, 1.68	2,3
lorazepam	2.8/-	7.89, 3.46	2,3
Olanzapine		6.6	2
Oxazepam		10.94, 1.68	2
Risperidone		7.89, 3.46	
Zolpidem		6.6	2
Anesthetics, analgesics, antiepileptics, anti-Parkinson and psychanaleptics			
Acetaminophen		9.62, 8.31	2
4-Aminoantipyrine	0.1 / 2.45	13.90	1
Buprenorphine		11.21, 1.57	2
Caffeine		8.4	2
Carbamazepine		9.46, 6	
Clonazepam	3.0/ -	8.8	2, 3
Codeine		8.43	2
Dihydroergotamine		4.23	2
Donepezil	3.7/ -	8.86	2,3
Fentanyl		3.73	2
Ketoprofen		10.42	2
Loperamide		9.86	2
Mefenamic acid	3.4/ -	6.95	2,3

Memantine	2.3/ -	9.28	2,3
Paracetamol		9.86	2
Pizotifen		6.95	2
Tramadol		9.28	2

1-Yang *et al.,* 2011; 2-Manallack 2009; 3-Hörsing *et al.,* 2011

The prescription of *antidepressants* has increased from 72 DDD/1000 inhabitants per day in 2006 to 86 DDD/1000 inhabitants per day in 2014 (Swedish National Board of Health and Welfare, 2014), reflecting the increasing treatment of mental illnesses. Sertraline is one of the most used antidepressants, accounting for 24 DDD/1000 inhabitants per day in 2014 (compared to 14 in 2006). Antidepressants account for the main part of the overall increased prescription of drugs for the nervous system (which increased from 208 to 248 DDD/1000 inhabitants per day between 2006 and 2014) followed by *neuroleptics, hypnotics and sedatives*, which are dominated by zopiklon, sertraline, propiomazine and zoldipem, and *analgetics,* dominated by paracetamol, kodein and tramadol. There is also a steady but weak increase among other sub-groups e.g. anti-Parkinson agents, psychostimulants, and agents used for ADHD, in particular methylphenidate.

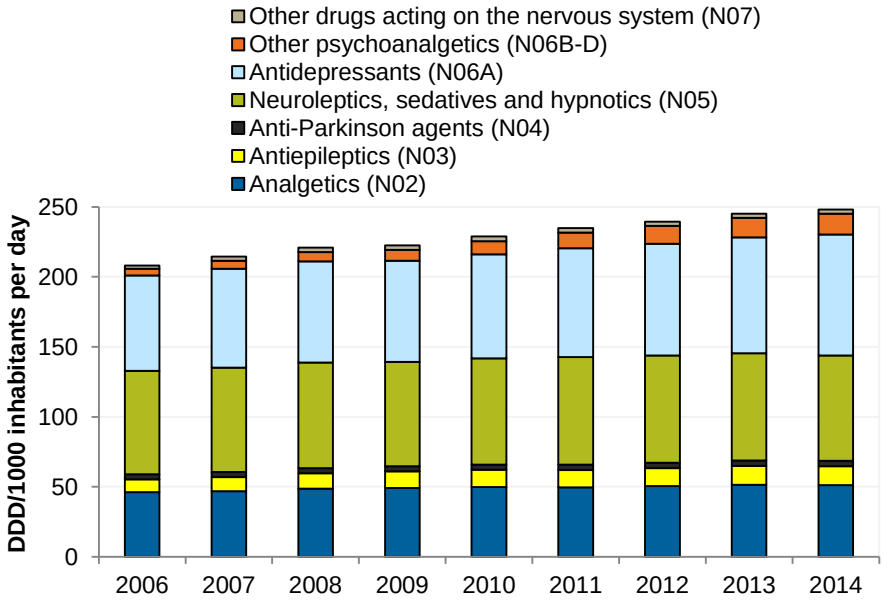


Figure 4.3. Total DDD/ 1000 inhabitants for drugs acting on the nervous system (Swedish National Board of Health and Welfare, 2014).

Environmental impact

Antidepressants have been shown to cause different disorders in the environment (see LOEC-values in Table 4.4). Fong *et al.* (2015) recently reported that venlafaxine boosts locomotion in marine snails while fluoxetine reduces it. In a review by Fong and Ford (2014), they report impact of various antidepressants on e.g. swimming activity in amphipods and induced spawning in zebra mussel.

Fate and behaviour in sewage treatment plants
Sertraline is one of the most commonly occurring antidepressants in STP effluents (<10 – 49 ng/L), reflecting the high prescription numbers of this API. Venlafaxine, a substance of increasing use and citalopram are also frequently detected, the former in the highest concentration of all antidepressants (417 ng/L) and the latter in levels of 34-480 ng/L (see Table 4.4). Carbamazepine, codeine and tramadol are frequently detected in STP effluent analysis.

Paroxetine, paracetamol and risperidone and to some extent fluoxetine have all been shown to be reduced in the biological treatment. Citalopram and sertraline have an even higher negative reduction of -25 and -50 %, respectively (Falås *et al.,* 2012a; Hörsing *et al.,* 2014). Zoldipem can partly be removed in existing Swedish STPs.

Outlook
Due to the increasing prescription of drugs acting on the nervous system, the discharge of these APIs is likely to continue. In order to reduce the amount of APIs discharged today e.g. ozone, chlorine dioxide and activated carbon can be used. Activated carbon has potential to reduce amytrypteline, bupropion, chlorpromazine, citalopram, clomipramine, clonazepam, donepezil, duloxetine, fluoxetine, maprotiline and venlafaxine (Hörsing *et al.,* 2014). Also, fluphenazine is assumed to adsorb strongly (Hörsing *et al.,* 2011) and could thus be removed using activated carbon. Chlorine dioxide has a potential to reduce citalopram and venlafaxine and has some effect on amytrypteline, maprotiline, but no effect on bupropion, fluoxetine (Hey *et al.,* 2012b; Hörsing *et al.,* 2012, 2014). Ozone can be used to reduce citalopram, clomipramine and fluoxetine. In order to increase the reduction for more persistent drugs, e.g. buprenorphine, carbamazepine, codeine pizotifen and tramadol, haldoperidol, hydroxyzine and oxazepam, advanced oxidation processes such as ozone or activated carbon may be applied (Hey *et al.,* 2014; Hörsing *et al.,* 2012, 2014). Also UV-light and Fenton have been shown to reduce citalopram (Hörsing *et al.,* 2012).

Table 4.4. Concentrations of antidepressant drugs, neuroleptica, ataractics, hypnotics and sedatives, anesthetics, analgesics and antiepileptics measured in Swedish STP-effluents (and other locations in parenthesis) and lowest observed effect concentration (LOEC), or other ecotoxicological information.

Substance	Mean concentration (ng/L)	LOEC[#]	Ref.
Antidepressants			
Amitriptyline	9.4	EC50 0.8-36.6 mg/L	1
Bupropion	19.1		1
Citalopram	282.3 (33.8 - 173)	4 mg/L	1,2,5,6,20-23,26
Clomipramine	10.9		1
Duloxetine	3.8		1
Fluoxetine	28.5 (2 - 11)	540 ng/L - 447 µg/L	1-3,16,26,27
Maprotiline	9.4		1
Mianserin	22	250 µg/L-250 mg/L	1
Mirtazapine	176.6		1
Nefazodone	10		1
Paroxetine	10.2	0.44 mg/L, 10^{-6} M	1,27
Sertraline	14.3 (2.1 – 21)	15µg/L -4.5 mg/L	1,5,6,26,27
Venlafaxine	416.9 (140)		1,3
Neuroleptica, ataractics, hypnotics and sedatives			
Alprazolam	66.3 (3 - 5)		1-3
Chlorpromazine	11.3	EC50 0.92-1.60 mg/L	1
Flunitrazepam	7.8		1
Flupentixol	8.3		1
Fluphenazine	11.4		1
Haloperidol	5.7		1
Hydroxyzine	10.3		1
Levomepromazine	31.8		1
lorazepam	(27.5)		1
Olanzapine	Not detected		3
Oxazepam	438 (30 - 633)		1,4-13
Perphenazine	6		1
Risperidone	6.8 (6.9)		1,3,5,7,13
Zolpidem	57.3 (1.5)		1,5
Anesthetics, analgesics and antiepileptics			
Acetaminophen	(10)		3,14,15
4-Aminoantipyrine	(690)		3
Buprenorphine	27.2		1
Caffeine	(10)		14,16
Carbamazepine	389.7 (21 - 832)	10ng/L-100 mg/L	2,5,6,15,17-19
Clonazepam	3.6		1
Codeine	358.2 (8 - 837)		1,4,5,8,9,20-25
Dihydroergotamine	25		1
Donepezil	8.8		1
Fentanyl	2.3		1
Memantine	23.8		1
Pizotifen	8		1
Tramadol	1686.9 (48 - 256)		1,10,16,23,24

[#] Compiled in Wikipharma http://www.wikipharma.org/welcome.asp Accessed 2014-12-16

1-Fick *et al.,* 2011; 2-Yuan *et al.,* 2013; 3-Gracia-Lor *et al.,* 2012; 4-Baker and Kasprzyk-Hordern, 2013; 5-Loos *et al.,* 2013; 6-Golovko *et al.,* 2014; 7-Kosma *et al.,* 2014; 8-van der Aa *et al.,* 2013; 9-Bijlsma *et al.,* 2012; 10-Kosjek *et al.,* 2012; 11-Hass *et al.,* 2012; 12-Margot *et al.,* 2013; 13-Vergeynst *et al.,* 2015; 14-Behera *et al.,* 2011; 15-Luo *et al.,* 2014; 16-Sun *et al.,* 2014a; 17-Patrolecco *et al.,* 2013; 18-Bahlmann *et al.,* 2014; 19-Yu *et al.,* 2013; 20-Acuña *et al.,* 2015; 21-Santos *et al.,* 2013; 22-Urtiaga *et al.,* 2013; 23-Collado *et al.,* 2014; 24-Rodayan *et al.,* 2014; 25-Yargeau *et al.,* 2014; 26-Lajeunesse *et al.,* 2012; 27-Hedgespeth *et al.,* 2012

4.1.3 Drugs for the cardiovascular system

Properties and use

The cardiovascular agents include e.g. β-blockers, diuretica, calciumantagonists, ACE-inhibitors. They have one or more functional groups, and are either weak acids or weak bases. Their physical-chemical properties, which are presented in Table 4.5, indicate that preferably partition to the water phase.

Table 4.5. Physical-chemical properties for some drugs for the cardiovascular system.

Substance	LogKD / LogKow	pKa	Ref.
Amiodarone		8.73	2
Atenolol	3.2/-	8.0-9.6	1,3
Atorvastatin		4.5-4.95	1, 2
Bezafibrate	2.0/-	9.2-9.6	1,2,3
Bisoprolol	2.0/-	8.06	2,3
Cilazapril	3.5/-	9.72	2,3
Clofibric acid		2.73	2
Diltiazem	2.6/-	9.53	2,3
Ezetimibe	3.4/-	5	2,3
Felodipine		8.9-9.75	1,2
Flecainide		4.31	2
Gemfibrozil		9.1-9.6	1
Metoprolol		3.7- 5.6	1
Pravastatin	2.6/-	9.98, 8,35	2,3
Propanolol	2.6/-	8.92	2,3
Rosuvastatin		3.7- 5.6	1
Sotalol	2.6/-	9.98, 8,35	2,3
Verapamil	2.6/-	8.92	2,3

1-Schönherr *et al.,* 2015; 2-Manallack. 2009; 3-Hörsing *et al.,* 2011

The total number of expedited prescriptions in this group is presented in Figure 4.4 for the years 2006-2014. The main contribution comes from diuretics, β-blockers and angiotensin antagonists (Swedish National Board of Health and Welfare, 2014).

Environmental impact

A recent study showed that, based on the green algae test, propranolol and metoprolol can be considered to be toxic ($10<EC_{50}>100$ mg L^{-1}) to aquatic organisms, according to EU directive 93/67EEC (Maszkowska *et al.,* 2014). Bezafibrate have been shown to cause oxidative stress in mussels when exposed to concentrations in the same level as found in STP effluents (Contardo-Jara *et al.,* 2011).

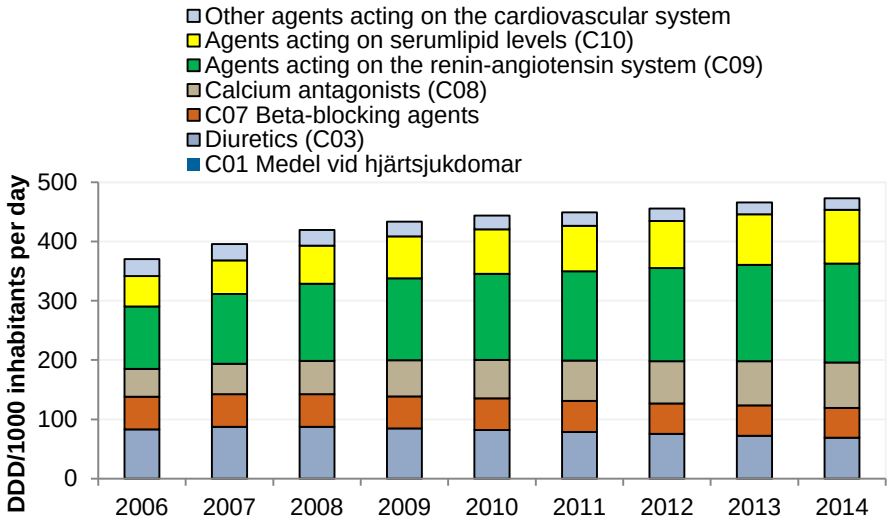


Figure 4.4 Prescriptions of agents for the cardiovascular system (Swedish National Board of Health and Welfare, 2014).

Fate and behaviour in sewage treatment plants

Most of these pharmaceuticals can be found in the water phase in the STP. There are however exceptions, such as amidorone that sorbs strongly to sludge (Hörsing *et al.*, 2011; Hörsing *et al.*, 2014). Table 4.6 presents concentrations of cardiovascular agents measured in STP effluents in Sweden and elsewhere. β-blockers, such as metoprolol and atenolol, are detected in high concentrations both in Sweden and in other countries.

Table 4.6. Concentrations of cardiovascular agents in Swedish STP-effluents (and other locations in parenthesis) and lowest observed effect concentration (LOEC), or other ecotoxicological information.

Substance	Mean concentration (ng/L)	LOEC[#]	Ref.
Amiodarone	25‡		1
Atenolol	461.5 (264 - 1860)	3.2-10 mg/L	1,2-9
Atorvastatin	45.8(20)	19 -1000 µg/L	1,10
Bezafibrate	200 (160)		10-12
Bisoprolol	107.8		1
Cilazapril	4.3		1
Clofibric acid	40 (2)		2,11,12
Diltiazem	42.7	EC50 8.2-407.4 mg/L	1
Ezetimibe	25‡		1
Felodipine	5‡		1
Flecainide	123		1
Gemfibrozil	17	1.5 µg/L-6.25 mg/L	2,10,12
Metoprolol	1621.5 (3 - 410)		1-7,9,13
Pravastatin	(100)	EC50 2 g/L	10
Propanolol	90	0.0005-5 mg/L	11
Rosuvastatin	100.8		1
Verapamil	13.5	7.77-403 mg/L	1

[#] Compiled in Wikipharma http://www.wikipharma.org/welcome.asp Accessed 2014-12-16
‡ reported value is ½ LOQ
1-Fick *et al.,* 2011; 2-Behera *et al.,* 2011; 3-Acuña *et al.,* 2015; 4-Santos *et al.,* 2013; 5-Urtiaga *et al.,* 2013; 6-Collado *et al.,* 2014; 7-Margot *et al.,* 2013; 8-Al Aukidy *et al.,* 2012; 9-Kostich *et al.,* 2014; 10-Gracia-Lor *et al.,* 2012; 11-Falås *et al.,* 2012a; 12-Luo *et al.,* 2014; 13-Nam *et al.,* 2014

Outlook

Beta-blockers are not removed in STPs within existing treatment processes. Minor improvements may be obtained by extending the biological treatment (Falås *et al.,* 2012b). In order to reduce metoprolol, atenolol, sotalol and bisoprolol, activated carbon may be applied. Further, ozone has shown to be efficient in reducing metoprolol. Chlorine dioxide may be used for reduction of sotalol but not for bisoprolol. Ciprazil and dilatiazem may be reduced by ozone, chlorine dioxide or activated carbon. For verapamil, both ozone and activated carbon showed a good reduction (Hörsing *et al.,* 2014).

4.1.4 Agents acting on the genitourinary organs and sex hormones

Properties and use

Physical-chemical properties of sex hormones and agents acting on the genitourinary organs are presented in Table 4.7, and indicate that the compounds are distributed towards the water phase and are either neutral or bases.

Table 4.7. Physical-chemical properties for some drugs for genitourinary organs and sex hormone agents.

Substance	Log K_D/ Log K_{ow}	pKa	Ref.
Afluzosin	3.1		1
17 α-ethynylestradiol	2.5 / 3.67	10.4	2
17 β-estradiol		10.27	3
Estrone	-/3.43	10.77	4,5
Etonogestrel		neutral	3
Finasteride		neutral	3
Levonorgestrel	2..4	neutral	1,3
Medroxyprogesterone	2.1	neutral	1,3
Megestrol	2.8	neutral	1,3
Progesterone	3.0	neutral	3

[#] Compiled in Wikipharma http://www.wikipharma.org/welcome.asp Accessed 2014-12-16
1-Hörsing *et al.,* 2011; 2- Yang *et al.,* 2011; 3-Manallack. 2009; 4-Ying *et al.,* 2002; 5-Lewis and Archer, 1979.

Within the number of expedited prescriptions for genitourinary organ and sex hormones agents, sex hormones agents are dominating, where contraception pills account for the majority. The total amounts of expedited prescription in Sweden of these agents are presented in Figure 4.5.

Environmental impact

The environmental impact caused by this group is well known, e.g. contraception pills causing feminisation of male fishes and frogs. Progesterone in environmental relevant concentrations can cause disruption in sex differentiation in zebra fish (Liang *et al.,* 2014).

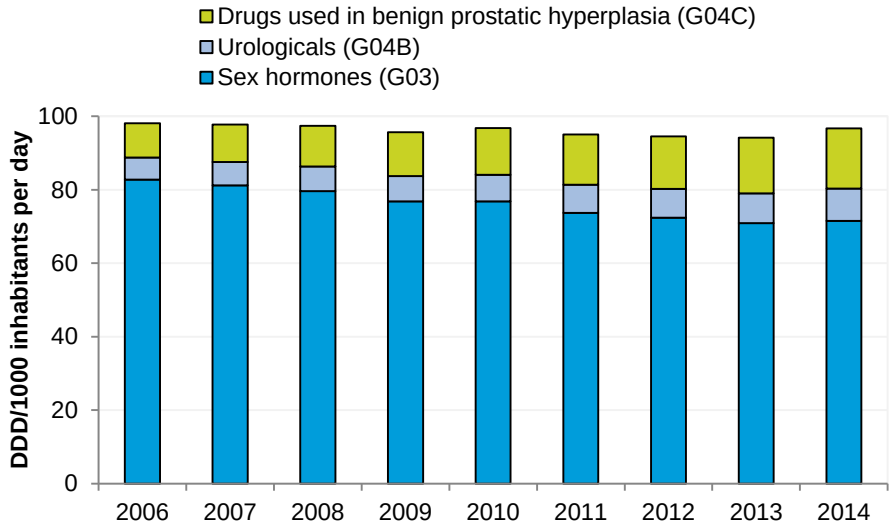


Figure 4.5. Prescriptions of agents acting on genitourinary organs and sex hormones (Swedish National Board of Health and Welfare, 2014).

Fate and behaviour in sewage treatment plants

For 17 α-ethinylestradiol and medroxyprogesterone the detection limit is a problem, with reported concentrations often below LOQ. For the Swedish measurements, LOQ is 10 ng/L, while Japanese studies have reported LOQs of 0.5 ng/L (Ihara *et al.,* 2014). Concentrations of hormones are reported from around the world and are ranging from < LOQ to ~400 ng/L and from < LOQ - ~2000 ng/L for 17 β-estradiol and estrone, respectively. For some of the APIs the concentrations approach levels in similar order magnitude as the LOECs (Table 4.8).

Table 4.8. Measured concentrations of different hormones in Swedish STP-effluents (and other locations in parenthesis) and lowest observed effect concentration (LOEC), or other ecotoxicological information.

Substance	Mean concentration (ng/L)	LOEC[#]	Ref.
Afluzosin	55.3		1
17 α-ethynylestradiol	5[‡] (0.4)	1.1 ng/L – 1 mg/L	1,2,3
17 β-estradiol	5[‡] (20 – 28)	0.9 ng/L-272 µg/L	1,3-6
Estrone	(3 – 242)	8 ng/L – 318 ng/L	2,4-6-10
Etonogestrel	156.9		1
Finasteride	9.46		1
Levonorgestrel	13.2	0.8-156 ng/L	1
Medroxyprogesterone	5[‡]		1
Megestrol	28.4		1
Progesterone	18.7(9)		5,11

[#] Compiled in Wikipharma http://www.wikipharma.org/welcome.asp Accessed 2014-12-16
[‡] reported value is ½ LOQ
1-Fick *et al.,*2011; 2-Ihara *et al.,* 2014; 3-Ogus and Kankaya 2013; 4-Behera *et al.,* 2011; 5-Manickum and John 2014; 6-Pessoa *et al.,* 2014; 7-Luo *et al.,* 2014; 8-Margot *et al.,* 2013; 9-Yu *et al.,* 2013; 10-Migowska *et al.,* 2012; 11-Köck-Schulmeyer *et al.,* 2013

Outlook
Even though the existing biological treatment seems to have the capacity to reduce ethinylestradiol, estradiol, estrone and estriol further improvement is needed. Progesterone, for example, is not reduced in existeing treatment systems, but may be reduced by activated carbon. Ozone or chlorine dioxide could also have a reducing effect on ethinylestradiol. Chlorine dioxide may also be used for estrone for which activated carbon is not very effective. Chlorine dioxide is however, not a good choice if finasteride is the targeted compound, then activated carbon may be an option (Hörsing *et al.,* 2014).

4.1.5 Agents for blood and blood forming organs

Properties and use
Agents for blood and blood forming organs include e.g. anticoagulants, (mainly antiplatelet drugs). Another group with high-expedited prescriptions is anti-anemic agents where folic acid and its derivatives are the main agents' contribution to the high prescriptions. Figure 4.6 presents the expedited prescriptions in Sweden during the years 2006-2014. Individual APIs in this group are dipyridamole with at pKa 6.4, vitamin K, enzymes, thrombin inhibitors, amino acids and vitamin B12.

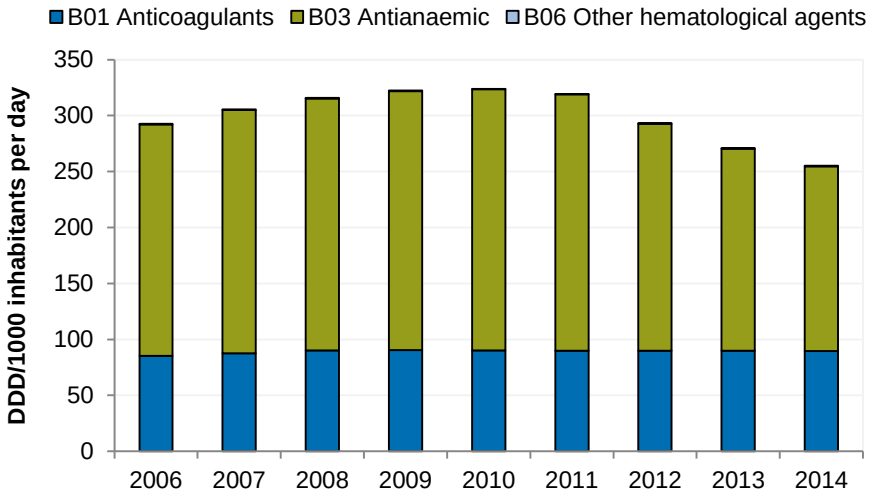


Figure 4.6. DDD/1000 inhabitants regarding agents for blood and blood forming organs (including the two largest groups of agents, anticoagulants and agents for anemias, which explains the high total DDD/ 1000 inhabitants; Swedish National Board of Health and Welfare, 2014).

Environmental impact
Warfarin, which is a vitamin K antagonist i.e. an anticoagulatia, has been found to interfere with many biological processes in zebrafish and to cause e.g. haemorrhage in brain and skeletal in zebrafish larvae (Fernández *et al.,* 2014).

Fate and behaviour in sewage treatment plants
Measurements of pharmaceuticals belonging to this group in STP effluents are scarce. In Sweden, dipyridamole is included in the national environmental monitoring

program, however, the concentrations reported are below LOQ (50 ng/L) (Fick *et al.*, 2011).

Outlook
Even though the prescriptions of blood forming agents shows a decreasing trend the DDD / 1000 inhabitants per day are high, thus the release is likely to continue. There will therefore be a continued great need for efficient wastewater tretment.

4.1.6 Agents against tumors and disorders of the immune system

Properties and use
The APIs in this group are either acids or weak bases, which have one or more functional groups. Their pKa-values are given in Table 4.9.

Table 4.9. Agents against tumors and disorders of the immune system.

Substance	pKa	Ref.
Cyclophosphamide	2.84	1
Doxorubicin	7.35, 8.31, 11.9, 8,68	1
Flutamide	neutral	1
Ifosfamide	1.44	1
Methotrexate	3.76, 4.83, 5.6	1

1-Manallack 2009

The prescriptions of agents against tumors and disorders of the immune system have increased from 12 to 16 DDD/1000 inhabitants per day. It should be noted that pharmaceuticals requisitioned for inpatients and outpatients, i.e. patients hospitalized and patients not hospitalized for 24 hours or more but who visits a hospital, for diagnosis or treatment, respectively, are not included.

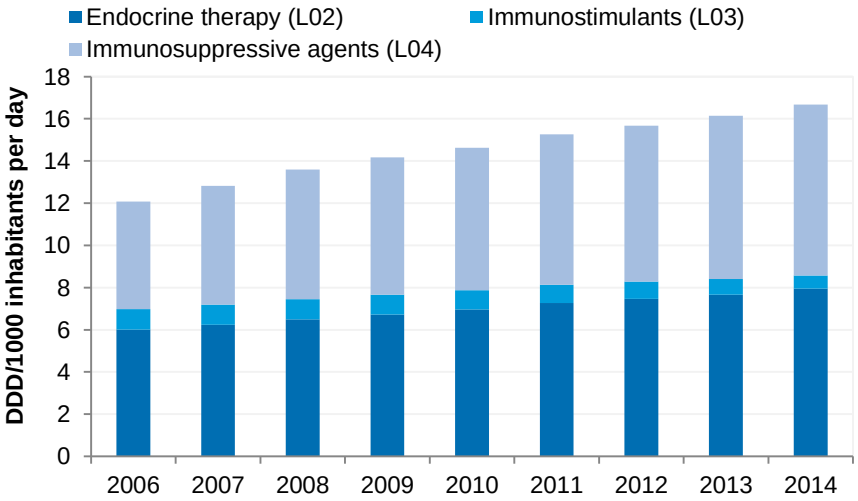


Figure 4.7. Prescriptions of agents against tumors and disorders of the immune system in Sweden (contain drugs for endocrine therapy and immunosuppressive agents, Swedish National Board of Health and Welfare, 2014).

Environmental impact
The environmental impact of APIs in this group is largely unknown.

Fate and behaviour in sewage treatment plants
The environmental measurements of cytostatics are scarce. The majority (10 out of 15) of the cytostatic drugs are not biodegradable, according to a review by Kosjek and Heath (2011). Some of these agents have been measured in wastewater effluents (Table 4.10).

Table 4.10. Measured concentrations agents against tumours and disorders of the immune system in Swedish STP-effluents (and other locations in parenthesis) and lowest observed effect concentration (LOEC), or other ecotoxicological information.

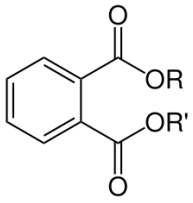
Substance	Mean concentration (ng/L)	LOEC[#]	Ref.
Bleomycine	11-19	0.05	1
Capecitabine	(7.7)		2
Cyclophosphamide	(2.1 – 9)	18-1000 mg/L	1,2
Doxorubicin	Not detected	74 µg/L -10 mg/L	2
Flutamide	9.8	0.28 µg/L – 1 mg/L	3
Ifosfamide	(8.9)		1,2
Methotrexate	(12.6)		1,2
Metabolites:			
(Z)-4-hydroxytamoxifen	Not detected - 5.8[#]		2
6(α)-hydroxypaclitaxel	Not detected - 3.7[#]		2

[#] Compiled in Wikipharma http://www.wikipharma.org/welcome.asp Accessed 2014-12-16
[#] Min-Max values
1-Kosjek and Heath 2011; 2-Negreira *et al.* 2014; 3-Fick *et al.,* 2011.

Outlook
In a review by Zhang *et al.* (2013), pilot studies of MBR, reverse osmosis and nanofiltration followed by granular activated carbon have shown that these techniques are able to reduce e.g. cyclophosphamide. With electrolysis, e.g. methotrexate was reduced. Furthermore, UV-light and the combination of UV-light and H_2O_2 were shown to reduce cyclophosphamide and methotrexate in pure water, deionized water and natural waters. In another study reduction of methotrexate and doxorubicin applying ozonation with or without combination was investigated showing 80 % reduction of methotrexate using both techniques and for doxorubicin <50 % reduction (Zhang *et al.,* 2013).

4.2 Plasticisers - Phthalate esters
Properties and use
Plasticisers are used to increase the plasticity of a material. Phthalate esters are used in plastics. Phtalate esters are colourless liquids with varying physical-chemical properties depending on the length of the carbon chains attached to their phthalate backbone (general structure in Table 4.11). Staples *et al.* (1997) stated that their octanol-water partition coefficient (K_{OW}) spans over eight orders of magnitude and their vapour pressure over four orders of magnitude, depending on the number of carbons attached. They also concluded that true solubilities were severely overestimated in the literature, particularly for the longer chain phthalates. A compilation of physical-chemical properties is shown in Table 4.11.

Table 4.11. Calculated physical-chemical properties of selected phthalate esters at 25 degrees Celsius (Cousins *et al.,* 2003).

Abbreviation	logKow	Water solubility (mg/L)	Vapour pressure (Pa)	General structure
DMP	1.61	5220	0.263	
DEP	2.54	591	6.48×10^{-2}	
DPP	5.12	77	1.75×10^{-2}	
DnBP	4.27	9.9	4.73×10^{-3}	
DIBP	4.27	9.9	4.73×10^{-3}	
BBP	4.7	3.8	2.49×10^{-3}	
DEHP	7.5	2.49×10^{-3}	2.52×10^{-5}	
DnOP	8.1	2.49×10^{-3}	6.81×10^{-6}	
DINP	8.6	3.08×10^{-4}	6.81×10^{-6}	
DIDP	9.46	3.81×10^{-5}	1.84×10^{-6}	
DUP	10.3	4.41×10^{-6}	4.97×10^{-7}	

In a global perspective, Phatalate esters are the most commonly used plasticizers, which is their main use. In Western Europe, about one million tonnes of phthalates are produced annually and the main use area is in PVC plastics and include applications such as wall covering, flooring and medical applications, but also to a lesser extent in certain personal care products (e.g. nail polish and perfume), sealants, pigments, adhesives and tool handles (Cousins *et al.,* 2007). The Swedish use of phthalates underwent a dramatic shift between 2000 and 2001, when di-ethylhexyl phthalate (DEHP) was subject to a voluntary phase-out by industry and was replaced by di-iso-nonyl phthalate (DINP) and di-iso-decyl phthalate (DIDP) which have accounted for the majority of the phthalate use during the last decade. Continued focus on the potential health effects of phthalates in Sweden led to yet another shift in 2011 towards other alternatives (see Figure 4.8). In 2012, the combined use of the major 'traditional' phthalate components (DIDP, DINP, BBzP, DIBP, DEP DEHP, DINP and DIDP) was 4500 metric tonnes (Figure 4.8).

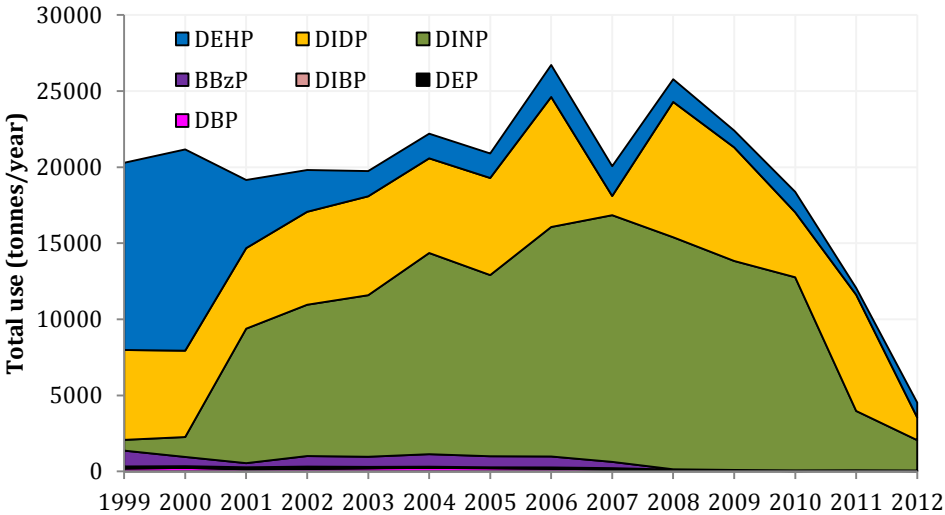


Figure 4.8. Use of major phthalate substances in Sweden (SPIN, 2014).

Environmental impact

The main concerns for phthalates in the environment are their potencies as endocrine disruptors in humans, and concerns have been raised that they may generate effects such as reduced sperm count in males (Andrade *et al.,* 2006; Borch *et al.,* 2006) and short "ano-genital-distance" (AGD) in male babies (Swan *et al.,* 2010; Swan *et al.,* 2005). Some evidence exists, that phthalates (DEHP, DINP) are potential carcinogens (David and Gans, 2003), the carcinogenic effect being generally a non-genotoxic mode of action. The Swedish Chemicals Agency has identified DEHP as a CMR (carcinogenic, mutagenic, reproduction disturbing) substance. Although most studies have been performed in rats, whereby their relevance to humans is unclear, the accumulating amount of incidental evidence causes the WHO and UNEP to identify phthalate esters as likely endocrine disruptors (Bergman *et al.,* 2013).

Bradlee and Thomas (2003) reviewed studies on the aquatic toxicity of phthalate esters and concluded that higher phthalate esters (chain length ≥C6) do not pose intrinsic toxicity to aquatic organisms. Phthalate esters are rapidly metabolised in biota and their water solubility is low, reducing their bioavailability.

Thus, the main concern for phthalates is related to human exposure, which primarily occurs via diet, but where the indoor environment is likely to play an important role. Because of the extensive use of phthalates in a large variety of consumer products, they occur everywhere in the environment, despite their relatively fast metabolisation rates, causing a general contamination of the food chain.

Fate and behaviour in sewage treatment plants

Phthalates belong to the most extensively surveyed substance groups in the environment and substantial research have focussed on understanding the environmental fate of phthalate esters. An extensive review on phthalate behaviour was published in the late 90's by Staples *et al.* (1997), who stated that the environmental behaviour varies substantially between the different phthalates due to their varying physical-chemical properties. They are fairly rapidly metabolised but due to the high usage their presence in the environment is ubiquitous. In their review, Staples *et al.* (1997) also concluded that biodegradation is likely the dominant removal process for phthalates in the environment as well as in STPs. In a more recent study, Zolfaghari *et al.* (2014) explored the literature on occurrence, fate and effects of DEHP in STPs. They summarized a large body of literature from all over the world covering data on DEHP occurrence in environmental samples between the years 1984 – 2013. The European sites included in their study were situated in Finland, Germany, England, Norway, Denmark and the Netherlands, and they reported data sampled between 1996 and 2006, with levels in STP effluent water ranging from 1.7-246 µg/L. Recent monitoring activities (after 2010) in STP effluents are less frequent. The most recent Swedish and European data reported are presented in Table 4.12, which to some extent also covers data from the previous decade. Considering a dilution factor of 10, both the median and the mean concentration in Sweden are below the EQS-value (Table 4.12) whereas the maximum concentration of DEHP for Europe exceeds the EQS for surface water even if the dilution factor of 10 is applied.

The common occurrence of phthalates in indoor and outdoor environments calls for extreme caution during sampling and analysis, and it is crucial that blank controls of all sampling equipment are performed, and that all stages of sampling and analysis are carefully protected (using phthalate free sampling equipment and aluminium foil to avoid contamination from indoor air) and checked for possible contamination.

Table 4.12. Monitoring data of phthalate esters in Swedish and European STP effluent water.

Substance	Country	n	Min (ng/L)	Max (ng/L)	Median (ng/L)	Mean (ng/L)	AA-EQS (ng/L)
DBP	Sweden	10	<50	185	130	105	
	Various European	126	0.54	4830	648	880	
DEHP	Sweden	10	<100	3005	360	1698	1300
	Various European	189	1.6	14200	963	2865	1300
DEP	Sweden	7	30	1470	60	286	
	Various European	5	0.2	2580	20	680	
DIBP	Sweden	7	46	210	100	118	
	Various European	2				5240	
BBzP	Sweden	10	62	110	15	69	
DiA(C7-C9) P	Sweden	3	<50	<50		<50	
DIDP	Sweden	3	<50	370		223	
DINP	Sweden	3	170	530		397	
DOP	Sweden	3	21	59		42	
DIunDP	Sweden	3	<20	<20		<20	
BBP	Various European	5	0.36	3130	76	700	
DMP	Various European	3	0.062	115	0.19	38	

Sources: Deblonde *et al.,* 2011; Gardner *et al.,* 2012; SEPA, 2014; Sun *et al.,* 2014b

Outlook

The consumption of 'traditional' phthalate esters is steadily decreasing. In Sweden, DEHP has been phased out almost entirely, and in the last few years the use of DINP and DIDP has also gone down. Instead, the consumption of 'new' phthalates and alternative plastizicers has increased. In 2012, the combined use of the sum of eight traditional phtahalates (see Figure 4.8) was 4500 tonnes, whereas the use of diisononyl-cyclohexane-dicarboxylate (DINCH) and bis (2-propylheptyl) phthalate (DPHP) was nearly 19000 and 21500 tonnes, respectively (Figure 4.9). Adipates are another group of potential replacements for phthalates, but their use so far is more limited (Figure 4.9). It is thus possible that the levels of traditional phthalates in STPs will gradually decrease even so this may take time due to the large amounts already existing in the technosphere. The concentrations of new plastizicers will increase in the future. At this stage, analytical methods for many of the new alternatives are still missing, and their physical-chemical properties and potential environmental impact are largely unknown.

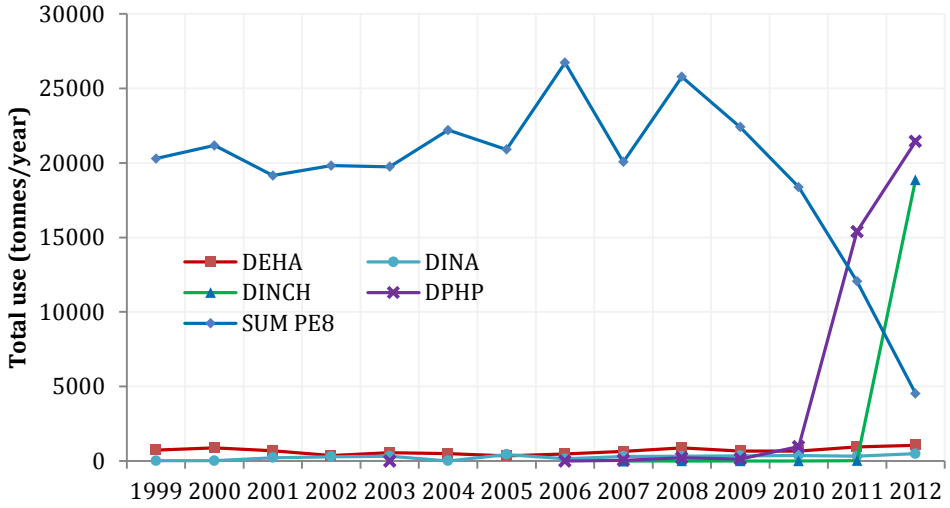


Figure 4.9. Use of "new" phthalates and alternative plasticizers in Sweden, in comparison to the traditional PEs (SUM PE8) (SPIN, 2014).

4.3 Flame retardants

Flame-retardants (FRs) are sometimes referred to as one group of chemicals, although they comprise a vast number of chemicals with different physical-chemical properties. Some of the substances may also be used as e.g. plasticizers. A total of 96 brominated (BFRs), chlorinated (CFRs) and phosphorous flame retardants (PFRs) were identified by Bergman *et al.* (2012), who also launched the categorization as either established, emerging, novel or potential FRs. Here, the focus is mainly on some of the established FRs, such as the polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCDD) and the organophosphates, but also some of the emerging substances.

Properties and use

Naturally, the properties of 'flame retardants' vary greatly depending on the type of substance. In a recent review, Liagkouridis *et al.* (accepted) estimated physical-chemical properties for a large number of BFRs and PFRs. Most of the FRs are hydrophobic and non-volatile substances with high values of the octanol-water (K_{OW}) and octanol-air (K_{OA}) partition coefficients (the latter is calculated from K_{OW} /K_{AW}), which makes them particularly susceptible for partitioning to organic carbon-rich matrices, i.e., particles, soils, sludge and sediments. This is not true for the entire group, however. In particular, some of the PFRs actually prefer the aquatic phase, as do some of the CFRs. In addition to their varying partitioning properties, FRs also display a large variation in environmental degradability or persistence. Established BFRs (PBDEs, TBBPA, HBCDD) have long half-lives in air (>2 days) and water (>60 days) whereas some of the emerging BFRs (1,2-Bis(tetrabromophthalimido)ethane (EBTEBPI), 1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE), Decabromodiphenyl-ethane (DBDPE)) are less persistent in air (~1 day) and water (~1 day) (Liagkouridis *et al.*, accepted). Regarding the CFRs, chloroparaffins may degrade in the atmosphere via OH radical reactions (indirect photolysis), with theoretical half-lives ranging from 0.5-1.8 days (Muir *et al.*, 2000), but half-lives as high as 10.5 days have been reported,

indicating a relatively high persistence in air (UNEP, 2010). In water, direct hydrolysis is believed to be negligible, but may occur in the presence of catalysts. The most important degradation pathway for the chloroparaffins is believed to be via microbial biodegradation (Muir *et al.,* 2000). The emerging CFR Dechlorane Plus (DDC-CO) displays fairly low atmospheric half-life (0.45 days) but is more persistent in water (180 days), predicted by the EPIWEB software (USEPA, 2011), but nevertheless, the substance has been repeatedly detected in remote air (Xian *et al.,* 2011). The PFRs are fairly reactive in air (half-life 0.1-1.8 days) but in general have high stability in the aquatic phase (9-180 days) (Liagkouridis *et al.,* accepted).

The ***PBDEs*** are used in products such as plastics, textiles and upholstered furniture. The use of some groups of PBDEs is restricted within the EU (Commission regulation (EC) No 552/2009; Directive 2002/95/EC (RoHS); the Court of Justice 2008/C 116/02). It is, however, still possible for industries to apply for exemptions for certain applications. The use of ***HBCDD*** and ***TBBPA*** has declined substantially in Sweden during the past decade (Figure 4.10a). Due to the ban and phase-out of these established BFRs, the consumption of alternative or 'emerging' FRs (e.g. DBDPE, HCBCH-DCAnh, DCP) has increased as indicated in Figure 4.10. Far from all alternative FRs are used regularly, and most of them have not yet reached the market, but some of them have now started to appear in environmental samples worldwide. So far, the use of the new alternatives included in this review appears to be much lower than the previous use of the established BFRs.

The ***chloroparaffins (chloroalkanes)*** are used partly as flame retardants, partly in other applications as lubricants and as additives in adhesives, paints, rubber and sealants (Muir *et al.,* 2000), which may explain their high usage relative to other individual FRs (Figure 4.10 b). The use of these substances also appears to be declining since the mid 00's. ***DDC-CO***, a proposed alternative FR, is used in a variety of polymeric materials (Xian *et al.,* 2011).

The ***PFRs*** comprise a large number of individual organophosphorous substances, serving as flame retardants, plasticizers, antifoaming agents and as additives in lubricants and hydraulic fluids. Their use in Sweden has been fairly constant over the past decade and appears to remain on the same level (Figure 4.10c).

Apart from those included in Figure 4.10, the SPIN-register does not include statistical data for any of the other emerging and novel FRs included on the list by Bergman *et al.* (2012).

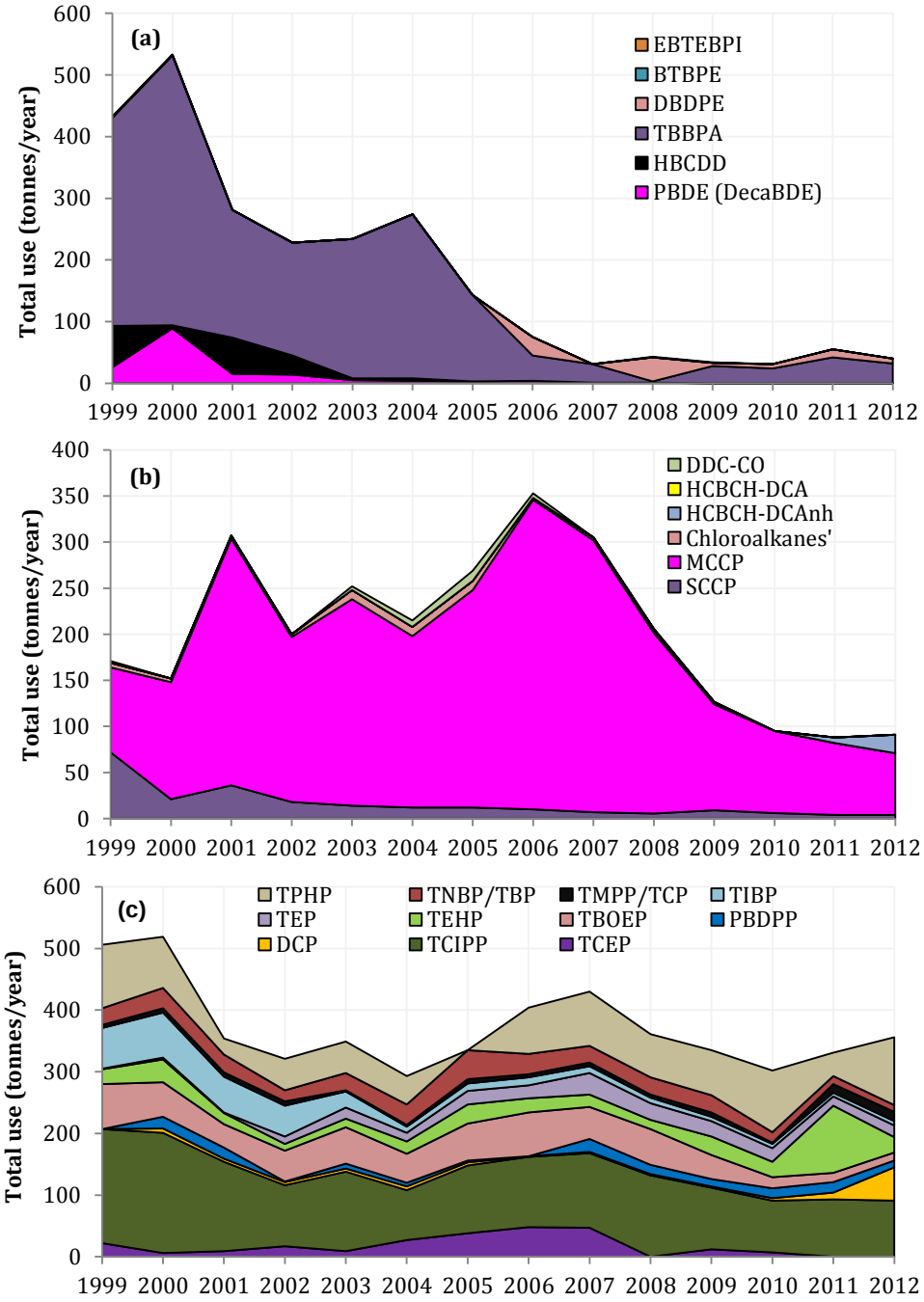


Figure 4.10. Use of (a) BFRs; (b) CFRs; and (c) PFRs in Sweden (SPIN, 2014).

Environmental impact

The PBDEs have raised concern for over a decade, due to their persistence, bioaccumulation potential and their potency as endocrine disruptors. Already in the 90's, Swedish studies revealed the presence of PBDE in sludge, sediment and biota (Sellström, 1999) and de Boer *et al.* (1998) reported occurrence of PBDEs in deep water marine mammals, indicating a ubiquitous presence of these substances. Since then,

numerous studies have investigated the toxicity and potential health effects of PBDEs. As an example, disturbances on the thyroid system have been observed in birds and mammals with high levels of PBDEs (and PCBs) and PBDEs have been identified by WHO and UNEP as endocrine disruptors (Bergman *et al.,* 2013). Consequently, they are now banned (penta- and octaBDE) or subject to strict regulations (DecaBDE) within EU and the US. PentaBDE is listed under the Stockholm Convention for persistent organic pollutants (POPs), and thus subject to a global ban.

Regarding TBBPA and HBCDD, the former has shown low toxicity in experimental test systems and very high doses are required for effects to be visible (Darnerud, 2003). TBBPA is regarded as a persistent substance but with low bioaccumulation potential and low toxicity. It is absorbed in humans but efficiently eliminated through faeces and breast milk. Some effects on the renal system have been observed in rats after high dosage and a NOAEL of 40 mg/kg/day was determined (KEMI, 2006). HBCDD is a ubiquitous pollutant with particularly high levels near point sources, where the main concern for potential risks to humans and wildlife lie in addition to work environments (Covaci *et al.,* 2006), but the actual effects on human health have rarely been studied (Chao *et al.,* 2014). Weak thyroidal disruption was observed in a study by Chao *et al.* (2014). Despite uncertainties related to exposure and effects, UNEP considered the incidental evidence to be sufficient for a qualification as a POP under the Stockholm Convention. This decision entered into force on 26 November 2014.

Chloroalkanes or chlorinated paraffins, in particular the short-chained ones (SCCPs) are regarded as persistent toxic substances by UNEP and are classified as possibly carcinogenic to humans. They have also shown to bioaccumulate in biota (BCF range: 1900-138000) and have been categorized as a 'severe marine pollutant' by the International Maritime Organization (IMO) (Bayen *et al.,* 2006). According to UNEP (2010), aquatic invertebrates appear particularly sensitive to SCCPs, with a chronic NOEC of 5 µg/L for *Daphnia magna*. A number of cancer-related effects have also been observed in mammals. UNEP states that based on the available evidence, SCCPs are likely to lead to significant adverse effects to humans and wildlife, and thus they are proposed for listing in the Stockholm Convention for persistent organic pollutants (POPs) (UNEP, 2010).

In a recent review, González-Alzaga *et al.* (2014) concluded that prenatal exposure to *organophosphate pesticides,* some of which are also used as FRs can lead to negative effects on child mental development. An even more recent study showed no correlation between PFRs and development of asthma in children (Canbaz *et al.,* Submitted). So far, no comprehensive review has been published regarding the environmental impact of PFRs, but incidental evidence exists that warrants precaution.

For most of the 'emerging' FRs, the effects on humans and the environment are still unknown.

Fate and behaviour in sewage treatment plants

To illustrate the generic fate of the FRs in a typical STP, their main removal pathways were estimated using the STPWIN program which is incorporated into the EPIWEB software (USEPA, 2011), and builds on the model developed by Clark *et al.* (1995) and Seth *et al.* (2008). The outcome of the model can be used to compare STP fate of

different organic substances and provide a general picture of the likely dominant removal pathways in the STP – thus generate an overview of where potential improvements should be focused. Figure 4.11 shows the outcome of the STPWIN program for selected FRs. As shown in the figure, many of the FRs, in particular BFRs will mainly partition to municipal sludge due to their hydrophobicity. Due to equilibrium partitioning, small amounts will always exist in the aquatic phase, even though often at levels lower than current analytical detection limits (Sörme *et al.,* 2013). The BFRs are also generally quite resistant to biodegradation. PFRs, in particular the chlorinated ones display a different behaviour, in that they partition to water to a larger extent, thus they are commonly detected in wastewater effluents (Table 4.13), and the non-halogenated PFRs are generally more susceptible to biodegradation in the STP, which is also true for some of the CFRs (the chlorinated paraffins). This assessment indicates that to improve STP treatment technologies, focus should lie on sludge treatment for the BFRs (indeed, application of PBDE-containing municipal waste sludge on farmland is proposed to be one of the main release pathways to the environment (Andersson *et al.,* 2012) and DDC-CO, whereas adjustments to the biological step could potentially improve the removal of non-halogenated PFRs. For the halogenated PFRs, as well as triethyl phosphate (TEP) and Tris(isobutyl)phosphate (TIBP), the major efforts should be directed towards the aquatic phase.

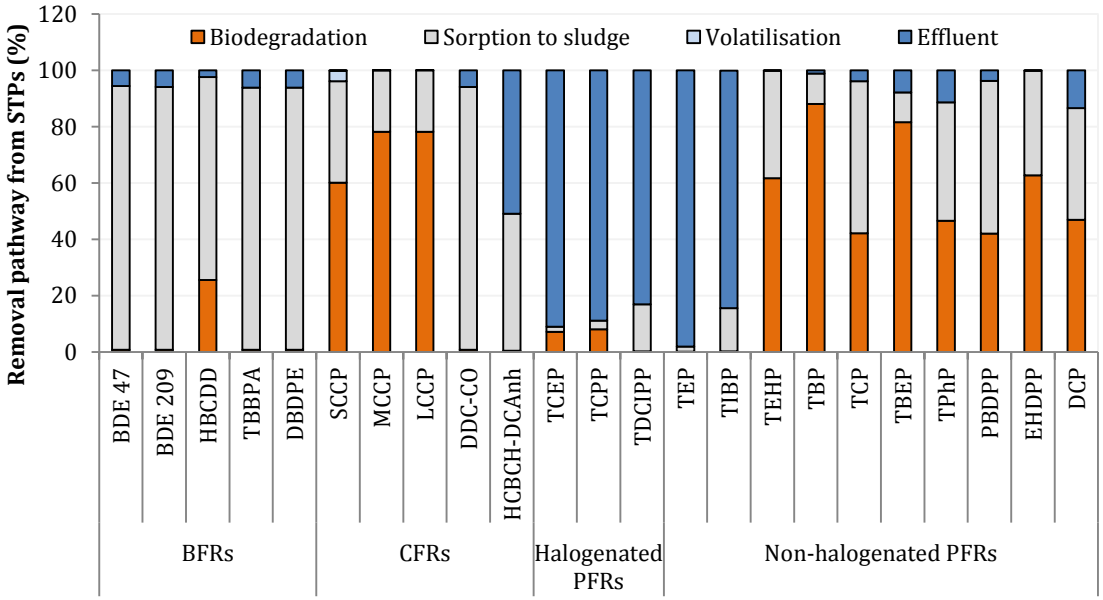


Figure 4.11. Estimated STP removal pathways of FR substances, as predicted by the STPWIN program incorporated in the EPIWEB estimation software (USEPA, 2011).

A summary of recently measured levels of FR substances in Swedish and European wastewater treatment plants is presented in Table 4.13. The PBDEs have been monitored in Swedish wastewater sludge for many years and are included in the national monitoring programme for sludge. Measurements on influent and/or effluent water from municipal wastewater treatment plants are scarce, however, but some studies have been published, e.g. by Ricklund *et al.* (2009). Measurements were also performed within the Baltic collaborative project COHIBA (Kaj *et al.,* 2011) and within the national screening programme (Kaj *et al.,* 2010; Lilja *et al.,* 2010; Remberger *et al.,*

2014). Overall, the substances are often close to detection limits but the most common BDEs have all been detected in effluent water at some point. Judging from Table 4.13, there is a risk that current levels in effluent water may lead to exceedance of the EQS. However, it should be noted that the sum of LOQ-values also result in a value near the EQS, thus it is important that the analytical methods are sensitive enough to detect levels near the proposed EQS-value. The median and mean level of HBCDD are both at least a factor of 10 lower than EQS, and considering the dilution factor of 10 also the max-level was below the EQS. Therefore, there is currently no legislative reason to take specific measures for this substance. DBDPE has been detected in one sample of STP effluent.

For the CFRs, the data availability is limited to chloroparaffins, which are also used for many other purposes. They are commonly found in effluents in Sweden as well as in Europe often exceeding the established EQS value. Considering a dilution factor of 10 however, all levels reported in Table 11 are below the EQS.

The PFRs are commonly found in STP effluents in Sweden as well as in Europe, but at present, there is no established EQS value to use for risk evaluation. To precede potential future risks associated with these substances, minimisation of their releases to the STPs and via the STPs should be prioritised. For the use of sludge on arable land, threshold values have been proposed for the fully brominated PBDE, BDE209 and SCCP by the Swedish EPA (SEPA 2013).

Table 4.13. Summary of measurements of flame retardant substances in influent and effluent water at Swedish and other European (within brackets) STPs. Single values represent mean concentrations.

Substance	Type	Range (ng/L)	AA-EQS (ng/L)
BFRs			
BDE-17	Effluent	(<0.03-0.06)	
BDE-28	Effluent	(<0.03)	
BDE-47	Influent Effluent	21 <0.15-5.0 (<0.03-3.2)	
BDE-66	Effluent	(<0.03-0.18)	
BDE-85	Effluent	<0.15 (<0.03-0.08)	
BDE-99	Influent Effluent	26 <0.15-4.8 (<0.03-3.8)	
BDE-100	Influent Effluent	4.3 <0.15-0.87 (<0.03-0.16)	
BDE-153	Effluent	<0.15 (<0.03-0.38)	
BDE-154	Effluent	<0.15 (<0.03-0.16)	
∑pentaBDE	Effluent	<0.75-11 (<0.18-8.0)	0.2
BDE-183	Effluent	<0.15 (<0.03-1.0)	
BDE-203	Effluent	(<0.03-0.45)	
BDE-209	Influent Effluent	26 <0.15-180 (0.13-8.8)	
HBCDD	Effluent	<0.05-3.6 (α-) (<0.01-2.0) (β-) (<0.01-1.0) (γ-) (<0.01-11)	1.6 (8)
DBDPE	Influent Effluent	<35 <25-420	
CFRs			
MCCPs	Effluent	<LOD-16000 (140-10010)	
SCCPs	Effluent	240-1500 (83-2670)	400

Non-halogenated PFRs		
TCEP, TCPP	Effluent	(200)
TCEP	Effluent	190-1800 (131)
TCPP	Effluent	230-610
TDCIPP	Effluent	4-820 (176)
Halogenated PFRs		
TIBP	Effluent	29-2800 (133)
TBP	Effluent	19-390 (260)
TCP	Effluent	(<LOD)
TBEP	Effluent	240-16000 (2220)
TPhP	Effluent	15-120
TPP	Effluent	(36)
EHDPP	Effluent	9.2-69 (93)
Total OPFRs	Effluent	7900-26500 (23.5-3850)

Data sources are Gardner *et al.* (2012), Lilja *et al.* (2010), Nakari *et al.* (2011), Ratola *et al.* (2012) and (SEPA, 2014), Ricklund *et al.* 2008.

Outlook

The PBDEs keep appearing in municipal STP sludge and recipient samples although the use in Sweden has gradually decreased down to zero (SPIN, 2014). Due to their long chemical persistence and their occurrence in products with long service lifetimes and due long-range atmospheric transport they are likely to remain a common pollutant, but due to the global ban and strict regulations the levels should gradually decrease. Since 2009, decreasing concentrations of PBDEs in STPs as well as in human breast milk have been observed in the city of Stockholm (http://miljobarometern.stockholm.se). For the future, it is likely that the alternative FRs (e.g. HCBCH-DCAnh) and the PFRs will be the most commonly occurring pollutants in STP effluents.

4.4 Phenolic substances

Properties and use

The group of chemicals here referred to as 'phenolic substances' is not a homogenous group of substances when it comes to usage. However, their properties are fairly similar in that they are soluble to moderately soluble in water (at least at neutral or high pH), but also have a tendency to partition to organic carbon rich matrices, such as soils, sediment and sludge. The assessment of properties for alkylphenols is complicated by the fact that they are reported under several different CAS-numbers and sometimes consist of several different isomers. Table 4.14 lists physical-chemical properties for the substances included as estimated using the EPIWEB estimation software (USEPA, 2011). Long-chain alkylphenols (i.e. octyl-, nonylphenols and their ethoxylates) have a straight or a branched alkyl chain attached to the phenol, and the name depends on the position, length and branching of the alkyl chain. In the past, CAS no 25154-52-3 referred to all nonylphenols, but has been redefined to only contain NPs with a straight chain, however not necessarily in a para-position as is the case for CAS no 104-40-5. Whereas triclosan has properties similar to the alkylphenols, bisphenol A is more water soluble and less hydrophobic, thus is likely to partition to water to a greater extent.

Table 4.14. Estimated physical-chemical properties of phenolic substances (USEPA, 2011).

Abbreviation	CAS	MW	$logK_{OW}$	Water solubility (mg/L)	Vapour pressure (Pa)
4-OP	1806-26-4	206.3	5.5	3.1	0.013
OP1EO	9002-93-1	250.4	4.5	5.3	932
4-n-OP1EO	51437-89-9	250.4	4.9	5.4	932
4-n-OP2EO	51437-90-2	294.4	4.8	3.3	3.3×10^{-6}
OPEO	9036-19-5	426.6	3.8	5.3	2.4×10^{-9}
NP	25154-52-3	220.4	5.8	7.0	9.1×10^{-2}
4-NP	104-40-5	220.4	5.8	7.0	9.1×10^{-2}
4-NP, branched	84852-15-3	220.4	5.8	1.5	1.3×10^{-2}
NP1EO	104-35-8	264.4	5.6	1.1	2.4×10^{-5}
NP2EO	20427-84-3	308.5	5.3	1.0	1.2×10^{-6}
BPA	80-05-7	228.3	3.3	120	3.0×10^{-5}
Triclosan	3380-34-5	289.6	4.8	4.6	6.2×10^{-4}

The main use of alkylphenols is in the production of long-chain ethoxylates, thus alkylphenols and short-chained ethoxylates found in STPs are mainly degradation products. The use of alkylphenols has gone down from around 200 tonnes per year in 1999 to about 50 tonnes per year in 2012 (Figure 4.12), and nonylphenol is now mainly imported as additives in paint, or for production of ethoxylates to be applied in paints. Outside the EU nonylphenol ethoxylates are used in the production of textiles. A lot of the nonylphenol in the Swedish STPs originates from the washing of imported textiles (Månsson *et al.,* 2008). The use of octylphenols mainly occurs in the form of ethoxylates in the production of paints (KEMI, 2014). The use of bisphenol A has decreased in later years from the peak in the mid 00's of 140 tonnes to 18 tonnes in 2012, possibly as a result of recent concerns for external exposure via e.g. canned food items, baby bottles and receipts. The declined use of BPA is however less pronounced than for the alkylphenols. According to the SPIN register, the use of alternative bisphenols from the "bisphenol family" is still limited. Triclosan has not been used in chemical products in Sweden in recent years according to the SPIN register. The decreasing use trend of triclosan, with the voluntary out-phase of triclosan from tooth pastes as the main factor, is confirmed by decreasing levels in municipal sludge in Stockholm from 4.2 µg/g dw sludge in 2009 to 0.3 µg/g dw sludge in 2013 (Miljöförvaltningen, 2014). Continued occurrence in sludge may be expected as a result of trace amounts incorporated in imported articles.

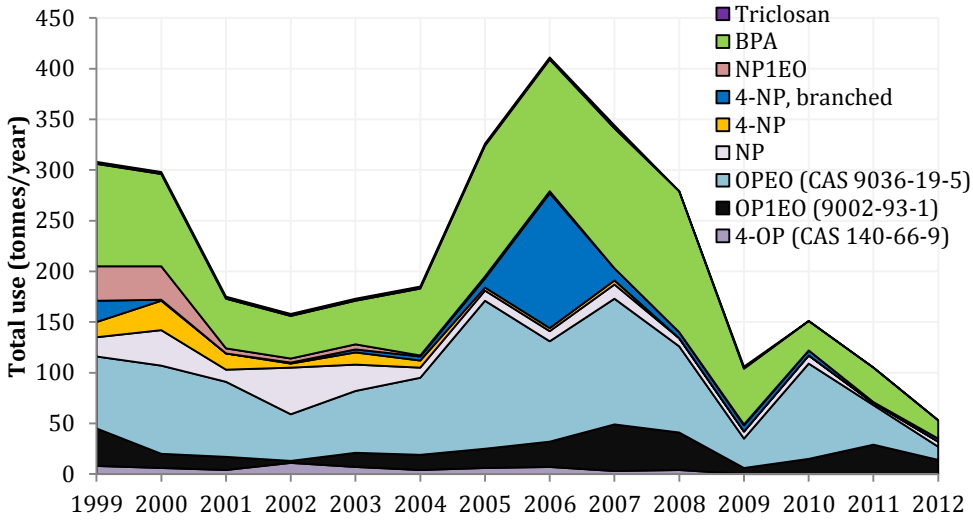


Figure 4.12. Use of phenols and phenolic substances in Sweden (SPIN, 2014).

Environmental impact

The concern about phenolic substances such as alkylphenols and their ethoxylates is mainly related to their estrogenic effects (White *et al.,* 1994) and their widespread occurrence in the environment (Ying *et al.,* 2002) leading to observed estrogenic effects in fish outside STPs (Purdom *et al.,* 1994). Similar effects have been observed for bisphenol A in laboratory studies of prosobranch snails (Oehlmann *et al.,* 2000) and studies have indicated adverse effects on rodents at levels at or below current acceptable daily intake levels (Rubin, 2011). On the other hand, other studies have shown no effects (Ryan *et al.,* 2009; Tinwell *et al.,* 2002; Tyl *et al.,* 2002). There has been a long-lasting debate about the potential estrogenic effects of BPA and in an attempt to untangle this apparently 'infectious' debate Sharpe (2010), suggested that most studies with proven effects of BPA have used exposure routes that are not relevant to humans, such as injections or implants, whereas the more large-scale studies (showing no effect) have assessed oral exposure, which is likely the predominant pathway to human exposure. Indeed, Kitraki (2014) stated that a large body of literature provided incomparable results due to the experimental design of the toxicity studies. The failure to reproduce studies showing effects caused Sharpe (2010) to conclude that scientific evidence for BPA as a potent endocrine disruptor is lacking, but that it could provide a (minor) contribution to the additive mixture effects of EDCs. Nevertheless, BPA is on the list of potential EDCs and has been highlighted by the WHO (Bergman *et al.,* 2013), thus the debate will likely continue.

Fate and behaviour in municipal treatment plants

Figure 4.13 shows the generic fate of selected phenolic substances as predicted by the STPWIN program. As shown in the figure, many of the phenols are predicted to be biodegraded to a large extent. This may be somewhat misleading, since alkylphenols ethoxylates generally degrade to their corresponding phenols, thus degradation may not lead to ultimate removal. Nevertheless, because of their general susceptibility to biological transformation it is possible that adjustments in the biological step could lead to enhanced removal of these substances. For some of the "new" bisphenols (which are currently of limited use), as well as triclosan, sludge sorption is predicted to be the

main removal route, thus prolonged residence time followed by sludge treatment may be more effective for these, perhaps in combination with actions directed towards the aquatic phase.

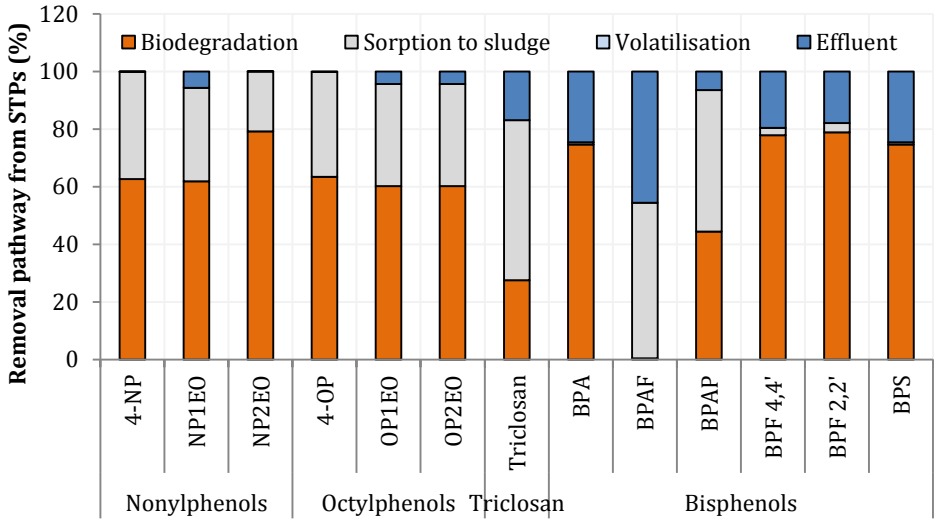


Figure 4.13. Estimated STP removal pathways of phenolic substances, as predicted by the STPWIN program incorporated in the EPIWEB estimation software (USEPA, 2011).

A summary of recent measurements of phenolic substances in Sweden and Europe is presented in Table 4.15.

Sun *et al.* (2014b) conducted a global review of estrogenic chemicals in effluent water and found that median levels of NP varied between 70 and 6780 ng/L between different countries (Australia, Canada, China, Germany, Italy, Japan, Korea, Spain, UK and USA), with highest median concentrations observed in Canada, whereas BPA levels varied between 20 and 3150 ng/L, with highest levels observed in Spain. Deblonde *et al.* (2011) reported levels of BPA varying between 6 and 4090 (median 50) ng/L in an international review covering 15 samples collected sometime between the years 1997-2010. Additional studies/reviews have been conducted by Barco-Bonilla *et al.* (2013), Gardner *et al.* (2012) and Loos *et al.* (2013), and for the Baltic States within the COHIBA project (Nakari *et al.,* 2011).

In Sweden, alkylphenols were screened in effluents in 2009, showing levels between 25-270, 2-67, <LOQ-110 and 2.5-1900 ng/L for 4-NP, 4-t-OP, triclosan and BPA respectively (Lilja *et al.,* 2010). Nonylphenol has also been regularly monitored in Stockholm STP sludge since the early 90's and there is a clear decreasing trend, with levels declining from 110 µg/g dw sludge (3-year average) to 11 µg/g dw sludge in 20 years (Miljöförvaltningen, 2014). The decline was most pronounced between 1993 and 1999, after which levels have continued to decrease but at a much lower rate. As mentioned above, the levels of triclosan are also decreasing in Stockholm (from 4.2 µg/g dw sludge to 0.3 µg/g dw sludge the last 4 years).

Table 4.15. Summary of recent measurements of phenolic substances in influent and effluent water at Swedish and other European (within brackets) STPs. Single values represent mean concentrations.

Substance	Range(ng/L)	AA-EQS (ng/L)
4-Nonylphenol	25-270 (30-22000)	300
4-nonylphenol monoethoxylate	<50-110 (<50-500)	
4-nonylphenol diethoxylate	<20-70 (<20-189)	
Bisphenol A	2.5-1900 (10-5790)	1600 (PNEC)
4-t-Octylphenol	2.3-310 (40-89740)	300
Octylphenol monoethoxylate	<20-510 (<20-36)	
Octylphenol diethoxylate	<20-240 (<20)	
Triclosan	<0.2-110 (40-780)	50*
2,4,5-TCP	(<11-100)	
2,4,6-TCP	(<11-160)	
PCP	(<11)	

Main data sources are: (Barco-Bonilla *et al.,* 2013; Deblonde *et al.,* 2011; Lilja *et al.,* 2010; Loos *et al.,* 2013; Nakari *et al.,* 2011; Sun *et al.,* 2014; Yang *et al.,* 2012).
*proposed PNEC according to Swedish EPA.

Outlook

According to the SPIN register, the use of most phenolic substances of current environmental concern, including nonylphenols, BPA and triclosan is decreasing, and this is supported by observed decreasing levels in Swedish sewage treatment plants. No clear replacements can yet be distinguished from the reported use patterns. The toxic potencies of BPA for humans are under debate, but the estrogenic effects of alkylphenols and BPA on aquatic species appears to be uncontroversial. Whereas the concentrations of NP in Swedish effluent water are generally below the EQS, levels of octylphenol, BPA and triclosan occasionally exceed the proposed limit values for surface water. Considering the dilution factor of 10, however, all levels recently measured can be considered 'safe'. This is however not the case in European waters (Table 4.15). The development in Sweden is promising but nevertheless, the proposed regulation of nonylphenol ethoxylates in imported textiles should enhance the decline of this substance. Ozone was shown to remove >99% of triclosan from STP effluents (Hernández-Leal *et al.,* 2011). NP was also efficiently removed using by ozone and activated carbon (Hernández-Leal *et al.,* 2011). Future wastewater treatment technologies should thus address the removal of phenolic substances, particularly since large mutual benefits can be expected, "if you remove one, you remove them all". This, together with the observed estrogenic effects on aquatic species, calls for treatment technologies that minimise the release of these substances to all surface waters.

4.5 Per- and polyfluoroalkyl substances (PFAS)

Properties and use

PFAS is the joint term for a large group of substances, which have been used, for commercial purposes since the 1950's (Kissa, 2001). PFAS include substances with different functional groups and with carbon chain lengths spanning from C1 to C20 or even higher. They all have an aliphatic carbon chain of varying length where the hydrogen atoms attached to at least one carbon atom have been replaced by fluorine atoms, represented by the formula $CF_3[CF_2]_n[CH_2]_m$- (Buck *et al.,* 2011). This moiety gives the PFAS oleophobic properties and the strength of the C-F binding causes them to be extremely stable, which have given them unique technical properties and resulted in an extensive and increasing use in technical applications and articles since the start

of the production in the 50's. Main application areas have been in impregnation agents for clothes and textiles, in cleaning agents, ski waxes, as insect repellent and in fire-fighting foams, but also in the surface treatment industry including the development of fluoropolymers used in water-repelling clothes and frying pans (e.g. Vestergren 2011).

Many of the PFAS substances have negligible vapour pressures and will thus not partition to air, however a large number of precursor compounds, such as the fluorotelomer alcohols and the perfluoroalkane sulfonamidoethanols do. Generally, the organic carbon-water partition coefficient K_{OC} is used to describe the partitioning between water and solid matrices, but the mechanisms for sorption differ from those of "traditional" pollutants, since PFAS tend to bind to membranes and proteins rather than fatty tissues and octanol-like matrices.

The substances of main public interest are the perfluorooctane sulfonate (PFOS) and the perfluorooctanoate (PFOA) due to their extreme persistence, their frequent occurrence in environmental samples and their toxic properties as well as the extensive historical uses together with the fact that many precursor compounds eventually break down to form e.g. PFOS and PFOA (e.g. Prevedouros *et al.,* 2006). In 2001, the production of PFOS, PFOA and related compounds ceased in the western world (Europe and North America), and was replaced by other, equally persistent but less bioaccumulative PFAS, in particular those that degrade to the four-carbon alternative PFBS. However, production of the long-chain alternatives still occurs in some countries, including e.g. China.

The SPIN register does not reveal any figures about the use of individual PFAS in Sweden. However, the Swedish Chemicals Agency has reported a total use of 24 tonnes of perfluoroalkane sulfonates (PFSAs; Buck *et al.,* 2011) and perfluoroalkyl carboxylic acids (PFCAs) in the year 2004 (KEMI, 2006b).

Environmental impact

Naturally, the extensive use of PFAS in a large number of different consumer products has also resulted in environmental releases and, as a consequence, exposure to humans and wildlife. Initially regarded as biologically inactive, it was gradually discovered that PFAS could cause adverse toxic effects in animals, and the observation of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in human samples throughout the world led to deep concerns about their potential impact on human and animal welfare. Due to their unusual binding mechanisms in biological tissues, resulting from their oleophobic nature (they bind to proteins rather than adipose tissue), they have extremely long elimination half-lives in humans and animals (3-5 years), thus have long time for concentrations to build-up in humans and wildlife , which may eventually lead to adverse negative effects (e.g. Vestergren 2011).

Fate and behavior in sewage treatment plants

The total release of PFOS via Swedish sewage treatment plants to inland surface waters and coastal seawater has been estimated to 6 and 9 kg/year, respectively (Andersson *et al.,* 2012a). Becker *et al.* (2008) assessed the fate of PFOS and PFOA in four STPs from Bavaria, Germany, and concluded that whereas PFOA increased about 10-fold during treatment (due to formation from precursors), half of PFOS was retained in sludge. Also, PFOS was formed during the biological treatment step, and released in high

amounts. Largest contribution was observed for STPs with heavy industrial load. The levels in both Swedish and European effluent waters are generally above the EQS, even if the dilution factor of 10 is applied (Table 4.16). In Stockholm, the concentrations of PFOS in municipal sludge have decreased from 0.053 to 0.017 µg/g dw between 2009 and 2012 (Miljöförvaltningen, 2014). A recent Swedish study investigated the origin of perfluoroalkyl acids (PFAAs) in wastewater influents and concluded that the contribution from tap water was substantial for the highly urbanized Stockholm region but not for the more rural areas. This implies that a large part of some of the influent PFAAs is a result of old sins and environmental recirculation rather than primary use of the substances (Filipovic and Berger, 2014). For the use of sludge on arable land, threshold values have been proposed for PFOS by the Swedish EPA (SEPA 2013).

Table 4.16. Summary of recent measurements of PFAS in effluent water at Swedish and other European (within brackets) wastewater treatment plants. Single values represent mean concentrations.

Substance	Range (ng/L)	AA-EQS (ng/L)
PFOS	0.78 - 79 (<0.5 - 640)	0.65
PFOA	2.5 (<0.5 - 255)	
PFOSA	<0.02 - 0.18	
PFHxA	0.55 - 22 (<0.5 - 304)	
PFDA	0.22 - 7.1 (<0.5 - 24)	
PFDcA	6 - 13	
PFHxS	0.58 - 10 (49)	
PFHpA	1 - 17 (83)	
PFNA	0.24 - 7.6 (35)	
PFBS	0.5 - 21	
PFBA	0.87 - 10	
PFDS	0.48 - 2	
PFDoA	0.15 - 4.2	
FOSA	0.06 - 1.8	
PFPA	2.4 -14	
PFUnDA	0.17 - 1.7	

Main data sources are: (Lilja *et al.,* 2010; Loos *et al.,* 2013; Nakari *et al.,* 2011; SEPA, 2014)

Outlook

Because of the extreme persistence of substances such as PFOA and PFOS, combined with the extensive historical use, it is likely that they will keep occurring in STP influent, effluent and sludge for a long time onwards. Due to the phase-out of PFOS and related substances, however, the potentially remaining effective reduction measures concerning PFOS are limited. Because of the replacement of long-chained alternatives with shorter chained substances (C4-substances) it is likely that such substances will increase in STPs in the future. Initiatives have been raised to address the general problem associated with the PFAS family and scientists have called for political actions on this matter[1,2]. The future development regarding these substances is thus to some extent dependent on the political actions.

[1] http://www.svd.se/opinion/brannpunkt/miljoskandal-av-historiska-matt_3992791.svd
[2] http://www.nyteknik.se/nyheter/energi_miljo/miljo/article3828678.ece

4.6 Synthetic sweeteners

Properties and use

Synthetic or artificial sweeteners are used as replacements for sugar in a vast amount of food items and beverages worldwide. Because of their negligible or lacking energy content, they are common ingredients of dietary products. The properties of some commonly occurring sweeteners are listed in Table 4.17. Because of their anthropogenic origin, their high water solubility and their inertness, artificial sweeteners are useful markers of wastewater, but some of them are also precursors of oxidation products that can be formed during ozonation (Lange *et al.,* 2012).

Table 4.17. Physical-chemical properties of artificial sweeteners (Lange *et al.,* 2012).

Substance	Abbreviation	CAS	MW	$\log K_{OW}$	Water solubility (mg/L)	ADI (mg/kg bw)
Sucralose	SUC	56038-13-2	397.6	-0.5	283	15
Acesulfame	ACE	33665-90-6	163.1	-1.3	270	9
Saccharine	SAC	81-07-2	183.2	0.91	4	3.8
Cyclamate	CYC	100-88-9	179.2	-1.6	133	7
Aspartame	ASP	22839-47-0	294.3	0.07	10	40

Environmental impact

Current environmental concentrations are well below the safe limits for human consumption via drinking water. This has been shown in numerous studies, some of which have been compiled in a review by Lange *et al.* (2012). The ecotoxicological profile is less well studied but standard toxicity tests show no risks of sucralose to aquatic organisms (Huggett and Stoddard, 2011; Stoddard and Huggett, 2014; Tollefsen *et al.,* 2012). However, some non-standard tests have shown behavioural effects in crustaceans following short term exposure (Hjorth *et al.,* 2010; Wiklund *et al.,* 2012), followed by a recently proposed explanation that exposure to sucralose leads to alterations in Acetylcholinesterase (AChE) and oxidative status (Wiklund *et al.,* 2014). Thus, while most studies indicate no concern for humans or aquatic species, some studies indicate that despite the lack of bio concentration, sucralose in natural waters may still generate behavioural effects amongst crustaceans. Further studies are thus needed to explore this phenomenon further. No studies exploring the ecotoxicity of other artificial sweeteners have been found.

Fate and behaviour in sewage treatment plants

Sucralose and acesulfame are extremely persistent and water soluble substances and pass through STPs virtually unchanged whereas saccharine and cyclamate undergo transformation processes in the treatment plant (Lange *et al.,* 2012). Aspartame has not been detected in wastewater.

Table 4.17. Summary of recent measurements of artificial sweeteners in wastewater at Swedish and other European (within brackets) wastewater treatment plants, and the acceptable daily intake levels (ADI).

Substance	Range (ng/L)	ADI (mg/kg/bw)
Sucralose	1700-10800 (<100-8800)	15
Acesulfame	(11000-46000)	9
Saccharine	(<100-3200)	3.8
Cyclamate	<10-940 (400-1900)	7
Aspartame	<100	3.8

Data sources are Lange *et al.* (2012); Loos *et al.* (2013); SEPA (2014).

Outlook

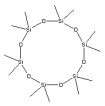
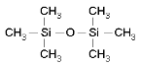
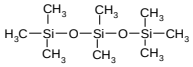
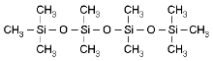
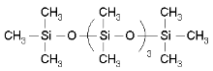
The use of sweeteners is likely to continue, and thus they will persist in sewage effluents. Their limited observable effects motivate a lower priority when evaluating treatment options, however, the recent findings of behavioral alterations among aquatic species call for additional follow-up studies.

4.7 Siloxanes

Properties and use

Siloxanes are chemical substances containing units with the general formula R_2SiO, with R representing hydrogen or a hydrocarbon group. They may be straight chains or cyclic compounds and vary in weight from a few hundred to several hundred thousand g/mol. The siloxanes of main interest from an environmental perspective are the volatile methylsiloxanes, having a short SiO backbone, in particular the cyclic siloxanes octamethyl-cyclotetra-siloxane (D4), decamethyl-cyclopenta-siloxane (D5) and dodecamethyl-cyclohexa-siloxane (D6) and the linear siloxanes hexamethyl-disiloxane (MM or HMDS), octamethyl-trisiloxane (MDM), decamethyl-tetrasiloxane (MD_2M) and dodecamethyl-pentasiloxane (MD_3M). A compilation of physical-chemical properties is shown in Table 4.18.

Table 4.18. Calculated physical-chemical properties of selected siloxanes at 25 degrees Celsius retrieved from the EPIWEB estimation software (USEPA, 2011).

Abbreviation	logKow	Water solubility (mg/L)	Vapour pressure (Pa)	Structure
D4	6.74	0.005	140	
D5	8.03	0.017	26.7	
D6	9.06	0.0051	3	
MM	5.25	0.93	5610	
MDM	6.6	0.034	465	
MD_2M	8.21	6.7×10^{-3}	64.8	
MD_3M	9.61	6.6×10^{-5}	9.39	

Out of these commercially used siloxanes; D4, D5, and MM are chemicals of high production volume within the European Union. The two former are the most commonly used siloxanes in the Nordic countries (SPIN, 2014). They are mainly used in industrial and consumer products such as fuel, car polish, cleaners, anti foamers, car waxes, personal care and biomedical products. In Sweden, the use of siloxanes has increased gradually since the early 00's, with the exception of 2002, when unusually high amounts of D4 appear to have been used. Otherwise, D5 is the dominant

substance in use and since the mid 00's also the use of D6 and MM has increased (Figure 4.14). In 2012, the combined use of the major siloxane components (D4, D5, D6, MM, MDM and MD2M) was 70 metric tonnes. The use of MD3M was registered as confidential.

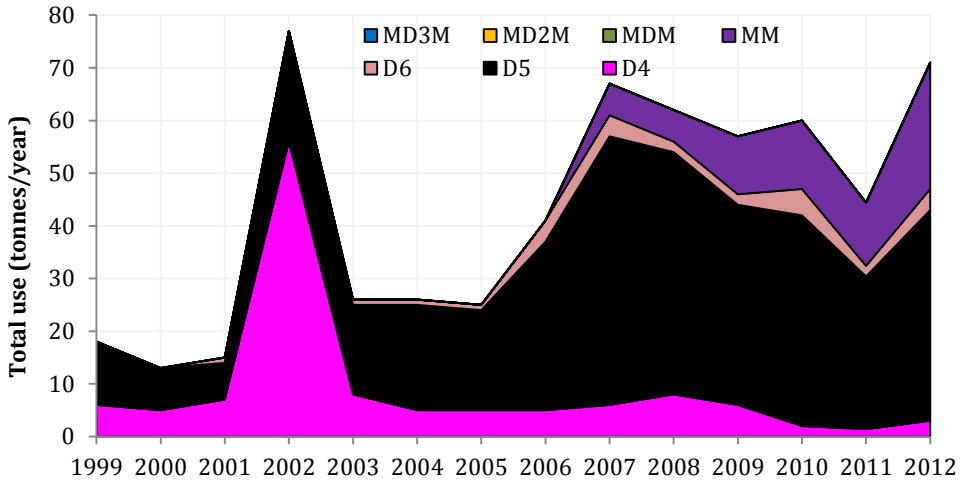


Figure 4.14. Use of siloxanes in Sweden (SPIN, 2014).

Environmental impact

The widespread use of siloxanes, their broad application, their environmental persistence as well as their high volatility and potential for toxic effects has raised the concern for these compounds within various disciplines of environmental science. The aquatic toxicity of cyclic siloxanes was recently reviewed (Wang *et al.,* 2013a), suggesting potential effects for in particular D4 to some aquatic species (effects on mortality, reproduction), albeit at much higher levels than current environmental levels. For D5 and D6 no significant effects were found up to their approximate water solubility. The authors suggested that the bioaccumulation potential of D4 and D5 should be further explored. For chronic effects, the liver has been identified as the main target organ for D4 whereas effects of D5 are related to the lung, whereas kidney and liver were the main target organs for MM. Chronic Values (ChV) were developed for fish for a number of siloxanes by Lassen *et al.* (2005). Furthermore, xenoestrogenic effects and effects on the reproductive health on humans have been suggested for D4 based on a number of studies on rats (He *et al.,* 2003; McKim *et al.,* 2001; Quinn *et al.,* 2007). Screening studies indicate that siloxanes may be found everywhere in the environment, and STPs have been identified as important indirect sources of release, leading to elevated levels in the vicinity of such plants (Cousins *et al.,* 2009).

Fate and behaviour in sewage treatment plants

As a consequence of their low water solubilities, siloxanes will mainly associate with sludge and particles in the STP, thus their occurrence in STP effluents will be dependent on the water residence time as well as the levels of suspended particles in the effluent. They are generally stable in the environment and may thus be resistant to biodegradation in the STPs. In the generic STP fate assessment, biodegradation is estimated to account for 15-60 % of the removal (Figure 4.15), but this result should be treated with caution, since it is largely dependent on the model predicted degradation

half-lives, which are highly uncertain. The overall removal efficiency from the water phase is predicted to be near 100%, which is confirmed for the cyclic siloxanes by a recent Canadian study which showed mean removal efficiencies of 98-99% for D4, D5 and D6 (Wang *et al.,* 2013b). Relative to the other siloxanes, MM appears to be the more biodegradable, and they should neither way be toxic to wastewater microbial communities. Other studies have shown that outdoor degradation in soils is more likely due to abiotic processes rather than biodegradation (Clarke and Smith, 2011). Some volatilisation is also expected to occur for the more volatile, linear siloxanes (Figure 4.15). This assessment indicates that to improve STP treatment technologies, focus should lay on sludge treatment, but it is possible that adjustments to the biological step could also improve the removal of siloxanes.

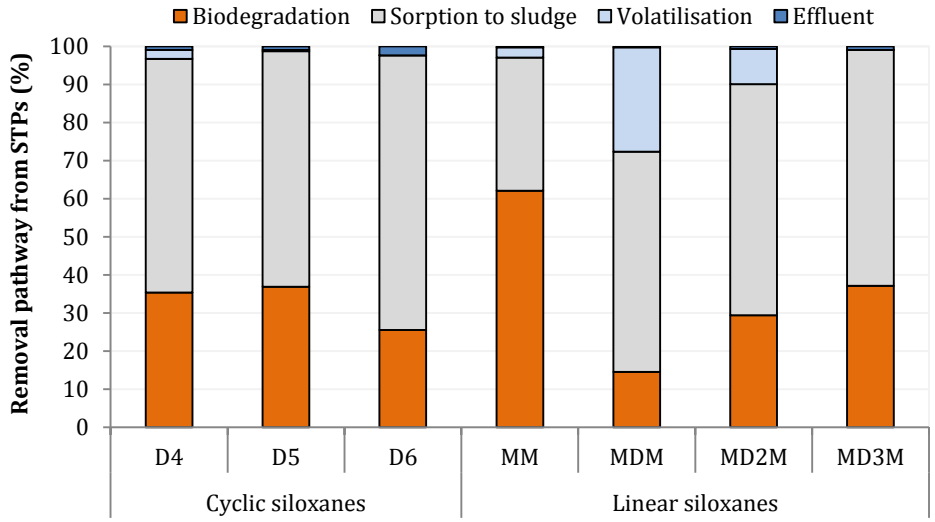


Figure 4.15. Estimated STP removal pathways of siloxanes, as predicted by the STPWIN program incorporated in the EPIWEB estimation software (USEPA, 2011).

Table 4.19. Summary of recent measurements of siloxanes in influent and effluent water at Nordic and Canadian (within brackets) wastewater treatment plants. Single values represent mean concentrations.

Substance	Type	Range (ng/L)	ChV* (ng/L)
D4	Influent	0.25-3.7 (282-6690)	58000
	Effluent	<0.06-0.11 (<9-45)	
D5	Influent	0.33-26 (1350-7750)	21000
	Effluent	0.063-0.98 (<27-1560)	
D6	Influent	0.12-3.8 (1530-2690)	
	Effluent	0.02-65 (<22-93)	
MM	Influent	<0.004-0.12	62000
	Effluent	<0.004-2.1	
MDM	Influent	<0.004-0.014	28000
	Effluent	<0.001-0.3	
MD2M	Influent	<0.004-0.078	
	Effluent	<0.0005-0.8	
MD3M	Influent	<0.004-0.23	
	Effluent	<0.004-1.7	

Data sources are Kaj *et al.* (2005), Lilja *et al.* (2010) and Wang *et al.* (2013b).
Chronic values were derived by Lassen *et al.* (2005).

Outlook
There are no signs of any decrease in the usage of siloxanes, thus it is likely that the substances will keep occurring in STP influents and sewage sludge. Effluent levels measured in the Nordic countries have so far been very low, and well below any potential effect levels. In addition, the removal efficiency of siloxanes is high, thus they should be relatively easily controlled also using future treatment methodologies. Increasing concentrations of siloxanes in fish at various sites in the Baltic Sea (Havsmiljöinstitutet 2014) still indicate that either the removal efficiency in STP is not sufficient or that siloxanes are transported to recipients by other pathways, i.e. atmospheric depositions. Siloxanes should, however, be relatively easy to mitigate using upstream source control measures since they are used in consumer products to a large extent.

4.8 Biocides

Properties and use
Biocides are used to prevent biological infestation and growth of various kinds. They include a variety of substances often grouped in pesticides, e.g. fungicides, herbicides, etc., and antimicrobials, e.g. antibiotics, antibacterials, antifungals, etc. Thus, most relevant biocides are included in the pharmaceutical and other emerging substances in the sections above. Diuron is on WFD's list of priority substances and together with Mecoprop used as an indicator substance by Jekel *et al.* (2015), which shows their relevance in other European countries. They have however not been detected in Swedish STP effluents. Biocides such as Irgarol (banned algicide) and Didecyldimethylammoniumchloride (DDAC) that are both stable, can bio-accumulate and have relatively low NOEC, were detected in the effluent of Swedish STPs (Kylin 2005; SEPA 2014b).

Environmental impact
Because of their intrinsic properties, biocides can pose risks to humans, animals and the environment (SEPA 2014b).

Fate and behaviour in sewage treatment plants
The removal of the biocides Atrazin and Mecoprop have been investigated within evaluation studies using ozonation and various filter techniques (incl. GAC, UF etc.) by Baresel *et al.* (2015). However, measurements are rare and observed concentrations are low. Therefore, biocides others than those included in the description in previous sections are determined not to be of concern for Swedish STP effluents. Currently ongoing measurements in STP-effluents in Southern Sweden will provide more data either to support this evaluation or to induce a re-evaluation.

Outlook
Some pharmaceutical biocides such as the fungicide Propiconazole to cure fungal infections in humans may be included in future screenings if their usage increases significantly. This implies also for a number of other fungicides for the same purpose. Substances such as Carbamazepine detected in STPs- effluent are breakdown products of biocides used in agriculture and can thus reach the STP though sewage leakage. Significant changes in the use and application of biocides may require their observation also in Swedish STP-effluents.

4.9 Microorganisms

Properties and use

Potential pathogens are common in STP influents and include a variety of enteric bacteria and viruses found in human faeces.

Environmental impact

Pathogenic bacteria and viruses pose a risk for disease spreading and especially, antibiotic resistant bacteria and their resistant genes have become a major concern.

Fate and behaviour in sewage treatment plants

The efficiency of microbial removal by treatment systems is usually evaluated using traditional faecal indicators (faecal coliforms, Escherichia coli, enterococci) (USEPA, 2004; WHO, 2006). Robustness of systems aiming to remove pathogens is an important aspect and multiple barrier systems may be preferable. Although STPs normally reduce the number of heterotrophic bacteria by up to 3 log (>99%), studies at STPs show that STPs with no complementary treatment cannot remove all organisms (Marín *et al.,* 2015; Mattsson *et al.,* 2009). This implies that high numbers of bacteria may still be discharged into recipients. Bacteria resistant to antibiotics were reported to be removed completely in STPs by Mattsson *et al.* (2009) but other studies suggest an increase of antibiotic resistance in effluent waters (Kwak *et al.,* 2015). This is in agreement with other findings that already low antibiotic concentrations may cause an enrichment and maintenance of resistance in bacterial populations (Gullberg *et al.,* 2011; RiSKWa 2015).

Filtration by sand filters, which combines size-exclusion and adsorption, is one of the most effective methods for the removal of microorganisms in existing STPs. Otherwise, special removal techniques such as the most common disinfection with chlorine, ozonation or ultraviolet light (UV) disinfection may be applied. Important to notice is that these methods may reduce the number of pathogens but not completely. A combination of oxidation and filtering may be necessary (Lüddeke *et al.,* 2015). MembraneBioReactors (MBRs) as an advanced separation technique with small pore sizes generally provide a high removal of a wide range of microorganisms (RiSKWa 2015).

Re-contamination of treated water due to conditions in the following distribution system may occur and require an additional disinfection step with lasting effect, if the effluent water is to be used for reuse applications. Re-contamination of water may for example take place even after complete removal of microorganisms through membrane separation. Due to contact between the downstream process parts and the atmosphere, which itself contains microorganisms, these can re-establish themselves in the treated water.

Outlook

While the removal of pathogens in general can be solved using existing technology, the increasing problem with multi-resistant bacteria caused by the increased use of antibiotic will required further research and developments efforts. The removal of antibiotics and pathogens from STP effluent alone may not be sufficient (e.g. RiSKWa 2015).

4.10 Microscopic debris particles

Properties and use

The presence of microscopic debris particles in the aquatic environment has received considerable attention, both in the media and in environmental research (Claessens *et al.,* 2011; Eriksen *et al.,* 2013; Magnusson and Norén, 2011; Vianello *et al.,* 2013). The sources of micro-debris in limnic and marine waters are far from understood, but there is a suspicion that STPs are important discharge points because of their function as endpoints for much of society's waste flow (Browne *et al.,* 2011; MCS. Beachwatch 2005). All particulate matter that is intentionally or accidentally released into sinks and sewers end up in the wastewater, thus forming potential micro debris sources. Examples of this are the micro-plastic particles present in many household hygiene and cleaning products in order to have an abrasive effect, or synthetic and non-synthetic fibers released during the washing of textiles (Fendall and Sewell, 2009; Magnusson and Wahlberg, 2014).

Environmental impact

Microscopic debris particles in the aquatic environment may be swallowed by animals, either inadvertently or because they are mistaken for food, and can cause various types of problems. Many plastic particles are inert, i.e. they are not directly toxic but can still cause mechanical problems for animals if caught on the gills, gut walls or other. Some plastics are non-toxic in their polymeric form, but can release toxic monomers (the building blocks that make up the plastic). Examples are polycarbonate, which releases the hormone-disrupting substance bisphenol A and polystyrene leaking the carcinogenic substance styrene (Saido *et al.,* 2012; Sajiki and Yonekubo, 2003). Many plastics also contain toxic additives, e.g. flame retardants, plasticizers or UV filters, that are added to give the material different desirable properties. These additives can leach out from the plastic material into the environment, which makes them available for uptake in the tissues and cells of living organisms. In addition to their content of toxic monomers or additives, microplastics can adsorb various other organic pollutants present in the surrounding to their surface, and thus act as carriers for these compounds (Desforges *et al.,* 2014; Zarfl and Matthies, 2010). If discharged to a recipient via STP effluent water, debris particles may therefor act both as carriers for compounds in the wastewater to the recipient, but also as carriers within the recipient (Ogata *et al.,* 2009), nonindigenous organisms (Barnes 2002), and potentially harmful microorganisms that colonize the surface of the plastic (Maso *et al.,* 2003). Even natural organic particles can act as carriers, but because they are generally more easily degradable than debris particles, their adsorption capacity is lost faster.

Fate and behaviour in sewage treatment plants

In a recent publication, it was shown that Swedish STPs remove from 95 to 100 % of microscopic debris particles larger than 300 µm from the water phase and from 74 to 99 % of particles larger than 20 µm (Magnusson and Wahlberg, 2014).

Outlook

Various aspects as production trends, usage patterns and changing demographics suggest that the amount of plastics debris and microplastics will increase in the future

(Andrady, 2011). As emissions sources and potential threats are not yet known, there is a need to quantify the magnitude of these potential impacts and the precautionary principle should demand for removal of these particles at STPs if possible.

5 Detection and quantification of pharmaceutical residues and other emerging substances and their effects

5.1 General

Well-designed sampling procedures and analytical methods guarantee the collection of samples with high representativeness and integrity and the acquisition of quality measured data for substance concentrations in wastewater. Ultimately, only quality measured data can be used to evaluate and optimize relevant wastewater treatment technologies and to conduct relevant risk assessments. Depending on the type of substances and measurements of interest, various aspects have to be taken into account within the process of sampling, sample handling, and analysis as described in the following sections.

5.2 Sampling

To guarantee good assessments the sampling needs proper planning, preparations, and handling.

5.2.1 Sampling media and sampling points

When planning the sampling program, it is important to consider the physical and chemical properties of the substances, since the properties govern the partitioning to different environmental media within the STP, i.e. air, water or sludge. Volatile substances tend to partition to air and soluble substances tend to dissolve in water. Figure 5.1 displays a generalized partition diagram indicating typical partitioning behaviour, e.g. substances with a Log Kow<3 preferably partition to water and substances with a Henrys law constant>1E-05 prefers the air compartment. Water samples are thus more appropriate than sludge samples for water-soluble substances such as most pharmaceuticals. Figure 5.1 is, however, a simplification as chemical spaces are not as clearly defined as indicated in the figure. In reality, intersecting areas between the different spaces exist.

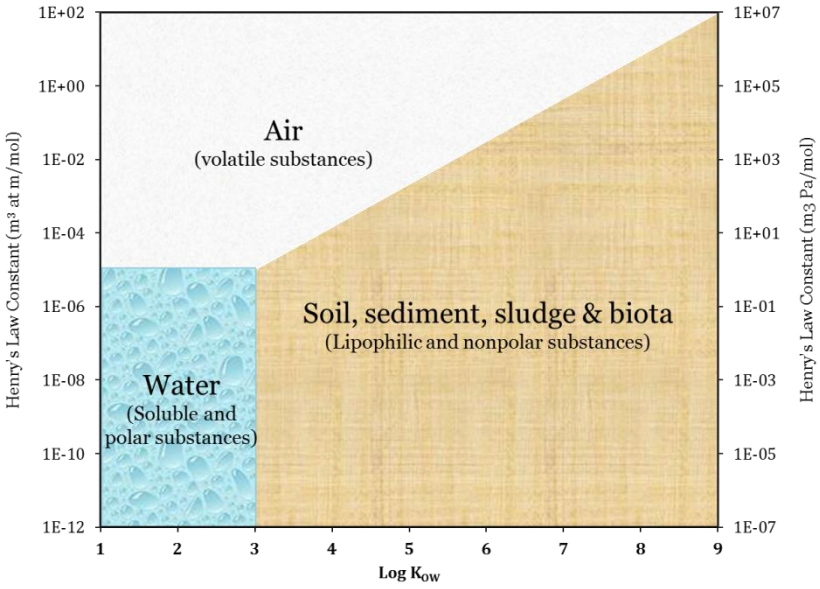


Figure 5.1. Hypothetical chemical space characterizing the major media to which different substances mainly partition in a STP environment.

Determine the sampling points by considering the *overall goal of the sampling*. When the goal is to construct mass balances or evaluate the treatment efficiencies, sampling of influent, effluent, sludge and possible side streams of a process is needed. If the aim is to evaluate the discharged concentrations or amounts into the receiving waters, it is sufficient to sample the effluent only. Proper sampling points are important for the representativeness of samples. For example, collecting samples from inactive zones of a reactor would result in unrepresentative analytical results.

5.2.2 Sampling duration, frequency and type

Different combinations of sampling duration and frequency can address different questions depending further on target substances, sample representativeness, and sampling goal. Regarding the EQS values for priority substances and specific pollutants, both annual average values and maximum concentrations measured at single occasions are relevant to determine. Figure 5.2 illustrates hourly, daily and monthly concentration profiles of pharmaceuticals in an STP influent. The concentration of some substances such as painkillers may increase during working hours (see Figure 5.2a). Hourly concentrations of other substances may be relatively stable due to stable usage and release, e.g., beta-blockers. To reveal daily fluctuations, shorter sampling duration and higher sampling frequency are needed but often not realistic to perform. Adequately, long sampling duration and low sampling frequency can ensure to reveal seasonal variations of concerned substances, e.g., antibiotics that are frequently prescribed for common cold and acute purulent rhinitis in the winter, and antidepressants that are more prescribed during the winter in Scandinavian countries (Figure 5.2c). In addition, other supporting tools may be used when planning sampling campaigns, e.g. the free trend tool GoogleFlu (google.org/flutrends).

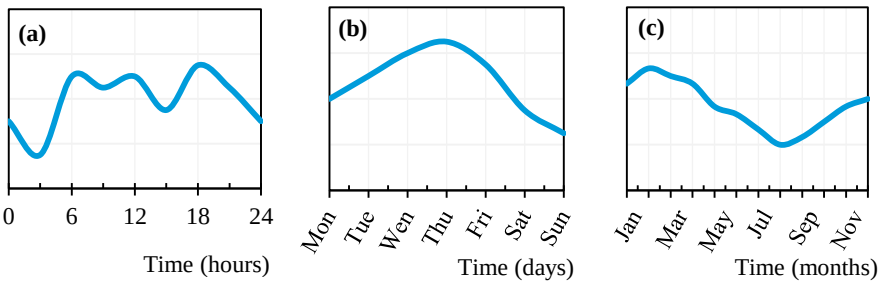


Figure 5.2. Illustrative concentration profiles of pharmaceuticals in STP influent with (a) hourly, (b) daily, and (c) monthly resolution.

The sample type determines the representativeness of the sampled medium at the time of sampling. *Grab samples* refer to a single discrete sample in time. *Composite samples* are collected over time by continuous sampling or mixing discrete samples. Composite samples represent the average conditions of sampled medium during the compositing period. At each sampling, the volume of collected samples can be related only to time or flow, i.e., *time composite sample or flow proportional composite sample*. The latter can consist of constant sample volumes at varying time intervals or varying sample volumes at a constant time interval. Furthermore, the retention time of the treatment process has to be considered for grab samples if concentrations variations are expected. If a sampling campaign aims to collect comparative samples of influent and effluent of a process, e.g. determining reduction efficiencies, then the sampling in the effluent is started with a delay corresponding to the retention time of the process. In general, however, composite samples are recommended, which also implies that time delays become insignificant.

Manual sampling is generally only recommended for collecting discrete grab samples when a minimum of contamination is required. Regardless of the targeted substance and sampler, proper cleaning to minimize cross contamination, and avoiding a direct contact of the sampler with the media sampled is required.

5.2.3 Sample handling and storage

Sample handling and storage after collection will inevitably cause changes to sample composition, especially regarding ozonized samples. However, changes can be limited with the proper handling and storage, best decided by the employed analytical laboratory but briefly described here (Figure 5.3).

The sample containers need to be of suitable materials to prevent adsorption on the container wall and to avoid contamination from leaching of the material. If the target substances are sensitive to light, dark bottles can be used to prevent photolysis. For easily contaminated organic substances, it may be necessary to pre-clean and burn the sample container, which excludes the possibility of using plastic containers (see Figure 5.3).

Samples that contain biodegradable analytes need to be preserved prior to analysis. Direct conservation of collected samples can be achieved by either freezing or by the addition of chemicals (see Figure 5.3). Bottle acidification, for example, can help

preserve trace metals, reduce precipitation, microbial activity and sorption losses to container walls. Some pharmaceuticals and organic materials are readily degradable, thus it is recommended to freeze these samples after collection. Note that sampling bottles should not be top-filled if samples are frozen, due to expansion of the sample media. Transportation time pose a challenge to handle samples that cannot be conserved by freezing or chemicals, i.e. for biological analysis. For non-conserved samples, minimized transportation time to the laboratory is very important.

The properties of target substances determine the general requirements and considerations. However, it is worth noting that sampling media can determine the selection of sample containers as well. For example, when sampling solid samples, containers such as wide-opening bottles are recommended.

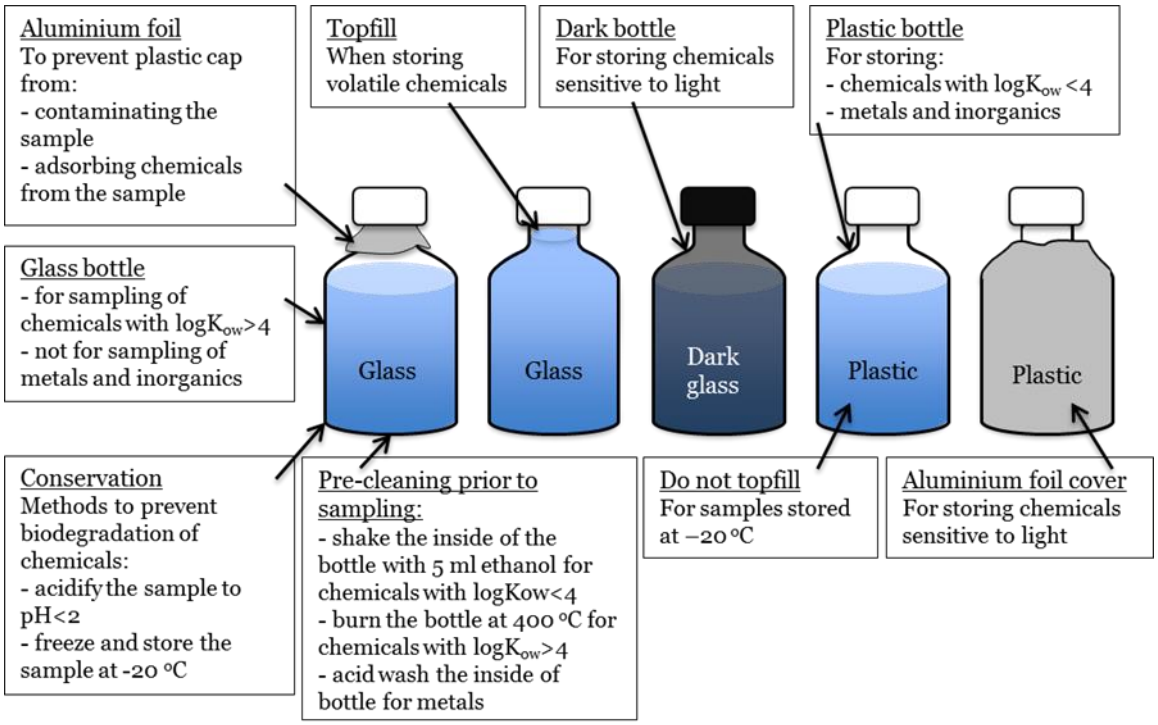


Figure 5.3. Collection media and sample handling with respect to different substances in wastewater.

Preparing a composite sample from many single samples or collecting a smaller amount of sample volume for analysis from a large sample volume requires care. Receiving representative samples includes aspects such as sedimented or floating fractions in the collected samples, which may contain more or less of the targeted substance. Improper extraction of samples for analysis will affect the substance quantifications significantly. Generally, gentle stirring of collected samples before extraction is recommended.

Finally, all unplanned, unexpected events in connection to sampling, such as clogging of pipes, stops in samplers or irregular operation of the treatment system, should be noted and used in analysis assessment since such events otherwise can lead to

misinterpretations of the actual composition of targeted substances in the water treatment system.

5.3 Chemical analysis

The aim when conducting a chemical analysis is to collect the chemical or physical information of a sample. The substances of interest in the sample are usually called analytes, and the residue of the sample is called matrix. Chromatographic methods are commonly used to determine the concentrations of pharmaceuticals and other emerging substances in environmental samples. A common analytical detection method is mass spectrometry, MS.

5.3.1 Sample treatment before analysis

Due to the complex matrix, wastewater samples cannot directly be injected into an analytical instrument without extensive clean up. Various pre-cleaning and extraction techniques such as filtration, centrifugation, sedimentation, solid phase extraction, liquid-liquid extraction, dilution, evaporation, soxhlet, microwave, ultrasonic extraction, and supercritical extractions as well as combinations are used to remove particulate matter and matrix interferences in liquid samples and organic analytes. Method blanks can be used to check if those materials are free from interferences.

5.3.2 Concentrations of interest

Samples of wastewater are always composed of suspended solids and solute with fractions of organic matter. Partitioning of substances between the fractions depend on the substance properties and solute properties. The potential risk of environmental effects from substances associated with organic matter is usually lower than the risk from the dissolved fraction, and a separation of the substance concentrations between the fractions is thus of large interest.

5.3.2.1 Total, bioavailable, and bioaccessible concentrations

Substances in wastewater are to a greater or less extent dissolved in the water phase and reversibly or irreversibly bound to dissolved organic matter (DOM) or particulate organic matter (POM). It is always a matter of distribution (Figure 5.4). The dissolved and reversibly bound fractions are usually of concern, as they are accessible to biota under environmental conditions.

The standard procedure to exclude particles from interfering with the analytes is to filtrate the sample before analysis. However, regardless of the pore-size of the selected filter, the remaining amount of an analyte in the water phase is not the same thing as the dissolved concentration of a substance, but rather a pre-defined assumption made of the size of a particle. For example, humic substances, such as humic acids and fulvic acids, present in waste- and receiving waters are often small and even partly dissolved in the water phase. This makes them impossible to separate from the water with normal filter techniques.

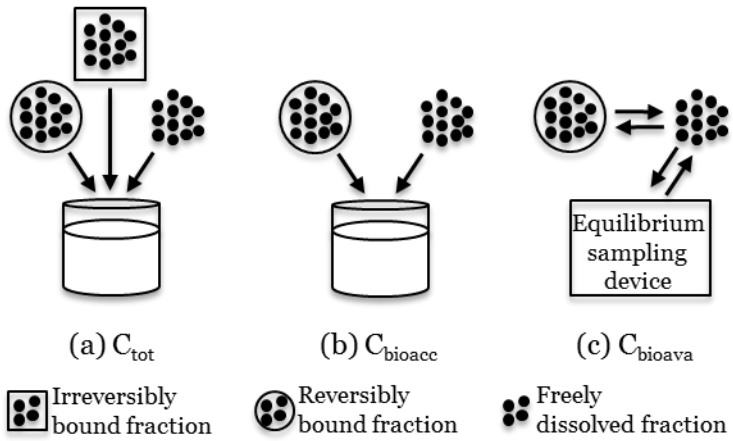


Figure 5.4. Distribution of substances in a sample and different extraction approaches: (a) Exhaustive extraction using strong solvents to establish the total concentration (C_{tot}); (b) Gradient extraction using weak solvents to establish the bioaccessible concentration (C_{bioacc}); (c) Equilibrium sampling techniques to estimate the bioavailable fraction (C_{bioava}).

5.3.2.2 Matrix effects and quantification

Analytical methods such as chromatography coupled to mass spectrometry are the primary choice for quantification of pharmaceuticals and other emerging substances in environmental samples. However, impurities (caused by substances present in the sample, not impurities caused by faulty handling of sample) in samples may result in inevitable issues during method development, validation and routine analysis. I.e. the co-elution of sample impurities can cause matrix effects such as ion suppression or ion enhancement of the analyte of interest during the mass spectrometric determination. This may *mask the true concentration* of the target analyte in the sample. There is no universal solution for matrix effects due to limited knowledge of their origin and mechanism. However, in order to remove or minimize matrix effects, different strategies including adapted example preparation methodology can be used by the employed analytical laboratory. The employed analytical laboratory should be able to assess and discuss the possible matrix effects in detail.

5.3.2.3 Substances spectrum

Analyzing duplicate samples is an effective internal method for determining the precision of an analysis. The duplicate samples can be taken from a single gross sample. The differences of results based on duplicates are derived and compared with accepted values.

5.4 Reporting analysis results

The reporting of chemical analysis represents an important part when handling problem quantification and mitigation related to pollution aspects. This chapter describes the procedure of reporting analysis results from laboratories back to the STPs. Even accredited laboratories use different methods in the process of sample conservation and preparation, and to require full knowledge of these procedures is thus necessary to make correct conclusions and provide possibilities to compare results.

5.4.1 Procedure documentation

It is important to report all the activities on sampling, sample preparation and analysis clearly and accurately. A good analysis report does not only offer opportunities for backtracking errors or mistakes, but serves as the basis for other following-up data-based assessments. For example, as sample composition is inevitably changed during sample analysis, what measures have been taken to minimize alterations to samples must be clearly recorded, e.g., acidification, freezing, filtration, blanks, standards etc. E.g. filtered samples will only give a fraction of the total composition of the substances unless they are completely in the dissolved fractions.

5.4.2 Analytical method limits

Limit of detection (LOD) is defined as the lower limit when it is possible to *detect* a specific component in the sample. The limit of quantification (LOQ) is defined as the lower limit when it is possible to *determine the concentration* of a specific component in the sample.

The LOD is normally derived using different methods including several standard deviations (STDs) of the results from repeated analysis of blanks, mean of blanks, difference between the mean and the expected concentration, weighing, calibration series etc. The LOQ is normally derived using similar methods. Each method is appropriate for specific conditions and the description how LOD and LOQ is determined should be described in the descriptions of methods and in the report of the results.

5.5 Quantification of Ecotoxicity

Wastewater is a complex cocktail of substances, which may cause severe effects on the aquatic environment when treatment is incomplete. The aim of the treatment is to protect the aquatic environment, and it is a challenge to assess the risk of effects of the substances in the effluent on the environment or in the recipient considering dilution factors. Even if adverse effects on the aquatic environment eventually may effect human health, e.g. through the food chain, ecotoxicity tests are the primary tool for impact assessment for STP effluent. This is partly because, e.g. human toxicity tests are far more advanced, cost-intensive and may not provide the most relevant information as they may represent impacts at a more downstream location.

With respect to assessing ecotoxicity, despite recognized shortcomings, the *single substance approach (SSA)* has been and still is widely adopted to determine the impact of pharmaceuticals and emerging substances on ecosystem health, e.g., effects on the aquatic organisms living downstream STPs. The substances whose effects have been assessed individually may account for only a small fraction of the harmful effects caused by the mixture. There is increasing concern about the potential toxic effects of chemical substance often referred to as “cocktail-effects”. Combined effect of a mixture of chemicals, can be larger than the effect of each of the single substances. To determine if the treatment is good enough using chemical analysis and single substance ecotoxicological tests, is a costly and in practice impossible task, due to the large amount of known and unknown substances in the wastewater. When assessment of combinations of chemicals should be carried out, *mixture substance assessments*

(MSA) may be used if considering the approach limitations. The use of ecotoxicological *whole effluent assessments (WEA)* of standardized test organisms or effect tests have been developed to account for unknown substances and combined cocktail effects.

5.5.1 Single-substance ecotoxicology effect studies

The assessment of the risk of effects on the ecosystem species is predicted on single substance level using comparison of the predicted concentration of the effluent (Predicted Environmental Concentration, PEC) to the predicted concentration that will not give unacceptable damage to the aquatic environment (Predicted No Effect Concentration, PNEC). This assessment is presented as a ratio:

PEC/PNEC < 1 (no predicted ecotoxicological effect)

PNEC is determined from effect studies, usually ecotoxicological tests performed in laboratory environment. The results from the tests are normally expressed as effect concentrations, usually median values (EC50- or LC50-values) or the highest concentration that does not have any observable effects, NOEC-values (No Observable Effect Concentration). Effects are studies on selected species from different habitat and trophic levels. For the PNEC value to be representative to as many organisms as possible in the ecosystem, an assessment factor is applied on the ecotoxicological test results. The assessment factors take into account the sensitivity between individuals of the same species, the different trophic level and habitats. The more sensitive a test is and the more extensive tests on several species and trophic level that have been applied, the lower the assessment factor (Table 5.1). The effect concentration value is divided with the assessment factor to produce the acceptable concentration PNEC for each substance.

PNEC = [ecotox test concentration (e.g. lowest EC50)]/assessment factor

Table 5.1. Assessment factors proposed for deriving PNEC water for saltwater for different data sets (Table 25 in TGD on risk assessment part II (ECHA 2003))

Data set	Assessment factor
Lowest short-term L(E)C50 from freshwater or saltwater representatives of three taxonomic groups (algae, crustaceans and fish) of three trophic levels	10 000
Lowest short-term L(E)C50 from freshwater or saltwater representatives of three taxonomicgroups (algae, crustaceans and fish) of three trophic levels, + two additional marine taxonomic groups (e.g. echinoderms, molluscs)	1 000
One long-term NOEC (from freshwater or saltwater crustacean reproduction or fish growth studies)	1 000
Two long-term NOECs from freshwater or saltwater species representing two trophic levels (algae and/or crustaceans and/or fish)	500
Lowest long-term NOECs from three freshwater or saltwater species (normally algae and/or crustaceans and/or fish) representing three trophic levels	100
Two long-term NOECs from freshwater or saltwater species representing two trophic levels (algae and/or crustaceans and/or fish) + one long-term NOEC from an additional marinetaxonomic group (e.g. echinoderms, molluscs)	50
Lowest long-term NOECs from three freshwater or saltwater species (normally algae and/orcrustaceans and/or fish) representing three trophic levels + two long-term NOECs from additional marine taxonomic groups (e.g. echinoderms, molluscs)	10

Defined Environmental Quality Standard values (EQS, see Section 3) would then work here. However, wastewater may contain substances for which results from toxicological effects are not available, or it may contain unknown substances. Thus, the *whole effluent tests* are recommended to assess the effects of the effluent on the aquatic environment.

5.5.2 Mixture substance assessments

For mixtures of similarly acting substances, effects can be estimated directly from the sum of the doses/concentrations, scaled for relative toxicity (dose/concentration addition). For mixtures of independently acting substances, effects can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological responses (effects addition). Both concepts are based on the assumption that substances in a mixture do not influence each other's toxicity. Such substances can either elicit similar responses by a common or similar mode of action, or they act independently and may have different endpoints and/or different target organs.

Both concepts have been suggested as default approaches in regulatory risk assessment of chemical mixtures (EC 2012b). In reality, however, chemical mixtures are rarely composed of either only similarly or of only dissimilarly acting substances. Instead, the combined effect of two or more substances as stronger (synergistic, potentiating, supra additive) or weaker (antagonistic, inhibitive, sub additive, infra additive) than would be expected on the basis of dose/concentration addition or response addition is common. Interactions may therefore vary according to the relative dose levels, the route(s), timing and duration of exposure (including the biological persistence of the mixture components), and the biological target(s).

5.5.3 Whole effluent assessments

The *whole effluent assessment (WEA)* directly measures the effects of STP effluent on the survival, growth and reproduction of organisms. It can be used as a first screening that is followed up by more detailed assessment tests when indications are given for negative effects in the tested effluent. In principal, WEA refers to biological tests using the whole effluent. Then, the toxicity of known and unknown substances and combination effects is assessed. The species tested can be single or multiple species in laboratory conditions or in situ, e.g., caged studies or artificial streams. Toxic effects on organisms of different trophic levels (bacteria, algae, benthic fauna, fish etc.) can be assessed as acute or chronic effects depending how fast the effects appear at exposure. It needs to be noted that parameters such as ammonia, pH and conductivity can affect these types of assessment, and the results should therefore be handled with care.

It can be generally expected that STP-effluents are only occasionally acutely toxic. Chronic tests comprise the assessments of impacts on organisms' vital functions or life-cycle stages, e.g., reproduction, growth, and hormonal impacts or effects on their genetic material (Table 5.2). Principally, they should include major parts, most sensitive stages or the complete lifecycle of the organism. Thus, the duration of a chronic test depends on the organism used. A review of the WEA methodology with regard to, amongst others, STP-effluents is provided by the COHIBA project (COHIBA 2010).

Table 5.2. Examples of WEA tests suitable for wastewater.

Type of test	Test organism	Duration
Acute tests		
Bacteria	Vibrio fisheri Luminescent bacteria ISO 11348-3	30 min
Fish	Brachydanio rerio (zebrafish) toxicity eggs ISO 15088	14 d
Crustaceans	Nitocra spinipes Immobility test SS 02 81 06	96 h
	Ceriodaphnia dubia Immobility test SS 02 82 14	48 h
	Daphnia magna Immobility test OECD 202, SS-EN ISO 6341	48 h
Algae*	Pseudokirchneriella subcapitata Growth inhibition ISO 8692	72 h
	Phaeodactylum tricornutum Growth inhibition SS-EN ISO 10253	72 h
	Ceramium tenuicorne Growth inhibition ISO 10710	7 d
Higher plants	Lemna minor Growth inhibition ISO 20079	7 d
Chronic and subcronic tests		
Fish	Brachydanio rerio (zebrafish) embryo and larvae test SS 02 81 93	≤ 14 d
Crustaceans	Nitocra spinipes Larval Development Rate Breitholtz et al. (2007)	6-8 d
	Ceriodaphnia dubia Reproduction test ISO 20665	7 d
	Daphnia magna Reproduction test ISO 10706	21 d
Algae*	Pseudokirchneriella subcapitata Growth inhibition ISO 8692	72 h
	Phaeodactylum tricornutum Growth inhibition SS-EN ISO 10253	72 h
	Ceramium tenuicorne Growth inhibition ISO 10710	7 d
Effect tests		
Hormones	Yeast Estrogen Screen (YES) Routledge and Sumpter 1996.	72 h
	Yeast Androgen Screen (YAS) Sohoni and Sumpter 1998	72 h
Genotoxicity	Ames test ISO 16240	
	UMU-test ISO 13829	
Biochemical tests		
Biomarkers in fish	For example EROD-activity test, Vitellogenin induction test, Glutathione transferase (GST)	

*Tests with algae can be counted both as acute and chronic tests since the test period covers several generations

The COHIBA project suggested a number of tests, suitable for wastewater analysis with most of them also standardized according to ISO standardization procedures and results normally presented as effect concentrations. The established recommendation is to perform WEA tests with 3-5 different organisms on different trophic levels or functional groups with dilution series to account for the variations of the sensitivity of the species and different trophic levels and habitat. Sometimes, only the most sensitive life stages are used in order to streamline the test procedure. These shortened chronic tests are sometimes referred to as "short-term chronic tests". The duration of acute toxicity test is usually shorter (72 h or less).

In order to characterise and test the toxicity of effluent industrial water or wastewater, a test scheme has been recommended by the Swedish EPA (SEPA 2011). Degradation tests may be performed before doing the ecotoxicity-tests in order to simulate the effects in the environment under natural conditions. However, degradation tests are time-consuming and the degradation rates site-specific. Thus, a “worst case” schemes including acute toxic, chronic toxic, bioaccumulation, and selected mutagenicity or hormone effect-tests are recommended. Performing only a small selection of tests makes the results more uncertain, because the sensitivity of all naturally occurring and site specific species cannot be predicted. The PNEC value can be calculated for the WEA using the same principle as for single substances. To account for test uncertainties and an improved comparability of test results to effects in the natural ecosystem, assessment factors have been recommended to be used together with the ecotox test results (Table 5.3). However, the proposed assessment factors for WEA are lower than

for single substances, thus single substance assessment factors therefore represents a more uncertain method.

PNEC = [ecotox test concentration (e.g. lowest EC50)]/assessment factor

Table 5.3. Table Assessment factor proposal for wastewater effluent to the aquatic environment (SEPA 2011, Handbook 2010:3).

Data set	Assessment factor
EC(LC)50 only from test using bioluminescence bacteria	1000
Lowest short-term EC(LC)C50 from at least one freshwater or saltwater representative of algae, crustaceans or fish	100
Lowest acute tox test EC(LC)50 from at least one fresh- or saltwater representatives on three trophic levels with at least on species of algae, crustaceans and fish	10
Lowest EC10 or NOEC from at least three long-term tox test of algae, crustaceans and fish	5

WEA and laboratory test comparison results in the COHIBA project were used to derive a proposal for toxicity-based discharge limits to protect the Baltic Sea aquatic environment (Nakari *et al.,* 2011). COHIBA proposed limits for maximum allowable acute toxicity stated as follows: 30% inhibition of algae growth at 80% test concentration, 20 % immobility of Daphnia magna at 95% test concentrations (48 h exposure), and 30% inhibition of luminescent bacteria (30 min exposure) at 80 % test concentration.

However, presence of persistent, bioaccumulative, and chronically toxic substances put the ecosystems at risk of long-term chronic effects and a build-up of persistent substances in the environment. The use of PNEC values and the COHIBA proposed limit values may in that case be too uncertain. The threshold value (0.5 mg/l or 0.05 kg/day as C20) of the bioaccumulation test EGOM (extractable organic material possible to separate with gas chromatography) has been recommended by the Swedish EPA as specific criteria for in-depth analysis of the chemicals causing the bioaccumulation and possible toxicity (SEPA, 2011).

WEA can be used to access the impact of a treatment process on the toxicity of wastewater and in that sense assesses its risk potential. After the initial WEA screening and/or characterization it is possible, and sometimes necessary, to conduct Toxicity Identification Evaluation (TIE) and Toxicity Reduction Evaluation (TRE) as suggested by the COHIBA project. The aim of TIE is to identify the substances or waste water fractions responsible of the effluent's toxicity. The objective of TRE to identify the sources of these substances and to plan adequate reduction measures for the substances in question.

The most important limitations of WEA (COHIBA 2010) include the fact that WEA as such only identifies potential risk and cannot be used alone to conduct an entire ecological risk assessment. Further, it is not possible to identify the exact substances causing the adverse effects even so WEA can identify e.g. which fraction that is responsible for detrimental effects. As for all analytical methods, also WEA results are bound to variability, which, however, can be reduced by using standardized or validated methods. Ethical aspects when using living organisms may be of importance too.

However, as far as there are no methods of similar sensitivity and of ecological relevance such tests should be accepted. Living organisms have species–specific requirements for the culture conditions, which may necessitate adjustment of the sample pH or salinity, for example. These actions may have an effect on the bioavailability or solubility of certain hazardous substances.

5.5.4 Inhibition of process organisms

In certain cases, the biological step at the STP itself may indicate if the treated water contains toxic substances. This fact is already today accounted for by STPs upstream activities to avoid emissions of process-disturbing substances from various sources. In certain setups such as e.g. an ozonation prior to biological processes, the bacteria activity can be used as a "screening test" to detect toxicity caused by the influent water and thus in this case the ozonation. Such a simplified indicator is, however, not a measure of the toxicity of the effluent water. The fact that a substance is not toxic to microorganisms in the biology does not imply that it cannot be toxic to higher organisms downstream. The usefulness of such test was demonstrated, e.g. by using nitrification Inhibition (ISO 9509) and respiration inhibition (ISO 8192) tests as indicators when investigating ozonation before the final denitrification of the sewage (Sehlén *et al.,* 2015). The Swedish EPA (SEPA 2011) has suggested $PNEC_{STP}$ specific ecotox tests and assessment factors for STP influents, using test species from the biologic STP treatment step to protect the STP microbiology.

6 Technologies for the removal of pharmaceutical residues and other emerging substances in sewage treatment plants

This section aims to give an overview of the state-of-the art of upcoming promising treatment technologies focussing on the removal of pharmaceuticals and other emerging substances from municipal wastewater. Special emphasis will lie on observed reduction rates for different substance groups, in combination with observed side effects such as formation of unwanted substances or other negative impacts. The targeted removal rate or effluent concentration is strongly affecting the choice of removal technology.

Most of the treatment technologies described in the following sections have been focusing on the efficiency of removing pharmaceuticals. However, there are reasons to believe that other substances with similar molecular structure and physico-chemical properties will behave in the same way.

6.1 Effluent vs. Sludge handling

Most studies on the removal of emerging substances in STPs focus on the removal of compounds from the aqueous phase by comparing inflow and outflow concentrations without discussing the fate of the removed compounds. This is not a problem if the substances are either totally biodegraded or removed by a physical sequestration as in an activated carbon filter where the sorbent is treated afterwards. If compounds instead are removed by attaching to sludge particles their fate is often unknown. The impact of a possible transport and degradation of persistent substances in soil after sludge application is largely unknown.

The discussed technologies here will also focus on the removal of substances from the STP-effluent, after biological treatment. However, modified biological systems or addition of powdered activated carbon (PAC) will also influence which compounds are found in the excess sludge, which may then become a more significant pathway of emerging substances. The sludge treatment and handling, however, needs to be reassessed especially if the stabilized sludge is spread on agriculture land. Difficulties in analytical methods and the understanding of various processes during sludge stabilization imply limitations in follow up of substances sorbed onto sludge (Malmborg 2014).

6.2 Upstream work

The most effective way to decrease emissions of priority and emerging substances in STP effluents is to prevent them from entering the sewer system. This can be done with upstream source control, directed information campaigns but also by legislation and/or voluntary actions to substitute harmful substances to less toxic, bioaccumulating and/or persistent alternatives if possible. Historically, focus have been on industrial point sources but nowadays there is an understanding of the many diffuse emissions that occur from smaller enterprises and other activities in the society; such as hospitals, airports, traffic, building- and construction work, as well as from households. The tools

for mitigation include the use of legislation, substitution, green procurement, voluntary agreements, financial initiatives, eco-labelling, etc. Additional benefits of upstream source control include improved sludge quality and the protection of the working environment, the material in the sewerage network and the microorganisms in the biological treatment. However, the control of new compounds before they are introduced is not always fast or efficient enough. One compound is often replaced by another with similar or new negative effects. Imported goods might contain substances not allowed in Sweden or the EU. One example is the presence of nonylphenol ethoxylates (NPE) in textiles produced outside the EU. NPE emitted from textiles into the washing waters contribute with a substantial part to the influent volumes of NPE to the STPs. However, many textile importers have nowadays set voluntary limits for NPE in their textiles, which have reduced influent amounts of NPE to the STPs. There is now a proposal within EU to restrict the use of NPE in all imported textiles, having a maximum possible NPE level using the REACH restriction procedure.

While upstream source control can be applied on many priority substances, it is more difficult in the case of active pharmaceutical ingredients (APIs). The large amounts that end up in the STP via urine and faeces are harder to avoid. Legally an API cannot be denied marketing authorization based on negative environmental properties, hence other mitigation methods have to be used until the regulating EU directive has been changed. Green Pharmacy aims to develop efficient products with minimal use of resources, causing minimal amounts of waste, having little negative side effects for the patient and that are easily degradable after use. The health sector is also an actor where for example doctors are urged to; if possible, prescribe drugs with less environmental impact and not in bigger packages than necessary. Restricted prescription of antibiotics is important and it should in the future be possible to put prescription requirements on environmentally harmful API:s, such as diclofenac.

To reduce the waste source of leftover pharmaceuticals in the STP influent, campaigns ask the public to return all leftover to pharmacies for proper destruction. Today most pharmaceuticals are correctly handled in Sweden.

One possible way to work upstream from the STP is to have separate wastewater treatment for *targeted wastewater*. In systems separating black water (toilet water) from grey water (washing water), most pharmaceuticals would be found in the black water much more concentrated in a considerably smaller volume of water than the total household wastewater. This might improve the possibilities to remove them with local black water treatment. However, most personal care products and compounds from washing of clothes would end up in the grey water, and have to be treated there.

Separate wastewater treatment for hospitals has also been tested in large-scale (Kovalova *et al.,* 2013; Köhler *et al.,* 2012; Nielsen 2014). However, even if the concentrations of some pharmaceuticals are much higher in hospital effluent the amount of pharmaceuticals used in hospitals is just a small fraction of the total amount used. In 2010, only about 3 % of all the pharmaceuticals on the Swedish market were used within the health care sector (Castenson 2010). To target the largest flows of emerging substances, investments in advanced treatment are thus needed in public STPs where in addition to pharmaceuticals also other emerging substances will be affected. However, a majority of the most potent antibiotics are used in hospitals.

6.3 Removal efficiency in existing Swedish STPs

This section mainly deals with data for Swedish STP. However, presented data should be relevant for all STPs with similar design and about the same composition of influent sewage. The first compilations of data regarding pharmaceuticals from early screening projects by IVL Swedish Environmental Research Institute were published by Svenson *et al.* (2003) and Woldegiorgis *et al.* (2007). A recent summary of relevant data is provided by Hörsing *et al.* (2014) based on data from the Mistra Pharma project (Falås *et al.,* 2012a) and The Stockholm Vatten project (Wahlberg *et al.*, 2010). These compilations indicate that inlet concentrations generally vary from some tenth of µg/L to a few ng/L, while the outlet figures vary from a few µg/L to a few ng/L or less. There is further a great variation in removal efficiency between both different compounds and different treatment methods. For different compounds, it is obvious that some are readily biologically degradable or transferred to the sludge phase depending on their chemical structure and physical properties. A good example is paracetamol, which is sufficiently degraded in any biological system that is not overloaded.

Another group of compounds is more slowly biodegraded, or demand more specific conditions in the biological step. These can be higher sludge age, as in nitrification steps or systems with carrier material, or possibly specific factors like anoxic conditions or nitrifying bacteria (see also section 6.4). For this group of compounds the removal efficiency will vary from 0 to 100 % depending on the process configuration and the load. Examples are naproxen and probably ibuprofen.

Some pharmaceuticals seem to pass traditional STPs without any obvious change in concentration, e.g. diclofenac and oxazepam. They are neither biodegraded nor transferred to the sludge phase and therefore some kind of complementary treatment system is necessary if these compounds are to be removed from the effluent. A group of compounds seems to increase in concentration over the STP. One reason for this is that normally only the free compound is detected with the analytical method. In many cases the compound is in some way conjugated or modified in the influent sewage and will not be detected in the analysis while in the effluent it has reverted to its parental form (see also section 0). Another explanation is the uncertain analysis of influent wastewater due to large matrix effects.

Other emerging pollutants are often lipophilic and thus largely particle bound in contrast to most pharmaceuticals. This is true for most of the heavy metals, which are to more than 95 % found in the sludge at Henriksdal STP in Stockholm. Other examples are the flame-retardants dekabromodiphenyl ether and dekabromodiphenyl ethane. A study at Henriksdal STP showed that only about 1 % of both substances were released with the treated wastewater while the bulk was sequestered into the digested sludge (Ricklund *et al.,* 2008). Previous studies indicate the same situation for PCBs, PAHs and PCDD/Fs. There are however other substances, such as the perfluorinated substances and many pesticides, that are more water soluble with a behavior similar to pharmaceuticals.

6.4 Secondary and tertiary treatment technologies in Sweden

Swedish STPs are built and constructed differently depending on size and location, which affects the need of extended nitrogen removal. Secondary and tertiary treatment

in Swedish STPs implies both carbon, phosphorous and nitrogen removal. Swedish regulation states that STPs larger than 10 000 pe (person equivalents) discharging effluent to larger recipients south of a line from the southern border of Norway to the Baltic Sea 50 km north of Stockholm should undergo extended nitrogen removal (Statistic Sweden 2014). In total Sweden in 2012 had 411 STPs divided in size classes: 298 plants of size 2001-20 000 pe, 94 plants of size 20 001-100 000 pe, and 19 Plants with a size larger than 100 001 pe. Four of the STPs have only biological treatment, 234 STPs have conventional biological and chemical treatment, 20 STPs have complemented biological and chemical treatment and 115 STPs have biological and chemical treatment with extended nitrogen removal (Statistic Sweden 2014).

Thus, the main part is equipped with a combination of biological and chemical treatment focusing on the removal of easily degradable organic material and nutrients. Depending on the process-characteristics and the fact that most unwanted substances in wastewater are organic, a certain removal of such substances may be achieved by secondary treatment of wastewater.

6.4.1 Enhanced biology

All organic substances can potentially be degraded. In existing STPs, a better removal may be achieved by an enhanced biological process (e.g. Suárez *et al.,* 2008). For this, additional biological activity can for example be created by adding carriers or increasing the sludge retention time. Both actions, however, have their limitations as adding carriers requires adaptions of the process and increasing sludge age goes hand in hand with increased process volumes if considering traditional active sludge processes. In addition, this approach presupposes that bacteria or other microorganisms exist that actually can degrade the specific compound, without requiring very specific conditions.

Falås *et al.* (2012b) demonstrated that some of a number of pharmaceuticals tested could be degraded more effectively in existing activated sludge treatments by adding carriers. The study indicates a faster degradation (per unit of biomass) for diclofenac, ketoprofen, gemfibrozil, clofibric acid and mefenamic using carriers. For ibuprofen and naproxen, no significant effect was observed. In addition, Falås *et al.* (2013) found various effects for a few more compounds. However, the breakdown of the six studied substances, including carbamazepine, was also observed in active sludge processes without carriers. On the other hand, Wahlberg *et al.* (2010) did investigate a MBBR (Moving Bed BioReactor) and traditional active sludge system in pilot-scale at Hammarby Sjöstadsverk using the same wastewater and did only see a marginal difference in removal performance.

The performed studies indicate that while some substances may be removed more efficiently by enhance biology; other substances are only marginally affected and some not at all. This is true not only for systems with extra carriers or increased sludge residence time but also for systems with shifting redox-conditions such as in complete nitrogen removal (Hörsing *et al.,* 2014). To secure an acceptable removal of most pharmaceutical compounds it seems more realistic to complement with a separation/degradation step, i.e., activated carbon or advanced oxidation as described

in following sections. This is probably true also for other emerging substances, although data in the literature is scarcer for these compounds.

6.4.2 MBR – Membrane BioReactor

A MembranBioReactor separates the active sludge from the water phase by a membrane, which implies the possibility for much higher sludge content and increased sludge retention times in the process. This certainly leads to an increased removal efficiency of organic substances and thus more persistent organic substances. Comparisons of conventional activated sludge treatment and pilot-scale membrane bioreactors in eliminating various pharmaceutical residues belonging to different groups and with diverse physico-chemical properties showed that investigated MBRs exhibited an enhanced elimination of several pharmaceutical residues poorly removed by traditional processes (Lipp *et al.,* 2009; Radjenović *et al.,* 2009; Sipma *et al.,* 2010; Wahlberg *et al.,* 2010). The elimination of some compounds, however, was observed to be less efficient for the MBR-processes than for conventional systems. As particles in general and inorganic/plastic micro-particles are more efficiently removed by a MBR-process, also persistence substances using such particles as carrier are removed (Magnusson and Wahlberg, 2014). On the other hand, some compounds normally adsorbed to the activated sludge may be free in the MBR because of the lower sludge production and higher mineralization of the sludge.

However, also an MBR-process will not be able to efficiently remove all emerging substances but completing treatment methods will be necessary (RiSKWa 2015). The advantages of a MBR prior to any following polishing step are obvious; lower concentrations of disturbing elements such as suspended solids, nutrients and organic matter. In addition, some persistent organic substances may already be removed or partly cracked down by the stronger biological process (Tambosi *et al.,* 2009). This implies more flexibility and decreased demand in efficiency of the following treatment methods and thus decreased footprint and cost. The operation and control of such treatment processes may also be easier due to a better and uniform effluent quality after the MBR. Ozone treatment, for example, may be easier to monitor and control, as online measurements on MBR-effluent are much more robust than on other effluents, which pilot-studies, among others, at Hammarby Sjöstadsverk indicate (Baresel *et al.,* 2014; Sehlén *et al.,* 2015; see section 6.5). Fewer particles in the effluent will also decrease the clogging problems in a bed of granulated activated carbon (GAC).

The removal efficiency of bacteria, virus and pathogens by membrane separation has been shown, e.g. by Marti *et al.* (2011). Depending on the pore size of the membranes used, almost complete removal for vegetative pathogenic and indicator bacteria (>0.5 μm wide and >2.0 μm long), the spores of bacterial indicators (≈1–5 μm), helminth eggs (>20 μm wide and >25 μm long) and protozoa can be removed by exclusion. Even so, most human viruses are smaller than most typical pore dimensions; they are partly retained because of biofilms on membranes or adsorption into the biomass. The MBR-process may also have some potential to be adapted in a way to facilitate an enhanced internal removal of unwanted substances by, e.g. adding powder activated carbon (section 6.7.3).

6.4.3 Other technologies

Partly anaerobic treatment consisting of an UASB (Upflow Anaerobic Sludge Blanket) was investigated by Wahlberg *et al.* (2010) using pilot treatment plants at Hammarby Sjöstadsverk. The system showed comparable removal efficiency as traditional active sludge systems.

6.5 Complementary treatment technologies

Priority and emerging substances have different partitioning between liquid and solid phase, in the case of STP, between water and sludge. In a survey covering 75 pharmaceuticals it was shown that only a few sorb to sludge and the main part of the studied pharmaceuticals would be found to more than 80% in the water phase (Hörsing *et al.,* 2011). Complementary treatment options include advanced techniques that can complement the existing secondary and tertiary treatment and by that improve the removal efficiency of emerging substances. Such technologies may consist of single stand-alone treatment steps or a combination of several treatment technologies. Complementary treatment methods are sometime also referred to as fourth treatment step (quaternary treatment).

6.5.1 Ozonation

The most common advanced oxidation process today is the treatment with ozone. Ozone treatment uses the direct chemical reaction of the ozone molecule as well as indirect reactions with hydroxyl radicals, which breaks specific chemical bonds within the targeted substances. There exist several full-scale installations of a complementary treatment step by ozone to oxidize pharmaceutical residues and other organic compounds. Results are reported from several lab-scale (Wert *et al.,* 2007), pilot-scale (Abegglen *et al.*, 2010; Baresel *et al.,* 2014, 2015; Ek *et al.,* 2013; Gerrity and Snyder, 2011; Magdeburg *et al.,* 2012, 2014; Reungoat *et al.*, 2011; Sehlén *et al.,* 2015; Stalter *et al.,* 2010b; Wahlberg *et al.,* 2010) and full-scale applications (Altmann *et al.,* 2012; Arge 2013; Gerrity and Snyder, 2011; Maus *et al.,* 2014; Stalter *et al.,* 2010a). Applied ozone doses range between 0.3 and 1.2 g O_3/g DOC (about 3-12 g O_3/m^3 water) and a significant breakdown of most of the studied compounds was observed in these studies. However, required ozone doses vary for different substances and for some (e.g. Ibuprofen) a sufficient removal could not be reported even at very high doses. Normal ozone doses (0.6-1.1 g O3/g DOC) decreased the estrogenic effect by about 98% and the androgenic by 56% as reported by Altmann *et al.* (2012) and Baresel *et al.* (2014).

One main advantage of ozone treatment is that the water is disinfected, however, the main disadvantage of ozone treatment is the fact that the process does not completely degrade most substances but transforms them into other substances, normally without aromatic structures. Some of these metabolites might be more or less toxic. Thus, risks for the formation of toxic compounds, bromate and NDMA (N-Nitrosodimethylamine) have been indicated by several studies and negative effects have been observed by a few ecotoxicological tests (Abegglen *et al.*, 2010; Gerrity and Snyder, 2011; Magdeburg *et al.,* 2012, 2014; Stalter *et al.,* 2010a, 2010b; Wert *et al.,* 2007). An extra treatment step introduced after the ozone treatment in order to reduce the possible toxic oxidation products may or may not reduce such concentrations to acceptable levels as shown by

several of these studies. At the same time, a number of studies did not indicate any increase in toxicity (Altmann *et al.,* 2012; Sehlén *et al.,* 2015).

6.5.1.1 Ozonation dose-response studies

Recent studies in Sweden (Baresel *et al.,* 2014, 2015; Ek *et al.,* 2013; Sehlén *et al.,* 2015; Wahlberg *et al.,* 2010) indicate comparable dose-response profiles despite the difference in treated wastewater. The studies include traditional active sludge processes (Henriksdal STP & Hammarby Sjöstadsverk), MBR-treated wastewater (Himmerfjärden STP & Hammarby Sjöstadsverk) and partially treated wastewater (Nykvarn STP Linköping). Contact times in all studies have been between 10-20 min but concentrations of pharmaceuticals and COD before ozonation vary between the various studies and within studies. Further, the number of substances included differs between studies and are assigned equally importance in the presented reduction.

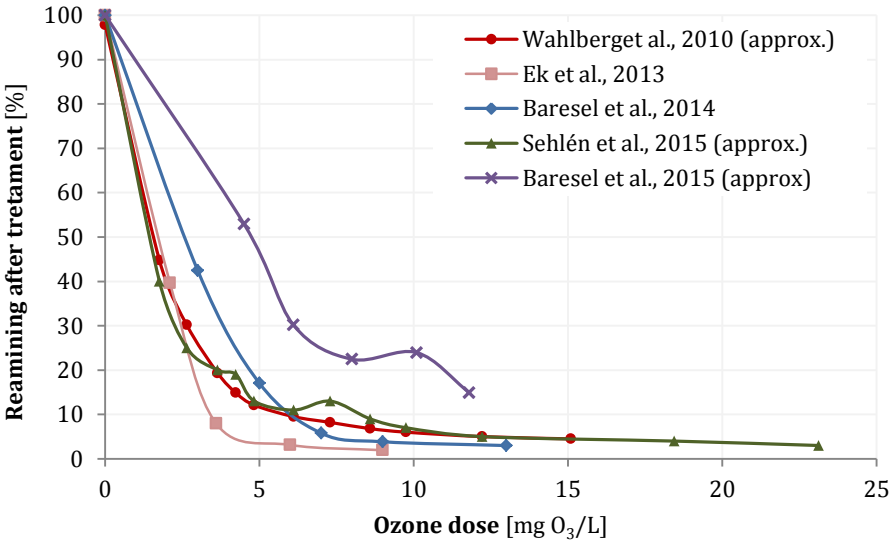


Figure 6.1. Dose-response profiles of recent wastewater ozonation studies in Sweden (based on averaged results of detectable pharmaceuticals in treated wastewater. Note that concentrations of pharmaceuticals and COD vary between the various studies and within studies).

Already medium dosages of ozone (5-7 mg ozone/L) give a very good removal of most analyzed substances and increasing BOD concentrations in the effluent analysis in some of the studies suggested that the more complex compounds are broken down into more biodegradable substances. This means that nature can more easily take care of these substances after discharge. At high dosage, all investigated compounds were removed almost completely. However, the figure also illustrates that the dose-response may vary with specific process characteristics and matrix of the treated wastewater. The chemical analysis of other compounds such as a number of hormones has yet problems with sufficient sensitivity (section 0). However, using the biological YES or YAS test for total estrogenic or androgenic effect can provide an indication that such effects are significant removed already at medium ozone dosage (Baresel *et al.,* 2014). Phenols may be removed similar as pharmaceutical residues except for octylphenol and nonylphenol that are more difficult to oxidize (Baresel *et al.,* 2014).

Although ozone doses of e.g. 7 mg O_3/L remove up to 94% of most pharmaceuticals (Figure 6.1), some extra persistent substances (e.g. oxazepam) can be detected even at very high ozone doses. The decision of how large doses to apply, should thus also consider other aspects, such as; effluent concentrations relative to observed effect concentration in combination with the current minimum dilution in the receiving water (see section 3). Another aspect is that ozonation is an energy-intensive process and a resource efficient treatment of persistent organic substances should take into account the total environmental impact of the process. This means that lower doses may be preferable to both achieve a significant transformation and limiting the risk for the formation of other toxic pollutants. Ozone residuals in effluent water and emitted gas as observed in some of these studies, indicates potential for further improvements. Extended retention times and/or more efficient distribution of ozone in the water phase can improve both the process efficiency and avoid an active destruction of residual ozone. At studied ozone doses, the energy demand for ozonation should not exceed 0.1-0.2 kWh/m^3 for high capacity installations.

6.5.1.2 Ozonation dosage control

Although Figure 6.1 indicates a good general dose-response behavior for ozone treatment, the actual optimal ozone dosage is not given. This is because the water varies in composition over time. The control of ozonation using current residues of targeted substances is not possible due to the absence of real-time online analytical methods for these low levels. This further implies that facilities probably tend to overdose to be on the safe side. However, both high costs, resource-efficiency and increased risk of formation of eco-toxic transformation products, requires a better approach. There has been much research on possible control concepts to optimize the use of ozonation with varying success (Eawag, 2013; Ikehata *et al.,* 2008; Snyder *et al.,* 2006; Snyder, 2008). Few strategies have been established as standard controls strategies. One of the reasons for this may be the need for reliable real-time monitoring of water parameters before, after or at both locations around the ozone treatment. Sehlén *et al. (*2015) tested ozone residues in the gas-phase as well as absorbance, as control parameter. Using COD control failed because of the mentioned problems with the ability for robust real-time measurements. The absorbance at 254 nm may be the most promising control strategy and, as recent test indicate, easier to implement on effluents of higher quality such as MBR-effluent (Baresel *et al.,* 2014). The decrease in absorbance, a rough measure of compounds with aromatic rings, showing a clear dose-response relationship and its online measurement is relatively easy and robust when particles have been removed. Pharmaceutical substances represent a very small fraction of the compounds responsible for the absorbance and further research and tests are required to establish good control strategies. Furthermore, each application will require a specific absorbance profile in order to evaluate if absorbance can be used in that configuration and the specific water matrix. As expected, wastewater with high concentration of aromatic compounds demand higher doses of ozone to give a certain removal of pharmaceuticals, compared to water with normal concentrations (Hörsing *et al.,* 2014)

6.5.1.3 Other considerations

Experiences from pilot and full-scale applications indicate that a characterization of the wastewater to be treated, including the creation of ecotoxicological compounds by ozonation, should be carried out as a first step evaluation before designing a full-scale

facility (Baresel *et al.,* 2014, 2015; Ek *et al.,* 2013 Maus *et al.,* 2014; Sehlén *et al.,* 2015). A full-scale facility should further have the option to apply a range of different doses and different residence times. The observed increase in BOD due to ozonation at some occasions should be evaluated at each application in order to avoid effluent criteria conflicts. Applying ozonation prior to a biological step (e.g. Sehlén *et al.,* 2015), residual ozone and increased oxygen concentrations need to be accounted for in subsequent processes.

Ozonation is a well-established technology that provides a flexibility to adapt to changing water composition etc. Main challenges are to ensure a good mixing and contact when adding ozone even at dynamic dosage regulation and the entire lifetime. This may be different for different mixing techniques used. Further, robust monitoring and control strategies needs to be developed. Further, the application of ozone at other process locations than usually applied may be worth to investigate. Finally, the potential formation and removal of toxic transformation products requires a better understanding.

6.5.2 Activated Carbon

Powdered and granular activated carbon (PAC and GAC) are common technologies to remove priority substances from all kinds of polluted waters. The main advantage of using activated carbon is that no by-products are produced and that priority substances are actually removed and not transformed into other compounds such as is the case of biological and oxidation methods. In comparison to ozone treatment, a disadvantage of using activated carbon is that the water is not disinfected. GAC-filters also act as physical barriers between the treatment process and the recipient. In addition, the regeneration of activated carbon implies a complete oxidation of the removed organic compounds. Especially in treatment of fresh water for drinking water production, technical systems using either PAC or GAC have been applied for many years. Thus, significant knowledge on setup and operation of removal systems is available.

The addition of PAC in secondary treatment implies that the PAC will end up in the sludge and thus negatively affect the possibilities of using sludge on agricultural land. Regeneration also becomes more difficult as the separation of PAC and biosolids is difficult. An advantage of such application of PAC, on the other hand, is that no additional equipment or installation is required and problems with clogging are normally not reported. Clausen *et al.* (2014) report that the dosage of 10 mg PAC/L into the active sludge process at the STP Düsseldorf-Süd (Germany) showed a significantly better elimination of Carbamazepine, Diclofenac and Metoprolole than without PAC-dosing. For other substances such as Benzotriazole and Sulphamethoxazole, on the other hand, no significant improvement of removal efficiency was observed. Further, increasing the PAC-dosage to 20 mg/L implied no improvement at all. The average contact time during the 12-month operation was about 30 hours.

PAC may also be used as a tertiary treatment step in a separate reactor, which avoids the carbon/sludge mixture (Alt and Mauritz, 2010; Boehler *et al.,* 2012; Arge 2013; Kovalova *et al.,* 2013; Luo *et al.,* 2014; Metzger *et al.,* 2014). A separation step has to be included often followed by a final filtration with e.g. sand filter, to avoid activated carbon discharges. Löwenberg *et al.* (2014) report good results using Ultra filtration in

PAC-applications. PAC dosage after the regular treatment process in the Mannheim STP (Alt and Mauritz, 2010) and a number of STPs in Baden-Württemberg, Germany (Arge 2013; Metzger *et al.,* 2014) report estimated cost in the range of about 0.5-1.8 SEK/m^3 water, or 20 -80 SEK/pe annually. It must be noted that 50 m^3/(pe·yr) were used in this study compared to 150 m^3/(pe·yr) used in Sweden. Cost would therefore be three folded. Two years of full-scale operation suggest that about 10 mg PAC/L are required to remove at least 80% of most of the investigated substances at average contact times of about one hour. However, 80% removal might not be enough and one-hour contact time takes a lot of space if it not mixed into the biological step.

Theoretically, the capacity of a system with activated carbon in a fixed bed should be significantly higher than that of activated carbon in a total-mixed system in equilibrium with a low concentration of dissolved compounds. GAC as tertiary filter systems may be operated as fixed bed filters in the same way as common sand filters but only partial backwash may be applied in order to maintain the concentration profile in the filter bed. However, results from Ek *et al.* (2014) showed no decrease in removal efficiency of totally backwashed and only partial backwashed systems. Totally mixed GAC filters further exists as upflow (fluid bed) filters. Full-scale investigations by Grover *et al.* (2011) showed >98 % removal of diclofenac, 64 % removal of estrone, >43 % removal of both 17β-estradiol and 17α-ethinylestradiol. The removal of carbamazepine and propranolol were only 23 and 17 %, respectively.

Furthermore, it is possible to attain a higher carbon capacity by setting up a number of sequential columns. The activated carbon in the first filter could then be used until the maximum effluent concentration of prioritized substances is reached in the outflow of the last filter (Ek *et al.,* 2014). This means that the first carbon-column would have a capacity equivalent to a relatively high concentration of pollutants. The capacity in equilibrium (PAC or completely mixed GAC) with low pollutant concentrations would be much lower. This implies a much better utilization of the carbon but requires also more installations. According to cost estimations for such a system, cost would be in the same range as for ozone treatment of about 0.6 SEK/m^3 in a high capacity plant.

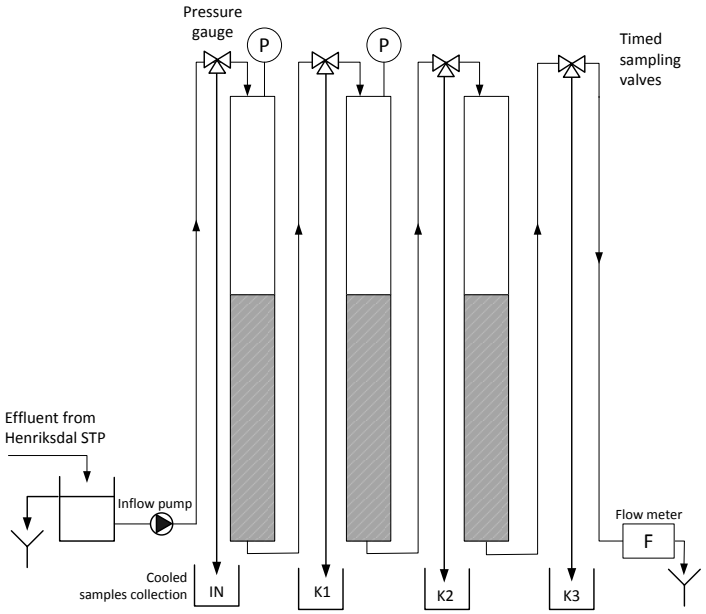


Figure 6.2. Schematic illustration of a GAC multi-filter system (Ek *et al.,* 2014).

Recent test with GAC-filter systems at Hammarby Sjöstadsverk and Swedish STP show good removal efficiency especially for MBR-effluent (Baresel *et al.,* 2014, 2015; Ek *et al.,* 2013a, 2013b, 2014). Of more than 37 pharmaceutical residues and a number of phenolic substances, the GAC performed generally well and better than with comparable ozone treatment for some substances and investigated loadings (Baresel *et al.,* 2014; Ek *et al.,* 2013b). Also phenolic compounds like Triclosan were removed. A moderate effect of the GAC-filter was observed for Bisphenol A and nonylphenol, but octylphenol was removed to a high degree. Coliforms were low already after the MBR-process, but declined further by 80-85% over the GAC-filter. Other research shows that activated carbon is the most effective technology for cytotoxicity removal Stalter *et al.* (2011).

For traditionally treated wastewater, about 25 mg GAC/L were estimated to be required in a single filter (Ek *et al.,* 2013a; 2014) even though earlier studies report much higher amounts (Wahlberg *et al.,* 2010). However, utilizing multiple- filter systems as presented in Figure 6.2, the efficiency of the system can be multiplied. Also a higher quality of the secondary effluent by e.g. MBR-systems will requires less GAC per treated cubic meter of wastewater. Empty bed contact times (EBCT) of about 12-14 minutes have been observed to be sufficient (Baresel *et al.,* 2014; Ek *et al.,* 2013a, 2013b, 2014). Recent results indicate however that even lower EBCT (10 min) may provide comparable removal efficiencies (Baresel *et al.,* 2014). Wahlberg *et al.* (2010) applied EBTC between 10 - 60 minutes but did not report any specific results for this.

Systems based on activated carbon will in most cases also lead to a biological breakdown of adsorbed substances and removal of other organic compounds (e.g. COD) and nutrients, etc. and therefore become biological activated carbon (BAC) systems. This is in agreement with common understanding that biological activity will

establish if the necessary conditions exist. This can be observed in common sand filters too. Results from e.g. Ek *et al.* (2013a; 2014) show a degradation/transformation of several of the investigated pharmaceutical residues. Also Reungoat *et al.* (2011) conclude that BAC filtration (with or without pre-ozonation) could be implemented as a low cost advanced treatment option to improve STP effluent chemical quality. However, it is generally difficult to determine if substances have been broken down totally, or if they are only partially converted to metabolites that either are left in the water phase or adsorbed to the filter. The biology in a GAC-filter may adapt to the specific compounds in the influent water and thus enhance the removal efficiency. Biological activity, however, is besides suspended solids in the inlet the main reason for clogging problems that are the main operational challenge for fixed GAC-filter systems. Here, MBR-treated water or other particle-free process waters are generally easier to handle.

Main aspects regarding the technical setup of activated carbon systems is to address hydraulic capacity problems caused by microbial growth in the system and backwashing properly. For this, required retention times and the removal of other organic compounds have to be assessed for each water matrix in order to implement successful treatment systems. Systems may be designed as either pressurized or open flow systems.

The potential for improvement in production and characteristics of activated carbon, such as the use of STP sludge to generate BioAC (biochar) or surface-treatment to modify activated carbon (ModAC), represents another advantage of this technology. Also a resource-efficient monitoring of the removal efficiency using ultraviolet transmission (UVT) (Altmann *et al.,* 2014; Baresel *et al.,* 2014) may help for the overall implementation of activated carbon systems and in the case of PAC-dosing even facilitate an active control. Several of these approaches are currently investigated at Hammarby Sjöstadsverk in collaboration with international companies and STPs.

6.5.3 Combined systems – ozone & filter

The combination of several of mentioned technologies is of course an efficient way to take advantage of single techniques and at the same time trying to compensate their adverse effects. The most obvious combination is ozonation and an activated carbon or sand filter. Many studies have shown that simple treatment steps after the ozone treatment reduce any harmful concentrations to acceptable levels (Abegglen *et al.*, 2010; Gerrity and Snyder, 2011; Lee *et al.,* 2012; Magdeburg *et al.,* 2012, 2014; Stalter *et al.,* 2010a, 2010b; Wert *et al.,* 2007). Yet it remains to investigate what the most resource-efficient step after ozonation would be. A simple increase of the contact time that allows for aging of the ozone- treated water may be sufficient; otherwise, biofiltration can remove the organic oxidation products of ozonation. Although the use of activated carbon in combination with ozonation may seem to be an optimal alternative; simpler systems may provide more resource efficient. Besides reducing the risk of harmful concentrations from ozonation, following filter steps can also reduce other compounds in the effluent, e.g. organics, nutrients and other substances.

Swedish research and competence includes activities within the Mistra Pharma project performing pilot-tests at various STPs with a combined ozone/GAC treatment. Such

systems have also been evaluated in the collaboration project ReUse between IVL and Xylem at Hammarby Sjöstadsverk (Baresel *et al.,* 2015; Wieland and Lazic, 2014) as well as ozone/BAF (Biological active filter) and ozone/sand filter. Even so, more research and tests are planned to further optimize these systems, the most resource-efficient solution that also provided the lowest total environmental impact and total costs (installation and operation) was transformed into a compact stand-alone technology consisting of a combined ozonation and filter (Oxelia process, Xylem Leopold). This combined system of ozonation and activated carbon as also identified as one of the most suitable technology for micropollutant removal in the RiSKWa-project (RiSKWa 2015).

6.5.4 Other advanced oxidation process (AOP)

Besides ozone treatment, the application of UV-light in different combinations with hydrogen peroxide (H_2O_2) and titanium dioxide (TiO_2) represent other advanced oxidation processes (AOP). Biologically treated and relatively particle-free water is an advantage for these methods and their use is therefore limited to tertiary treatment steps. A recent review of the literature on treatment with UV light and TiO_2 by Tong *et al.* (2012) contains more than 150 references to studies ranging from lab-scale to full-scale observations with real or conditioned wastewater. The main conclusion is that while some substances may be mineralized completely, others are not removed. Further, formation of toxic intermediates was observed. For the implementation, factors such as the type and amount of TiO_2, radiation dose, pH and water matrix are important. However, optimal conditions differ between different compounds. A general conclusion is that ozone alone seems to be at least as good as the combinations to remove a broad spectrum of compounds in a relatively simple process.

Wahlberg *et al.* (2010) reported lower removal efficiency for UV/H_2O_2 than for e.g. ozone treatment of the same water. Only at very high doses of H_2O_2 could comparable removal rates as for ozone be achieved but at a cost of unwanted high residue concentrations of hydrogen peroxide in the effluent.

On more concentrated wastewaters, i.e. hospital wastewater, UV irradiation with varying dosages of H_2O_2 as tertiary treatment after an MBR-process showed good removal efficiency (Köhler *et al.,* 2012). On the other hand, Kovalova *et al.* (2013) observed that only high doses of UV could provide sufficient removal efficiencies for the same hospital water type. Miranda-García *et al.* (2011) and Prieto-Rodriguez *et al.* (2012) reported good removal results using TiO2 but for low concentrations of substances in prepared wastewater and high TiO2 concentrations, respectively.

Such significant differences in sensitivity between compounds for the various treatment methods make a resource-efficient implementation of these already cost-intensive techniques difficult if the target is the removal of as many compounds as possible. Increasing the intensity of the treatment may not be an alternative as long as it is not known which compounds are most important to remove. In general, such removal systems may only be an alternative in combination with other techniques, i.e. as integrated systems, also in an attempt at cost reduction (Laera *et al.,* 2012; Kovalova *et al.,* 2013; Wols *et al.,* 2013; Miralles-Cuevas *et al.,* 2014).

Peracetic acid (PAA) is another oxidant evaluated for removal of pharmaceuticals in wastewater effluents. In a comparative study between ClO2 and PAA, PAA came out as a weak oxidant for removal of pharmaceuticals in wastewater. Wastewater with low, medium and high COD was investigated applying PAA doses up to 50 mg/L. In the wastewater with high COD limited removal was found, for example diclofenac was reduced by 25% applying 50 mg/L of PAA (Hey *et al.,* 2012). Thus, PAA is not an oxidant, which will be useful for removal of organic priority substances.

Within RiSKWa test with a boron-doped diamond (BDD) electrode as AOP method for the degradation of specific pharmaceuticals (e.g. diclofenac) from various water matrices were carried out (RiSKWa 2015).

6.5.5 Chlorine dioxide

Chlorine dioxide (ClO_2) is widely used as a disinfectant in public water systems e.g. swimming pools and cooling systems. ClO_2 may also be useful as an oxidant treating wastewater effluents. Recent work shows that ClO_2 can reduce the concentration of pharmaceuticals from different therapeutic classes in STP effluents even though the reactivity varied (Hey *et al.,* 2012a, 2012b). As an example, it can be mentioned that 38 out of 56 investigated pharmaceuticals were reduced with at least 90 % by applying 8 mg/L ClO_2 to a wastewater with low COD, and in wastewaters with high COD, the same dose ClO_2 oxidized 33 out of 56 pharmaceuticals (Hey *et al.,* 2012b). It was also noted that the removal of pharmaceuticals in STP effluents with extended nitrogen removal (i.e. low COD), was better than in an STP with high COD (Hey *et al.,* 2012b).The reactivity of the organic substances depends on the reactive functional group present. Pharmaceuticals with electron-withdrawing functional groups seem to be more resistant towards ClO_2 (Hey *et al.,* 2012b). ClO_2 has been proven to be rapidly consumed, in less than one minute, depending on the wastewater matrix and the concentrations of the target priority substances in the water (Andersen, 2010; Andersen *et al.*, 2007; Hey *et al.*, 2012b; Lee and von Gunten, 2010).

Drawbacks and risks of using ClO_2 are the inorganic by-products chlorite (ClO_2^-) and chlorate (ClO_3^-), which are toxic to human and the environment (Aieta and Berg, 1986; Veschetti *et al.,* 2005). Also, the risk of formation of adsorbable organic halogens (AOX) needs to be considered. However, with careful dosing and improvement in the production technology of ClO_2, the formation of these by-products can be minimised and controlled (Veschetti *et al.,* 2005). ClO_2 rapidly oxidizes Fe(II) to Fe(III), which precipitates as iron-hydroxides (Aieta and Berg, 1986). Fe(II) has also been proven to remove ClO_2^- when ClO_2 is used as disinfectant for drinking water and a mixture of Fe(II)-Al(III) (Katz and Narkis, 2001; Shin, 2011).

The running cost using chlorine dioxide as disinfectant may be higher compared to ozone but new research indicates that the costs can be lowered. Commercially chlorine dioxide production is today based on $NaClO_2$, but recent research shows that both $NaClO_2$ and NaCl can be used for production of ClO_2, which would lower the running cost (Tsai *et al.,* 2014).

6.5.6 Coagulation/ flocculation

Coagulation or flocculation is usually used in order to reduce particulate matter and colloids. Luo *et al.* (2014) has shown that the process may also remove some priority substances. However, the removal varies a lot and is generally poor, e.g. ibuprofen (4-12 %), galaxolide (16-79 %), nonylphenol (90 %). Since most pharmaceutical residues are water-soluble and normally not associated to particles this is as expected. Further, sludge containing the removed substances is produced and has to be handled.

6.5.7 Membrane filtration

Various membrane filtration technologies can be used as tertiary treatment. The most common technologies are Microfiltration (MF), Ultrafiltration (UF), Nanofiltration (NF) and Reverse osmosis (RO). MF and UF can remove suspended matter and disinfect the treated water. However, besides particle-bound compounds no efficient removal of pharmaceutical residues or other priority substances is provided. An efficient removal of such substances requires Nanofiltration (NF) or Reverse osmosis (RO). Even though these filtration techniques are commonly used in drinking water treatment, their stand-alone applications in wastewater treatment are rare. Wahlberg *et al.* (2010) tested both NF and RO in pilot-scale at Hammarby Sjöstadsverk (2010) and results indicate poor removal efficiency of pharmaceuticals for NF but a high (about 95 %) removal rate by RO. Löwenberg *et al.* (2014) report good results from UF-systems in combination with PAC. PAC-UF treatment was also considered the most suitable option in comparison with ozone/sand filter, despite its current higher cost (Margot *et al.,* 2013). Generally, the process is dependent on several factors such as the characteristics of the priority substances, operating conditions, membrane characteristics etc. (Luo *et al.,* 2014).

A recent study shows a more efficient removal of pharmaceutical residues in a RO-pilot if compared to ozone and activated carbon treatment (Baresel *et al.,* 2014; Bergström *et al.,* 2014). Considering the energy demand of membrane filtration, especially RO, as well as the need for a further treatment of the residual concentrate, membrane technologies may currently not represent the first alternative as tertiary treatment technology but imply considerable advantages when applied in secondary treatment such as in a MBR-process or other new approaches.

6.6 Component combination

Different combinations of the described techniques are of course possible. This comprises both secondary and tertiary treatment methods as well as new emerging or yet unknown techniques. As the removal- and resources-efficiency of most tertiary removal steps are directly correlated to the quality of the secondary effluent, especially the MBR-process may present a number of advantages in technology combinations. Other methods may be a today missing step after the secondary treatment and prior to the polishing step. There a number of different technical solutions such as disk-filter, sand-filter etc. may be applied.

6.7 Technologies under development

The following methods to remove pharmaceutical residues and other emerging substances are either still in the early stage of development with fundamental tests

performed, or have only been tested within limited studies. Some of these approaches may however represent potential solutions in the future, both as stand-alone techniques or in combination with other treatments.

6.7.1 Fungi

A relatively new approach is to use white-rot fungi for the degradation of pharmaceutical residues (Marco-Urrea *et al.,* 2009; Rodarte-Morales *et al.,* 2011). These fungi are known to use extracellular enzymes to break down many stable compounds such as lignin and chlorinated phenols. Rodarte-Morales *et al.* (2011) report on experiments with three different fungi and eight drug compounds. Six of the eight compounds were removed completely. However, the test setup was far from an applicable technical system and therefore cost estimates for this approach are not yet possible. The fact that the process involves extracellular enzymes complicates the design of a technical system. Another investigation using white-rot fungi for degradation of various priority substances in wastewater has shown that X-ray contrast agent iopromide and a fluoroqinolone antibiotic ofloxacin can be reduced in hospital wastewater using a defined medium and in an air-pulsed fluidized bed bioreactor. After treatment with white-rot fungi, toxicity were less or equal with the initial toxicity the author suggest that the treatment can be a good strategy for degradation of pharmaceuticals in hospital wastewater (Gros *et al.,* 2014). Also Nguyen *et al.* (2013) report efficient removal of some substances by white-rot fungi that otherwise are resistant to bacterial removal. However, the tested MBR-system with a mixture of bacteria and fungi showed a lower performance on other compounds such as ibuprofen than conventional active sludge systems.

General applicability, removal efficiencies and associated costs of this removal method are at the current state impossible to provide. A general problem with systems with selected organisms is the need of aseptic conditions if the organisms are not competitive enough. White-rot fungi also demand different conditions for primary metabolism (growth) and for secondary metabolism (extracellular enzyme production), at least for lignin degradation (de Souza-Cruz *et al.,* 2003).

6.7.2 Fenton

Fenton processes, iron catalyzed hydrogen peroxide reactions, have been studied for removal of substances from different matrixes. Traditionally Fenton processes are carried out at low pH. In a recent study results from a comparison between photo-Fenton at pH3 and a modified photo-Fenton carried out at neutral pH with minimal Fe (5 mg/L) and minimal initial H2O2 (50 mg/L) for removal of priority substances in wastewater was presented (Klamerth *et al.,* 2013). Their study showed 95 % removal of the priority substances for both cases; however, the treatment time was shorter at pH 3. Treatment at pH 3 has the disadvantage that the wastewater has to be acidified before treatment and neutralized afterwards. The modification made for photo-Fenton at neutral pH consisted of using complexing agents such as humic acids or ethylenediamine-N,N′-disuccinic acid (EDD) to keep the iron in solution (Klamerth *et al.,* 2013). However, there is need of more research in order to develop the Fenton processes by decreasing the amount of chemicals needed and the sludge production.

6.7.3 Advancements in using activated carbon

Using activated carbon facilitates the removal of pharmaceutical residues and other emerging substances but also toxicity and more traditional compounds such as nutrients (see section 6.5.2). No matter of where and how activated carbon is used, there exist a number of potential advances. While other technologies such as ozonation and membrane separation are limited to progresses in material features, control and operational strategies, respectively, the use of activated carbon offers a number of development possibilities. One of these alternatives is the production of activated carbon from sewage sludge, preferably onsite to minimize environmental impacts. This would not only provide a resource efficient and sustainable utilization of local resources, but it would also contribute to a more positive carbon emissions balance for STPs as emissions from organic carbon (BAC) would not be accounted for because of their biogenic origin. In addition, STPs may turn the common problem with discharging the sludge into a valuable resource that can be used for polishing treatment (as BAC). It has yet to be determined if this is more preferable than reuse of the humic substances and nutrients as fertilisers in agricultural land. During recent years already a number of studies have investigated the production of biochar from sludge (e.g. Agrafioti *et al.,* 2013; Hossain *et al.,* 2011). Little work has been done on other applications although the unique properties (e.g. high specific surface area, microporosity, and sorptive capabilities), and the highly variable and customizable surface chemistry of the material (Xie *et al.,* 2014). Also in Sweden, initial studies have been performed by a number of STPs, partly in collaboration with IVL. So far, results from these studies are not published and more work is currently carried out.

The second potential development is magnetic activated carbon (MAC, Chen *et al.,* 2011), due to practical aspects only considered for PAC applications. The advantages become obvious reviewing the main problem applying traditional PAC in separation of the carbon from the sludge or water. A magnet could easily replace more advanced and costly systems and guaranty a recovery of PAC. If produced from STP sludge, as currently investigated within some projects, MAC may become an attractive alternative for the removal of prioritized substances mainly in tertiary treatment but if a good separation of MAC from sludge flocks can be achieved, possibly also in secondary treatment.

Advances in surface modification of traditional activated carbon resulting in improved characteristics represent the third potential improvement area, the ModAC. The efficiency of activated carbon filters depends highly on the properties of the activated carbon itself. Even so, with different carbon products based on fossil sources (coal) or organic sources (coconut), no significant differences in removal efficiency were observed (Wahlberg *et al.,* 2010). However, specific carbon and surface modification may increase both the stability, capacity and regeneration efficiency of the material. The increased environmental impact and cost because of this modification may be compensated by a higher capacity, an increased number of possible regenerations and decreased losses during regeneration. This is a research area under development but first results from a long-term pilot test at Hammarby Sjöstadsverk indicate a good potential for further improvements.

6.7.4 Enzymes

Enzymes could be designed to break down the specific organic pollutants in the same way as white-rot fungi use extracellular enzymes to break down many stable compounds. A number of oxidative enzymes from bacteria, fungi and plants may already now play an important role in numerous waste treatment applications even though such processes are not specifically described (Durán *et al.,* 2000). There are examples of research on engineered enzymes capable of breaking down some pollutants, but it has yet not been applied for advanced wastewater treatment (Gavrilescu *et al.,* 2005). If specific enzymes could be identified and developed being capable of degradation of pollutants, this could be a potential removal alternative. It is quite possible that a limited number of different enzymes can degrade a broad spectrum of compounds. The enzymes have to be attached to a matrix material to create a filter that then can be dimensions to needed requirements. Multiple matrix material would be possible. Efficiency, capacity, contact time, stability, etc. are yet not known.

The potential, technical applicability, limitations and costs are currently investigated at the R&D-facility Hammarby Sjöstadsverk.

6.7.5 Electrochemical treatment

According to some recent reviews, direct or integrated electrochemical processes may be considered as an alternative due to the significant improvement of the electrode materials and the coupling with low-cost renewable energy sources (Sirés and Brillas, 2012). Electrochemical advanced oxidation processes (EAOPs) like anodic oxidation (AO), electro-Fenton (EF), and photoelectro-Fenton (PEF) has been used to remove pharmaceuticals. Best removal efficiencies were achieved for ibuprofen, paracetamol and diclofenac (Feng *et al.,* 2013). There are two types of electrochemical treatment processes, electrochemical separation technologies, which only isolate the pollutants from water, and electrochemical degradation technologies. Advantages of electrochemical technologies may be that the main reagent, the electron, is a clean reagent. Further, it may be relatively easy to handle, automated, and safe. Obvious drawbacks are the high amount of energy, the possible formation of by-products as for other oxidation methods, and fouling of electrodes due to the deposition of organic material on their surface. Furthermore, the low conductivity of wastewaters may require the addition of electrolytes and pH regulation.

Electrochemical treatment may be sued in combination with other technologies as reverse osmosis concentrates (Zhou *et al.,* 2012) or nano-/ultra-filtration concentrates (Wang *et al.,* 2012).

7 Recommendations

Below, the main recommendations from the authors out of the different discussed subjects are given. Together they will supply the reader with the main findings that, the authors find match the general understanding and consensus on all the various small but crucial parts that need to be considered when targeting pharmaceutical residues and other merging substances in sewage.

7.1 Effluent quality – Removal objective

As clear legislations has yet to be defined for most substances and the main actions rely on the understanding of engaged organizations, well-defined objectives that comprise the overall goal of improving the situation in e.g. recipients are crucial for a successful implementation of relevant and sustainable removal systems. However, the precautionary principle should be considered when discussing emissions of pharmaceutical residues and other emerging substances.

A relevant mitigation objective is defined by the following aspects and is to be considered for each STP:

1. First, a thorough investigation of current emissions to the recipient and the recipient characteristics is necessary to **define the most relevant substances** and their characteristics.
2. **Use Environmental Quality Standard values** (AA EQS and MAC EQS) whenever available to assess the risk of effect on the aquatic ecosystem.
3. For substances where EQS values are not available, **use the Predicted No Effect Concentration** (PNEC) and assessment factors of targeted substances when available.
4. **Consider the actual dilution** of the effluent within the recipient to get realistic predicted environmental concentrations (PEC).
5. Also **consider the "worst-case end of pipe"** PEC in case targeted protected species can be expected in the mixing zone at the effluent release to the recipient.
6. In case many different or **unknown substances** are targeted, **whole effluent tests** that measures the effects of STP effluent on the survival, growth and reproduction of organisms, may in some cases be used as a first screening test, but must be followed by substance specific tests.
7. For very **persistent, bio accumulating and/or reproduction disturbing substances** defined by REACH, **minimum emissions** should be targeted.
8. Additional margins of safety may be applied to live up to the **precautionary principle**.

For a more complete discussion, see Chapter 3.

7.2 Prioritized pharmaceuticals residues and other emerging substances

The list of prioritized substances that STPs and authorities should focus on will of course always be a dynamic list changing with new knowledge gathered. The following list, established by the authors, includes substances already recognized and/or regulated in legislations, ECHAs candidate lists or WFD watch lists as priority substances or selected pollutants, but it also includes other substances and media strongly correlated to emission problems and thus in focus. Note that some substances may appear in different categories, such as for example, triclosan that is here categorized as a phenolic substance but that also has been classified as biocide or personal care product in other studies. The categorization in this report was based either on function or on physico-chemical characteristics depending on how they are commonly reported. Selection criteria include the frequent use/detection of a substance, e.g. DDD, stability, if the substance can be representative for a larger group of substances, available characterizations and documented ecotoxicology.

- **Pharmaceutical residues:** including representative substances (based on information on lowest observed effect concentration (LOEC) and observed concentrations in STP-effluents) for the groups of
  - *Antibacterial substances such as ciprofloxacin, clarithromycin, doxycycline, norfloxacin, sulfamethoxazole, and trimethoprim*
  - *Anti-inflammatory substances such as diclofenac, ibuprofen, ketoprofen, naproxen and paracetamol*
  - *Antidepressants such as citalopram, fluoxetine and sertraline*
  - *Antipsychotic hypnotics, sedative etc. such as oxazepam (few LOEC available)*
  - *Stimulants such as carbamazepine*
  - *Antihypertensives (cardiovascular agents) such as atenolol, bisoprolol, metoprolol och propranolol*
  - *Sex hormones such as 17 α-ethynylestradiol, 17 β-estradiol, estrone, finasteride, levonorgestrel and progesterone*
- **Phtalate esters and their alternatives** (here especially DEHP, DINCH and DPHP due to their increasing use)
- **Flame retardants** (especially PFRs and some of the new CFRs, e.g. HCBCH-DCANh, as well as chloroparaffins. The PBDEs are mainly relevant for monitoring in sludge.)
- **Phenolic substances** (including alkylphenols, 4-nonylphenol, BPA and triclosan)
- **Per- and polyfluoroalkyl substances/***Surfactants* (PFAS, with perfluorooctane sulfonate (PFOS), perfluorobutane sulfonate (PFBS), and perfluorooctanoate (PFOA)).
- **Pathogens such as** bacteria and viruses but especially antibiotic resistant bacteria and their resistant genes

More substances representing different groups can be found in Chapter 4 on priority substances measured at STPs and Chapter 6 on experiences from removal tests. Other

substances may be of importance in specific locations but not of general interest and are therefore not included in the list above.

The removal efficiencies of siloxanes are very high and effluent levels are low, thus they need not be prioritized for future treatment options. Upstream work is more relevant for these substances to reduce the influent amounts.

Microscopic debris particles including synthetic fibers and other plastic particles that may release toxic monomers or contain toxic additives but also non-toxic plastics that can act as carriers for other targeted substances may be acknowledged but of minor significance and therefore not included in the list above.

7.3 Sample handling, analysis and assessment

Analysis of many of the listed substances is a real analytical challenge, not only because of the diversity of physico-chemical properties, but also because of generally low concentrations. However, following the recommendations below, as a guideline, will provide the best possible analysis results:

1. When planning the sampling campaign, consider the best way to achieve **representative samples** depending on the overall goal of the sampling.
2. Follow the **instructions for sampling** commonly agreed by the chemical laboratory. Without proper sample collection, storage, handling and preparation of samples, which may differ for different substances, even an accredited sample analysis is just as good as all the prior steps allow. Note that laboratories do not always inform the sampler about proper handling. Always contact the analytical laboratory before sampling.
3. **Provide all relevant information regarding the samples to the laboratory.** Relevant information is i.e. sample point, influent or effluent etc., process problems affecting specific samples, expected possible matrix effects such as suspended solids amount or particulate matter, expected concentrations.
4. **Require chemical analysis with relevant limit of quantification (LOQ).** The relevant LOQ should be low enough to be able to assess effluents concentrations against limit values, as EQS or PNEC values. When effluent concentrations are below EQS or PNEC values, trends are important to follow continuously, to be able to mitigate degradation of effluent quality with time.
5. **Require a clear description of the analytical methods** used for the various substances or group of substances in the analytical report.
6. **Require clear description of the sample conditioning and preparation** prior to analysis performed, as this may have a significant impact on the analysis outcome.
7. **Require complete and correct reporting** of results with all related accuracy, precision, and sensitivity limits.
8. Perform/require a **proper assessment** of the presented analytical results with regard to sample conditioning and preparation, what concentration is measured and how this may be influenced by matrix effects or quantification issues.

9. **Be aware of test limitations when quantifying ecotoxicity**. Discuss with laboratories, which ecotoxicity-test is suitable and meaningful for your problem and water and what information the results will provide. Require intercalibration results of ecotoxicology tests applied or an extensive description of the methods used and any uncertainties or limitations they may include. Whole effluent assessments can be used as a first screening completed with more detailed tests when indications for negative effects are detected.
10. **Questioning** - always include anonymous blank samples to get better control of analysis.

For complete instructions, see Chapter 5.

7.4 Removal technologies

As described in Chapter 6, a number of methods exist for removing some or all of the listed pharmaceutical residues and other priority substances. Many of these methods have been tested within various projects and intensive work is on-going. The main recommendations for which methods that should be considered for implementation and further development comprise the following items:

1. **Upstream activities** to reduce emissions of relevant substances, are the first priority, but have a natural **limitation** especially for some pharmaceuticals.
2. **On-site tests** to gain knowledge about STP specific preconditions and requirements are **necessary** and **recommended**.
3. Some prioritized pharmaceutical residues and many other emerging substances in the influent end up in sewage sludge. **Sludge handling** becomes an important aspect.
4. **Advances in secondary sewage treatment processes** may become an important part in the removal of prioritized pharmaceutical residues and other emerging substances. Here the MBR process may be mentioned as especially promising due to a combined enhanced degradation and separation of substances.
5. To secure an acceptable removal of most compounds however, **complementary treatment** in form of separation and/or degradation processes are required.
6. As today, **activated carbon and advanced oxidation with ozone** are the most relevant and established methods. Both, however, have their disadvantages and open questions to be solved. Further, new technologies and advances in activated carbon e.g. AC produced from biomass such as STPs own sewage sludge (BAC), magnetic activated carbon (MAC), modified activated carbon (ModAC) and other new technologies provide the potential **for more sustainable and economic removal solutions**.
7. **Combinations** of different tertiary and secondary treatment methods to complete treatment systems may be necessary to accomplish complete removal of some targeted substances.

8. Removal of prioritized pharmaceutical residues and other emerging substances must be handled with a **system perspective** to implement the most **sustainable solutions** (see also next section).

For a complete review of the different removal methods, their advantages, disadvantages, and potential, see Chapter 6.

7.5 Example substances for assessment support

Given the high and steadily increasing number of priority and emerging substances and thus growing complexity of their quantification and removal, some few indicator substances may be used instead. The indicator approach has also been applied for different pathways both for indication of various sources or process performance (Jekel *et al.,* 2015). Such indicator substances have to represent the most significant groups of priority and emerging substances as listed above, have similar characteristics with respect to application, source, physicochemical properties or reactivity as the group they represent, and have a high detection frequency in STP effluents. They must further comprise the complexity of priority and emerging substances handling.

There is an obvious risk that specific indicator substances may not represent the majority of all interesting substances. When parameters like acid/base properties, electron dense regions, other reactive groups and possible biodegradation pathways are included, very few substances might be actually represented by a certain indicator substance. If the list of indicator substances will be too long, it is probably better to work with single substances selected from factors like expected EC/PNEC, risk for bioaccumulation or other criteria. However, this will be discussed in the project parallel to completing the table with important substances and parameters.

Therefore, certain substances should exclusively be used as examples for an initial assessment support. By using example substances, both sampling, problem assessment and removal options by various technologies can be described and evaluated. Using example substances may help to present a larger number of substances even though fewer substances are assessed. This is because these example substances clearly state an indication whereas common assessments normally apply a battery of available substance analyses (analysis packages for pharmaceuticals provided by IVL Swedish Environmental Research Institute include a selection of the 42 most relevant substances, Umeå University includes more than 90 substances). Using example substances in the first stage may help to focus on the overall problem rather than on the specific substances.

Table 7.1 provides example substances as proposed by the authors and includes apart from pharmaceutical residues other priority or emerging substances. The table provides information about observed removal rates in Swedish STPs and projects performed on Swedish wastewater (e.g. Baresel *et al.,* 2014, 2015; Ek *et al.,* 2013a, 2013b, 2014; Hörsing *et al.,* 2014; Sehlén *et al.,* 2015; Wahlberg *et al.,* 2010). As such, information may be lacking for some substances and one of the outspoken goals of the current project is to complete this information (see Chapter 9). It is further important to note that removal rates exclusively include removal from the water phase, which may imply both degradation and transfer to the sludge. Only substances relevant for Swedish STP

effluents are considered. Many substances such as the phthalate ester DINCH (not included in Table 7.1) or pharmaceuticals such as Sertraline etc. have a high or very high affinity to sludge. Even though, focus here is on STP effluent, the sludge aspects cannot be neglected when discussing the handling of pharmaceutical residues and other priority and emerging substances in STPs. Also, PFOS is an exception and in addition phased out. However, replacement substances may imply increasing emissions from STPs. This is also true for DEHP, 4-nonylphenol and Bisphenol A. Multiresistance is to be understood as the removal of potential pathogens/bacteria using traditional faecal indicators (see section 4.9) and the removal of antibiotics (e.g. ciprofloxacin and sulfamethoxazole in the table below). As indicated by recent research, eve the complete or almost complete removal of pathogens/bacteria may not guaranty that multiresistant organisms can evolve downstream of STP-effluent (see section 4.9).

Table 7.1. Selected example substances, characteristics and reported removal efficiencies for various treatment techniques.

Substance	Group	LogD (pH=7.4)	Sampling	Affinity to sludge	Removal STP	O_3	GAC	RO	High EC/PNEC
4-nonylphenol	Phenols	6.13	GC/GS	++					
Atenolol	Antihypertensives	-1.85	PC/CS	-					
Benzotriazole	Drug pecusers	2.09	PC/CS	-					
Bisphenol A	Plastic monomers	3.63	GC/GS	+					
Carbamazepine	Stimulants	2.28	PC/CS	--					
Ciprofloxacin	Antibacterials	-2.23	PC/CS	++					x
DEHP	Phthalate esters	7.91	GC/GS	++					
Diclofenac	Anti-inflammatory	1.37	PC/CS	--					x
Estrogenic effect	Hormones WEA		PC/CS						
Estron	Hormones	3.38	PC/CS	--					x
HBCDD	Flame retardants	6.41	GC/GS	++					
Ibuprofen	Anti-inflammatory	0.45	PC/CS	--					
Metoprolol	Antihypertensives	-0.25	PC/CS	--					
Multiresistance	Pathogens/bacteria		PC/GS						
Oxacepam	Sedatives	2.06	PC/CS	--					x
PFOS	Surfactant	0.66	PC/CS	+					
Sertralin	Antidepressants	3.14	PC/CS	+					
Sucralose	Sweetener	-0.17	PC/CS	-					
Sulfamethoxazole	Antibacterials	-0.56	PC/CS	--					x
TEP	Flame retardants	1.01	GC/GS	--					
Triclosan	Phenols	5.13	GC/GS	++					
Venlafaxin	Antidepressants	1.43	PC/CS	-					x

Removal efficiency (%): RED <20; YELLOW 20-80; GREEN >80
Sampling: PC - Plastic container; GC - Glass container; CS - Composite sample; GS - Grab sample
Affinity to sludge: very low -- to very high ++

The removal efficiencies shown in the table are indications only as the water matrix to be treated significantly influences the removal efficiency. Removal indication for reverse osmosis are based on only a few Swedish tests but are supported by general process characteristics. The removal efficiency with RO is probably high also for substances without data in the table. Combined oxidation and filtration systems are not specifically listed but a relevant indication is provided by summing the effects of both techniques. Toxicological or ecotoxicological (and human health) risks as discussed in

section 5.5 and to some extent included in EC/PNEC. YES is representing an effect test rather than a substance, and therefore not included in the example substance list. Whole effluent assessments as described and presented in one of the recommendations should be used as a first screening when indications of negative effects on the recipient by STP effluent are aimed for.

7.6 System perspective and sustainability

In order to consider only the most sustainable removal solutions both from an economic and environmental impact perspective, all solutions have to be assessed based on both their economic cost and their environmental impact. This is most important for complementary treatment systems such as the advanced oxidation with ozone or activated carbon systems, but ideally, the complete treatment processes including both main and secondary treatment should be assessed. If quantifications are difficult or too cost-intensive to perform, simplified Life Cycle Assessments (LCA) and Life Cycle Cost assessments (LCC) should be applied to get an understanding of the pros and cons of the considered system. Such an assessment will also facilitate the identification of the most significant items of a system and possible improvements. New solutions, such as activated carbon produced from STP sludge, may then be assessed in a similar way in order to investigate potential benefits of such new techniques (even though they may require initial R&D efforts).

8 Future activities within this project

The further work in the on-going project ***Systems for the purification of pharmaceutical residues and other emerging substances***, of which this compilation is the first deliverable, will focus on several of the discussed open questions. The activities to be carried out will be based on the recommendations provided (see Section 0). This includes the following actions:

- **Development of analytical methods** including detection limits if those are missing or in need of improvement. This enables a better evaluation of ”actual” removal efficiencies, artefacts due to the complex matrixes, metabolites and more, but also an increased sensitivity in analysis (e.g. estrogen hormones and antibiotics).
- **Update of STP removal efficiencies** for improved measurements and thus knowledge of existing treatment processes with different configurations i.e. MBR, advanced and partial N-removal. Measurement campaigns will all be based on the, in this report, described fundamentals of sampling and analyzing, which often is not the case, as the current review has shown. Reliable evaluations of the status and actions needed are otherwise difficult.
- **New and completing tests of various removal techniques** to optimize, verify and answer open questions of the most relevant technologies; ozonation and activated carbon. The MBR process, as the emerging technology for larger STPs in Sweden, will be tested in combination with activated carbon and ozone. Potential environmental beneficiary adaptions of traditional systems will be tested including innovative ozonation control, BAC, MAC, ModAC etc.
- A **complementary mapping of ecotoxicity after treatment with oxidation** will be done to investigate if oxidation increases ecotoxicity by transformation- and byproducts, and so far unknown and unidentified components. Opportunities to reduce this potential ecotoxicity with and without subsequent polishing step will be examined.
- **System alternatives for the removal** of pharmaceutical residues and other emerging substances in the effluent of sewage treatment plants will be established for different conditions at various STPs. This includes developing technical recommendations for the most effective system solutions for different STP types including CAS and MBR, regarding both treatment systems and their control.
- **Environmental impact analysis and cost estimates** on the most relevant system alternatives will be carried out to ensure the implementation of the best alternatives from life-cycle and cost perspective. Life cycle assessment (LCA) and Life Cycle Cost Assessment (LCC) will include both setups that are more traditional and possible future improvements (BAC, MAC, ModAC etc).
- **Implementation documentation** of the selected system alternatives will be provided to STPs as a basis for the implementation. This activity brings together technical, environmental and economic aspects and includes cost retrieval and procurement data. This will also lead to an increased understanding of alternatives at consultants and producers.

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