Guidance for future monitoring based on final criteria for and preparation of pharmaceutical lists to be monitored

Report of D. T1.3.2

.

Nature Needs No Pill

2023

Project LLI-527

"Pharmaceuticals in wastewaters – levels, impacts and reduction" MEDWwater

Project aims to increase the efficiency of pharmaceutical substances pollution management and to increase cooperation between governmental institutions and wastewater treatment plant operators.

Total projects size	Out of them co-funding of European Regional Development Fund	Project duration:
673 773 EUR	**572 707 EUR**	**February 1, 2021 – December 31, 2022**

PROJECT PARTNER:

- Latvian Institute of Aquatic Ecology Agency of Daugavpils University, ***www.lhei.lv***
- Kurzeme Planning Region, ***www.kurzemesregions.lv***
- Latvian Environment, Geology and Meteorology Centre, ***www.videscentrs.lvgmc.lv***
- University of Klaipeda, ***www.ku.lt***
- State Agency of Medicines of Latvia, ***www.zva.gov.lv***
- State Medicines Control Agency under the Ministry of Health of Republic of Lithuania, ***www.vvkt.lt***

Project is co- financed by

Interreg V-A Latvia – Lithuania Programme 2014-2020

www.latlit.eu

Nature Needs No Pill

Authors: Ieva Putna-Nīmane, Anete Kubliņa, Ilga Kokorīte, Sergej Suzdalev, Anda Ikauniece

1) Latvian Institute of Aquatic Ecology
2) Latvian Environment, Geology and Meteorology Centre
3) Klaipeda University

Year of issue: 2023

This document has been produced with the financial assistance of the European Union. The contents of this document are the sole responsibility of Latvian Environment, Geology and Meteorology Centre / Klaipeda University / Latvian Institute of Aquatic Ecology and can under no circumstances be regarded as reflecting the position of the European Union.

Glossary

API - active pharmaceutical ingredient

AWT - advanced water treatment (e.g. ozonation)

CEC - chemicals of emerging concern

EQN - environmental quality norm

EQS - environmental quality standard

HELCOM - The Baltic Sea Marine Environment Protection Commission

LoQ - limit of quantification

OMP - organic micropollutant

PE - people equivalent

PNEC - predicted no effect concentration

UWWTD - European Union urban waste water treatment directive 91/271/EEC

WWTP - wastewater treatment plant

Contents

Introduction

This report is prepared in the frame of Latvia – Lithuania Interreg project "Pharmaceuticals in wastewaters – levels, impacts and reduction" (LLI-527) (*MEDWwater*).

The aim of this document is to give suggestions on future monitoring active pharmaceutical ingredients (further - API) monitoring and pharmaceutical lists to be monitored.

Existing knowledge and good practices on choosing and monitoring APIs and pharmaceuticals in selected European countries and from the previous projects has been summarised. We have reviewed experiences from Switzerland, Sweden, Netherlands and Germany, as well as Interreg BSR project CWPharma and Interreg South Baltic project MORPHEUS.

For future monitoring aspects the foreseen developments in the European Union and in the framework of Helsinki Commission have been checked. The requirements of the binding EU Directives have been taken into account.

We have reviewed the general challenges for monitoring of pharmaceuticals and APIs, and have concluded on necessary additions in current frameworks of activities.

1. Existing and planned requirements for API monitoring

This chapter contains API monitoring official requirements, that were summarised in MEDWwater report D.T3.1.1. "An overview of policies / strategies for applying advanced cleaning technologies" and all potential upcoming monitoring tasks from European level legislation proposals.

All required API for future monitoring are summarised in Annex 1 of this report. Annex include API, that are requested to monitor in environment in proposals of new Urban Waste Water Treatment Directive, proposal of directive of the European parliament and of the council amending directives 2000/60/EC, 2006/118/EC, 2008/105/EC Decision on the surface water watch list, and HELCOM indicator requirements, and that were problematic for water environment according to results of MEDWwater project.

Based on the mechanism introduced by the Directive 2013/39/EU, the watch list aims to better assess risks from chemicals found in surface water. Member states have to monitor these substances at least once per year for up to four years[1]. The draft Commission Implementing Decision on the surface water watch list[2] in the next few years to gain necessary knowledge requires for monitoring of such API in three **inland surface water** monitoring stations in Latvia and four monitoring stations in Lithuania:

1) to continue to monitor -

- Sulfamethoxazole – antibiotics;
- Trimethoprim – antibiotics;
- Venlafaxine - serotonin and norepinephrine reuptake inhibitors;
- O-desmethylvenlafaxine – metabolite (intermediate or end product of metabolism) of venlafaxine;
- Clotrimazole - antifungal medication;
- Fluconazole - antifungal medication;
- Miconazole - antifungal medication;

2) to start to monitor in 2023 -

- Clindamycin – antibiotics;
- Ofloxacin – antibiotics;
- Metformin - antidiabetic drug;

[1] European Commission adopts revised Surface Water Watch List, 2020. Available: https://watereurope.eu/european-commission-adopts-revised-surface-water-watch-list/

[2] Commission Implementing Decision (EU) 2022/1307 of 22 July 2022 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council

- Guanylurea - transformation product of the antidiabetic drug metformin[3].

European Commission has included these API in proposal of directive of the European parliament and of the council[4]: diclofenac, ibuprofen, carbamazepine, clarithromycin, erythromycin, 17-α–Ethinylestradiol (EE2), 17-β-Estradiol (E2), Estrone (E1)[5], azithromycin.

Although not legally binding the HELCOM strategy towards reduction of pharmaceutical substances in the environment includes several actions, *inter alia* aiming to have priority pharmaceuticals identified already by 2024. The existing core indicator list then should be updated with additional API besides current onliest diclofenac.

In Proposal of Urban wastewater treatment directive water utilities are intended to start monitoring the following organic pollutants, including some API, and achieve at least 80% removal for 6 of them. Whilst the Directive does not say whether these requirements will be considered as met if the removal is achieved without post-treatment, it is nevertheless assumed that post-treatment will be developed.

Category 1 (substances that can be very easily treated):
- Amisulpride (CAS No 71675-85-9)
- Carbamazepine (CAS No 298-46-4)
- Citalopram (CAS No 59729-33-8)
- Clarithromycin (CAS No 81103-11-9)
- Diclofenac (CAS No 15307-86-5)
- Hydrochlorothiazide (CAS No 58-93-5)
- Metoprolol (CAS No 37350-58-6)
- Venlafaxine (CAS No 93413-69-5)

Category 2 (substances that can be easily disposed of):
- Benzotriazole (CAS No 95-14-7)
- Candesartan (CAS No 139481-59-7)
- Irbesartan (CAS No 138402-11-6)
- mixture of 4-Methylbenzotriazole (CAS No 29878-31-7) and 6-methyl-benzotriazole (CAS No 136-85-6)

[3] Jacob S, Knoll S, Huhn C, Köhler HR, Tisler S, Zwiener C, Triebskorn R. Effects of guanylurea, the transformation product of the antidiabetic drug metformin, on the health of brown trout (Salmo trutta f. fario). PeerJ. 2019 Jul 11;7:e7289. doi: 10.7717/peerj.7289. PMID: 31338260; PMCID: PMC6626654.

[4] Proposal for a directive of the European Parliament and of the Council amending Directive 2000/60/EC establishing a framework for Community action in the field of water policy, Directive 2006/118/EC on the protection of groundwater against pollution and deterioration and Directive 2008/105/EC on environmental quality standards in the field of water policy (26.10.2022). Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0540

[5] Status update Impact Assessment on review priority substances lists under Environmental Quality Standards Directive (EQSD), Groundwater Directive (GWD) & Water Framework Directive (WFD). Presentation to Working Group Chemicals, 10.02.2022. Available: https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/f100cb29-fc48-43dc-b9e7-e066d0424f81/details

2. Good examples from other countries and previous projects

The need to develop and implement a holistic monitoring approach towards chemical status of European Union surface waters has been realised already a while ago, as the individual regulation of substances does not cover all possible chemical risks (Brack et al., 2018). Still, the capacity of countries to follow and react to mixtures of substances has to be developed yet, although the conceptual tools are in place[6]. Therefore, tracing and monitoring of single substances, in this case pharmaceuticals/APIs remains as the main option for surveying the chemical status of the water quality.

In this chapter we have included selected examples from the countries with already developed approaches for pharmaceutical substances or API monitoring - Switzerland, Germany, Sweden, Netherlands and suggestions for monitoring in the project area from relevant recent projects - Interreg BSR *CWPharma*, Interreg South Baltic *Morpheus*.

Switzerland

Switzerland has prioritised five indicator substances to reduce analytical costs of monitoring for an extensive list of chemicals of emerging concern (CEC). Out of a total of 250 substances (pharmaceuticals, pesticide and transformation products) identified in Swiss rivers, 47 indicator substances were identified through a selection process based on five criteria: i) partitioning of substances between water and solid phase; ii) persistence in the aquatic environment; iii) toxicity; iv) concentration patterns (continuous, periodic or intermittent); and v) probability of detecting a substance in surface waters.

To reduce the analytical costs for monitoring all 47 compounds, a subgroup of five indicator compounds was identified to be included in sampling programmes: carbamazepine (anticonvulsant or anti-epileptic drug), diclofenac (nonsteroidal anti-inflammatory drug), sulfamethoxazole (antibiotic), mecoprop (herbicide) and benzotriazole (anticorrosive agent). All of these substances can be measured with the same analytical method and are detectable in more than 90 % of all domestic WWTP effluents in Switzerland (Gotz et al., 2011).

Sweden

Sweden has proposed 17 pharmaceuticals for monitoring in addition to the WFD Watch List, based on PBT properties, large usage, and/or detection in fish, surface water, drinking water and sludge (MPA, 2015). In addition, Sweden has incorporated Environmental Quality Norms (EQN) for 4 pharmaceuticals (Ciprofloxacin, Diclofenac, E2

[6] https://www.solutions-project.eu/results-products/

and EE2) as river basin-specific substances according to the Swedish Agency for Marine and Water Management statues HVMFS 2018:17.[7]

The Swedish Environmental Protection Agency has clearly stated that it should be investigated where the technologies for advanced treatment in WWTPs should be introduced first, but also concluded that, with existing occurrence data, this is not possible to specify. Several factors are important to make adequate prioritizations on where the needs are greatest, and consideration must be taken of local conditions, such as the following:

- The amount of pharmaceutical residues that are discharged into the recipients;
- The recipient's water turnover;
- The number of WWTPs that discharge to the same recipient;
- The recipient's sensitivity;
- Variations over the year;
- Variations in discharged amounts from the WWTP.

So the actions are requested to be taken at the regional level, by counties. An example from County Scania has demonstrated some seasonal variation in outlet concentration from the largest WWTP in Kristianstad with a peak in January and a dip in July, but still with a consistent flow of pharmaceuticals all year around.

The Netherlands

In the Netherlands, nation-wide consumption-based hydrological modelling has given spatial insight on the impact of WWTP discharge on concentrations of pharmaceuticals in surface water bodies. The modelling and ranking exercise was undertaken to investigate and prioritise which of their 345 WWTPs should be upgraded to reduce the impact of pharmaceuticals on receiving water bodies (in particular to EU nature protection areas) and the risk to raw drinking water sources. The model was based on two components: i) a water quality model representing the Dutch surface water network and its key hydrological features; and ii) a consumption-based emission model to project the loads from WWTPs to receiving rivers during both low and high discharge conditions. Two pharmaceuticals with different characteristics (carbamazepine and ibuprofen) underwent a detailed spatial analysis.

The vast majority of the total impact of all Dutch WWTPs, during both high and low discharge conditions, was attributed to 19% of the WWTPs with regard to the drinking water function, and to 39% of the WWTPs with regard to the nature protected areas function. The model thus provides a spatially smart and cost-effective way to identify and

[7] https://www.oecd-ilibrary.org/sites/1207aa0a-en/index.html?itemId=/content/component/1207aa0a-en

prioritise WWTP upgrades to improve water quality and reduce adverse environment effects (Coppens et al., 2015).

Due to the fact that a number of pharmaceuticals in surface water exceed environmental risk limits and effects are shown in and near WWTP discharges, the Dutch government, together with many stakeholders from the health and water sectors, has developed a so-called *chain approach* to reduce the emission of pharmaceuticals into surface waters. Within this chain approach, the actors in the chain worked together to identify measures throughout the whole chain and, where feasible and effective, worked on their implementation. From the 2000 active ingredients on the Dutch market, only around 80 were monitored on a regular or project basis. Therefore, despite the identified lack of knowledge for most pharmaceuticals, the explicit choice was made not to wait until more research was performed on the topic, since the data available already showed risks. Thus, it was decided that time and resources should be used for the development of measures. One of the measures, started in 2020, included a programme to speed up improvements at WWTPs, funded by the national government and regional authorities. This programme includes research projects on new technologies and optimisation of existing technologies, full-scale implementation of additional treatment modules at existing WWTPs and impact studies. The WWTPs have been prioritised for full-scale improvement with the help of a hotspot analysis, to identify locations where the receiving water was most influenced by WWTP effluent. This resulted in 80–100 hotspot WWTPs (depending on the criteria used) out of the 314 Dutch WWTPs. The programme led to standardised monitoring of pharmaceutical residues at the WWTP, both in the way samples are taken as well as in the way the samples are analysed. Bioassay methods to determine toxicity of effluent were developed, as it is not feasible to analytically determine all pharmaceutical residues (Moermond & de Rooy, 2022).

Germany

In Germany the wastewater is treated in more than 10,000 sewage treatment plants. In general, municipalities are responsible for waste water treatment facilities. There are, however, also privately owned sewage treatment plants in industry. Around 9.4 billion cubic meter of waste water are treated annually in public waste water treatment facilities[8]. A list of 21 priority substances has been compiled and published in 2011, taking into account sales, predicted no effect concentrations (PNECs), maximum measured environmental concentrations (MECmax) and risk quotients (RQs) (Bergmann et al., 2011). WWTPs have been identified as a major source. Although the latest report on pharmaceuticals in the environment report on 269 substances above the detection limit

[8] https://www.bmuv.de/en/topics/water-resources-waste/water-management/wastewater/sewage-treatment-plant

in Germany, the provided numbers also show that the German system of three-step wastewater treatment is quite effective in reducing the concentrations[9]. In 2016-2022 Germany has been developing the Federal Emerging Substances Strategy (Spurenstoffstrategie des Bundes). During the creation process, *inter alia*, an orientation framework for further development of wastewater treatment process in WWTPs in the federal lands has been applied. The 4th cleaning stage is advised to be introduced in the WWTPs[10].

Results of the projects

Interreg BSR project **CWPharma** aimed to provide guidance on how to reduce the load of active pharmaceutical ingredients (APIs) entering the aquatic environment and especially the Baltic Sea. Municipal wastewater treatment plants (WWTPs) are relevant point sources of APIs as they treat the wastewater from public households, hospitals, and industry of the connected catchment area. However, conventional "state-of-the-art" WWTPs can only remove APIs that are either easily biodegradable and/or absorbable to activated sludge, whereas others can pass the treatment process with no or only minor reductions. Therefore, reduction of a broad range of APIs can only be achieved by using targeted advanced wastewater treatment (AWT) techniques, such as ozonation or application of powdered and granular activated carbon. All of these technologies for API removal are already used at full-scale WWTPs and have proven their practical and economical suitability. As an outcome of the project a document “Guideline for advanced API removal” was developed to provide an overview on how to plan, start, and operate AWT technologies for API elimination (Stapf et al., 2020). It has been also noted that membrane separation via dense membrane such as nanofiltration (NF) or reverse osmosis (RO) was not considered in this guideline, as both technologies produce a brine with high API concentrations. At coastal WWTPs, this brine might be discharged directly to the sea in order to protect freshwater ecosystems, but this would not reduce the API load to the Baltic Sea. Thus, the brine also requires treatment, which makes this approach less economical in comparison to the other established API removal technologies.

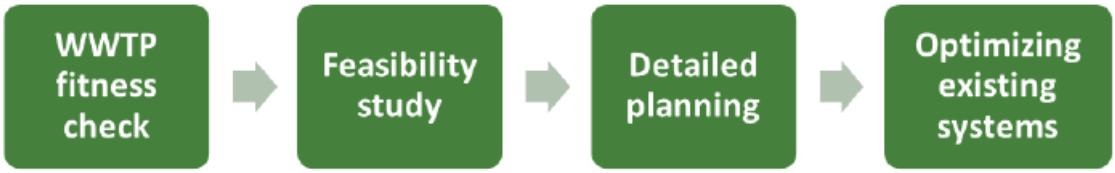
A comparison of AWT technologies based on available data and publications has been provided in the guidelines: ozonation, granular activated carbon (GAC), powdered activated carbon (PAC), and moving bed biofilm reactor (MBBR). Categories are very good (++), good (+), average (0), and bad/negative (-). It should be noted that API removal with the different technologies is always substance specific, thus, evaluation will strongly depend on the targeted substances.

[9] https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/2019-06-24_texte_67-2019_database_pharmaceuticals-environment_0.pdf

[10] https://www.umweltbundesamt.de/vom-stakeholderdialog-spurenstoffzentrum-2016-2021?parent=93380#vom-stakeholderdialog-spurenstoffe-zum-spurenstoffzentrum-des-bundes

Category	Ozone	GAC	PAC	MBBR
API removal	++	++	++	o / +
Technology maturity for API elimination	++	++	++	-
Process complexity	+	++	o	+
Reaction products from the water matrix	-	++	++	++
Transformation products or metabolites	-	++	++	-
Costs#	+	+	+	o
Operational energy required	-	+	o / +	+
Carbon footprint	o	o	-	+
Space requirement	++	+	- / ++	-
Subsequent sludge application in agriculture	++	++	-	++

The guidelines also describe four logical steps to prepare the WWTPs for AWT:



The *WWTP fitness check* includes defining the overall targets of the AWT, identifying potential barriers that might rule out certain technologies, and determining additional data or monitoring campaign needs. The *feasibility study* will assess the practicability of an AWT for API elimination, estimate costs for construction and operation, and evaluate different scenarios (e.g. using different technologies). When the favoured API elimination technology is selected, the *detailed planning* will reduce uncertainties regarding the final design and will bring detailed knowledge. Therefore this stage includes laboratory tests, on-site piloting and understanding what is needed for the process control. After the AWT stage has started to operate, still several aspects can be evaluated to *optimize this operation* and to maintain a stable API elimination, e.g. more frequent monitoring due to API flow variations and following the energy demand.

Results of Interreg project **MORPHEUS** included "Guidance document on the need of removal of pharmaceuticals from wastewater in the coastal regions of the South Baltic Sea"[11]. It has become obvious that to understand the impact of a specific WWTP on receiving water bodies the outflow concentrations of pharmaceuticals should be measured and seasonal recipient concentrations should be monitored. A minimum of two seasonal recipient samples is required, covering draught and high flow conditions. If resources are available, four seasonal samples are preferable. This information is vital to aid legislators and decision makers in the prioritization process of advanced treatment

[11] https://eucc-d-inline.databases.eucc-d.de/files/documents/00001259_MORPHEUS_Guidance%20document_2021.pdf

implementation. Experimental removal rates of selected pharmaceuticals calculated on the basis of these measurements and existing treatment technologies can help to find relations between removal efficiencies, treatment methods, WWTP sizes, inflow loads and/or sludge ages – and thus support the development of suitable strategies to reduce the pharmaceutical burden to the environment.

MORPHEUS measured and analysed the seasonal WWTP inflow, outflow and recipient concentrations of selected pharmaceuticals in 15 WWTPs in the project model areas. Removal rates of pharmaceuticals were also calculated. It has to be considered that wastewater treatment technologies in the model areas are mostly based on the activated sludge system and that average removal rates only serve as an indication of the degree of removal. Results showed high removal rates of certain compounds such as paracetamol, ibuprofen, ciprofloxacin (adsorbs to sludge) and estrone, while others such as carbamazepine and diclofenac only were removed to a very limited extent. These more difficult compounds can, however, be removed by the introduction of advanced treatment technologies at the WWTPs. Noteworthy is that there were no major effects observed between removal efficiency and the number of connected inhabitants, the daily flow or the sludge age used in wastewater treatment.

For assessing the actual chemical load to a WWTP, a comparison of predicted incoming load (PIL) values, using regional pharmaceutical consumption data, and measured incoming load (MIL) values determined by chemical analysis of incoming wastewater turned out to be a suitable approach.

While investigating potential correlations between consumption and occurrence, MORPHEUS results showed that carbamazepine is a good predictor of expected chemical loads to WWTPs. In addition, carbamazepine may also function as an indicator of the chemical burden of (persistent) pharmaceuticals in the environment since it had a very low removal efficiency value in the investigated 15 WWTPs – however, not unexpected as carbamazepine is known to be persistent in WWTPs and the environment.

Quantifying the consumption of specific pharmaceutical substances and re-allocating it to local levels is a fundamental prerequisite for understanding the pharmaceutical burden to the environment from the emission perspective and to build up a reasonable mass flow from the source (intake by individual humans). Moreover, investigating local consumption patterns helps to understand which pharmaceuticals are most relevant to monitor in specific regions.

MORPHEUS succeeded to apply country specific data of the total consumption of pharmaceuticals per year to region-specific yearly consumption loads as intake per inhabitant [mg/inh./a]. Furthermore, by combining it with the number of real-connected inhabitants instead of the usually applied personal equivalents (PE), the project showed that it is also possible to estimate a WWTP-related inflow of some pharmaceuticals.

3. Criteria for monitoring of WWTP effluents and surface water monitoring site selection

When suggesting criteria for choosing the monitoring of WWTP effluents and sites for surface waters, we have considered recommendations and requirements for EU Member States, the knowledge acquired in the projects and approaches used in model countries - Sweden and Switzerland.

Concerning the **wastewater** in general, the **European Union Directive of urban waste water treatment** (91/271/EEC; UWWTD) aims for collection, treatment and monitoring of the wastewater starting from those WWTPs, servicing 2000 PE (people equivalent). The secondary treatment of all discharges from urban areas of more than 2000 people, and more advanced treatment for urban areas of more than 10000 people in catchments with sensitive waters is required. Annex 1 of the Directive lists also the reference methods for monitoring and evaluation:

D. Reference methods for monitoring and evaluation of results

1. Member States shall ensure that a monitoring method is applied which corresponds at least with the level of requirements described below.

2. Flow-proportional or time-based 24-hour samples shall be collected at the same well-defined point in the outlet and if necessary in the inlet of the treatment plant in order to monitor compliance with the requirements for discharged wastewater laid down in this Directive

3. The minimum annual number of samples shall be determined according to the size of the treatment plant and be collected at regular intervals during the year:

2000 - 9999 PE: 12 samples during the first year (four samples in subsequent years, if it can be shown that the water during the first year complies with the provisions of the Directive ; if one sample of the four fails, 12 samples must be taken in the year that follows.

10 000 - 49 999 PE: 12 samples

50 000 > PE: 24 samples.

Regarding selection of **WWTPs to be monitored for APIs**, the experience of the ***MORPHEUS*** project indicated that several factors determine the occurrence and concentration level of pharmaceuticals in effluent. Those include consumption rate of the medicines in the area, size of the WWTP, removal efficiency of the WWTP, water flow of

the receiving rivers[12]. When addressing specifically WWTPs in the Klaipeda Region it has been concluded that priority in upgrading to advanced treatment and thus also regular monitoring of APIs should be granted to Klaipeda City WWTP due to following facts and assumptions:

- The discharge of treated wastewater has the largest volumes and releases the highest amount of pharmaceuticals to surface water bodies;
- Introduction of pilot-scale and/or on-site tests or even full-scale advanced treatment will have the least effects on water services prices;
- Water company has the greatest potential for recruiting qualified specialists for the maintenance and operation of advanced wastewater treatment systems[13].

The general recommendations towards WWTPs to be chosen for APIs monitoring then could be:

- The loads and discharges of wastewater are high, in most cases related to at least 10 thousand inhabitants in the service area, the data on pharmaceutical burden are existing or burden is obvious (receiving hospital wastewater);
- The location of WWTP is in the catchment area of lakes and/or rivers with an impact on drinking water resources;
- The WWTP has at least the secondary level treatment present and experienced personnel for e.g. sewage sludge management.

MORPHEUS also provided recommendations for choosing indicators for WWTP efficiency. To assess the efficiency of removal of the micropollutants, it is recommended to monitor the presence of indicator substances in the WWTP's influent and effluent. The indicators need to be chosen according to the following criteria:

- be present in sufficiently high concentrations in influent of targeted WWTPs with small load variation;
- their removal by conventional (biological) WWTPs should be little or non-existent;
- their removal by advanced treatment should be specific (high or low) to the method;
- they can be assessed simply, during a single run with LC/MS/MS.

When **discussing the reduction of API emissions**, project ***CWPharma*** recommends all Baltic Sea region countries to achieve the compliance with current UWWTD. It is noted that enforcement of the polluter-pays principle in certain member states requires stronger national environmental governance and regulations. Then, all countries should

[12] https://eucc-d-inline.databases.eucc-d.de/files/documents/00001235_morpheus_deliverable_4.1_pharmaceutical_burden.pdf
[13] https://eucc-d-inline.databases.eucc-d.de/files/documents/00001247_MORPHEUS_Roadmap_Klaipeda_Lithuania_final.pdf

be ensure that all wastewaters emitted to the Baltic Sea directly or indirectly though rivers and/or streams from WWTPs larger than 250 000 population equivalents (PE) are treated with an appropriate AWT technology removing APIs and other environmentally hazardous substances no later than between 2025-2030. Further on, also it should be ensured that all wastewater emitted to the Baltic Sea directly or indirectly from WWTPs larger than 50 000 PE are treated with an appropriate AWT technology removing no later than between 2035-2040.

On **monitoring of APIs**, the ***CWPharma policy action plan*** suggests that APIs posing environmental risks should be included in regular national or regional environmental monitoring programmes. The list of these APIs should be kept updated with the newest information about environmental concentrations and risks and also reflect what is on the current Surface Water Watch List.Screening campaigns of APIs should be performed regularly, preferably once every third year, and should focus on API concentrations in surface waters downstream of WWTPs and animal farms, as well as in sediments where API accumulation is expected, such as in lakes and Baltic Sea estuaries. In case API concentrations in surface water bodies exceed PNEC values, operators of WWTP and pharmaceutical plants should be additionally required to monitor their emissions and their impact on surface waters[14].

Swedish approach to advanced treatment and monitoring of APIs

In Sweden the most organic pollutants are not analysed regularly by wastewater treatment plants due to the complexity and costs involved. Within the environmental surveillance program "Miljögiftssamordning" sludge and water discharge from nine Swedish wastewater treatment plants are analysed each year focusing on a large number of environmental pollutants. The Swedish EPA has a specific screening pro- gramme that performs occasional sampling surveys and analyses focused on newly, potentially hazardous identified environmental pollutants. Screening operations at wastewater treatment plants include screening for pharmaceuticals, microplastics, flame retardants and highly fluorinated substances (PFAS)[15]. The Swedish EPA distributes investment funds for installation of advanced treatment of pharmaceutical residue and other micropollutants, in Swedish wastewater treatment plants as an assignment from the government. The funds have been granted since 2018. Municipalities can apply for up to 90 percent of the investment both in pilot study and full-scale installation. In 2020 the Swedish EPA granted 18 million SEK (ca EUR 1,5 M) for 6 pilot studies and one investment project. The investment funds will be granted until 2023 or until the money runs out. One

[14] https://www.cwpharma.fi/download/noname/%7BB6F3D5D6-D460-490E-9B01-FFD6118C7DCD%7D/164484

[15] https://www.naturvardsverket.se/4aaaec/globalassets/media/publikationer-pdf/8800/978-91-620-8896-5.pdf

of the latest screening study results (Naturvårdsverket, 2022) indicate that seven Swedish river catchments impacted by WWTPs showed distribution of organic micropollutants (OMPs) due to hydrology and anthropogenic pressures and impacts (agricultural, urban, and industrial). A total of 70 OMPs were detected in at least one sample, in mean concentrations ranging from ng/L to mg/L in wastewater samples and from ng/L to µg/L in surface water samples. Dominant compounds were tramadol, lidocaine, metoprolol and caffeine in all sampling sites. Upstream recipient samples showed on average ten times lower OMP concentrations compared to recipient samples downstream of the respective WWTP effluents. A number of Watch list compounds were detected including sulfamethoxazole, erythromycin and azithromycin, fluconazole and venlafaxine and its metabolite desvenlafaxine.

The Swiss National strategy for upgrading selected WWTPs

In 2014, the Waters Protection Act was revised, following agreement by Parliament, to further improve wastewater treatment for the removal of CECs (including pharmaceuticals). The revised Act involved three policy instruments:
i) a new technical wastewater treatment standard, and
ii) a nationwide wastewater tax, and
iii) public subsidies to fund technical upgrades of WWTPs.
The technical standard requires selected WWTPs to remove 80% of CECs from raw sewage, measured on the basis of 12 indicator substances, by 2040[16]. The indicator compounds are tested for at the inlet and outlet of the treatment plant. Since the goal of the regulations is also to improve treatment to deal with dissolved compounds not already removed, the indicator compounds are ones that are not substantially removed or degraded at the biological treatment stage. The indicator compounds also represent the chemical characteristics of micropollutants, such as having an aromatic group, and react with ozone or activated carbon. Also, this group of selected 12 indicator compounds can be assessed in a single laboratory test using a combination of HPLC and MS/MS[17].

Selection criteria for upgrading of 100 WWTPs are based on:

- the anticipated micropollutants load ;
- the capacity for dilution in the receiving water.

Installations treating 50-60% of Swiss wastewater:

- WWTP (>80 000 inhabitants) with high loads;
- WWTP (>24 000 inhabitants) in the catchment of lakes;

[16] (OECD, 2019) Pharmaceutical Residues in Freshwater
https://www.oecd-ilibrary.org/environment/pharmaceutical-residues-in-freshwater_c936f42d-en

[17] https://www.aquastrategy.com/article/expert-insight-switzerlands-early-lessons-micropollutants-wastewater

- WWTP (>8 000 inhabitants) on rivers with a fraction of wastewater > 10%;
- WWTP (>1 000 inhabitants) on rivers impacting drinking water resources

Thus, the Swiss approach contrasts with the approach to dealing with pollutants that is taken in, for example, the EU Water Framework Directive, where there is a focus on achieving particular concentrations for particular chemicals. For micropollutants, this presents a scenario where environmental regulators may set very low concentrations as a requirement and these may be difficult to achieve.

Summarising, the suggestions of **MEDWwater project** for WWTP effluent and surface recipient monitoring include:

- The WWTP covers at least 10 000 PE and receives high loads of micropollutants;
- The WWTP is in the relevant area for the water resources, including drinking water;
- The WWTP has a capacity for sampling.

4. Criteria for selection of pharmaceuticals to be monitored

When selecting the pharmaceuticals/API for monitoring, the selection criteria embraces the regulatory requirements, experience from the previous studies and projects and practical analytical feasibility. Thus, the **selection criteria by MEDWwater** project have been following:

- Inclusion in the Watchlists for EU-wide monitoring in the field of environmental policy;
- High consumption and sales amounts and/or top prescribed medicine in Latvia and Lithuania;
- Antiviral drugs used intensively during COVID-19 pandemic;
- PNEC (predicted no-effect concentrations) values (toxicity assessment data) of pharmaceuticals;
- Limits of quantification (LoQ) of pharmaceuticals;
- Excretion rate from WWTP;
- Laboratory capacities and possibilities to analyse the substances.

Application of criteria for the chosen pharmaceuticals and APIs is demonstrated in the Annex 1, with the legal justification, project results and monitoring matrices.

Proposal of UWWTD (2022) uses Swiss approach by selecting pharmaceuticals that are monitored also in Switzerland and that are like indicator substances - are representative

for organic micropollutants. These are not based on high risk chemicals (but, e.g. hormones are also abated) (McArdel, Brander, 2022[18]):

- Only parents compounds (no transformation products);
- Can be easily and routinely measured in one analytical method (at cantonal or private labs;
- Occurring in bigger WWTPs at measureable concentration (influent concentration 10x LOQ in effluent);
- Degraded to less than 50% in biological treatment;
- Similar abatement in advanced treatment (not favoring ozone or AC);
- Continuous discharge into WWTP.

From suggested API in UWWTD proposal we propose to include into wastewater monitoring such API, that propose risk to **wastewater and/or surface** water according to MEDWwater studies: diclofenac, carbamazepine, clarithromycin, venlafaxin (4 of 6 suggested API for monitoring). Suggested API to test in **sludge** that is prepared for use in agriculture: amoxicillin, diclofenac, ibuprofen. Suggested - **optional** API for **investigative monitoring** for screanings in **effluent, upstream and downstream effluent discharges** (on a base of MEDWwater results) are amoxicillin, ciprofloxacin and ibuprofen.

5. Sampling time and frequency

According to HELCOM Guidelines at the WWTPs regarding the effluent in general, sampling frequency should be optimized taking into account the variation of flow and concentration[19]. Samples from treated and untreated wastewater should always be taken as composite samples, which are prepared either automatically or manually. In both cases 24-hours-flow-weighted composite samples should be the target at a well-defined point in the outlet of the industrial plant. At plants with very small wastewater discharges the sampling period of the composite samples can be less than 24 hours (e.g. 8-12 hours).

For measurements at the outlet of industrial plants, the number of samples should be 12 times per year if water consumption is more than 500 m^3 per day, 4 times per year if consumption is 50-500 m^3 per day, and 2 samples a year if 5-50 m^3 water consumed per day.

If there are little day-to-day flow variations, then the particular time of day or day of the week for sampling is relatively unimportant. The solution then is to sample evenly

[18] McArdell, Christa S., Brander, A., 2022.Strategical planning of introduction of advanced wastewater treatment in Switzerland. February 23, 2022, online event. Available: https://videscentrs.lvgmc.lv/files/Par_LVGMC/Projekti/MEDWwater/Seminari/Prezentacijas_majas_lapai_23022022/2_Strategical_planning_introduction_AWWT_Switzerland_McArdell_EAWAG.pdf

[19] http://helcom.fi/Lists/Publications/PLC-Water%20Guidelines.pdf

throughout the year, but at any time of day and on any day of the week (these being chosen at convenience). If the identification of the nature and magnitude of peak load are important, sampling should be restricted to those periods of the day, week, or month when peak loads are known to occur.

The project **CWPharma** found that more antibiotics were detected in the winter sampling campaign than in the summer at 26 out of 36 sites, when the number of detected APIs and the sum concentration of antibiotics were used as indicators. (Ek et al., 2020.) Similar observations of higher antibiotic levels in winter related to seasonal respiratory infections have been described also elsewhere (e.g. Bijlsma et al., 2021). There is also a practice to carry out a year long intensive monitoring in order to detect the seasonality of patterns in the urban WWTP and then decide on a sampling regime (Miino et al., 2023). Shorter - of several months - and intensive sampling campaigns can be used to estimate the dynamics of specific WWTP and then a daily composite 24 hour sample is collected for this shorter period (Anliker et al., 2022).

6. Requirements for sample collection and storage prior analysis

As the sampling of micropollutants, including pharmaceuticals, is complicated due to their very low concentrations the standard protocols do not exist and methods are different in some aspects. As an example - freezing of samples is described by Malnes et al., 2022 and non-freezing recommended by guidelines in Germany[20]. Still, some general general approaches are valid and are recommended to be observed.

Sampling directly affects the results of the analysis. The results will naturally depend first of all on the type of sampling, whether it is a grab sample or a composite sample, which in turn can be a time-proportional or a flow-proportional composite sample. Here, 24h composite samples (in some cases also 48h and 72h samples, collected as 24h composite samples) rather than grab samples should be preferred. The results are also affected by the sampling instruments used. Some of the micropollutants may be adsorbed to tubes, seals or vessels of automated sampling devices and released again when certain conditions change. This will directly affect the pollutant concentration in the sample. That is why results that are higher than usual must be viewed critically. Since some of the micropollutants are biodegradable, the reduction in their concentration in the sample should be avoided by filling the sample bottle to the full to avoid excessive aeration, and the sample should be placed immediately in cold, at ca 4° C, freezing of the samples is not recommended. More detailed description is available as the MEDWwater Report of D.T3.3.1.

As of the procedures from the project **CWPharma**, the collected wastewater samples were protected from light and frozen within a few hours after the collection. The samples were delivered to the laboratory as frozen and stored under -20 ± 2 °C prior to the analysis. Samples were analysed within six months after arrival to the laboratory (Ek et al. 2020). Sampling and analytical steps for water sampling compiled below, for full table see Ek et al., 2020, Table 3.1.

[20] Spurenstoffe im Abwasser, eine Handlungsempfehlung for Kommunen, Kompetenzzentrums Spurenstoffe, Oktober 2020.

Sample type	Sample amount (g)	Extraction method	Final volume (mL)	Detection method	Number of APIs
WWTP influent	1	Direct	1	UHPLC-MS/MS	75
	50	SPE	1		
WWTP effluent	1	Direct	1	UHPLC-MS/MS	76
	100	SPE	1		
Surface water	500	SPE	1	UHPLC-MS/MS	60
Estuary water	1000	SPE	0.3	UHPLC-MS/MS	54

SPE - solid phase extraction, UHPLC MS/MS - ultra high-performance liquid chromatography combined with multiple reaction monitoring mass spectrometry.

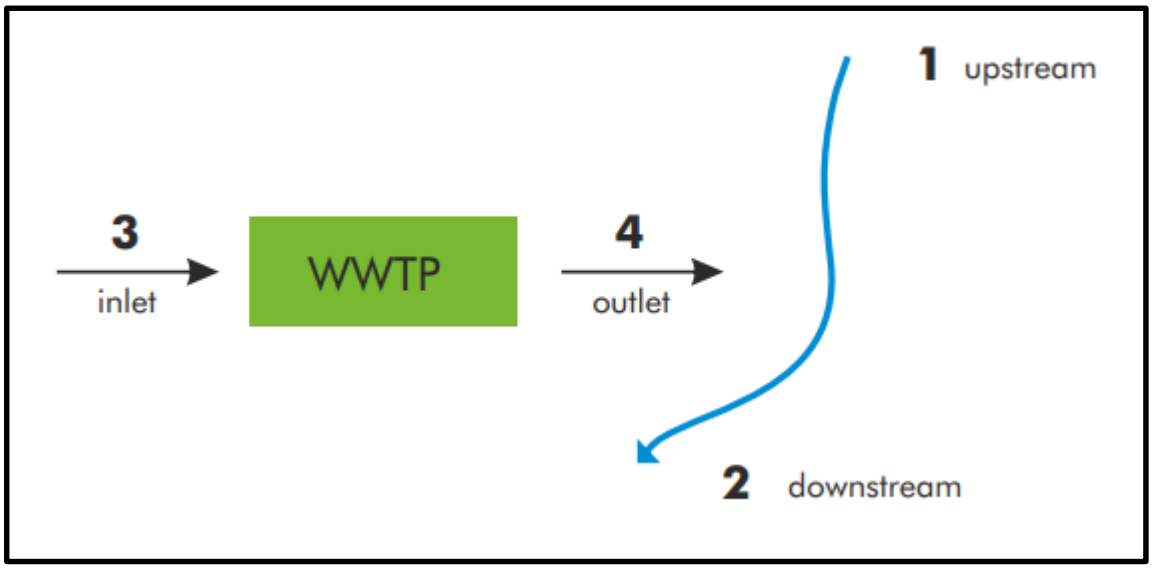
Example of MEDWwater project:

The procedure related to the analysis of pharmaceuticals includes 3 important steps:

[1] Source: https://www.waters.com/waters/en_US/Most-sensitive-mass-spectrometer-for-LC-MS-MS-in-the-clinical-laboratory/nav.htm?locale=en_US&cid=134831529

Step 1 - Sampling

Where: Take samples in the river: upstream (1), downstream (2), in the WWTP: inlet (3), outlet (4).



Sampling scheme proposed by MORPHEUS project (http://www.morpheus-project.eu/)

When: The seasonal differences for sampling respective pharmaceuticals/APIs should be taken into account, cf. Section 5.

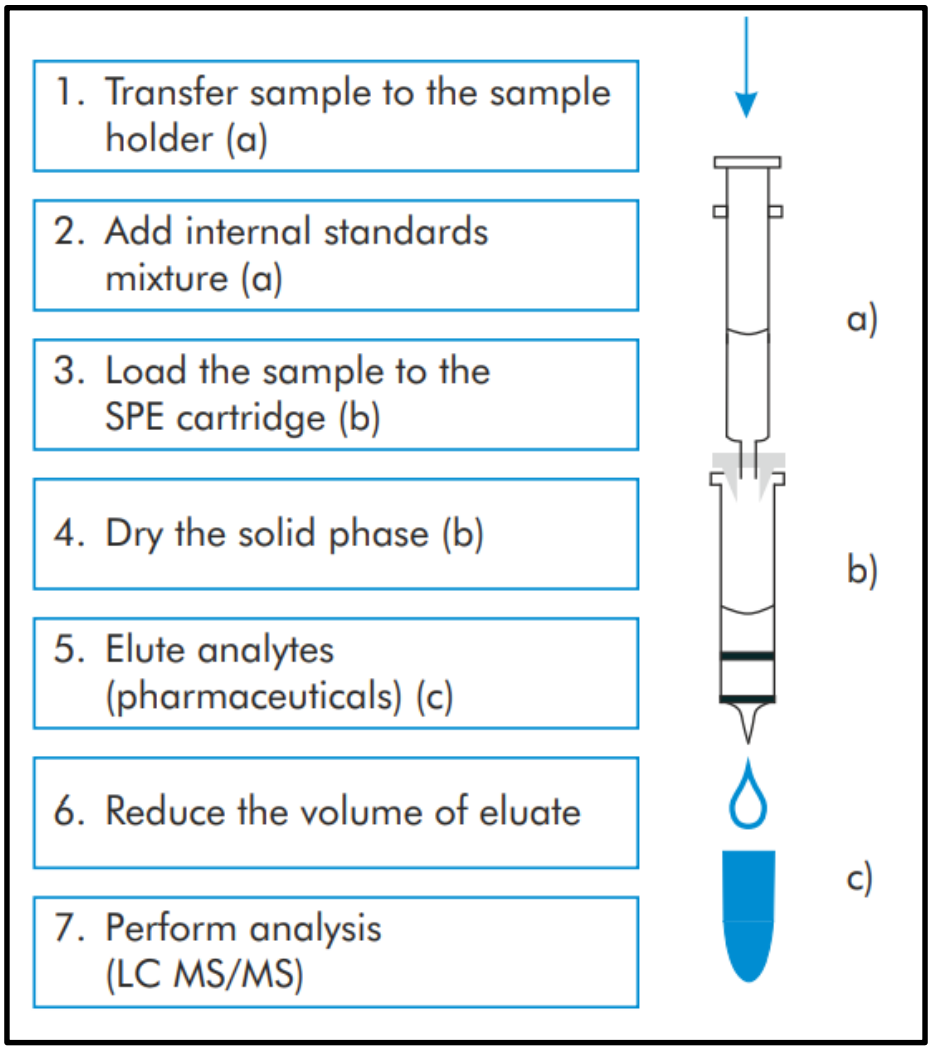
What: Select the substances that shall be monitored according to the EU watchlist or other relevant substances.

Sampling techniques: Use the national/regional sample material as recommended by authorities. Wear protective gloves. Prepare the sampling container, position yourself in shallow waters—about knee high, rinse the container 3 times with the sample (water stream), hold the jar near the bottom and plunge it below the water surface, turn the submerged container into the current / water stream and collect the sample, cover the full container while it is submerged and remove it from the water.

Step 2 - Sample preparation

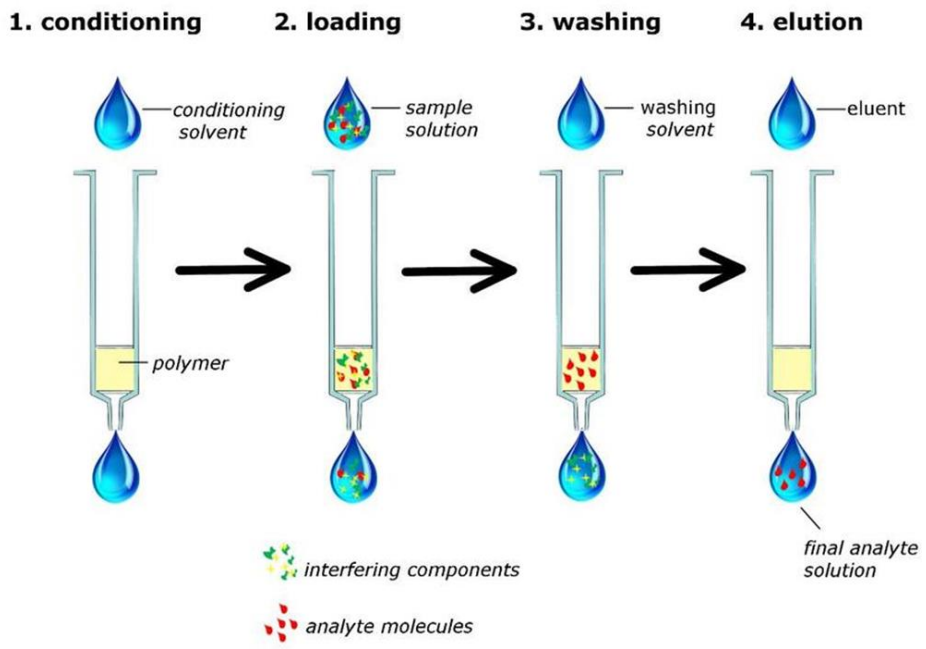
Store the samples at 4 °C for a maximum of 48 h before analysis. If immediate analysis is not possible, samples should be stored at -20 °C. The choice of storage might dictate the sample volume and sample bottle type (amber glass or HDPE). ISO 5667-3 Water quality – Sampling. Part 3: Guidance on the preservation and handling of water samples.

The general steps in a Solid Phase Extraction (SPE) procedure prior to final analysis is shown in the figure below. The SPE concentrates and cleans the samples.



General protocol for an SPA (according to MORPHEUS, http://www.morpheus-project.eu/

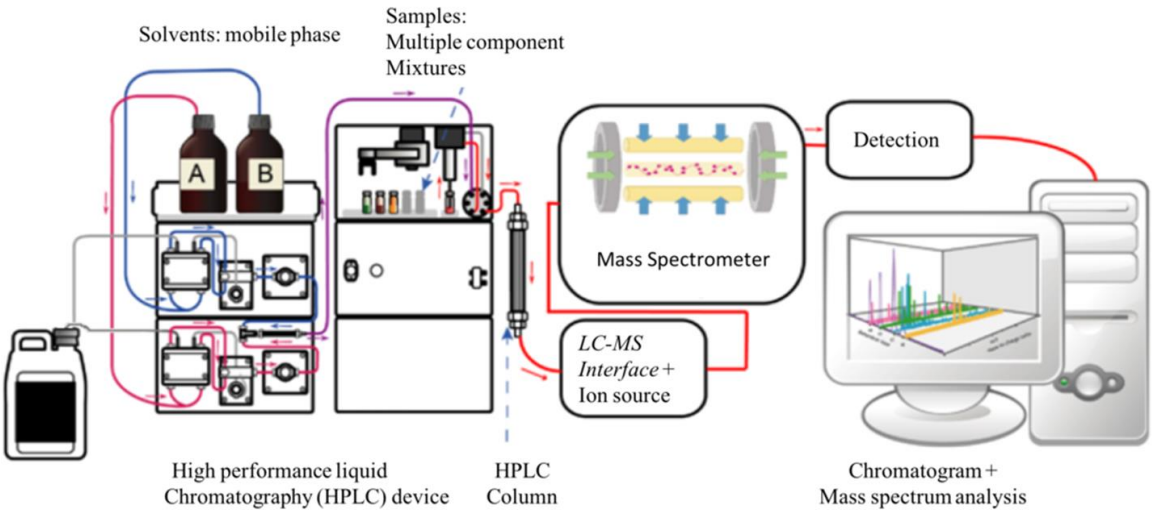
Solid phase extraction



Source: Maria Alexandra Sandoval Riofrio, Extraction of Phorbol Esters (PEs) from Pinion cake using computationally- designed polymers as adsorbents for Solid Phase Extraction, Master Thesis, 2016, University of Leicester

Step 3 - Final analysis

Samples must be sent urgently to the trace organic laboratory for further analysis, most commonly using the technique of SPE-LC-MS/MS or SPE-GC-MS/MS. Different laboratories use somewhat different methods, however the results should of course be the same. The LC and GC separate the analytes before the final analysis and detection in the mass spectrometer (MS/MS).



7. Existing analytical methods for selected pharmaceuticals

Analysing pharmaceuticals in polluted water, which in some cases occur at very low concentrations, requires advanced analytical methods. There are several analytical techniques used in the pharmaceutical industry, but the techniques commonly used are chromatography techniques such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS), gas chromatography (GC), and gas chromatography-mass spectrometry (GC-MS).

Validation of analytical methods and quality assurance

Prior to applications in environmental monitoring, the efficacy of the optimised analytical methods is often evaluated by spiking the environmental samples with analytes using the environmentally relevant concentrations. The performance of the analytical methods are evaluated based on sensitivity using the detection (LoD) and quantitation (LoQ) limits, accuracy by determining the percent recoveries and precision based on relative standard deviations (RSD)(Ngubane et al.). Commission directive 2009/90/EC[21] sets the minimum performance criteria for methods of analysis (Article 4): "Member States shall ensure that the minimum performance criteria for all methods of analysis applied are based on an uncertainty of measurement of 50 % or below (k = 2) estimated at the level of relevant environmental quality standards and a limit of quantification equal or below a value of 30 % of the relevant environmental quality standards. In the absence of relevant environmental quality standards for a given parameter, or in the absence of a method of analysis meeting the minimum performance criteria, Member States shall ensure that monitoring is carried out using best available techniques not entailing excessive costs".

We have compiled the information on performance of analytical methods with the available references as Table 7.1 for analysis of pharmaceuticals in the freshwater samples. Table 7.2 contains these data with references for analysis in the wastewater effluents. For full published references please check the respective chapter of this report. Analytical methods have been improved greatly during the past decades allowing identification of pharmaceuticals and their metabolites in the environment at trace levels. Steroidal oestrogens are strong endocrine disruptors, and their environmental occurrence should be monitored at ultra-trace levels, therefore development of more sophisticated analytical methods is necessary.

[21] Commission directive 2009/90/EC (31.07.2009) laying down, pursuant to Directive 2000/60/EC of the European Parliament and of the Council, technical specifications for chemical analysis and monitoring of water status. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32009L0090&qid=1689525269318

Table 7.1 Proposed EQS, lowest PNEC values and a range of quantification limits for pharmaceuticals in freshwater samples.

Compound	EQS[22], µg/L	Lowest PNEC, µg/L (Norman)	acceptable QL or DL, µg/L	QL range from studies, µg/L	refs for QL
17-α-ethinyl estradiol (EE2)	$1.7*10^{-5}$	0.000037	$5.1*10^{-6}$/$1.1*10^{-5}$	$8*10^{-5}$ $3.5*10^{-5}$	Zacs et al LVĢMC, 2016
17-β-estradiol (E2)	0.00018	0.0004	$5.4*10^{-5}$/$1.2*10^{-4}$	$8*10^{-5}$ $4*10^{-4}$	Zacs et al LVĢMC, 2016
Azithromycin	0.019	0.019	0.0057	0.0004 0.0011 0.09	Stapf, 2022 Langas et al LVĢMC, 2016
Carbamazepine	2.5	2	0.75/0.60	0.001 0.000005 0.0002	Stapf, 2022 Ek et al.2020 Langas et al
Clarithromycin	0.13	0.12	0.039/0.036	0.0006 0.001 0.0011 0.09	Stapf, 2022 Ek et al.2020 Langas et al LVĢMC, 2016
Clindamycin		0.044	0.044 (QL)	0.025	LVĢMC, 2016
Clotrimazole		0.03	0.02 (DL)	0.005	Peschka et
Diclofenac	0.04	0.05	0.012/0.015	0.0022 0.0012 0.0003 0.0021 0.01	Stapf, 2022 Ek et al.2020 Reinholds et Langas et al LVĢMC, 2016
Erythromycin	0.5	0.3	0.15/0.09	0.0004 0.0005 0.09	Stapf, 2022 Langas et al LVĢMC, 2016
Estrone (E1)	$3.6*10^{-4}$	$3.6*10^{-4}$	$1.08*10^{-4}$	$7.4*10^{-4}$ 0.0002 $4*10^{-4}$	Ek et al.2020 Langas et al LVĢMC, 2016
Fluconazole		1.04	0.25 (DL)	$4.6*10^{-5}$	Ek et al.2020

[22] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0540

Guanylurea		100	100 (QL)	0.03	LVǪMC, 2016
Ibuprofen	0.22	0.011	0.066/0.0033	0.005 0.001 0.01	Stapf, 2022 Reinholds et Langas et al
Metformin		160	156 (QL)	0.0198 $2.4*10^{-4}$ 0.03	Stapf, 2022 Ek et al.2020 LVǪMC, 2016
Miconazole		0.025	0.20 (DL)		
O-desmethylvenlafaxine		0.88	0.006 (DL)	0.005	Stapf, 2022
Ofloxacin		1.39	0.026 (QL)	0.010 0.025	Ek et al.2020 LVǪMC, 2016
Sulfamethoxazole		0.6	0.10 (DL)	0.0002 0.0013	Stapf, 2022 Langas et al
Trimethoprim		120	0.10 (DL)	0.0004	Stapf, 2022
Venlafaxine		0.88	0.006 (DL)	0.003 $3.4*10^{-5}$	Stapf, 2022 Ek et al.2020

Table 7.2 Proposed EQS, lowest PNEC values and a range of quantification limits for pharmaceuticals in wastewater effluents.

Compound	EQS, µg/L	Lowest PNEC (as for freshwater), µg/L (Norman)	acceptable QL or DL, µg/L	QL range from studies, µg/L	refs for QL
4-methyl benzotriazole		8.0	2.4	0.016	Huntscha et
6-methyl benzotriazole		150	45	0.016	Huntscha et
Amisulpride		140	42	0.0005	Pugajeva et
Benzotriazole		19	5.7	0.03 0.04	Voutsa et al Loos et al.,

				0.07	Huntscha et
Carbamazepine	2.5	2	0.75/0.60	0.001 0.0077 0.0002 0.0005	Stapf, 2022 Ek et al.2020 Langas et al Pugajeva et
Candesartan		100	30	0.011	Ek et al.2020
Citalopram		16	4.8	0.0011 0.01	Ek et al.2020 Ajo et al.
Clarithromycin	0.13	0.12	0.039/0.036	0.0006 0.016 0.0011 0.025 0.09	Stapf, 2022 Ek et al.2020 Langas et al Pugajeva et LVĢMC, 2016
Diclofenac		0.05	0.015	0.0022 0.022 0.0021 0.005 0.01	Stapf, 2022 Ek et al.2020 Langas et al Pugajeva et LVĢMC, 2016
Hydrochlorothiazide		100	30	0.110 0.05	Ek et al.2020 Ajo et al.
Irbesartan		700	210	0.070 0.0005	Ek et al.2020 Pugajeva et
Metoprolol		8.6	2.58	0.0004 0.002 0.029 0.0005	Stapf, 2022 Langas et al Ek et al.2020 Pugajeva et
Venlafaxine		0.88	0.006 (DL)	0.003 0.010 0.005	Stapf, 2022 Ek et al.2020 Pugajeva et

8. Challenges and conclusions

The concentration of pharmaceuticals in water bodies depends on a number of local factors such as consumption rate of medicines, size and removal efficiency of WWTPs, water flow of receiving rivers, and persistence of pharmaceuticals towards transformation or degradation. It has become obvious that information on these parameters should be collected regularly.

While the ideal environmental monitoring system would routinely include all three components (chemical analysis, bioassays, ecosystem/effect-based monitoring), resource limitations and other practical constraints generally dictate where they are employed on a case-by-case basis. Therefore a stepwise process is suggested to design and implement a strategic and integrated monitoring approach. The first step is to start with a problem formulation considering the existing information about the site, management goals and particular regulatory motivators. Once these basics are understood, strategic decisions about which specific monitoring tools should be employed are possible, which then allows for informed decision-making on what actions may (or may not) be required (Ekman et al., 2013).

The stepwise approach has also been suggested by projects *CWPharma* and *MORPHEUS*, stressing also that further development of activities and advancement of water treatment plants should be thoroughly discussed with all stakeholders. The next stages of AWT in most cases will require substantial investments, and this should also be communicated to responsible authorities. A study is available (Pistocchi et al., 2022) showing the reduction of discharge toxicity by 75% with AWT technologies and emphasising that achievement of these objectives would cost about 4 billion euro/year for the whole EU. Further research on the drivers of effluent toxicity, and a wider adoption of advanced treatment processes, may significantly improve the trade-offs between reducing effluent toxicity and controlling the costs of wastewater treatment. In addition, the defined EU policy toward zero carbon emissions in 2050 also should be considered when planning and implementing AWT.

CWPharma estimated that the cost for removing micropollutants from municipal wastewater ranges between 0.05-0.25 €/m3 (total costs including investment and operation) (Stapf et al. 2020). Costs are very site specific and can be affected by the following non-exhaustive list of factors: economy of scale, use of existing infrastructure, need for additional water hydraulics, organic matter background of treated water, cost for electricity, etc. In any case, the investments for the updating of WWTPs will be necessary in the very nearest future and it is important to include the need for funding in the policies and action plans (HELCOM, 2022).

We can conclude that **future costs** should be planned also for inclusion of **regular monitoring procedures of OMPs** in the national monitoring programmes, taking into account that analytical capacities of respective laboratories also should be in place. Potential of laboratories can be developed by participation in networks of the most recent knowledge exchange and training, e.g.

NORMAN Network[23]. The development of unified standards for OMP monitoring in the HELCOM area could also enhance the achievement of environmental objectives.

References

Ajo, P., Preis, S., Vornamo, T., Mänttäri, M., Kallioinen, M., & Louhi-Kultanen, M., 2018. Hospital wastewater treatment with pilot-scale pulsed corona discharge for removal of pharmaceutical residues. Journal of Environmental Chemical Engineering, 6(2), 1569-1577.

Anliker S., S. Santiago, K. Fenner, H. Singer, 2022. Large-scale assessment of organic contaminant emissions from chemical and pharmaceutical manufacturing into Swiss surface waters. Water Res., 215, 118221, ISSN 0043-1354, https://doi.org/10.1016/j.watres.2022.118221

Bergmann A., R. Fohrmann, F.A. Weber. 2011. Zusammenstellung von Monitoringdaten zu Umweltkonzentrationen von Arzneimitteln. In: UBA-FB 001525, Umweltbundesamt, pp. 1862-4804, ISSN, (Dessau-Roßlau).

Bijlsma L., E. Pitarch, E. Fonseca, M. Ibáñez, A. M. Botero, J. Claros, L. Pastor, F. Hernández, 2021. Investigation of pharmaceuticals in a conventional wastewater treatment plant: Removal efficiency, seasonal variation and impact of a nearby hospital. Journal of Environmental Chemical Engineering, Vol. 9, Issue 4, 105548, ISSN 2213-3437, https://doi.org/10.1016/j.jece.2021.105548.

Björklund E, Svahn O. 2021. Total Release of 21 Indicator Pharmaceuticals Listed by the Swedish Medical Products Agency from Wastewater Treatment Plants to Surface Water Bodies in the 1.3 Million Populated County Skåne (Scania), Sweden. Molecules. 2021 Dec 23;27(1):77. doi: 10.3390/molecules27010077. PMID: 35011310; PMCID: PMC8746806.

Brack, W., Escher, B.I., Müller, E. et al. 2018. Towards a holistic and solution-oriented monitoring of chemical status of European water bodies: how to support the EU strategy for a non-toxic environment? Environ Sci Eur 30, 33. https://doi.org/10.1186/s12302-018-0161-1

Commission Implementing Decision (EU) 2015/495,. (2015). Establishing a watch list of substances for union-wide monitoring in the field of water policy pursuant to directive 2008/105/EC of the European Parliament and of the Council. Official Journal of the European Union, 78, 40-42.

Coppens, L. et al. 2015. “Towards spatially smart abatement of human pharmaceuticals in surface waters: Defining impact of sewage treatment plants on susceptible functions”, Water Research, Vol. 81, pp. 356-365, http://dx.doi.org/10.1016/j.watres.2015.05.061.

Ek Henning, H., Putna.Nimane, I., Kalinowski, R., Perkola, N., Bogusz, A., Kublina, A., Haiba, E., Barda, I., Karkovska, I., Schütz, J., Mehtonen, J., Siimes, K., Nyhlén, K., Dzintare, L., Äystö, L., Sinics, L., Laht, M., Lehtonen, M., Stapf, M., Stridh, P., Poikāne, R., Hoppe, S., Lehtinen, T.,

[23] http://www.norman-network.net/?q=Home

Kõrgma, V., Junttila, V., Leisk, Ü. 2020. Pharmaceuticals in the Baltic Sea Region – emissions, consumption and environmental risks. Report no. 2020:28, Länsstyrelsen Östergötland, Linköping. Available at: https://www.lansstyrelsen.se/4.f2dbbcc175974692d268b9.html

Ekman, D. et al. 2013. "Biological Effects–Based Tools for Monitoring Impacted Surface Waters in the Great Lakes: A Multiagency Program in Support of the Great Lakes Restoration Initiative", Environmental Practice, Vol. 15/4, pp. 409-426, http://dx.doi.org/10.1017/S1466046613000458.

Götz, C., R. Kase and J. Hollender, 2011. Micropollutants - Assessment concept for organic trace substances from municipal sewage [In German], Swiss Federal Institute of Aquatic Science and Technology (Eawag), Dübendorf.

HELCOM 2022. Micropollutants in wastewater and sewage sludge. Baltic Sea Environment Proceedings No. 185. https://helcom.fi/wp-content/uploads/2022/04/Micropollutants-in-wastewater-and-sewage-sludge.pdf

Huntscha, S., Singer, H. P., McArdell, C. S., Frank, C. E., & Hollender, J. 2012. Multiresidue analysis of 88 polar organic micropollutants in ground, surface and wastewater using online mixed-bed multilayer solid-phase extraction coupled to high performance liquid chromatography–tandem mass spectrometry. Journal of Chromatography A, 1268, 74-83.

Loos, R., Carvalho, R., António, D. C., Comero, S., Locoro, G., Tavazzi, S., ... & Gawlik, B. M. 2013. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. Water research, 47(17), 6475-6487.

LVĢMC. 2016. Bīstamu ķīmisko vielu apsekojums Latvijas virszemes ūdeņos. [A survey of hazardous chemicals in the Latvian surface waters]. Project report, Nr. 1-08/425/2015 (in Latvian).

Malnes D., Ahrens L., Köhler S., Forsberg M., Golovko O., 2022. Occurrence and mass flows of contaminants of emerging concern (CECs) in Sweden's three largest lakes and associated rivers. Chemosphere, Volume 294, 133825, ISSN 0045-6535, https://doi.org/10.1016/j.chemosphere.2022.133825

Miino M.C., T. Macsek, T. Halešová, T. Chorazy, P. Hlavínek, 2023. Pharmaceutical and narcotics monitoring in Brno wastewater system and estimation of seasonal effect on the abuse of illicit drugs by a wastewater-based epidemiology approach, Science of The Total Environment, 891, 164386, ISSN 0048-9697, https://doi.org/10.1016/j.scitotenv.2023.164386

MPA (2015), Miljöindikatorer inom ramen för nationella läkemedelsstrategin (NLS). [Environmental indicators under the national drugs strategy (NLS)] Rapport från CBL-kansliet, Läkemedelsverket, Swedish Medicinal Product Agency, Uppsala, https://lakemedelsverket.se/upload/nyheter/2015/miljoindikatorer-rapport-NLS_2015-09-07.pdf.

Moermond, CTA, de Rooy, M. 2022. The Dutch chain approach on pharmaceuticals in water: Stakeholders acting together to reduce the environmental impact of pharmaceuticals. Br J Clin Pharmacol. 2022; 88(12): 5074- 5082. doi:10.1111/bcp.15509

Naturvårdsverket, 2022. Monitoring for organic micropollutants in the WFD Watch List 2021-2022. Överenskommelse NV-00325-21. https://www.diva-portal.org/smash/get/diva2:1698003/FULLTEXT01.pdf

Ncebakazi Primrose Ngubane, Devrani Naicker, Somandla Ncube, Luke Chimuka, Lawrence Mzukisi Madikizela, 2019. Determination of naproxen, diclofenac and ibuprofen in Umgeni estuary and seawater: A case of northern Durban in KwaZulu–Natal Province of South Africa, Regional Studies in Marine Science, Volume 29, 100675, ISSN 2352-4855, https://doi.org/10.1016/j.rsma.2019.100675.

Peschka, M., Roberts, P. H., & Knepper, T. P. 2007. Analysis, fate studies and monitoring of the antifungal agent clotrimazole in the aquatic environment. Analytical and bioanalytical chemistry, 389, 959-968.

Pistocchi A., H.R. Andersen, G. Bertanza, A. Brander, J.M. Choubert, M. Cimbritz, J.E. Drewes, C. Koehler, J. Krampe, M. Launay, P.H. Nielsen, N. Obermaier, S. Stanev, D. Thornberg. 2022. Treatment of micropollutants in wastewater: Balancing effectiveness, costs and implications. Science of The Total Environment, Volume 850, 2022, 157593, ISSN 0048-9697, https://doi.org/10.1016/j.scitotenv.2022.157593.

Pugajeva, I., Ikkere, L. E., Jansons, M., Perkons, I., Sukajeva, V., & Bartkevics, V. 2021. Two-dimensional liquid chromatography-mass spectrometry as an effective tool for assessing a wide range of pharmaceuticals and biomarkers in wastewater-based epidemiology studies. Journal of Pharmaceutical and Biomedical Analysis, 205, 114295.

Reinholds, I., Pugajeva, I., Zacs, D. et al. 2017. Determination of acidic non-steroidal anti-inflammatory drugs in aquatic samples by liquid chromatography-triple quadrupole mass spectrometry combined with carbon nanotubes-based solid-phase extraction. Environ Monit Assess 189, 568. https://doi.org/10.1007/s10661-017-6304-9

Stapf, M., Miehe, U., Bester, K., & Lukas, M. 2020. Guideline for advanced API removal. CWPharma project report for GoA3.4: Optimization and control of advanced treatment. Zenodo. https://doi.org/10.5281/zenodo.5069819

Voutsa, D., Hartmann, P., Schaffner, C., & Giger, W. (2006). Benzotriazoles, alkylphenols and bisphenol A in municipal wastewaters and in the Glatt River, Switzerland. Environmental Science and Pollution Research, 13, 333-341.

Zacs, D., Perkons, I. & Bartkevics, V. Determination of steroidal oestrogens in tap water samples using solid-phase extraction on a molecularly imprinted polymer sorbent and quantification with gas chromatography-mass spectrometry (GC-MS). Environ Monit Assess 188, 433 (2016). https://doi.org/10.1007/s10661-016-5435-8

Suggested API for future monitoring

API name	CAS No.	Application	Justification	Surface water	Wastewater	Sludge
17-α–Ethinylestradiol (EE2)	57-63-6	estrogenic hormones		+		
17-β-Estradiol (E2)	50-28-2	estrogenic hormones		+		
4-methyl benzotriazole and 6-methyl benzotriazole	29878-31-7 and 136-85-6	antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, analgesic properties; corrosion inhibitors			+	
Amilsulpride	71675-85-9	antiemetic and antipsychotic medication			+	
Amoxicillin	26787-78-0	antibiotic		+	+	+
Azithromycin	CAS_83905-01-5	antibiotic		+	+	
Benzotriazole	95-14-7	antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, analgesic properties; corrosion inhibitors			+	
Candesartan	139481-59-7	angiotensin receptor blocker			+	
Carbamazepine	298-46-4	anticonvulsant or anti-epileptic drug		+	+	
Ciprofloxacin	85721-33-1	antibiotic	LV	+	+	
Citalopram	59729-33-8	antidepressant			+	
Clarithromycin	81103-11-9	antibiotic	LV	+	+	
Clindamycin	18323-44-9	antibiotic		+		
Clotrimazole	23593-75-1	antifungal medication		+		
Diclofenac	15307-86-5	nonsteroidal anti-inflammatory drug		+	+	+
Erythromycin	CAS_114-07-8	antibiotic		+		
Estrone (E1)	53-16-7	estrogenic hormones		+		

API name	CAS No.	Application	Justification	Surface water	Wastewater	Sludge
Fluconazole	86386-73-4	antifungal medication		+		
Guanylurea	141-83-3	transformation product of metformin		+		
Hydrochlorothiazide	58-93-5	diuretic medication			+	
Ibuprofen	15687-27-1	nonsteroidal anti-inflammatory drug		+	+	+
Irbesartan	138402-11-6	angiotensin II receptor blocker			+	
Metformin	657-24-9	treatment of type 2 diabetes		+		
Metoprolol	37350-58-6	selective β_1 receptor blocker			+	
Miconazole	22916-47-8	antifungal medicine		+		
O-desmethylvenlafaxine	93413-62-8	human metabolite of (s)-venlafaxine		+		
Ofloxacin	82419-36-1	antibiotic		+		
Primidone	125-33-7	antiepileptic				
Sulfamethoxazole	723-46-6	antibiotic		+		
Trimethoprim	738-70-5	antibiotic		+		
Venlafaxine	93413-69-5	antidepressant	LT	+	+	

Justification explanations

	Watch list requirements; ammount of monitoring stations, where to monitor: LV (3), LT (4)
	HELCOM indicator
	UWWTD update plans
	2013/39/EU directive future (2022) update plans
	MEDWwater results: PNEC exceedances in effluent / surface water
	MEDWwater results: exceeded acceptable lengths of mixing zones
	MEDWwater reslts: PNEC exceedances for soil
	Directive of the EU Parliament and of the Council amending Directive 2000/60/EC establishing a framework for Community action in the field of water policy, Directive 2006/118/EC on the protection of groundwater against pollution and deterioration and Directive 2008/105/EC on environmental quality standard s in the field of water policy

Monitoring matrix explanations

+	requirements of regulatory acts, already in force
+	proposed requirements of regulatory acts in EU level, planned to be approved soon
+	proposed requirements of regulatory acts in EU level, planned to be approved soon (suggested on a base of MEDWwater project results as one of 6 substances)
+	proposed requirements of regulatory acts in EU level, planned to be approved soon (other possible substances)
+	suggested - optional for investigative monitoring - screenings in effluent, upstream and downstream effluent discharges