Pharmaceuticals in the Baltic Sea Region
– emissions, consumption and environmental risks

County Administrative Board of Östergötland (CAB) in collaboration with Latvian Institute of Aquatic Ecology (LIAE), Institute of Environmental Protection - National Research Institute (IOS, Poland), Finnish Environment Institute (SYKE), Latvian Environment, Geology and Meteorology Centre (LEGMC), Estonian Waterworks Association (EVEL), Berlin Center for Competence of Water (KWB) and Estonian Environmental Research Centre and Finnish medicines agency (EERC).

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Preface

Pharmaceutical residues are widespread in the environment. Some active pharmaceutical ingredients (APIs) are present at levels that may negatively affect organisms in surface water, sediment and soil. This report highlights results from the three year-project Clear Waters from Pharmaceuticals (CWPharma) funded by the EU's Interreg Baltic Sea Region Programme. The overall aim of the project was to decrease the emissions and adverse effects of pharmaceuticals in the Baltic Sea region. The County Administrative Board of Östergötland participated in the project together with other authorities, researchers and wastewater organisations from seven Baltic Sea countries. The project was divided into four work packages focusing on (1) emissions, consumption and environmental risks of APIs, (2) advanced wastewater treatment, (3) low-tech risk reduction measures of APIs, and (4) scenarios, conclusions and action plans.

The County Administrative Board of Östergötland coordinated the work of mapping the emissions, consumption and environmental risks of about 80 active pharmaceutical ingredients (APIs) in the Baltic Sea region. Sampling was performed in selected river basin districts in Sweden, Finland, Estonia, Latvia, Germany and Poland. Environmental samples were collected from lakes, streams, coastal waters and agricultural land. We also analyzed emissions of APIs from municipal wastewater treatment plants, hospitals, pharmaceutical manufacturing facilities, landfills, and fish and livestock farms. In Sweden, sampling was carried out within the Motala ström catchment area, from Lake Vättern to Bråviken Estuary.

This report presents all the results from the mapping of emissions, consumption and environmental risks of APIs in the Baltic Sea region. The widespread and, in some places, high prevalence of APIs in the environment shows that immediate measures are needed to reduce the risk of negative environmental effects and the development of antibiotic resistance.

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The County Administrative Board of Östergötland (CAB) would like to thank the lead partner Finnish Environment Institute (SYKE), the activity leaders at the Latvian Institute of Aquatic Ecology (LIAE) and the Institute of Environmental Protection - National Research Institute in Poland (IOS) and the other project partners that have contributed to this report. We are also grateful for the support from the project's associated organizations and everyone who has contributed to the project's outcome.

CAB's work in the project has, in addition to grants from the EU's Baltic Sea Program, been co-financed by the Swedish Agency for Marine and Water Management through the grant 1:11 Measures for a better marine and aquatic environment.

Förord (in Swedish)

Läkemedelsrester är vitt spridda i miljön. Vissa läkemedelssubstanser förekommer i nivåer som utgör en risk för organismer som lever i vatten, bottensediment och i jord. Detta visar resultat från det treåriga projektet Clear Waters from Pharmaceuticals (CWPharma) som finansierades av EU:s Interreg Baltic Sea Region Program. Syftet med projektet var att minska spridning av läkemedelsrester till Östersjön. Länsstyrelsen Östergötland deltog i projektet tillsammans med andra myndigheter, forskare och avloppsreningsverk från sju östersjöländer. Projektet delades in i fyra arbetspaket med fokus på (1) utsläpp, miljörisker och konsumtion av aktiva läkemedelssubstanser, (2) avancerad rening av avloppsvatten, (3) uppströmsåtgärder och (4) scenarier, slutsatser och handlingsplan.

Länsstyrelsen samordnade arbetet med att kartlägga utsläpp, miljörisker och konsumtion av ca 80 aktiva läkemedelssubstanser i östersjöregionen. Provtagningar genomfördes i utvalda avrinningsområden i Sverige, Finland, Estland, Lettland, Tyskland och Polen. Prover samlades in från sjöar, vattendrag, kustvatten och jordbruksmark. Vi analyserade även utsläpp av läkemedelsrester från avloppsreningsverk, sjukhus, läkemedelsindustri, fiskodlingar, djurbesättningar och deponier. I Sverige genomfördes provtagningar inom Motala ströms avrinningsområde, från Vättern till Bråviken.

I denna rapport presenteras samtliga resultat från kartläggningen av utsläpp, miljörisker och konsumtion av läkemedelssubstanser i östersjöregionen. Den utbredda och ställvis höga förekomsten av läkemedelsrester i miljön visar att det krävs omedelbara åtgärder för att minska risken för negativa miljöeffekter och utveckling av antibiotikaresistens.

Tack
Länsstyrelsen Östergötland vill rikta ett stort tack till lead partner Finnish Environment Institute (SYKE), aktivitetsledarna vid Latvian Intitute of Aquatic Ecology (LIAE) och Institute of Environmental Protection – National Research Institute (IOS) i Polen, samt övriga projektpartners som bidragit till denna rapport. Vi är även tacksamma för stödet från projektets associerade organisationer och andra som på något sätt hjälpt oss.

Länsstyrelsen Östergötlands arbete i projektet har, utöver bidrag från EU:s östersjöprogram, även medfinansierats av Havs- och vattenmyndigheten genom anslag 1:11 Åtgärder för en bättre havs- och vattenmiljö.

CWPharma

CLEAR WATERS FROM PHARMACEUTICALS

Pharmaceuticals in the Baltic Sea Region – emissions, consumption and environmental risks

This report is an output of CWPharma project's work package 2, activities 2.1 and 2.2.

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Contents

Summary

This report describes the contamination by pharmaceuticals and the environmental risks associated with their environmental levels in the Baltic Sea Region. Data were collected within the three-year project Clear Waters from Pharmaceuticals (CWPharma) funded by the EU's Interreg Baltic Sea Region Programme. Sampling was performed in the river basin districts of Vantaanjoki in Finland, Pärnu in Estonia, Lielupe and Daugava in Latvia, Vistula in Poland, Warnow-Peene in Germany and Motala ström in Sweden. Analyses were performed on surface water, coastal water, sediment and soil that was fertilized with sewage sludge or manure. Analyses were also performed on emissions from municipal wastewater treatment plants, hospitals, pharmaceutical manufacturing facilities, landfills, and fish and livestock farms. In total, the study covered 13 365 data points from 226 samples as well as collection of human and veterinary consumption data of selected active pharmaceutical ingredients (APIs).

Samples were screened for up to 80 APIs, representing antibiotics, antiepileptics, antihypertensives, asthma and allergy medications, gastrointestinal disease medications, hormones, metabolic disease medications, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, other cardiovascular medicines, psychopharmaceuticals, veterinary medicines and caffeine. The measured APIs were selected based on analytical capacity, consumption rates, identified data gaps and potential environmental risks. Literature and databases were screened for ecotoxicological information. Acute toxicity tests were performed for two APIs, nebivolol and cetirizine, for which ecotoxicological data were lacking. Measured environmental concentrations were compared with predicted no-effect concentrations (PNEC) to assess environmental risks of the selected APIs.

Environmental levels

This study showed a widespread prevalence of APIs in the environment. APIs were detected in all the studied rivers, lakes, coastal waters, sediments and soils. **Surface water** samples contained between 8–49 of 63 analysed APIs. The sum concentration of the detected APIs was 0.0018–12 µg/L, reflecting very different environmental conditions upstream versus downstream of emissions from e.g. municipal wastewater treatment plants and livestock farms. The most frequently detected API was an antiepileptic carbamazepine, which was quantified in 98% of the inland surface water samples and 100% of the coastal water samples. Other frequently detected APIs in surface water were tramadol and diclofenac (NSAIDs and analgesics), cetirizine (asthma and allergy medication) and venlafaxine and citalopram (psychopharmaceuticals).

Several APIs were also found in the **sediment** of Baltic Sea estuaries and Pärnu river. Each coastal sediment sample contained between 13–27 of 64 analysed APIs. The sum concentration of the detected APIs varied from 37 to 161 µg/kg d.w. Pärnu river sediment contained 41 APIs with a sum concentration of 188 µg/kg d.w. close to the river mouth. Five APIs were found in all sediment samples: metformin (metabolic disease medication), tramadol (NSAIDs and analgesics), oxazepam and risperidone (psychopharmaceuticals) and caffeine. Paracetamol (NSAIDs and analgesics) and xylometazoline (asthma and allergy medications) were detected at the highest concentrations in sediments, up to about 80 µg/kg d.w.

Soil samples from sludge or manure-fertilized agricultural fields contained between 18–25 of 64 analysed APIs. The sum concentration of detected APIs varied from 15 to 166 µg/kg d.w. Five APIs were detected in all soil samples: trimethoprim (antibiotics), paracetamol and tramadol (NSAIDs and analgesics), risperidone (psychopharmaceuticals) and fenbendazole (veterinary medicine).

Environmental risks

This study showed that some of the analysed APIs, especially some hormones and antibiotics, are present at levels that may pose a risk to the environment. At least one API was present at a concentration which may pose an environmental risk in over 75% of the surface water samples. The

highest risks were related to hormones estrone and norethisterone, antibiotics clarithromycin and ofloxacin and an NSAID diclofenac. Medicinal use of estrone appears to be negligible in the Baltic Sea region. Therefore, the estrone detected in the environment is likely naturally excreted from humans and animals. In addition, emamectin (veterinary medicine), mometasone furoate (asthma and allergy medication) and metformin (metabolic disease medication) were found at risky levels in some surface water samples.

The study also indicated that sediment and soil organisms can be negatively affected by pharmaceutical residues. The APIs that most frequently exceeded their PNECs in sediments were ciprofloxacin (antibiotic), metformin (metabolic disease medication) and paracetamol (NSAID and analgesic). In some sediment samples, risks were also observed related to diclofenac, emamectin (veterinary medicines), estrone and norethisterone (hormones), and clarithromycin, ofloxacin and the sum concentration of doxycycline and tetracycline (antibiotics). In soils, exceedance of PNECs were often observed for paracetamol and metformin. Single exceedances of PNECs were observed for ciprofloxacin, ofloxacin, diclofenac, estrone and the veterinary medicine ivermectin in soil samples. For some APIs the environmental risk cannot be excluded because their limits of quantification were higher than the PNECs.

In addition, several other APIs contributed to the combined ecological risk, although their concentrations did not exceed the PNEC. The sum risk quotients were high in many samples, especially in surface waters downstream of wastewater treatment plants. The results indicate an urgent need to decrease the loading and the environmental levels of APIs.

Consumption data of APIs

The collected data on **human and veterinary consumption** (in kg) showed that of all the studied APIs, the ones used for pain and fever (paracetamol and different NSAIDs), epilepsy (levetiracetam and gabapentin), and for major public health problems such as type II diabetes (metformin) and cardiovascular diseases (losartan, valsartan and metoprolol) were the most consumed. After intake, some medicines are metabolized, while others remain intact until they are excreted. As a result, large quantities of APIs and their metabolites are spread via the **wastewater treatment plants (WWTPs)** to receiving aquatic environments.

The expected load of APIs in wastewater influents was predicted countrywise based on the collected consumption data. The predicted loads were then compared to influent loads measured at the sixteen studied WWTPs in Estonia, Latvia, Finland, Germany, Poland and Sweden. This study showed that the **predicted and measured load of APIs in wastewater influents** were in good agreement for some APIs (e.g. diclofenac and paracetamol) in most countries, whereas load prediction for other APIs (e.g. carbamazepine) resulted either in an over- or underestimation. The agreement may be improved for instance by including more comprehensive consumption data and measurements.

Sources and pathways

This study showed that the analysed APIs are spread into the Baltic Sea environment mainly via **municipal wastewater treatment plants**, and to a lesser extent via hospitals, manufacturing facilities, landfills, and fish and livestock farms. Results from sixteen WWTPs showed the presence of 17–45 of the 75 analysed APIs in each influent, 19–37 of 75 analysed APIs in each effluent and 15–26 of 31 analysed APIs in each sludge sample. The sum concentration of the detected APIs was 53–1550 µg/L (median 300 µg/L) in influents, 14–1280 µg/L (median 40 µg/L) in effluents and 550–11600 µg/kg d.w. (median 2440 µg/kg d.w.) in sludge.

APIs detected in ≥90% of the **influents** were caffeine, codeine, diclofenac, fluconazole, gabapentin, hydrochlorothiazide, ketoprofen, levetiracetam, mesalazine, metformin, naproxen, oxazepam, paracetamol, sulfamethoxazole, trimethoprim, valsartan and venlafaxine. Six APIs were found in all influent samples: diclofenac, gabapentin, ketoprofen, metformin, naproxen and trimethoprim. The maximum influent concentration, up to 1000 µg/L, was measured for paracetamol in Finland

and Sweden. The APIs that were highly consumed (in kg) and/or excreted largely as unmetabolized had typically the highest concentrations in influents, while the detection frequency was also highly related to the limits of the analytical method of quantification.

APIs detected in ≥90% of the **effluents** were carbamazepine, citalopram, clarithromycin, diclofenac, erythromycin, fluconazole, hydrochlorothiazide, ketoprofen, metoprolol, naproxen, oxazepam, sotalol, tramadol, trimethoprim and venlafaxine. Three APIs were found in all effluent samples: diclofenac, metoprolol and oxazepam. In the effluents, ibuprofen had the highest concentration (up to 44 µg/L in Latvia), followed by diclofenac (up to 38 µg/L in Estonia) and caffeine (up to 32 µg/L in Latvia). Eight APIs were found in all WWTP **sludge** samples: diclofenac, carbamazepine, venlafaxine, metformin, caffeine, metoprolol, citalopram and sertraline. In sludge, the most abundant APIs were telmisartan (up to 8700 µg/kg d.w. in Estonia) and ofloxacin (up to 8600 µg/kg d.w. in Finland).

Wastewater treatment efficiency could be calculated for 50 APIs analysed in influents and effluents within the project. The calculations showed that 28 APIs had positive removal efficiencies in all the studied WWTPs, indicating they were at least partly removed in the WWTPs. Substances with high removal efficiency (≥90%) were allopurinol, caffeine, levetiracetam, mesalazine, metformin, nebivolol, olanzapine, paracetamol and simvastatin.

For 19 APIs, removal efficiencies depended on the WWTP. Ten APIs had zero or negative average removal rates (the average efficiency of all the studied WWTPs), which means that the conventional wastewater treatment plants cannot decrease their emissions. These ten substances were carbamazepine, diclofenac, hydrochlorothiazide, irbesartan, metoprolol, sotalol, telmisartan, primidone, ramipril and losartan. Three of these APIs showed negative removal rates in all the studied WWTPs: metoprolol, primidone and ramipril. Hence, this study confirmed that many APIs are incompletely removed at conventional WWTPs.

In this study, APIs were analysed in hospital wastewaters in Sweden (Linköping and Norrköping), Germany (Wismar) and Estonia (Pärnu). The sum concentration of the detected APIs in the **hospital effluents** varied between 75–1200 µg/L. Gabapentin, metformin and paracetamol were found at highest concentrations. The sum concentration of detected APIs (µg/L) was generally higher in hospital effluents compared to the sum concentrations in the influents of the connected WWTPs. Because of the comparatively low wastewater flow rates from the hospitals, the total load of the detected APIs (g/day) in the effluents from hospitals were only up to 3% of the overall load to the connected WWTPs.

Landfill leachates were analysed before and after treatment at the landfill's WWTP three times during one year. The untreated leachate contained 26 out of 74 analysed APIs, whereas treated effluents contained 21 out of 74 analysed APIs. The sum concentrations of detected APIs varied over the year from 3.5–172 µg/L in untreated leachate and from 1.1–41 µg/L in treated effluents, indicating an overall decrease of about 35–76% during the treatment. The APIs found in highest concentrations in the untreated leachates were hydrochlorothiazide (up to 79 µg/L), paracetamol (74 µg/L) and gabapentin (7.0 µg/L), whereas caffeine (8.8 µg/L), hydrochlorothiazide (4.4 µg/L) and erythromycin (1.8 µg/L) were the most abundant in the treated effluents. However, because the landfill WWTP treats relatively low amount of water per day, the total load of APIs (g/day) from the landfill WWTP was low compared to the API load from municipal WWTPs of the Vantaa case study area.

This study also covered analyses of APIs in surface waters and sediments at Finnish and Estonian **fish farms**. Temporarily elevated concentrations in surface water were found for the antibiotic trimethoprim near one of the fish farms after an onsite medication event. Otherwise, the number of

detected APIs and their sum concentration (0.005–0.09 µg/L) was about the same or lower in the fish farm waters compared to other studied surface waters.

The watercourses downstream a **pig farm and a poultry farm** in Latvia contained 7–21 of 59 analysed APIs. The sum concentration of detected APIs was 0.18–0.62 µg/L, which is within the range found in other surface water samples of the case study areas. However, the concentrations of the veterinary medicines tiamulin and toltrazuril were higher downstream the pig farm than in other surface water samples. Hence, this study suggests that at least some livestock farms may be significant sources of APIs used for veterinary purposes, an issue that needs further attention.

This report contributes to an increased knowledge about sources, environmental levels and risks of pharmaceutical residues in the Baltic Sea Region. Data will be further used as a **base for modelling of APIs within the Baltic Sea region and to identify efficient measures** to reduce the load and environmental risks of APIs.

Recommendations

The recommendations drawn from this study are summarized below.

- APIs should be included in regular environmental monitoring programmes, focusing on APIs that pose environmental risks. The API list should be continuously updated as we receive new information on environmental levels and risks.

- The analytical methods should be further refined and developed to make comprehensive estimates of API concentrations in the environment, including metabolites.

- The statistics on the usage of human and veterinary medicines should be improved, by making data publicly available in DDD format (defined daily dose) and in mass units (kg of API) for all types of medicines.

- Further studies should be performed on the use of veterinary medicines and their dispersal in the environment. Any unnecessary use should be restricted and best practices for manure storage and application on agricultural fields should be implemented.

- More ecotoxicological data are needed on single APIs and their metabolites as well on mixture toxicity to assess the combined ecological risks. Ecotoxicological studies should be performed on different trophic levels and on different matrixes e.g. freshwater, coastal and marine waters, sediment and soil. Also, knowledge on chronic effects from long-term exposure to APIs should be improved.

- Further studies should be performed on the environmental levels and risks of antibiotics, including the spread of antibiotic resistance genes.

- Emissions of APIs from landfill leachates should be further analysed, especially where household waste is or has been disposed of at landfills.

- The emissions of environmentally risky APIs should be reduced by improved wastewater treatment and upstream measures.

- The discharges of APIs via WWTP effluents should be followed up, focusing on APIs that pose environmental risks. The list of environmentally risky APIs should be updated regularly when new ecotoxicological data and risk assessments are available.

1 Introduction

Pollution caused by pharmaceuticals is an emerging problem due to the potential risks to ecosystems and humans. Residues of pharmaceutical products may enter the environment during their manufacture, use and disposal. As identified by e.g. UNESCO and HELCOM (2017)[1], and European Comission (2019) there are still data gaps about the consumption of pharmaceuticals, environmental levels and emissions from various sources. This report focuses on filling in some of these data gaps. The overall aim is to increase knowledge about the extent of contamination by pharmaceuticals and the associated environmental risks in the Baltic Sea Region.

Environmental levels and sources of active pharmaceutical ingredients (APIs) were studied in selected river basin districts of Vantaa in Finland, Pärnu in Estonia, Lielupe and Daugava in Latvia, Vistula in Poland, Warnow-Peene in Germany and Motala ström in Sweden. The measured concentrations of about 80 APIs were compared with ecotoxicological data to assess environmental risks. The APIs were selected based on analytical capacity, high consumption volumes, identified data gaps and potential environmental risks. This report also covers a compilation of human and veterinary consumption of the selected APIs.

The study was performed within the three year-project Clear Waters from Pharmaceuticals (CWPharma) funded by the EU's Interreg Baltic Sea Region Programme. Data will be further used as a base for modelling APIs within the Baltic Sea Region and to identify measures to reduce the load and environmental risks of APIs.

Lielupe river in the Latvian case study area. Photo: M. Tīrums, LEGMC.

[1] UNESCO and HELCOM, 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris.

1.1 Scope of the report

Data collection covered 13 365 data points from 226 individual samples from selected river basin districts of Finland, Estonia, Latvia, Poland, Germany and Sweden. The screening of APIs covered about 80 active pharmaceutical ingredients (APIs), representing antibiotics, antiepileptics, antihypertensives, asthma and allergy medications, caffeine, gastrointestinal disease medications, hormones, metabolic disease medications, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, other cardiovascular medicines, psycopharmaceuticals and veterinary medicines.
Literature and databases were screened for ecotoxicological data. Additional acute toxicity tests were performed for two APIs for which no ecotoxicological endpoints were found. The measured environmental concentrations in surface water, sediment and soil were compared to calculated predicted no effect concentrations of the selected APIs.
To summarize, this report contains new data on:

- Human and veterinary consumption of APIs
- Levels of APIs in:
    - rivers, lakes and Baltic Sea estuaries
    - sediments of Baltic Sea estuaries
    - influents and effluents from municipal wastewater treatment plants
    - sewage sludge from municipal wastewater treatment plants
    - soils where sludge or manure have been applied
    - coastal waters in the vicinity of fish farms
    - watercourses near pig and poultry farms
    - effluents from manufacturing facilities
    - effluents from hospitals
    - leachates from landfills
- Predicted no effect concentrations of the selected APIs.
- Assessments of environmental risks of the measured environmental concentrations.

The case study areas and the chemical analyses are described in Chapters 2 and 3. Chapter 4 presents the consumption data for the selected APIs. Chapters 5–7 are divided into matrix-specific subchapters including methods, results, discussion and conclusion. Predicted API load in WWTP influents, based on the collected consumption data, are presented in chapter 8. Calculations of risk quotients are presented in chapter 9. At the end of the report there are overall conclusions and recommendations (chapter 10), followed by annexes.

2 Case study area selection and descriptions

2.1 Finnish case study area

River Vantaanjoki runs to the Gulf of Finland in Helsinki. The river basin, its estuary and the Helsinki coast were selected as a case study area. The case study area consists of two geographically overlapping but separate entities: one is a large wastewater treatment plant (WWTP) Viikinmäki in Helsinki and the coastal area near its outlet pipe in the Baltic Sea Estaury (BSE), and the other one is river Vantaanjoki and its estuary.

The Vantaanjoki main riverbed is approx. 100 km long with several smaller tributaries (Figure 2.1). Its drainage area is about 1 700 km^2 with around half a million inhabitants, but over 70% of the inhabitants are linked to WWTP Viikinmäki. However, the headwater and mid-river cities Riihimäki, Hyvinkää and Nurmijärvi have four municipal WWTPs discharging their treated wastewater into the river. In addition, there are a couple of very small WWTPs where pharmaceuticals may enter the river: a small nursery type hospital WWTP Rinnekoti and a small WWTP of a landfill site Metsä-Tuomela. Urban and industrial areas cover approximately 15% of the river basin area, making the case area one of the most urban catchments in Finnish scale.

We selected two municipal WWTPs (WWTP Viikinmäki and WWTP Kalteva), a small WWTP of a landfill site (Metsä-Tuomela) and surface water sites in the river (an upstream site and three downstream sites), estuary (two sites) and two off-shore sites (one at the outlet pipe of WWTP Viikinmäki and another about a nautical mile from the outlet pipe). Figure 2.1 shows a schematic figure of the sampling locations. Information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2).

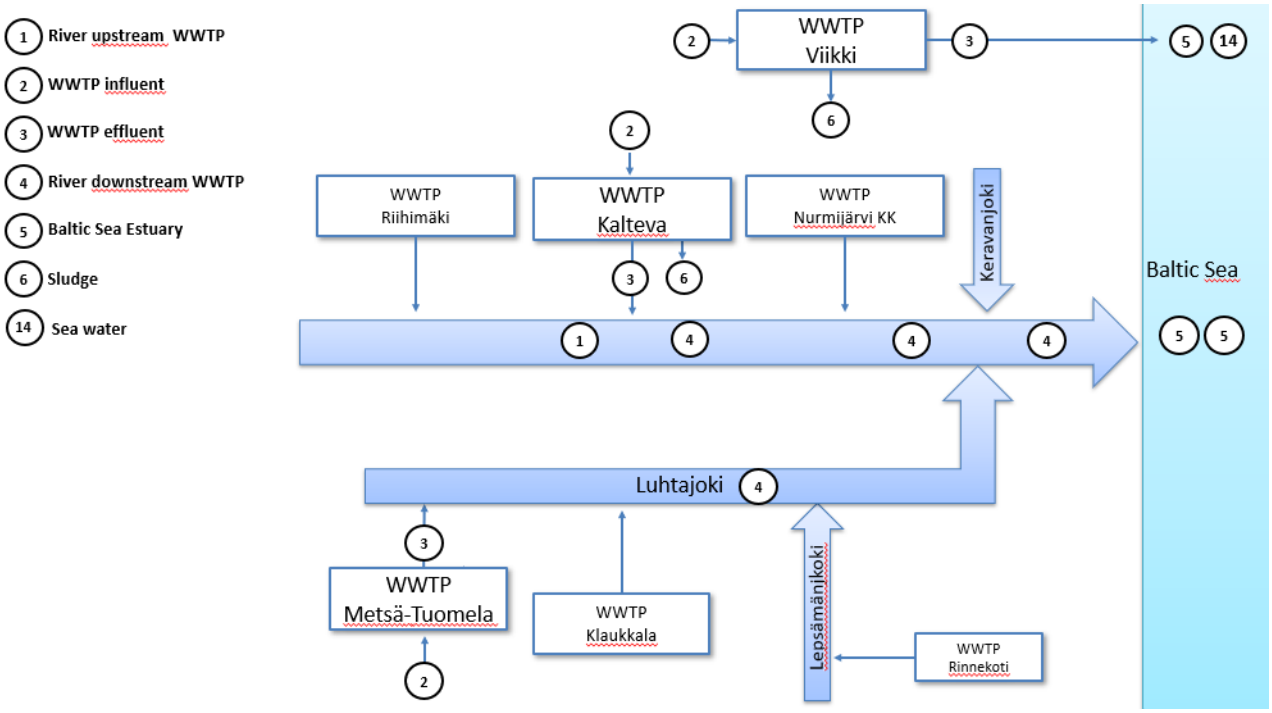


Figure 2.1. Schematic figure of the sampling locations within the Finnish case study area.

WWTP Viikinmäki is currently the largest WWTP in the Nordic countries, treating the sewage of over 800 000 inhabitants and several hospitals. The annual average volume of treated wastewater is 100 million m^3. Variation of daily sewage flow is presented in Figure 2.2. The treated wastewater is released to Baltic Sea via a 16 km long pipe. The pipe outlet is located roughly 7 km off the shore of the Helsinki peninsula at 20 m depth. The WWTP influent and effluent water samples were collected in December 2018, August 2018 and November 2018. Sludge samples were collected in December 2017 and August 2018.

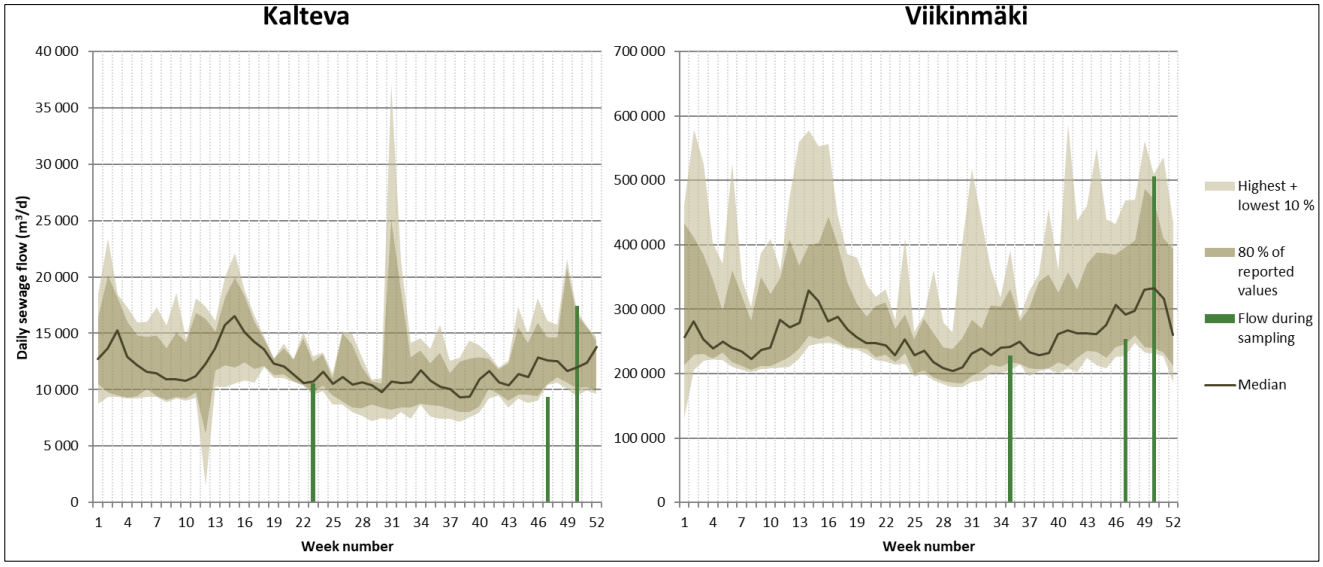


Figure 2.2. Variation in average daily sewage flow, calculated from reported weekly flows for the years 2003 – 2009 (Kalteva) and 2003-2017 (Viikinmäki). (Data: YLVA)

The medium-sized WWTP Kalteva (40 000 inhabitants and a hospital) is located 65 km north of the river mouth. From Kalteva the treated wastewater (almost 4 million m^3 per year) is directed into the River Vantaanjoki. The WWTP influent and effluent were sampled in December 2017, June 2018 and November 2018. One sample of undried raw sludge was taken in June 2018.

River samples were taken at one upstream and several downstream sites from Kalteva WWTP. About 20 km upstream from Kalteva is another WWTP, which treats the wastewater of approx. 38 000 inhabitants in Riihimäki and neighbouring cities and industrial waters. In addition, there are vacation homes not connected to any WWTPs and farms in the upstream drainage area.

Sampling was also performed at a landfill WWTP in Metsä-Tuomela. At the landfill site, APIs can leach from the treated (composted) sludge stored in the area or from the landfill. To balance the flows before the WWTP, there was a small pond that collected water from the landfill area and the surface runoff from composted WWTP sludge stored in the open air. The outlet of the WWTP effluent was in a ditch which runs to a tributane of river Vantaanjoki.

The weather conditions and Vantaanjoki river flow rates were very unusual in 2017–2018. The average flow measured at the lower reaches of the river Vantaanjoki is approx. 16 m^3/s (=1 400 000 m^3/d) being usually higher after snow melt and lower in summer. The first sampling campaign was carried out in December 2017, when the river flow was three times higher than average. The second sampling was in June 2018, when the flow was only ¼ of the average flow (Figure 2.3). A third sampling round was carried out in November 2018, but the flow was again lower than usual. Therefore, the portion of treated wastewater in the river water varied dramatically between the samplings.

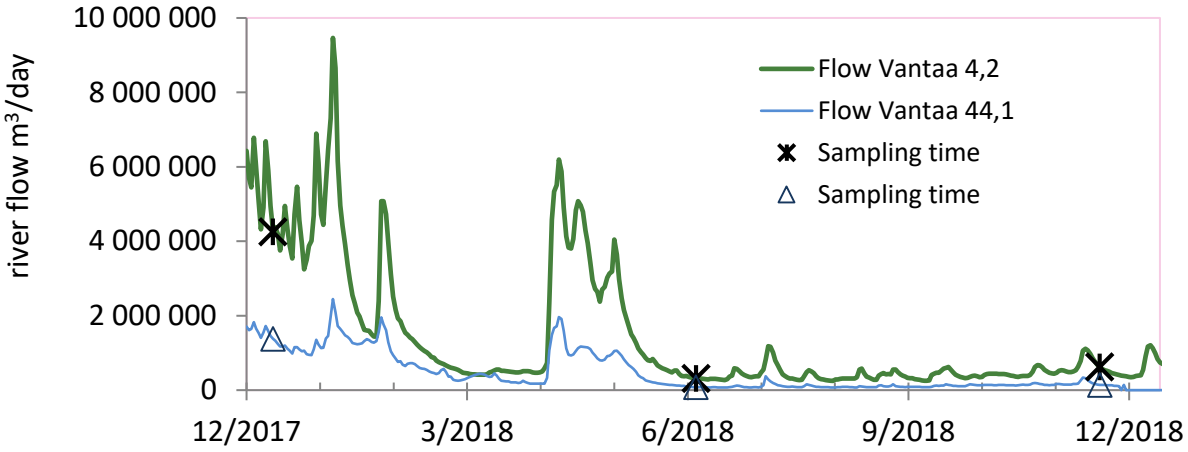


Figure 2.3. Daily flows of river Vantaanjoki close to the sampling sites Vantaa 44,1 and Vantaa 4,2 (Data: Hertta\Finnish Environment Institute).

The estuary and coastal samples were planned to be taken in the same week as river samples. However, the sampling sites were not reachable in December 2017 due to difficult weather conditions. In the beginning of March 2018 the coastal sampling site 'Katajaluoto 125' was reachable, but due to boat traffic the other coastal sampling site (Viikinmäki WWTP pipe outlet) was not. In Katajaluoto 125, samples were taken from three depths: 1 m from the bottom, in the mid-depth and a 1 m from surface. In June 2018 the same depths were used, and the outlet pipe site was sampled in the mid-depth (10 m). The two estuary sites were a bridge in the Vantaanjoki river mouth (Matinsilta, depth about 5 m; sampling in 1 m) and a site in the middle of Vanhankaupunginselkä (sampling in 1 m). They were sampled in March and June 2018, as well. Additionally, Matinsilta was sampled in November 2018 in the third river sampling round.

Sampling was performed in Vantaanjoki in Finland. Photo: Lauri Äystö, SYKE.

2.2 German case study area

The German Baltic Sea catchment region has a total area of about 30 307 km^2 and is mainly located in the Federal State of Mecklenburg-Vorpommern (21 960 km^2). The Warnow/Peene river basin district covers an area of 21 089 km². Main usage of the land area (13 452 km²) is agriculture with an area of 8774 km² (65% of land area). Besides the rivers Warnow and Peene, other large rivers are: Mildenitz, Nebel, Recknitz, Tollense and Trebel. The territorial unit has about 1.0 million inhabitants. The five largest cities are Rostock (204 300 inh.), Neubrandenburg (65 000 inh.), Stralsund (57 900 inh.), Wismar (44 100 inh.) and Greifswald (55 100 inh.).

In the Federal State of Schleswig-Holstein the Schlei/Trave river basin district discharges into the Baltic Sea. The Schlei/Trave river basin district has a total area of 9,218 km^2, 8,347 km^2 in Schleswig-Holstein and 871 km^2 in Meckelenburg-Vorpommern. Main usage of the land area (6184 km²) is agriculture with an area of 5,015 km² (81% of land area). Within this river basin region, about 1.25 million inhabitants are living. Largest cities are Kiel (235 700 inh.), Lübeck (211 500 inh.) and Flensburg (87 400 inh.).

The Warnow/Peene river basin region in Mecklenburg-Vorpommern was selected as case study area as it has the largest drainage area. There are 586 municipal WWTPs located in the Federal State of Mecklenburg-Vorpommern, with a total design capacity of about 3.3 million population equivalents (PE), of which 2/3 (about 2.2 million PE) are in the study area of the Warnow/Peene river basin district. The vast majority of the WWTPs (n = 514; 88%) have a smaller design capacity than 5000 PE, but only represent about 11% of the total treatment capacity. On the other hand, the 51 WWTPs with a treatment capacity of more than 10 000 PE cover 84% of the total treatment capacity. For the CWPharma measurement campaign three WWTPs of size class 4 (10 001–100 000 PE) and one WWTP of size class 5 (>100 000 PE) were selected. Information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2). All selected WWTPs are connected to the Baltic Sea directly (WWTP Greifswald with 59 232 persons connected, and WWTP Wismar with 42 963 persons connected) or indirectly via the river Tollense/Peene (WWTP Neubrandenburg with 63 761 persons connected) and river Warnow (WWTP Rostock with 209 191 persons connected). Information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2). Samples were taken in the influent and the effluent of the four WWTPs in autumn 2017 and summer 2018. Sewage sludge grab samples were also taken in autumn 2017 and summer 2018 from all four WWTPs.

Surface water samples were taken in two rivers (Tollense and Warnow) and in the estuary of the river Peene and river Warnow. The WWTP Neubrandenburg discharges into the river Tollense which is a tributary of the river Peene. Surface water samples of the Tollense were taken upstream and downstream of the WWTP Neubrandenburg. The Warnow surface water samples were taken upstream of the WWTP Rostock.

Effluent of the hospital Wismar was sampled in winter 2017 and summer 2018. The hospital effluent discharges to the WWTP Wismar. Soil samples were taken from an agricultural field outside of Rerik where sewage sludge of the WWTP Greifswald had been applied two years prior to sampling in summer 2018.

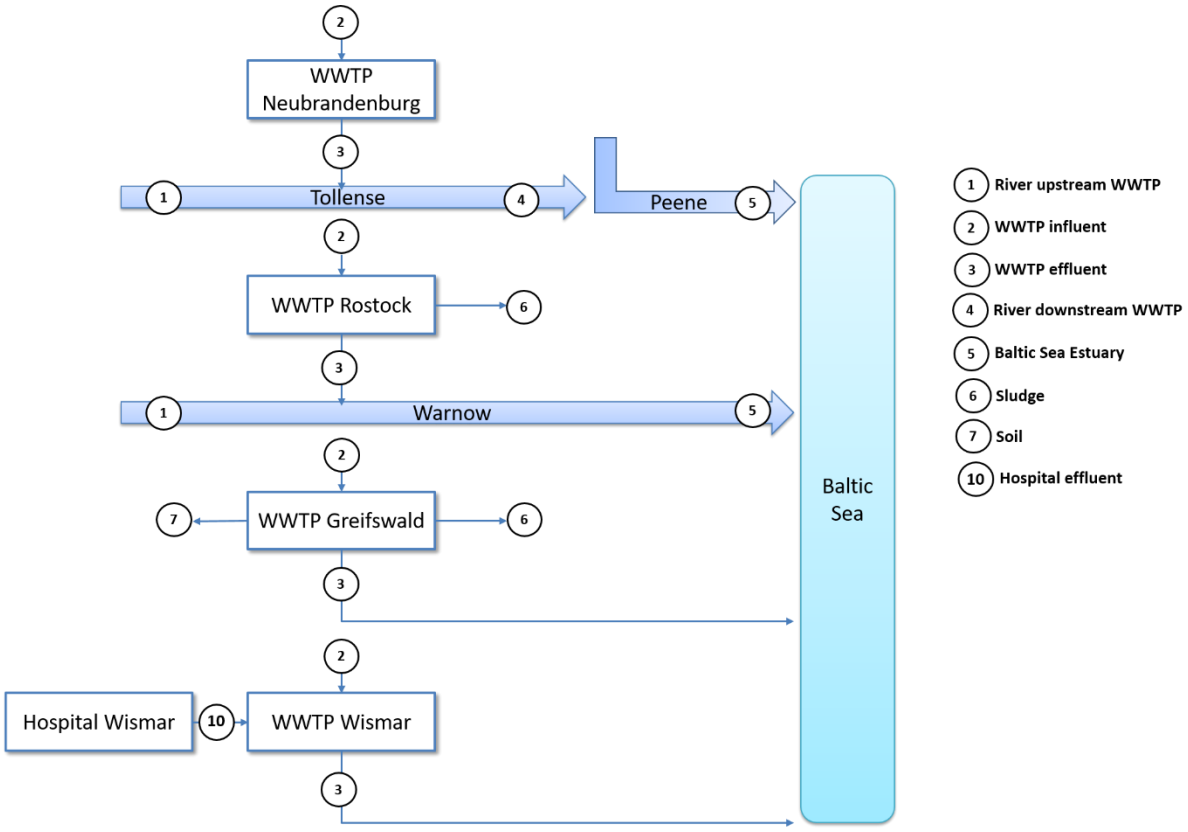


Figure 2.4. Schematic figure of sampling locations within the German case study area.

Collection of water sample upstream of WWTP Neubrandenburg in Tollense river, Germany. Photo: Jan Schütz, KWB.

2.3 Estonian case study area

The Estonian case study area was the Pärnu river, the second longest river in Estonia. The catchment area covers about 16% of Estonia. The Pärnu river catchment area is situated in Western Estonia and drains 6690 km² to the Bay of Pärnu. The river Pärnu (length 144 km) is a typical river for Estonia, characterized with spring snow-melting flood, autumn rain flood and minimal flow in summer and winter. The mean long-term runoff at the Pärnu - Oore hydrological station (representing 5160 km²) amounts 49 m³/s or about 9.5 l/s/km² or 300 mm per year. The river flow is regulated by several dams. Due to the lack of lakes in the river basin, the fluctuation of runoff is very large. 59% of the catchment area is covered by forests and natural grasslands. 30% of the total catchment area is arable land.

The population in the drainage area is about 179 000 inhabitants and 56% of them live in cities and towns. The main cities are Pärnu (41 000 inhabitants), Paide (8400 inhabitants) and Türi (5500 inhabitants). There are about 160 wastewater treatment plants in the catchment area, most of which are small. There are four wastewater treatment plants more than 2000 PE in the drainage area. Three of them were selected for the measurement campaign within CWPharma:

- Pärnu WWTP: 62 900 people, several industries, one hospital, several spas and sanatoriums are connected.
- Paide WWTP: 9 600 people, small enterprises, food proceeding industry, and one hospital are connected.
- Türi WWTP: 5 860 people and small industries are connected.

Information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2). Sampling locations in the Estonian case study area are presented in Figure 2.5. Samples were collected from surface water (upstream and downstream of WWTPs, and river estuary), river and estuary sediments, three WWTPs (influent, effluent and sewage sludge), Roosna-Alliku fish farm, Pärnu hospital sewage water, and the soils of two fields. All water and sediment samples were taken in December 2017 and in June 2018. Soil samples were collected in October 2018.

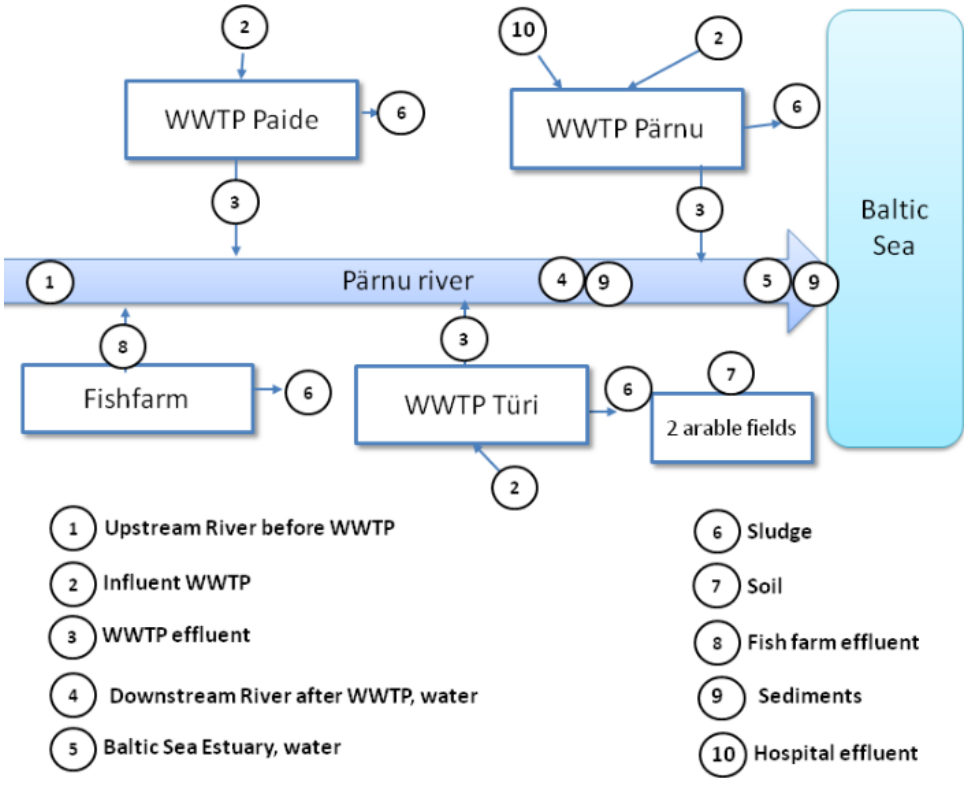


Figure 2.5. Schematic figure of sampling locations within the Estonian case study area of Pärnu river catchment area.

Pärnu river in the Estonian case study area. Photo: Vallo Kõrgmaa, EERC.

2.4 Latvian case study area

The Latvian case studies were carried out in Lielupe and Daugava river basin districts. Lielupe river covers many data gaps identified in the Status report on pharmaceuticals in the Baltic Sea region (UNESCO and HELCOM 2017). Lielupe river provides environmental data from both Latvia and Lithuania, as well as contributions to our understanding of API emessions from both veterinary areas and the pharmaceutical manufacturing industry:

1) Transboundary river basin district with Lithuania (8849 km^2 in Latvia and 8751 km^2 in Lithuania; 235 000 inhabitants in Latvia and 261 039 in Lithuania;
2) There are big poultry and pig farms;
3) There is pharmaceutical manufacturing industry ("Olainfarm").

There are also cities that discharge their wastewater into the river Lielupe. Biggest cities in the Lielupe river basin district are Jelgava, Jūrmala, Dobele, Bauska and Olaine. There are many WWTPs in the catchment area. Samples of influent, effluent were taken in two of them – WWTP 1 near Driksa river (a branch of the river Lielupe), where also sludge was taken, and WWTP 3 near Pupla river, to which in total 63 072 people were connected in 2018 (51 452 to WWTP 1 and 11 620 to WWTP 3). The amount of wastewater was 9140 m^3 per day at WWTP 1 in 2018, 2570 m^3 per day at WWTP 3.

There were also two sampling places in Daugava river basin district:

- WWTP 2 (samples of influent, effluent, sludge) receives wastewater from Riga city, as well as effluents from manufacturing facilities of API as, for example, "Grindeks", "Northern Synthesis", "Rīgas farmaceitiskā fabrika";
- wastewater effluent sample in one API manufacturing facility in Rīga;
- water and sediment sample in the Gulf of Riga near discharge of wastewater treatment plant.

In total 636 865 people were connected to WWTP 2 in 2018, and the amount of treated wastewater was 130 000 m^3 per day. Information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2).

Sampling locations in the Latvian case study are presented in the schematic figure 2.6. Surface water samples were taken in five rivers (Mūsa, Mēmele, Pupla, Lielupe and Vērģupe), and in a ditch downstream a pig farm, and in the Gulf of Riga. Sediment samples were taken in the Gulf of Riga. Surface water samples were taken in November 2017 (inland waters) or December 2017 (Gulf of Riga) and May 2018. Samples of WWTP influent, effluent and sludge were taken in December 2017 and May 2018. Soil samples were taken from agricultural field, where manure had been applied, in June 2018.

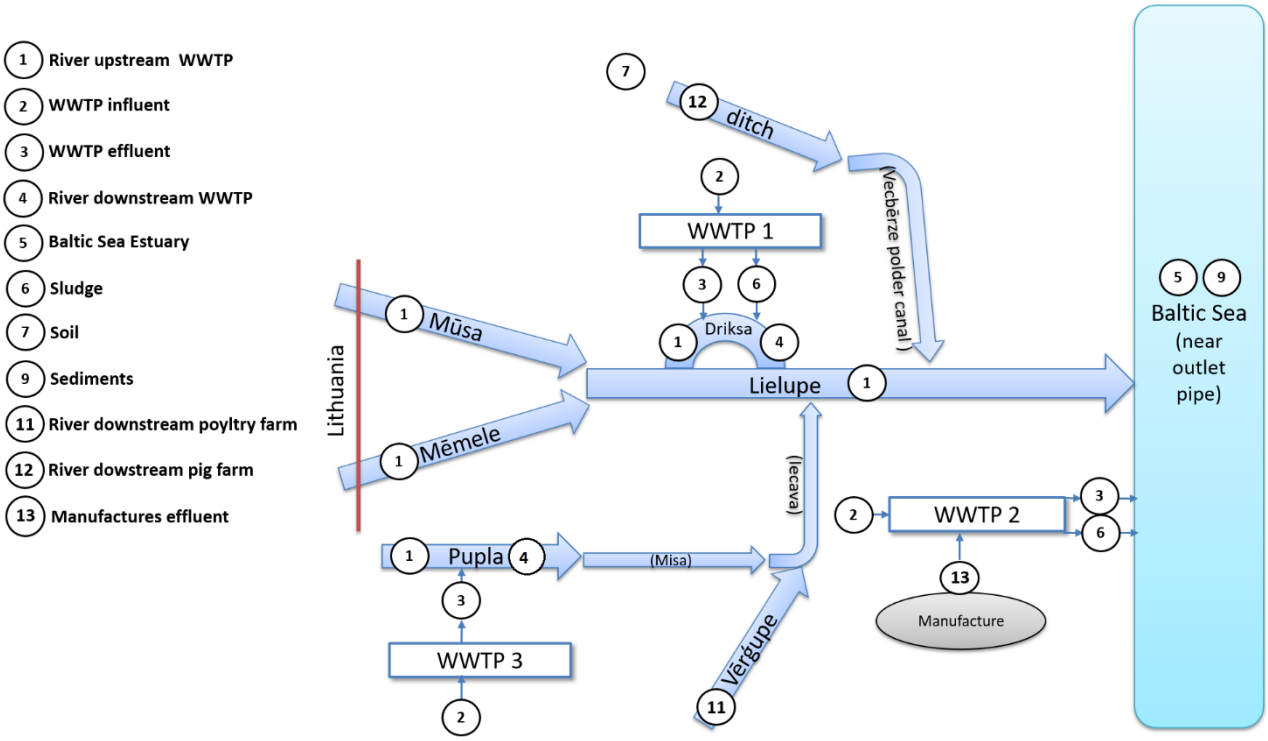


Figure 2.6. Schematic figure of sampling locations within the Latvian case study area of Lielupe river and Riga city.

Musa river at the Latvia-Lithuanian border. Photo: M. Tīrums, LEGMC.

2.5 Polish case study area

The Polish case study samples were collected from two locations (Figure 2.7): the Rokitnica river at the city of Błonie (Mazovian Voivodeship) and from the Vistula river at the village of Kiezmark (Pomeranian Voivodeship). Samples of raw sewage (WWTP influent), sewage sludge and treated sewage (WWTP effluent) were collected at the WWTP in Blonie. About 30 000 persons are connected to the WWTP in Blonie. The WWTP in Blonie discharges its effluents (2 000 000 m^3/year) in the Rokitnica Nowa River. Information on the treatment process and size (in PE) of the studied WWTP is shown in chapter 6 (table 6.2).

Discharge of treated wastewater from Miejskie Przedsiębiorstwo Wodociągów i Kanalizacji Sp. Zoo. - Błonie takes place about 3 km downstream of the WWTP in the Rokitnica Nowa river. The average water flow of Rokitnica Nowa River is below 1 m^3/s at the WWTP. The Rokitnica Nowa River is a kind of "relief" of the Rokitnica river, in the case of large flows.

The Rokitnica river is about 30 km long and the catchment area is 227 km^2. Surface water samples were collected from the Rokitnica River about 500 m upstream the WWTP and downstream the discharge of treated wastewater where the treated sewage is fully mixed with the waters of the Rokitnica Nowa River.

A surface water sample was also collected from the Vistula river, near the bridge in the village of Kiezmark. This is 930 000 km of the Vistula river's course, and the bridge is the last, northernmost bridge on the Vistula. The mouth of the river is located 12 km further down its course. The catchment area of this section of the river is 194 414 km^2.

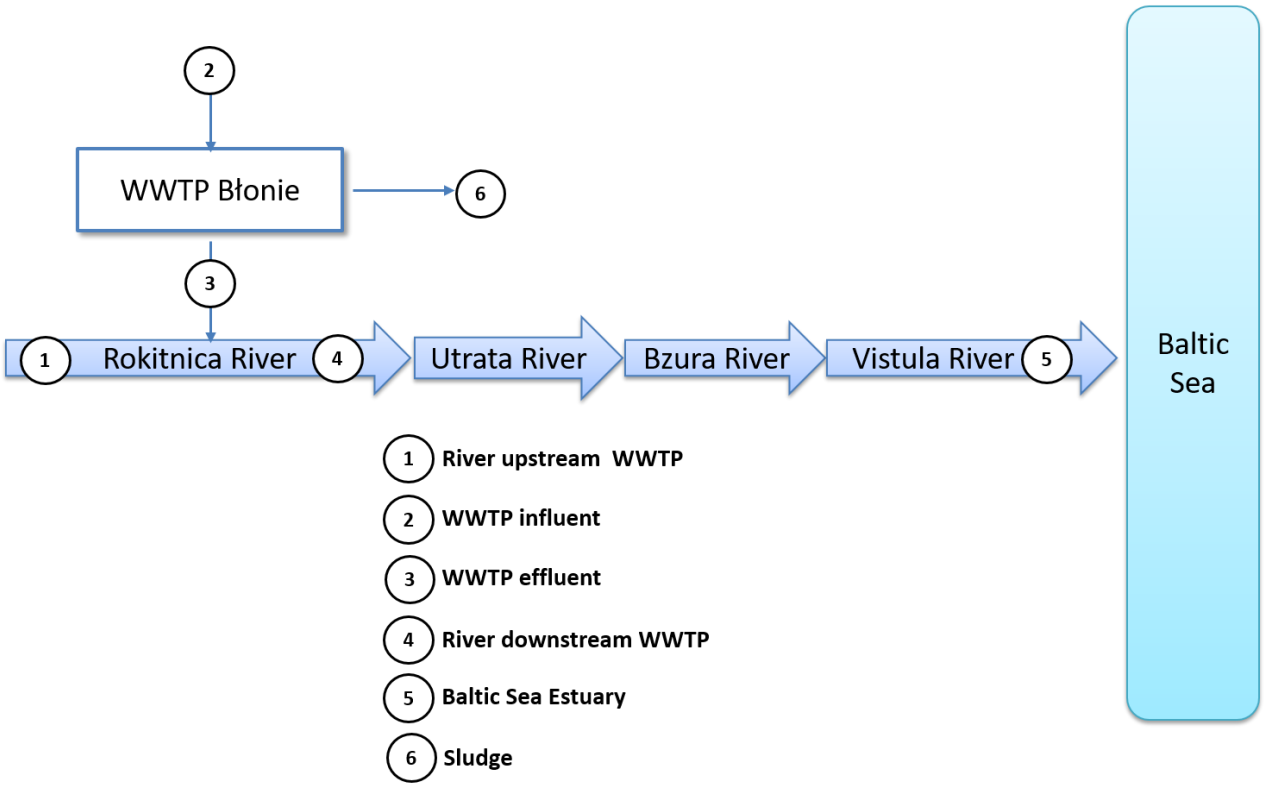


Figure 2.7. Schematic of sampling locations within Polish case study area.

Vistula river in the Polish case study area. Photo: Radoslaw Kalinowski.

2.6 Swedish case study area

The Motala Ström case study area is one of the largest catchment areas in Sweden, covering approximately 15 500 km² and with a population of approx. 650 000. The main cities are Linköping and Norrköping, where also the largest hospitals are located. The total length of the river Motala ström is about 100 km, stretching from Lake Vättern in Motala to Bråviken estuary in Norrköping. The average water flow of Motala ström is 92 m³/s at the mouth in Norrköping. Motala ström runs through three large lakes on its way to the Baltic sea: Boren, Roxen and Glan. Also, two other rivers flow into Lake Roxen: Svartån and Stångån.

There are several WWTPs in the catchment area. Samples of influent, effluent and sludge were taken at the largest WWTPs located in Motala, Linköping and Norrköping, to which in total 315 500 people are connected (i.e. almost the half of the population in the catchment area). The WWTP in Motala is located early in the river system, discharging its effluent (3 104 370 m³/year) into Lake Boren. About 32 500 persons are connected to the WWTP in Motala/Karshult. The WWTP in Linköping discharges its effluents (14 829 000 m³/year) in the river Stångån, near the mouth of Lake Roxen. About 147 500 persons are connected to the WWTP in Linköping. The WWTP in Linköping has installed advanced ozone treatment of APIs, but this treatment was not running during the sampling occasions. Finally, the WWTP in Norrköping/Slottshagen dicharges its effluents (1 6327 000 m³/year) to the river Motala ström close to the Bråviken estuary. About 135 500 persons are connected to the WWTP in Norrköping. Further information on the treatment process and size (in PE) of the studied WWTPs is shown in chapter 6 (table 6.2).

Sampling locations in the Swedish case study area are presented in the schematic Figure 2.8. Surface water samples were taken in four lakes (Vättern, Boren, Glan and Dovern), two rivers (Svartån and Stångån, upstream and downstream the WWTP in Linköping) and in the Bråviken estuary outside Norrköping. Sediment samples were also taken in the Bråviken estuary, approx. 7,5 km downstream the discharge of treated wastewater from the WWTP in Norrköping. All water and sediment samples were taken in December 2017 and in June 2018.

Samples of effluents were also taken from the two major hospitals in the catchment area: the university hospital in Linköping and the Vrinnevi hospital in Norrköping. The hospital effluents are discharged to the WWTPs in Linköping/Nykvarn and Norrköping/Slottshagen, respectively. Soil samples were taken from an agricultural field outside of Linköping where sewage sludge had been applied two years prior to sampling. The sampling of soil and hospital effluents were both performed in June 2018.

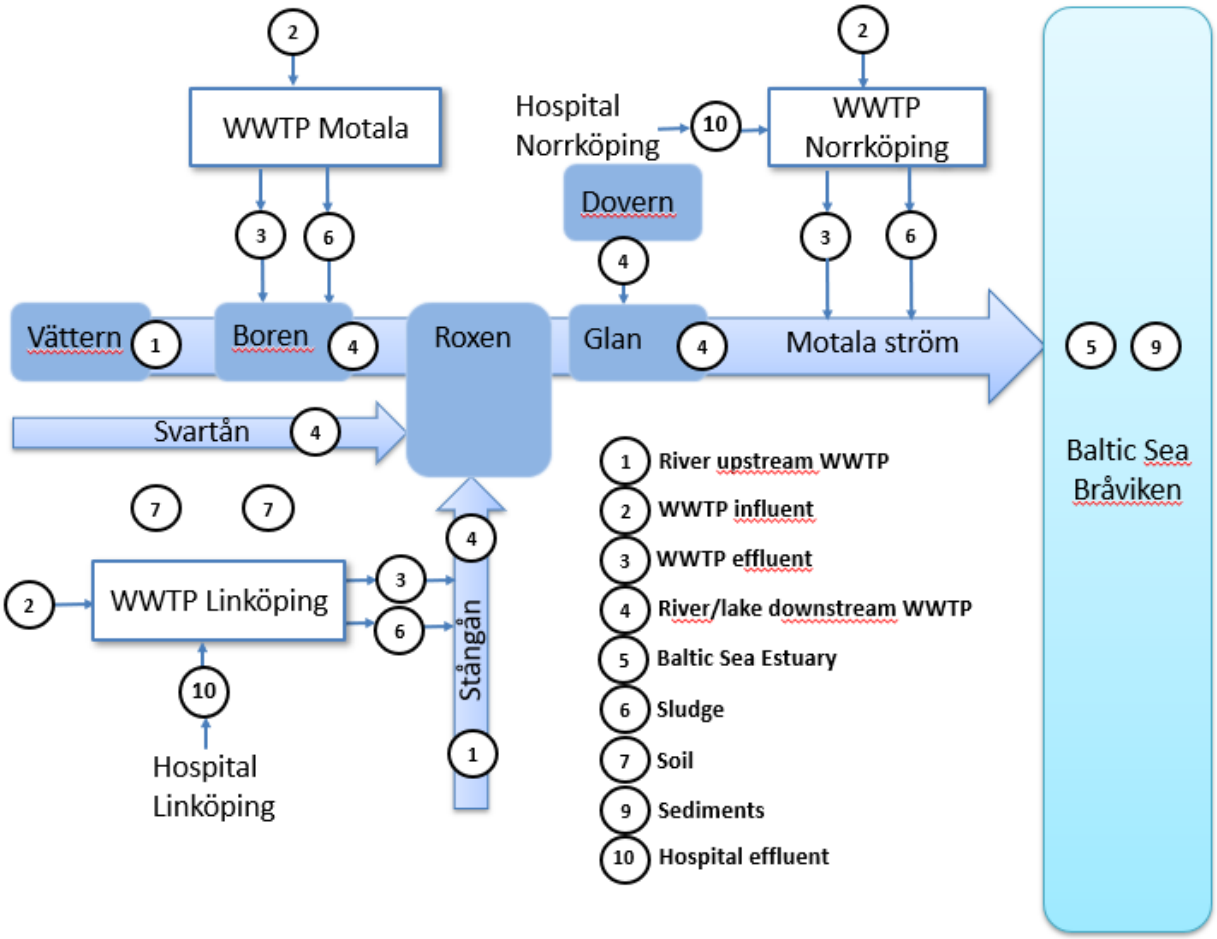


Figure 2.8. Schematic figure of sampling locations within the Swedish case study area of Motala ström.

Lake Roxen recives water from three rivers: Motala ström, Svartån and Stångån. Photo: Helene Ek Henning, CAB.

3 Sample storage and analysis

The APIs that were analysed from the case study samples were based on existing analytical methods in SYKE laboratory and amended with highly consumed or highly detected APIs and veterinary APIs. To find out the highly consumed or highly detected APIs, we reviewed the consumption and environmental concentration data from the Baltic Sea Region. This included a status report on pharmaceuticals in the Baltic Sea region (HELCOM and UNESCO 2017[2]), where certain APIs (allopurinol, gabapentin, levetiracetam, mesalazin, valsartan) with high consumption and no monitoring data were highlighted, and APIs that were suggested as priority substances in the BSR countries. To estimate the emissions from animal husbandry, we selected nine veterinary APIs that are used for farm animals and/or fish in the BSR countries. Five of the nine veterinary APIs are also used for companion animals. The selected veterinary APIs are used only for animals, except ivermectin which can also be used as an insecticide e.g. against hair lice.

Collected 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. Sludge, soil and sediment samples were lyophilized and stored under -20 ± 2 °C prior to the analysis. Samples were analyzed within six months after arrival to the laboratory.

The APIs were analysed from the case study samples in SYKE laboratory in Finland using an UHPLC-MS/MS instrument (Waters Acquity UPLC and Xevo TQ). Before the instrumental analysis, water samples were extracted with solid-phase extraction (SPE) using HLB discs (Atlantic HLB-M, 47 mm) for surface and estuary waters and HLB cartridges (Oasis HLB 60 µm, 6 cc, 500 mg) for wastewater influents and effluents. The wastewater influents and effluents were also analysed with direct injection. The solid samples (i.e., wastewater treatment plant sludge, soil and sediment) were freeze-dried and extracted with solid-liquid extraction using buffer solution and methanol. The extracts were further purified by SPE using strong anion exchange cartridges (Oasis MAX 60 µm, 6 cc, 150 mg). All the samples were filtered through a regenerated cellulose filter (RC, 0.2 µm pore size, Captiva, Agilent Technologies) prior to analysis with UHPLC-MS/MS. The LC-MS/MS method could not distinquish between enantiomers of APIs (e.g. citalopram end escitalopram). Also, the concentrations of tetracycline and oxycycline are given as sum parameter, because chromatographic separation of these compounds was not obtained, and the compounds cannot be separated by the mass spectrometer.

All samples were spiked with mass-labelled internal standards before extraction. To estimate the method overall recovery of the compounds for which mass-labelled surrogates were not available, all sample batches included at least one spiked sample. Contents were reported for those APIs having absolute recoveries in the range of 30–160%.

For quality assurance and control, blank samples and a control sample were analysed in each sample batch. In addition, we performed a stability test for wastewater effluent and river water to evaluate the effect of sample storage and transportation to the API concentrations. The list of analysed APIs, and the performance of the analytical methods, including recovery correction method, recoveries of the spiked control samples and the limits of quantification (LOQ), are presented in Annex 1.

[2] UNESCO and HELCOM, 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris.

Table 3.1. Analysis of APIs from water, sludge, soil and sediment samples.

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
WWTP sludge	0.5	SLE+SPE	1	UHPLC-MS/MS	31
Soil	2	SLE+SPE	1	UHPLC-MS/MS	65
Sediment	2	SLE+SPE	1	UHPLC-MS/MS	65

SLE = Solid-liquid extraction, SPE = Solid-phase extraction, UHPLC-MS/MS = Ultra high-performance liquid chromatography combined with multiple reaction monitoring mass spectrometry

4 Consumption data of APIs

4.1 Methods

Drug consumption data for the 83 selected APIs was collected based on the available statistics in each Baltic Sea country. Data are presented in kg for the years 2015-2017. The complete human consumption data are presented in Annex 2. The consumption data are based on different sources and is of different quality described for each country below. Information on the consumption of veterinary medicines was also collected through a questionnaire organized in collaboration with HELCOM. The results from this questionnaire are incorporated into this chapter when appropriate.

4.1.1 Finland

Drug consumption statistics are based on the amount of medicines sold by drug wholesalers to pharmacies and hospitals. Drug consumption statistics are available publicly at the Finnish Medicines Agency (Fimea) website[3], expressed as defined daily doses (DDD) per 1000 inhabitants and per day. This figure offers estimation of what proportion of the population theoretically receives a certain drug treatment during a certain period. In the statistics drugs are sorted using the latest Anatomical Therapeutic Chemical (ATC) classification. Due to the uncertainties of the DDD data, for this project, the Fimea database for consumption data of the 83 API was directly searched for more accurate calculation of consumption data. For each API, the corresponding ATC codes were queried from the database (see Annex 2). All formulations and strengths, including combination products were taken into account. The data represents the wholesale data in kg of the API. All pharmaceuticals, hospital and outpatient, both prescription and over the counter (OTC) medicines are included in the data.

4.1.2 Sweden

Statistics about pharmaceutical sales were ordered from the Swedish eHealth Agency. Anyone selling pharmaceuticals in Sweden is bound by law to provide regular reports of their sales to the eHealth Agency. The statistics include medicines registered for both human and veterinary use. Reported sales data covers both prescribed and non-prescribed medicines provided by pharmacy operators, retailers and wholesalers. The sales statistics consist of all retailers of pharmaceuticals (both in pharmacies and other stores with a license to sell non-prescribed drugs), medicines sold to healthcare and other goods that are subsidized in the high-cost protection. Pharmaceutical supplies to hospitals and healthcare institutions not dispensed through a pharmacy are not included. The sales data in kg of the API were calculated based on the sales statistics (i.e. sold packages) combined with the strength (i.e. amount of API in each package). All formulations and strengths, including combination products were included in the data.

4.1.3 Germany

The German statutory health insurances index (GKV-drug-index) was used for the calculation of the consumption data for human pharmaceuticals. Within the GKV-drug-index all pharmaceuticals are documented which have been sold at e.g. pharmacies and were (partly) paid by the German statutory health insurances. Thus, privately purchased pharmaceuticals are not included in the dataset. The GKV-drug index-dataset provides the total amount per active drug substance (mono as well as combination products) in DDD for each year. For the current dataset, the average amount of substance per DDD for different kind of intakes, defined by the ATC-Index, was calculated and multiplied with the DDD/year. For veterinary medicines data were only available for antibiotics. Data were provided by the German Federal Office of Consumer Protection and Food Safety. The dataset for veterinary medicines only provides the total amount per class of drugs and not per active drug substance (e.g. fenbendazole belongs to the class of benzimidazoles).

[3] https://www.fimea.fi/web/en/databases_and_registeries/consumption

4.1.4 Latvia

The calculations are based on quantities sold in Latvia and the consumption of all medicines is included: both topical and oral medications, non-combined and combined products, as well as registered and non-registered medicines. API consumption statistics are publicly available in DDD, but they do not include topical formulations. The calculations of sold quantities of APIs in kg were performed by the State Agency of Medicines of Latvia specifically for the needs of CWPharma-project. The calculations were not done based on the DDD values, but in the following way: for example, if a package contained 0.5 grams of diclofenac, then 0.5 g was multiplied with the number of sold packages and converted to kilograms.

4.1.5 Estonia

The statistics about Estonian annual drug consumption are based on wholesalers' reports. Drug consumption statistics are available publicly at the State Agency of Medicines (SAM) website[4]. All the wholesalers report their drug sales data to the State Agency of Medicines four times a year. The reports include the following data for each product: ATC code, ingredients, trade name, pharmaceutical form, strength, package size and the manufacturer. The sales data are presented in monetary value and by unit of volume (number of packages). The statistics of human and veterinary medicinal products include sales to general and hospital pharmacies and to other institutions, i.e. state and scientific institutions. The consumption results are presented in the number of DDDs per 1000 inhabitants per day. Due to the uncertainty of the DDD data, an inquiry was made to the Estonian Medicines Agency to obtain more accurate consumption data for the 83 active substances selected for the project. For each API, the corresponding ATC codes were queried from the database. All formulations and strengths, including combination products were considered. The data represents the wholesale data in kg of the pure API. All pharmaceuticals, hospital and outpatient, both prescription and OTC medicines are included in the data.

4.1.6 Lithuania

Statistics of the Lithuanian drug consumption as DDDs were received from the project MORPHEUS study on pharmaceutical consumption patterns in four coastal regions of the South Baltic Sea (Kaiser et al., 2019)[5]. The statistics are also available in the Baltic Statistics on Medicines 2013-2015 and 2016-2018, which are available on the websites of the Estonian, Latvian and Lithuanian medicines regulatory agencies.

4.1.7 Denmark

Statistics of the total sales of medicines in Denmark can be found at medstat.dk. Medstat.dk contains statistics on the sales of medicines in Denmark based on the data reported to the Register of Medicinal Product Statistics. It is mandatory to report the sales of medicines, and therefore the data covers all sales in Denmark. The data are reported by pharmacies and non-pharmacy outlets that sell medicines. Besides the medicines sold to individuals, the sales of medicines for use in practices and for medicine stocks at treatment centers are reported. This is the sales in the primary sector, and statistics are available from 1996 onwards. The Register of Medicinal Product Statistics also includes data about medicines sold to hospitals - the hospital sector - statistics are available from 1997 onwards. For the OTC sales from shops outside pharmacies the sales for 2016 and 2017 includes only the sales from the major retail chains (e.g. supermarket chains), because the data has not been yet checked for completeness. The statistics are available as DDD. For some groups of medicines for which DDD has not been defined by WHO, a national DDD has been defined.

4.1.8 Poland, Russia and Belarussia

No consumption data were available from Poland, Russia and Belarussia for 2015, 2016 and 2017. However, for a selection of the APIs studied in this project consumption data became available in a

[4] https://www.ravimiamet.ee/en/statistics-medicines

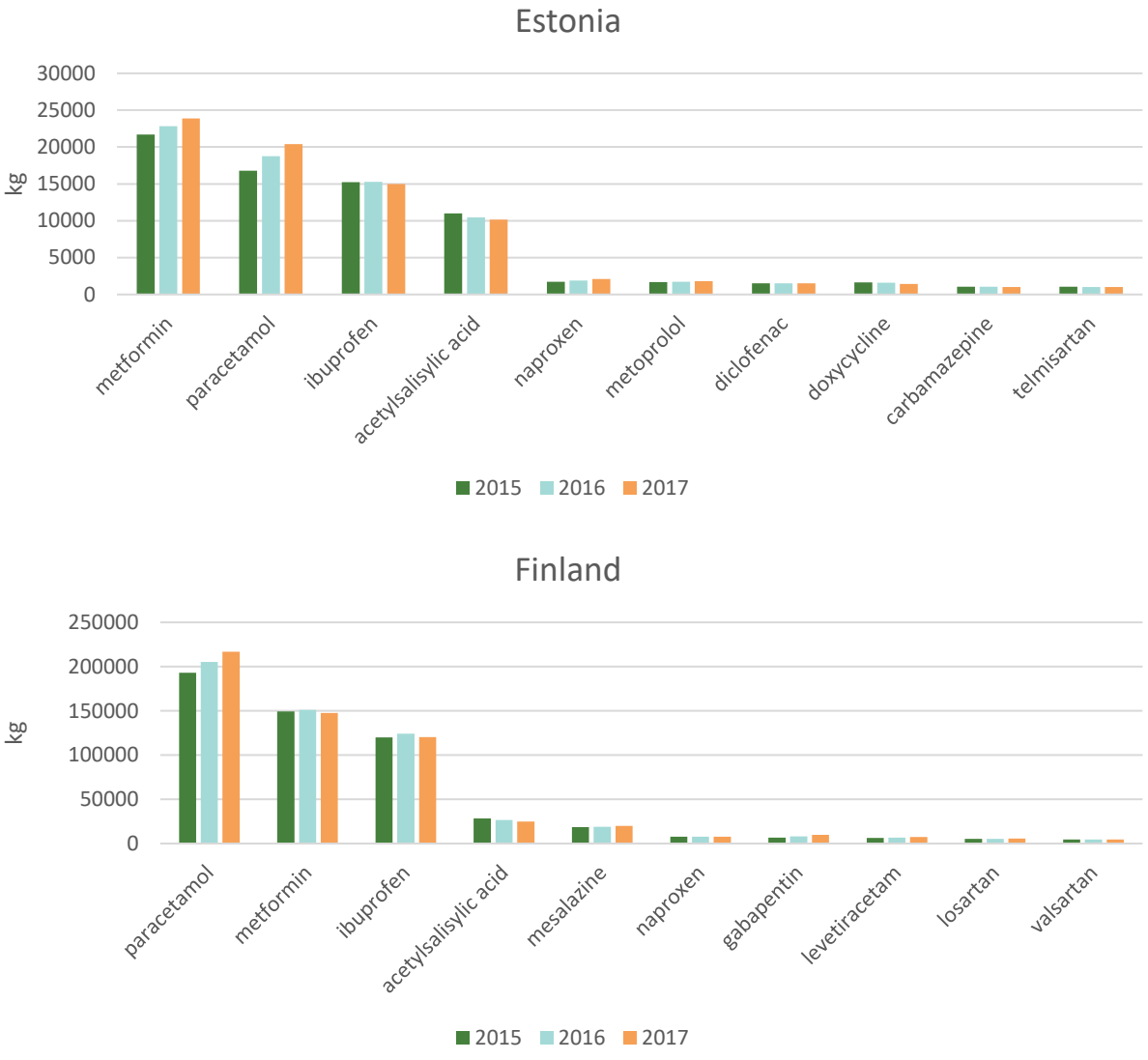
[5] Kaiser, A., Tränckner, J. et al. (2019). Pharmaceutical consumption patterns in four coastal regions of the South Baltic Sea. Germany, Sweden, Poland and Lithuania. Project MORPHEUS 2017 - 2019 Deliverable 3.1.Available at: https://eucc-d-inline.databases.eucc-d.de/files/documents/00001227_MORPHEUS_DEL3.1_Final.pdf

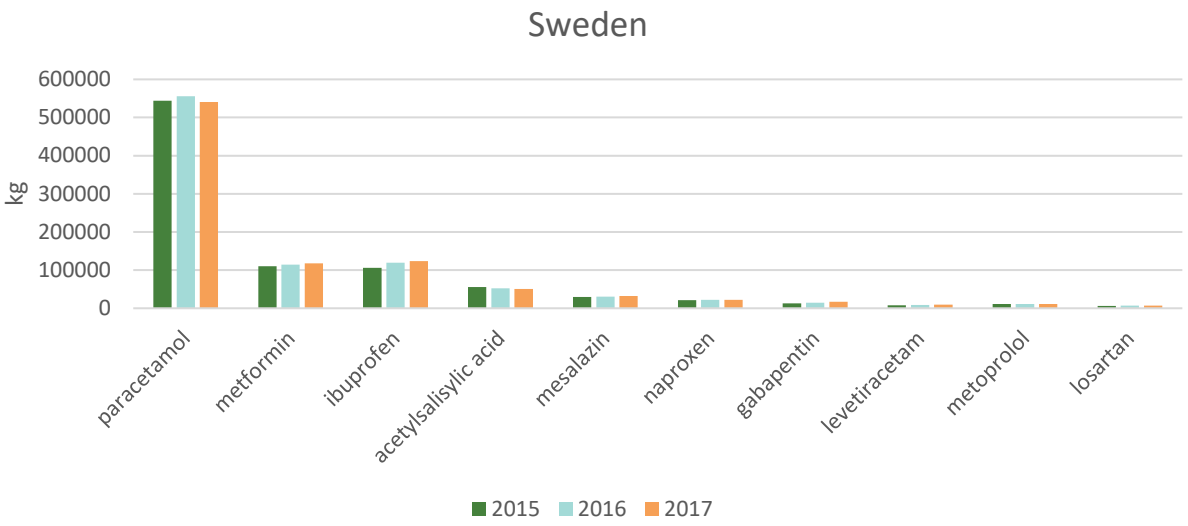
report about pharmaceutical consumption patterns in four coastal regions of the South Baltic Sea (Kaiser et al. 2019). In this report, data for 2015 was presented for the Pomeranian Voivideship (Poland) for 19 APIs. The 19 APIs in the MORPHEUS project largely overlapped the APIs selected for CWPharma. Therefore, this data could be used to extrapolate the consumption for the whole Poland. However, the consumption data were available only for reimbursed and prescribed medicines. Thus, the consumption of OTC products (e.g. ibuprofen and naproxen) was likely underestimated in this data.

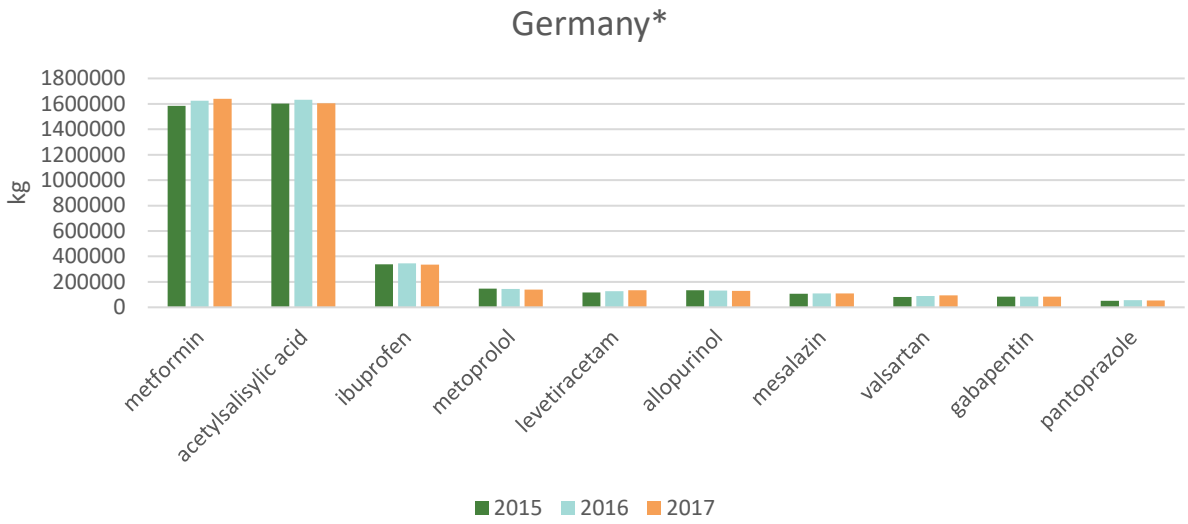
4.2 Results and discussion

4.2.1 Human consumption

74 of the 83 APIs studied in this project are primarily used in human medicine. The corresponding ATC codes and the grouping of the API are presented Annex 2. The top ten consumed APIs in kg per year for each participating country are presented in figure 4.1. For Lithuania and Denmark data for human medicines was only available in DDD format and therefore not presented here. The German data has been converted from DDD data and includes only data for reimbursed medicines. For Poland, very limited data were available, and therefore the data are not presented. For Russia and Belarussia no consumption data for 2015, 2016 and 2017 could be obtained from public sources.







* Only medicines paid by the German statutory health insurances are included

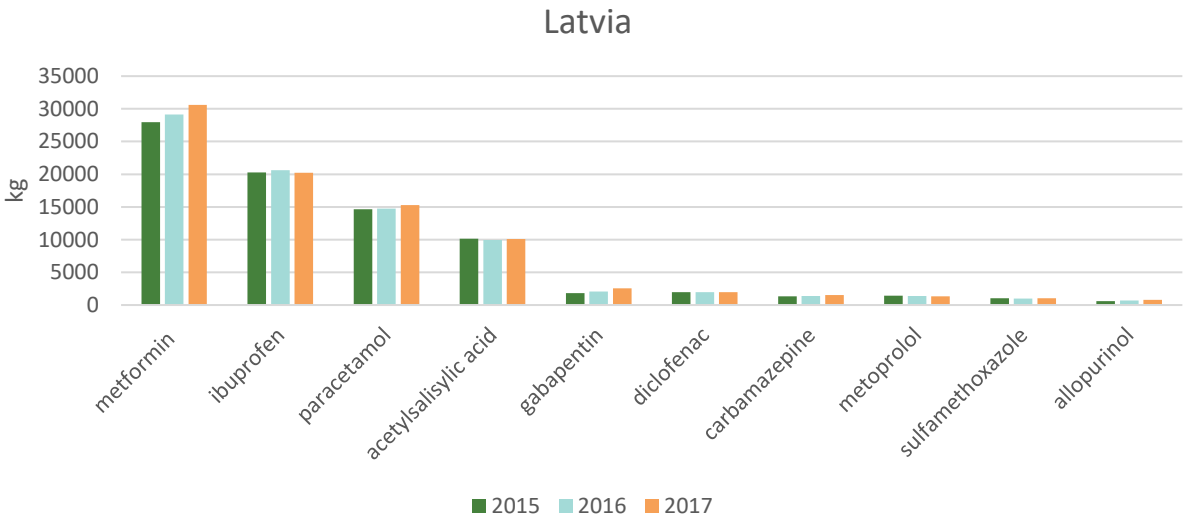


Figure 4.1. Pharmaceuticals with the highest consumption in kg for each participating country. Note different scales on the y-axis.

Antibiotics

The antibiotics for human use considered in this project were ciprofloxacin, clarithromycin, doxycycline, erythromycin, fluconazole, lincomycin, norfloxacin, ofloxacin, sulfadiazine, sulfamethoxazole, tetracycline and trimethoprim. Considering the overall antibiotics consumption, some of the most frequently used antibiotics, such as penicillins, amoxicillin, cefalosporins or azithromycin were not included in this project. Of note is that lincomycin appears to be predominantly used for veterinary medicine. In addition, doxycycline, sulfadiazine and sulfamethoxazole are also used in veterinary medicine, although most of the consumption comes from human use. In this project, only two antibiotics were among the 10 most consumed APIs. In Germany tetracycline was the 10th most used API, but this is most likely because only reimbursed medicines data were available. In Latvia sulfamethoxazole was the 9th most used API.

Antiepileptics

The antiepileptics considered in this project included carbamazepine, gabapentin, levetiracetam and primidone. Some of the commonly used antiepileptics were not included in this project, such as oxcarbazepine, topiramate, valproate, lamotrigine and pregabaline. Antiepileptics were included among the 10 most used APIs in each country: gabapentin and levetiracetam in Finland, Sweden and Germany, gabapentin and carbamazepine in Latvia and carbamazepine in Estonia.

Antihypertensives

Medicines used mainly to control high blood pressure, and considered in this project, were amlodipine, candesartan, enalapril, eprosartan, hydrochlorothiazide, irbesartan, losartan, ramipril, telmisartan and valsartan. Medicines used also for hypertension, but primarily for other cardiovascular indications, are included under *Other cardiovascular medication*. Although the antihypertensives can be used alone, they are commonly part of a fixed combination product. An antihypertensive combination product typically includes a diuretic component, (hydrochlorothiazide) and another blood pressure lowering active ingredient. The proportion of consumption coming from combination products varies greatly depending on the drug. Of the antihypertensives studied in this project, losartan was among the 10 most used API in Sweden, valsartan in Germany, telmisartan in Estonia and both losartan and valsartan in Finland.

Asthma and allergy medications

The active pharmaceutical ingredients that were considered in this project included cetirizine, fexofenadine, fluticasone, mometasone furoate and xylometazoline. Regarding the oral antihistamines it is important to consider also data for levocetirizine and hydroxyzine. Levosetirizine is the r-enenthiomer of cetirizine and approximately 45% of the orally administered hydroxyzine is metabolized into cetirizine. Detection of cetirizine in environmental samples therefore not only reflects the cetirizine use but also levocetirizine and partly hydroxyzine. Fluticasone and mometasone are used in inhalation products for allergy and asthma. Mometasone is also available in topical formulations for dermatological conditions. Xylometazolin is available alone and in combination with other pharmaceutical ingredients, in a nasal spray formulation for nasal congestion. None of the APIs studied in this group were among the 10 most used APIs in any country.

Gastrointestinal disease medications

The gastrointestinal disease medications included in this project included the proton-pump inhibitors esomeprazole, omeprazole and pantoprazole, which are used for conditions such as gastrointestinal reflux disease. Esomeprazole is the s-enanthiomer of omeprazole, which needs to be considered when looking at the environmental levels of these medicines. The detection methods used in this project were not able to distinguish between the enanthiomers. Mesalazine is used to treat ulcerative colitis and other inflammatory bowel diseases. Typical dose is 1.6 - 2.4 g per day, which results in rather high overall consumption of the medicine although the proportion of population using mesalazine is lower than those using e.g. proton pump inhibitors. Olsalazine is a molecule comprising of two mesalazine molecules and sulfasalazine, which is used for similar

indications, metabolises in humans partly into mesalazine. The consumption statistics of sulfasalazine and olsalazine should be taken into consideration when assessing environmental levels of mesalazine. Mesalazine was among the 10 most used API in Finland, Sweden and Germany.

Hormones

Hormones considered in this project were 17-α-ethinyl estradiol (EE2), 17-β-estradiol (E2), estriol, estrone, norethisterone, progesterone and testosterone. No consumption for estrone was reported from any country, suggesting that no medicinal product containing estrone for human is available in the countries involved. Like many of the hormones studied in this project, estrone is a naturally occurring hormone in humans and animals. In fertile aged females, the average production of estrone is between 0.45-1 nmol/day, depending on the stage of the menstrual cycle. The average production of estrone in males is 0.6 nmol/day.

EE2 is a component in many contraceptive medicines. It is available in contraceptive pills, plasters and vaginal rings. The total consumption of EE2 is overall quite low in kilograms, due to the very low amounts of hormones needed to get the desired efficacy. Estriol is available as oral formulations as well as vaginal cream and suppositories. Norethisterone is available in an oral formulation but is also available in plasters indicated for hormone replacement therapy. During the use of plasters, 6-18% of the norethisterone is absorbed and the rest remains in the plaster, which is discarded. Norethisterone metabolises partly into EE2, which results in a dose of 4-6 micrograms of EE2/1 mg of norethisterone, when taken orally.

Other hormones are also available in different formulations, such as oral, topical and injections. Interpretation of environmental levels of these medicines need to consider the metabolism and the normal excretion of these hormones by humans. For example, the human endogenic testosterone production is approximately 3.7 mg/day in males and 0.4 mg/day in women. Hormones were not among the 10 most used APIs in any country.

Metabolic disease medications

The metabolic disease medications considered in this project were the type 2 diabetes medication metformin, lipid lowering medications atorvastatin, simvastatin, bezafibrate and gemfibrozil and anti-gout medication allopurinol. Metformin is by far the most used oral antidiabetic medication. The daily dose can be as high as 3 g per day, and type 2 diabetes is a common condition, which explains the rather high overall consumption. Statins are the first line medical treatment for hypercholesterolemia. Atorvastatin and simvastatin are among the most frequently prescribed statins. Other commonly used statins, such as rosuvastatin, pravastatin, lovastatin and fluvastatin were not included in this project. Fibrates are used for hypercholesterolemia treatment in some specific situations and if statins are not tolerated. The fibrates included in this project were bezafibrate and gemfibrozil. One of the most commonly used fibrates, fenofibrate, was not included in this project. Allopurinol is the first line medical treatment for hyperuricemia that manifests as gout. Other medicines for the treatment of hyperuricemia, such as febuxostat, probenisid or benzbromarone were not included in this project.

NSAIDs and analgesics

The non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics considered in this project included acetylsalisylic acid, codeine, diclofenac, ibuprofen, ketoprofen, naproxen, oxycodone, paracetamol and tramadol. These are typically available in several different combination products and in various formulations, such as injections, oral formulations, topical creams, gels or sprays. Of the NSAIDs ibuprofen was by far the most used in the data collected for this project. Ibuprofen was among the 10 most used API in all countries. Diclofenac is widely used in topical formulations, and e.g. approximately 65% of the diclofenac sales in Finland are from topical formulations. There is no DDD defined for topical diclofenac products, and the consumption data, if only converted from DDD, is therefore not complete. Diclofenac was among the 10 most consumed API in two countries, Latvia and Estonia. Naproxen was among the most used API in 3 countries, Finland, Sweden and

Estonia. With regards to ketoprofen, also dexketoprofen is available, which is the s-enantiomer of ketoprofen. Paracetamol is the first recommended medicine for pain and fever in children, pregnant and elderly, and in long-term conditions such as arthritis. Paracetamol is available alone and in combination. Paracetamol is among the 10 most API in all countries but Germany. The German data only included reimbursed medicines and it is possible that paracetamol is mostly bought without prescription, and therefore not reflected in the German data. Acetylsalisylic acid is used for pain and fever, but also in lower doses for cardiovascular prevention indications. Due to the difference in dosing, the DDD for fever and pain is 3 g per day, whereas the DDD for cardiovascular indications is one UD, (unit dose) which can be, depending on product, for example 50 mg, 100 mg or 250 mg. Acetylsalicylic acid was also among the 10 most used medicines in all countries but Germany.

Other cardiovascular medications

Other cardiovascular medications considered in this project include beta-blocking agents atenolol, bisoprolol, metoprolol, nebivolol and sotalol. Dipyridamol is used in cardiovascular disease prevention and warfarin in the treatment and prevention of deep venous thromboembolism. Furosemide is a diuretic used to reduce fluid accumulation due to e.g. heart failure. Metoprolol was among the 10 most used APIs in Sweden, Germany, Latvia and Estonia. The other APIs in this group did not reach the top 10.

Psychopharmaceuticals

The following medicines used for psychiatric indications were considered in this project: antidepressants citalopram, sertraline and venlafaxine, antipsychotics olanzapine, quetiapine and risperidone and benzodiazepines oxazepam and temazepam. Citalopram, sertraline and venlafaxine are amongst the most frequently prescribed antidepressants. Escitalopram is the s-enanthiomer of citalopram and should be taken into account when environmental levels of citalopram are assessed. When considering the consumption and environmental concentrations of benzodiazepines, it must be noted that oxazepam is a metabolite of many other benzodiazepines (e.g. diazepam and temazepam) and temazepam a minor metabolite of diazepam. None of the medicines in this group reached the top 10 of most used API in any country.

Caffeine

Caffeine was included in this project as one API. However, caffeine from medicines may be negligible compared to other sources. In some countries, e.g. Finland there is no medicines registered with caffeine as primary API since 2016. On the other hand, coffee consumption in for example Sweden and Finland is 9-10 kg/person/year (each cup contains 80 mg/dl caffeine; 1 kg = 130 cups), resulting in more than several hundred tons of caffeine consumed each year in coffee. In addition, caffeine consumption from cola-drinks, energy drinks, chocolate etc. is likely significant, compared to medicines. Caffeine from medicines was not among the 10 most used API in any country.

Discussion on sales statistics

Information published on pharmaceutical consumption is often reported in DDD/100 inhabitants/day. Many pharmaceuticals are issued DDD-values that represent the most common daily dose for the ATC-code. These values are published e.g. by the World Health Organization (WHO 2018). The DDD/100 inhabitants/day values can thus be converted into mass (e.g. kg/year) using equation (1).

$$C_m = C_{DDD} \times Pop \times 365 \times DDD \times 10^{-6} \quad (1)$$

where
C_m = Sold amount in mass (kg)
C_{DDD} = Sold amount in defined daily doses (DDD)
Pop = Population
DDD = Defined daily dose (g)

However, there are several substances for which the DDD-values are given in some other unit than mass, or for which no DDD-values are given. This kind of consumption information, given in

DDDs, cannot be converted into mass. The problem applies also for APIs used in combination products, since these uses are seldom given DDD-values, and when they are given, they usually refer to only one of the active substances. Often the DDD value for combination products may refer to units, such as number of tablets. However, there are typically combination product tablets of different strengths available.

To demonstrate this problem, the consumption values calculated for the CWPharma-project from the Fimea sales register were compared to values calculated from publicly available DDDs to mass. The results are presented in figure 4.2. In the top 10 APIs sold in Finland, there are five APIs for which the error between the two data sets is <1%. However, the error for acetylsalicylic is >80%. The error in mass calculations in this set of products was most pronounced for acetylsalisylic acid, losartan, valsartan and metformin. Acetylsalisylic acid is typically included in combination products. As the ATC codes, such as ATC B01AC30 combinations, do not directly refer to acetylsalisylic acid, careful review of all available ATC codes must be performed in order to catch all possible products with acetylsalisylic acid for calculations. Losartan and valsartan are often used in combination with hydrochlorothiazide. For these combination products, the DDD is typically one tablet, but depending on the product, a tablet may contain 50–100 mg of losartan or 80–320 mg of valsartan. In case of metformin, at the time of preparation of this report there was no DDD defined for a number of combination products of metformin, thus leaving these products out of the calculated sales converted from published DDD consumption values.

Consumption data of 83 selected APIs were collected in each Baltic Sea country. Photo: Helene Ek Henning, CAB.

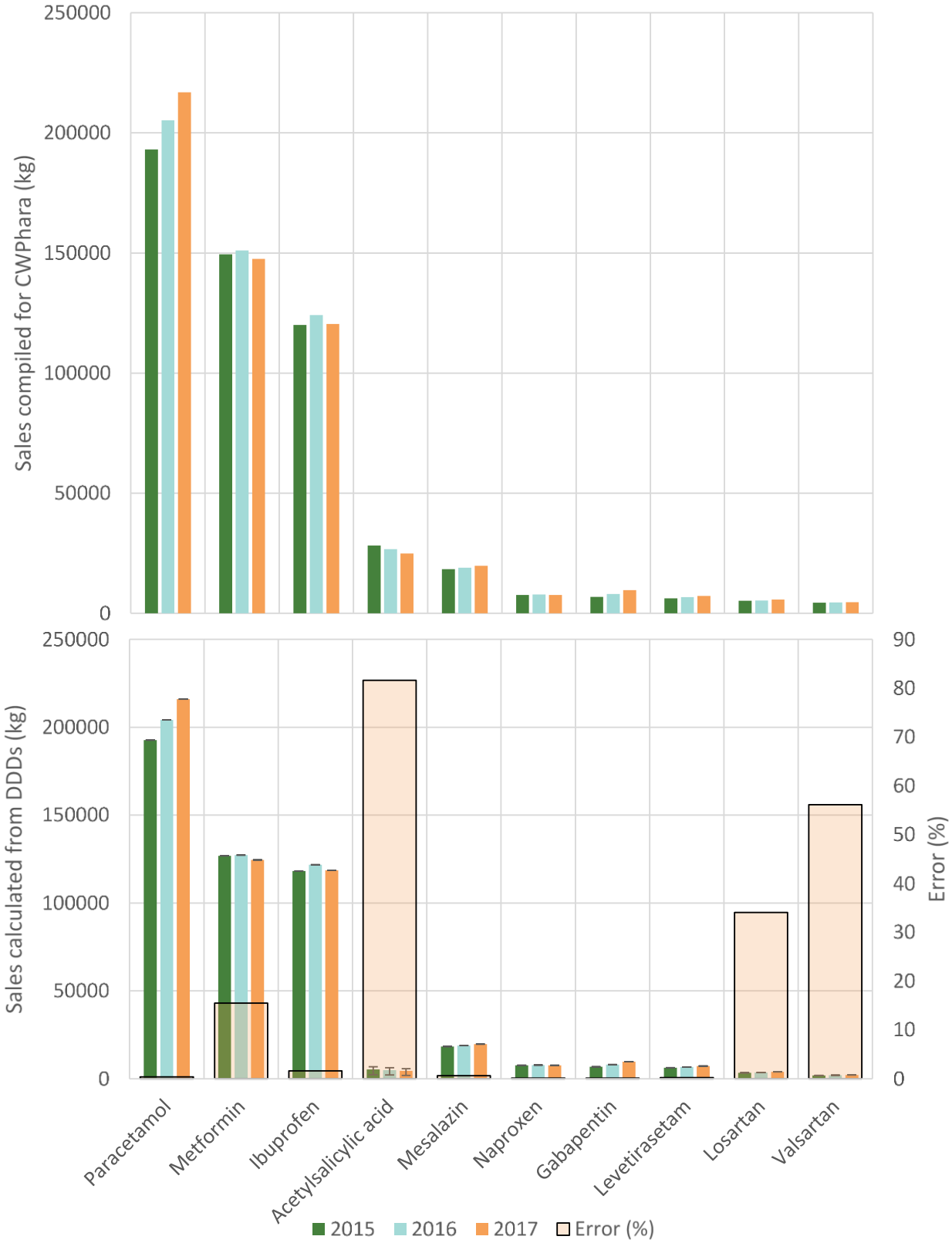


Figure 4.2. Sales calculated from wholesale data and from published DDD consumption data.

4.2.2 Veterinary consumption

9 of the selected 83 APIs in this project are primarily used in veterinary medicine. These included carprofen, an NSAID, antiparasite products emamectin, fenbendazole, ivermectin and toltrazuril and antibiotics florfenicol, tiamulin, and tylosin. Ivermectin, is used also in human medicine, but the use is likely quite limited. Several of the medicines that are used mainly for humans are also approved for use in veterinary medicine. At least doxycycline, lincomycin, sulfadiazine, sulfamethoxazole, tetracycline, furosemide, esomeprazole, omeprazole and ketoprofen are used in veterinary medicine. Some of these are even used in higher quantities in veterinary than in human treatment. Such examples are ketoprofen and sulfadiazine in Finland, trimethoprim and sulfadiazine in Sweden and doxycycline, tetracycline and omeprazole+esomeprazole in Latvia. Lincomycin is used in human medicine only in Latvia, so most of the consumption is veterinary use in the BSR.

The consumption data for veterinary use was more difficult to obtain than consumption data for human medicines. For some countries only data related to veterinary antibiotic use was available, and only for different classes of antibiotics and not for a specific API. Some data for veterinary medicines became available through a HELCOM data call on the use of veterinary medicines and the treatment of unused veterinary pharmaceuticals carried out 2018-2019. The questionnaire of the data call was formulated by CWPharma project. In the responses to the questionnaire, data for additional veterinary medicines that were not considered in this project, were also reported. The following tables summarise the available data for veterinary consumption for products where at least 1 kg/year of veterinary consumption was reported.

Table 4.1. Veterinary consumption of 9 APIs from the CWPharma project that are primarily used in veterinary medicines, in kg.

Country	Year	Florfenicol	Tiamulin hydrogenfumarate	Tylosin	Lincomycin	Fenbendazole	Toltrazuril	Carprofen	Emamectin-benzoate	Ivermectin
Finland	2015	72	23	518	116	1760	190	256	1	20
	2016	55	13	468.4	73	1586	199	274	1	14
	2017	97	14	341.1	258	1468	268	262	1	12
Sweden	2015	0	153	320	0	440	85	421	-	-
	2016	0	143	328	0	519	85	417	-	-
	2017	0	76	379	0	616	183	392	-	-
Latvia	2015	7	655	533	21	-	-	-	-	-
	2016	12	556	328	9	-	-	-	-	-
	2017	14	846	415	32	-	-	-	-	-
Estonia	2015	8	931	142	311	39	46	16	0	-
	2016	14	728	81	127	43	44	15	0	-
	2017	27	692	44	154	58	50	18	0	-
Denmark*	2015	1224	9754	7197	2329	-	-	-	-	-
	2016	1351	9647	7 926	2061	-	-	-	-	-
	2017	1481	9315	9203	2270	-	-	-	-	-
Lithuania*	2017	112	279	451	198	-	-	-	-	-
Poland*	2017	7752	37 789	19 807	6835	2159	698	259	-	-

*Data derived from the overview of the results of the HELCOM questionnaire on veterinary medicines

Table 4.2 Available veterinary consumption (≥ 1 kg/year) of APIs in CWPharma project that are primarily used in human medicine, in kg.

	Doxycycline	Sulfadiazine	Sulfamethoxazole	Telmisartan	Trimethoprim	Omeprazole/esomeprazole	Tetracycline	Furosemide	Ketoprofen	Progesterone
Finland										
2015	42	1761	10	0	376	54	0	24	646	21
2016	2	1745	1	0	364	54	0	24	637	21
2017	2	1714	0	0	362	60	0	25	642	21
Sweden										
2015	43	695	0	1	208	21	-	-	-	-
2016	37	654	0	1	208	40	-	-	-	-
2017	66	636	0	2	205	90	-	-	-	-
Latvia										
2015	1230	70	-	-	65	368	220	-	-	-
2016	711	71	-	-	47	384	247	-	-	-
2017	806	48	-	-	40	390	188	-	-	-
Lithuania*										
2017	0	-	-	-	-	-	-	-	-	-
Denmark*										
2015	17 745	-	-	-	-	-	-	-	-	-
2016	16 990	-	-	-	-	-	-	-	-	-
2017	10 955	-	-	-	-	-	-	-	-	-

*Data derived from the overview of the results of the HELCOM questionnaire on veterinary medicines.

4.3 Conclusions

Complete consumption data were available from only four of the eight Baltic Sea coastal countries (Estonia, Finland, Latvia, Sweden). In many cases data in kilograms is not available but needs to be converted from DDD data (Denmark, Germany, Lithuania). This is problematic because the conversion is not possible for certain products, such as combination products or topical products. The consumption of many products may therefore be underestimated. From Germany, data were only available for reimbursed products leaving over the counter medicines outside the statistics. In Germany paracetamol and acetylsalicylic acid, which were among the ten most used APIs in all other countries, did not reach the top ten. This could be due to most of these medicines being purchased over the counter.

It is recommended that public authorities in Baltic states make drug statistics publicly available, not only in DDD format but also in kg of API, including combination products and topical formulations. All medicines should be included, regardless of reimbursement status. Also, veterinary medicines consumption data for all APIs but especially for antibiotics, in kg, should be made available publicly for research purposes.

When consumption data are used for estimating the amount of specific APIs in the environment, several factors must be taken into consideration. If consumption is converted from DDD, significant underestimation of the consumption may result, in case the API is used in combination products or in e.g. topical formulations, patches and rings. The DDD may also differ according to the intended use, like in case of acetylsalisylic acid. Also, stereoisomers, which are often classified as a different API, need to be reviewed, and as some APIs metabolize to other APIs, the metabolism of the medicines needs to be considered. When selecting suitable candidates as model APIs for e.g. modeling the fate of pharmaceuticals, medicines which are commonly used, primarily used as single ingredient products, and which do not undergo major metabolism should be selected. A good example of such an API is metformin. Should the selection of the API be driven by factors such as environmental toxicity, the consumption data of the API should be carefully evaluated. In addition to stereosisomers and metabolism products of other parent APIs, also other sources need to be considered, such as natural excretion of hormones by humans and animals.

Collection of water samples in the Finnish case study area. Photo: Lauri Äystö, SYKE.

5 Environmental levels of APIs in the Baltic Sea region

5.1 Environmental levels of APIs in inland and coastal waters

5.1.1 Methods

Surface water samples were taken in six case studies in six countries (see chapter 2). Each case study consisted of several sampling sites, described as upstream or downstream from API sources like wastewater treatment plants. The sea samples were taken either in the estuaries or in the areas influenced by the WWTP outlet pipes. The case studies represented anthropogenic areas, where estimated potential environmental risks caused by pharmaceuticals was higher than average in each country. An overview of the sampling locations is presented in figure 5.1.

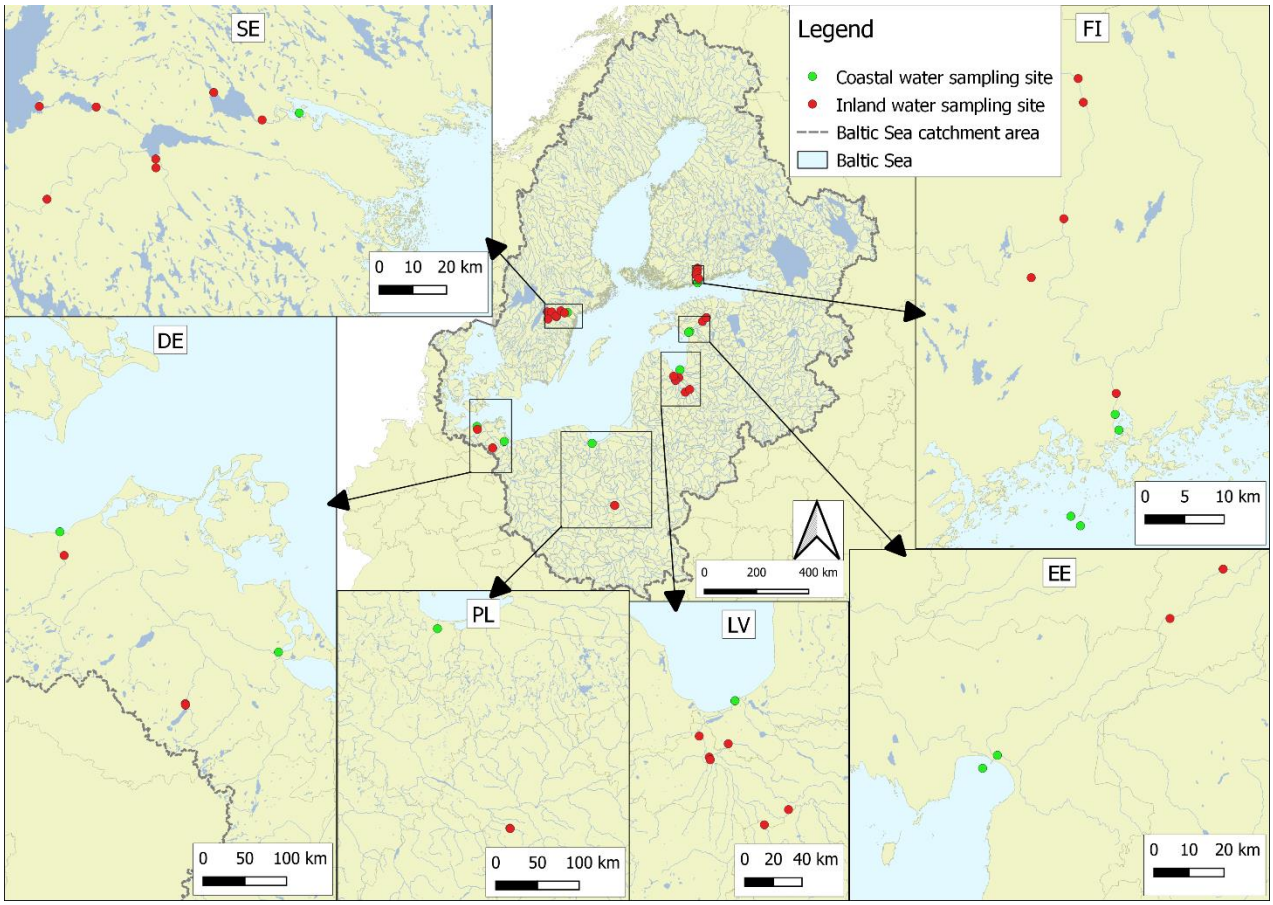


Figure 5.1. Overview of surface water sampling locations and their division into inland and coastal sites. (Sources: Catcment area: HELCOM 2018; rivers & lakes: European Commission - JRC 2007)

Each site was sampled twice, except the Finnish river Vantaanjoki was sampled three times because there were extreme flow conditions causing untypical API concentrations in the first two samplings (high flood in autumn 2017 and extremely low flow in summer and autumn 2018). Samples were taken as grab samples except the samples taken in Estonia. Information on sampling is presented in Table 5.1. The methods for chemical analyses are described in the chapter 3.

For many APIs high concentration peaks appeared occasionally, and in order to avoid biased view of concentrations of APIs in riverine surface waters, the median concentrations are presented with the minimum and maximum values. Due to limited number of coastal water samples, country specific average concentrations of APIs were calculated instead of medians. Because LOQs differed markedly between APIs and to some extent between sea water and freshwater samples, the concentrations below LOQs were treated as zeroes in all calculations.

The potential risk caused by the detected APIs were estimated by calculating a risk quotient (RQ), see chapter 9. RQ-values exceeding one give a signal of environmental risk. The RQs of all APIs in each water sample were summed to have a rought estimate of the combined effect of all detected compounds.

Table 5.1. Number and volume of samples, sampling depths and information concerning sampling.

Country	Number of samples (inland + coast)	Sampling depth	Subsamples (number x volume)	Notes
DE	6 + 4	1 m	6 x 500 mL	Sampling carried out using a standard water sampler (Ruttner, 1 L).
EE	4 + 2	Inland: 1 m Coast: 0.5 m	Inland: 64-96 x 50 mL Coast: 6 x 500 mL	Inland water samples were taken as time-proportionate composites.* Grab samples were taken using a bathometer.
FI	13 + 12	Inland: 0.3 – 1 m Coast: 1 – 25 m	Inland: 3 x 1 000 mL Coast: 2 x 1 000 mL	Samples were taken using a 2 L Limnos water sampler.**
LV	14 + 4	Inland: 0.5–1 m Coast: 1 / 12 m	Inland: 4 x 800 mL Coast: 2 x 1000 mL	Samples were taken using a horizontal bathometer.
PL	4 + 2	0.2–0.5 m	8 x 500 mL	Samples were taken using a bucket sampler.
SE	14 + 2	Inland: 1 m Coast: 1 / 10 m	2 x 1 000 mL	Samples were taken using a horizontal bathometer.

* Subsamples were taken every 15 minutes, using a composite sampler (MAXX TP6). Number of subsamples varied because of sampler malfunctioning due to cold weather.
** During winter sampling in estuary and coastal sites, the sampler froze several times between samples, and had to be rinsed with hot water to melt the ice.

5.1.2 Results and discussion

5.1.2.1 Observed occurrence and concentration levels of APIs

All measured concentrations are presented in Annex 3. 53 to 59 APIs were analysed in each sample and the number of detected compounds varied from 8 to 49 per sample. Altogether 60 out of 63 analysed APIs were detected in at least one sample. The high detection frequency (DF) was partly due to the low limits of quantification (LOQ) of the analytical method. For several compounds the LOQs were lower than 1/1000 of the predicted no effect concentration (PNEC) derived in chapter 9, see Table 5.2. The LOQs were lower than PNEC values for all other APIs except ciprofloxacin (antibiotic) and estrone (hormone). The low LOQs allowed reliable risk estimations of the analysed compounds.

In the following sub-chapters, the concentration levels are analysed by API groups. In the end of the chapter there is a summary table (Table 5.2) of detection frequencies (DF) and concentrations of each API.

Hormones

Each of the studied four hormones were detected both in inland surface waters and coastal waters. The most frequently detected hormone in both inland and coastal waters was norethisterone which was detected in 62% of both types of samples. The least frequently detected hormone in inland waters was estrone (DF=25%) and in coastal waters progesterone, with DFs of 25 % and 35 %, respectively. The variation of the concentrations of each hormone are presented in Figures 5.2 and 5.3 and Table 5.2.

The 95th percentiles of norethisterone were 2.1 ng/L in inland waters and 1.1 ng/L in coastal waters. Norethisterone is used in contraceptive pills, in hormone replacement therapy and for the treatment of gynaecological disorders.

Estrone 95th percentile concentration in inland and coastal waters were 7.2 and 5.1 ng/L, respectively. Estrone was not detected in Swedish samples, while it was the only hormone detected in Estonian coastal waters. The highest estrone concentrations (5.9–10 ng/L) were measured in Finnish river Vantaanjoki on a day when the flow in the river was about half of the annual average. In the same sites, concentrations were below detection limit (0.70 ng/L) during high flow conditions. In the BSE, the highest estrone concentration was observed in the summer sample taken in Warnow estuary.

The observed estrone concentrations were rather close to the EU watch list screening results (Loos et al. 2018), where the median concentration of 1358 samples was 2.5 ng/L and the 95th percentile 5.6 ng/L (see Table 5.5). Estrone is a naturally occurring hormone in humans and other mammals. It is available as a medicine as well but according to consumption statistics it is not on the market in the Baltic countries. Therefore, the detections are likely linked to natural excretion.

Estrone and norethisterone exceeded their PNEC values (0.008 ng/L and 0.50 ng/L, respectively) in both inland and coastal waters. Norethisterone concentration exceeded the PNEC in 33% of the samples. The LOQ of estrone was higher than the PNEC value determined in this study, and therefore all the detected concentrations were above PNEC. However, under the EU water policy, the PNEC value for estrone is 3.6 ng/L being 450 times higher (Loos et al. 2018). It was exceeded in 12% of the surface water samples. The detected exceedances give a strong indication of environmental risks caused by hormones.

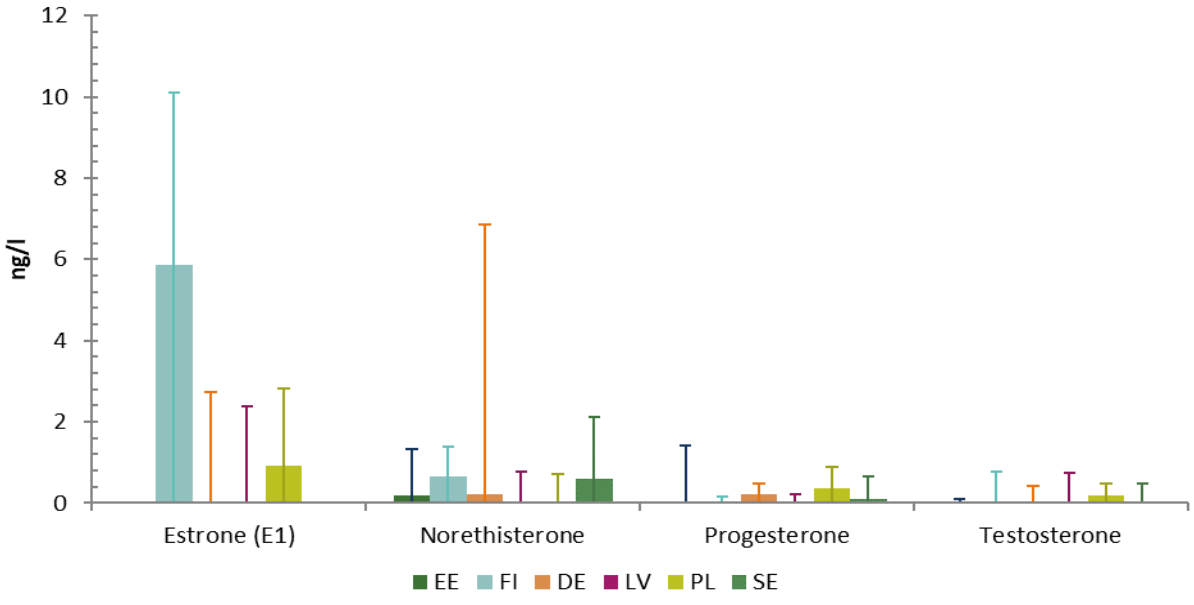


Figure 5.2. Median (wide bar) and minimum and maximum (whiskers) concentrations of hormones in inland waters in the BSR countries.

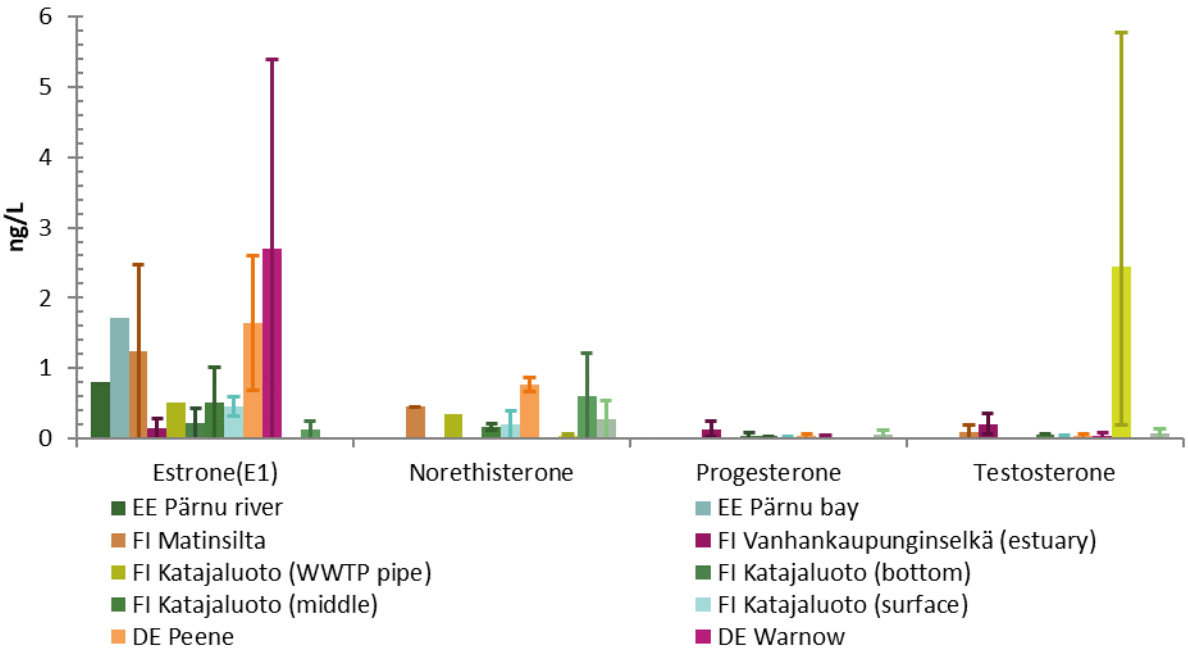


Figure 5.3. Average (wide bar) and minimum and maximum (whiskers) concentrations of hormones in coastal waters in the BSR.

Antibiotics

In inland waters the DFs varied from 0% (ciprofloxacin, n=2 and sulfadiazinem n=53) to 100% (erythromycin, n=2) (Figure 5.4). In coastal waters the DFs of these APIs varied from 4% (ofloxacin, n=24) to 65% (fluconazole, n=26) (Figure 5.5). Sulfadiazine was analysed only from three coastal samples and the quantification limit of ciprofloxacin was higher than its PNEC.

In the Polish river samples, the median concentrations of fluconazole (200 ng/L), clarithromycin (42 ng/L), trimethoprim (12 ng/L) and lincomycin (4.8 ng/L) were higher than in the other countries (Figure 5.4). Four of the five above mentioned antibiotics were detected in all Polish river samples (n=4) but trimethroprim only in sampels taken downstream from WWTP. The highest concentration of antibiotics (590 ng/L) was measured for clarithromycin in the downstream site of the River Rokitnica in Poland.

In coastal waters, the sampling site specific average concentrations of all studied antibiotics were below 12 ng/L (Figure 5.5). The highest concentrations were measured for the sum of tetracycline and doxycycline (23 ng/L) in sample taken in Bråviken (Sweden) and erythromycin (20 ng/l) in sample taken in the Finnish coast in the mid-depth (14 m) in winter sampling (March).

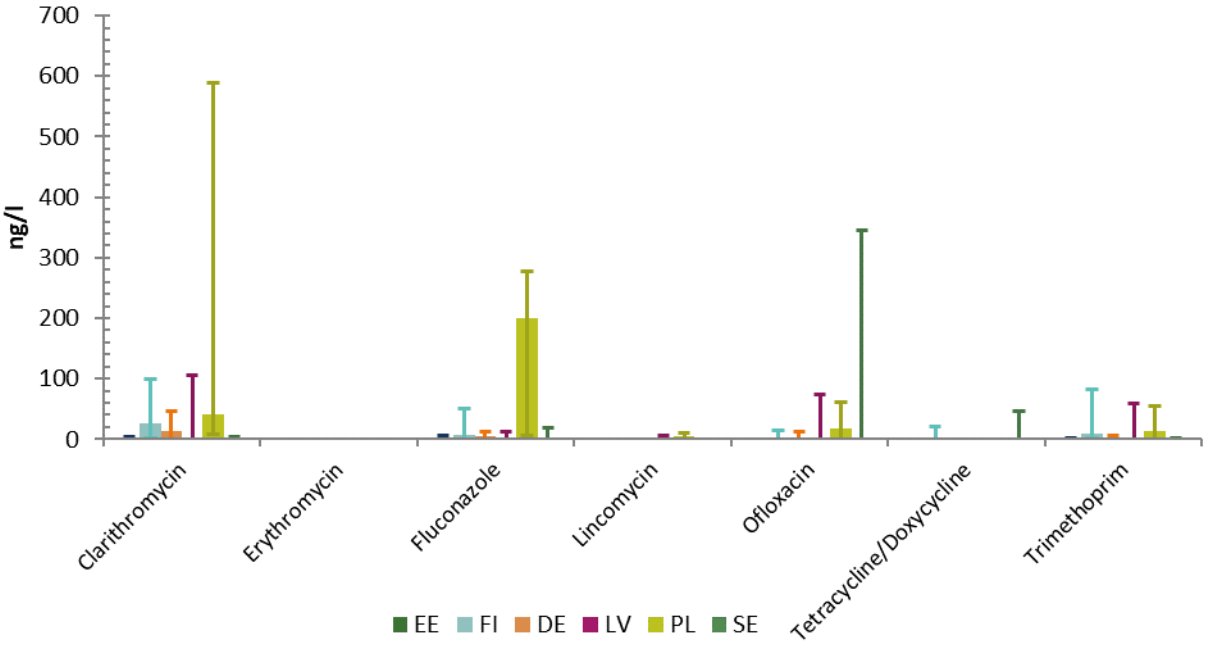


Figure 5.4. Median (wide bar) and minimum and maximum (whiskers) concentrations of antibiotics in inland waters in the BSR.

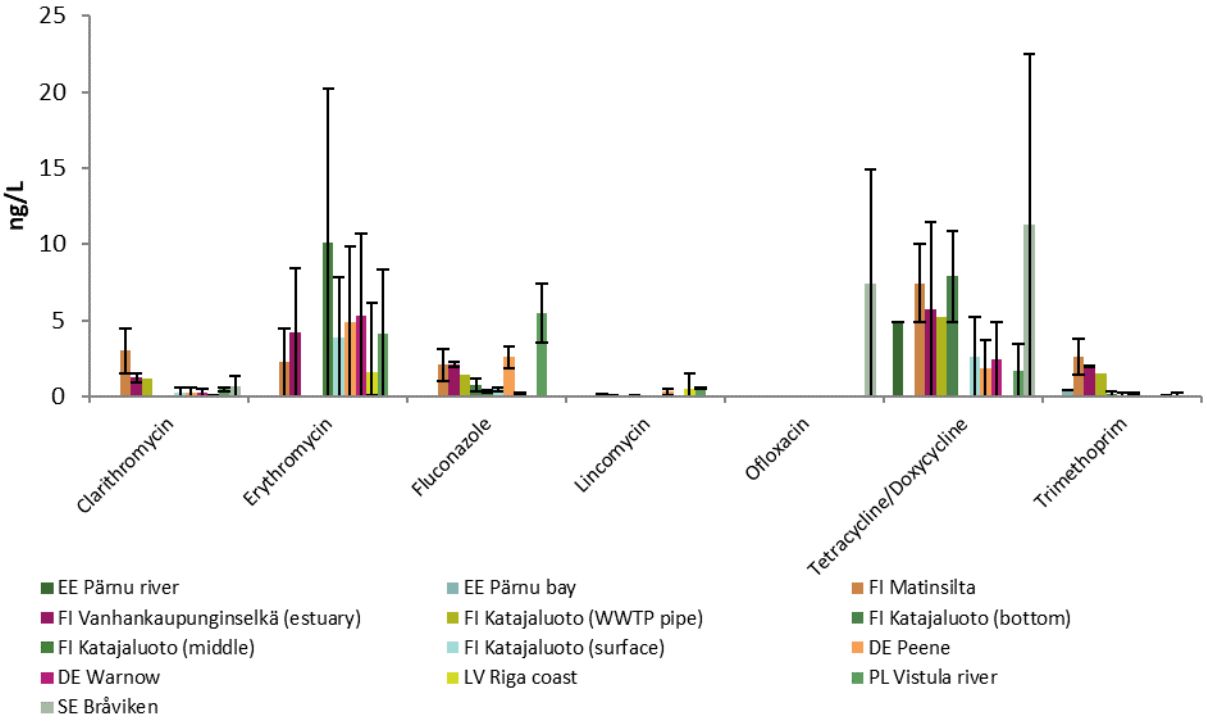


Figure 5.5. Average (wide bar) and minimum and maximum (whiskers) concentrations of antibiotics in sea waters in the BSR.

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. Either of the indicators showed different behaviour in six sites while in the remaining four sites the results were not clear (no difference between seasons or the two winter sampling times in Vantaanjoki under different dilution conditions gave contrasting results).

Clarithromycin concentrations exceeded the PNEC-value of 3.9 ng/L in 45% of inland water samples. Exceedances were detected in samples taken from all partner countries, except Sweden. The PNEC-value was exceeded most often in Poland and Finland, where the frequency of

exceedance was 100% (n=4) and 85% (n=13), respectively. In the Finnish case area, the PNEC-value was exceeded in every inland water sample during the second (6/2018) and third (11/2018) sampling campaigns taken during low-flow conditions. Clarithromycin exceeded its PNEC-value in only one coastal sample, taken at the River Vantaa estuary during the third sampling campaign. The PNEC value used under the EU water policy (120 ng/L, Loos et al. 2018) was exceeded in only one sample, taken in November 2017 downstream from the Błonie WWTP in Rokitnica river, Poland.

The median clarithromycin concentration in the EU watch list screening was 15 ng/L and the 95th percentile 130 ng/L (n=7443) (Loos et al. 2018). In this study, the inland median concentration was about one fifth of that (3.2 ng/L), while the 95th percentile (100 ng/L) was in the same order of magnitude as that reported by Loos et al. (2018) (see table 5.5).

Ofloxacin exceeded its PNEC-value (20 ng/L) in inland surface waters occasionally in Latvia, Poland and Sweden, with an overall frequency of exceedance being 15%. The highest number of PNEC exceedances were detected in Sweden (5 samples out of 14), all occurring during the first sampling campaign (12/2017). The sum concentration of tetracycline and doxycycline exceeded the PNEC of doxycycline (37 ng/L) but not the PNEC value of tetracycline (1730 ng/L) in a Swedish sample (Stångån upstream).

Antiepileptics

All studied antiepileptics were detected in the surface water samples (Figures 5.6 and 5.7). In inland surface waters, DFs varied from 25% (primidone, n=55) to 98% (carbamazepine, n=55) and in coastal waters from 19% (levetiracetam, n=26) to 100% (carbamazepine, n=26 and gabapentin, n=3; gabapentin was analysed in only one Finnish and two Swedish coastal water samples).

The median inland water concentrations of individual APIs varied from <LOQ (levetiracetam and primidone) to 3.7 ng/L of carbamazepine and 82 ng/L of gabapentin (Figure 5.6). Highest country-specific median inland water concentrations of gabapentin (900 ng/L), carbamazepine (620 ng/L) and primidone (12 ng/L) were detected in Polish samples and of levetiracetam (9.4 ng/L) in German samples. The highest concentration of antiepileptics (1 900 ng/L) was measured for gabapentin in the downstream site of the River Rokitnica in Poland.

In coastal waters, the concentrations of antiepileptics had 95th percentile of 33 ng/L. The median concentrations of carbamazepine and gabapentin, which were detected in every coastal water sample, were 2.0 ng/L and 82 ng/L, respectively. Concentrations of antiepileptics in coastal waters are presented in Figure 5.7. Case-specific average concentrations of all compounds were mainly below 7.0 ng/L, but higher values were measured for carbamazepine in Vistula river in Poland (35 ng/L) and in Peene in Germany (17 ng/L). The highest carbamazepine concentration (60 ng/L) in coastal waters was measured in the Vistula estuary in Poland.

Carbamazepine reached 95th percentiles of 440 ng/L and 48 ng/L in inland and coastal waters, respectively. The antiepileptic detected in highest concentrations in both inland and coastal waters was gabapentin, for which the 95th concentration percentile in inland waters was 1 700 ng/L (median 88 ng/L). In coastal samples gabapentin concentrations varied from 34 to 120 ng/L. Since gabapentin was only analysed from three coastal samples, more data would be needed for proper comparison between coastal and inland waters. Gabapentin was previously identified as an API for which there is very little screening data considering its high consumption (UNESCO & HELCOM 2017[6]). The average concentration in the BSR was reported to be approx. 80 ng/L (UNESCO &

[6] UNESCO and HELCOM, 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris.

HELCOM 2017), while concentrations reaching 1 300 ng/L have previously been reported from Germany (UBA 2016). The concentrations detected in the CWPharma-screening campaigns are well in line with these results.

Primidone was previously also identified as an antiepileptic of concern. The DF was reported to have reached 100% in water samples taken in Germany (UNESCO & HELCOM 2017), with the limits of detection ranging from 1 ng/L to 5.7 ng/L. In the CWPharma screening study, the overall DF was 25%, with LOQ ranging from 0.032 ng/L to 1.4 ng/L. The DF in German coastal water samples reached 100%, but the total number of samples was very low (n=4). However, considering the annual sales of primidone are estimated to reach 5 300 kg in Germany, while similar numbers are <100 kg for Finland, Sweden, Estonia, Latvia and Lithuania combined, it is reasonable to assume that primidone occurrence is higher in Germany than in the rest of the BSR.

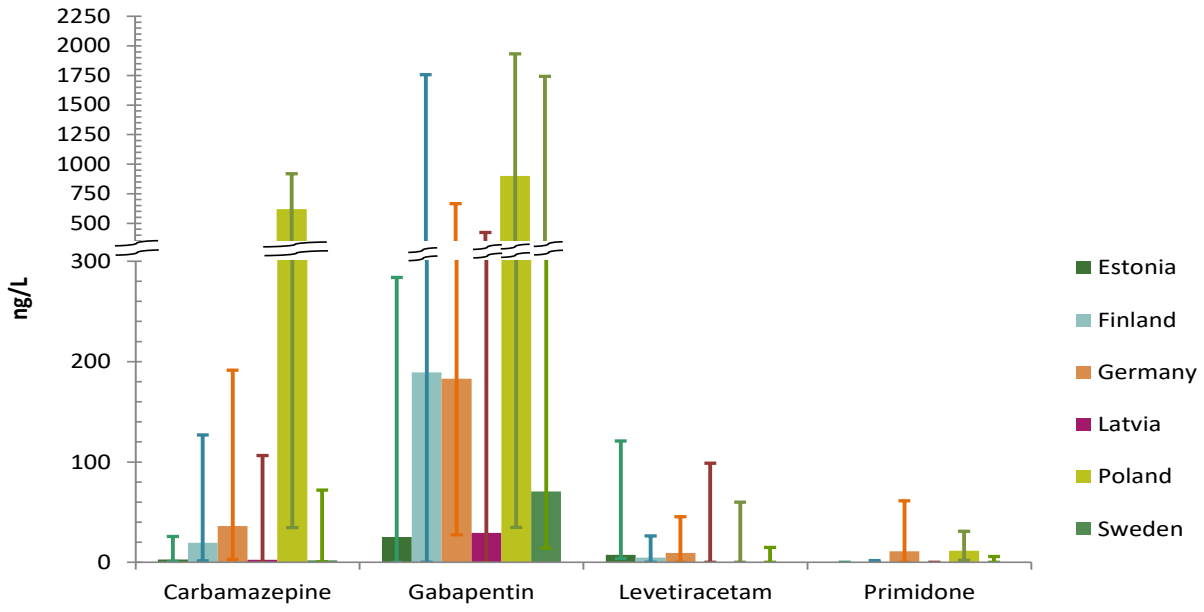


Figure 5.6. Median (wide bar), minimum and maximum (narrow bar) concentrations of antiepileptics in inland waters in the BSR.

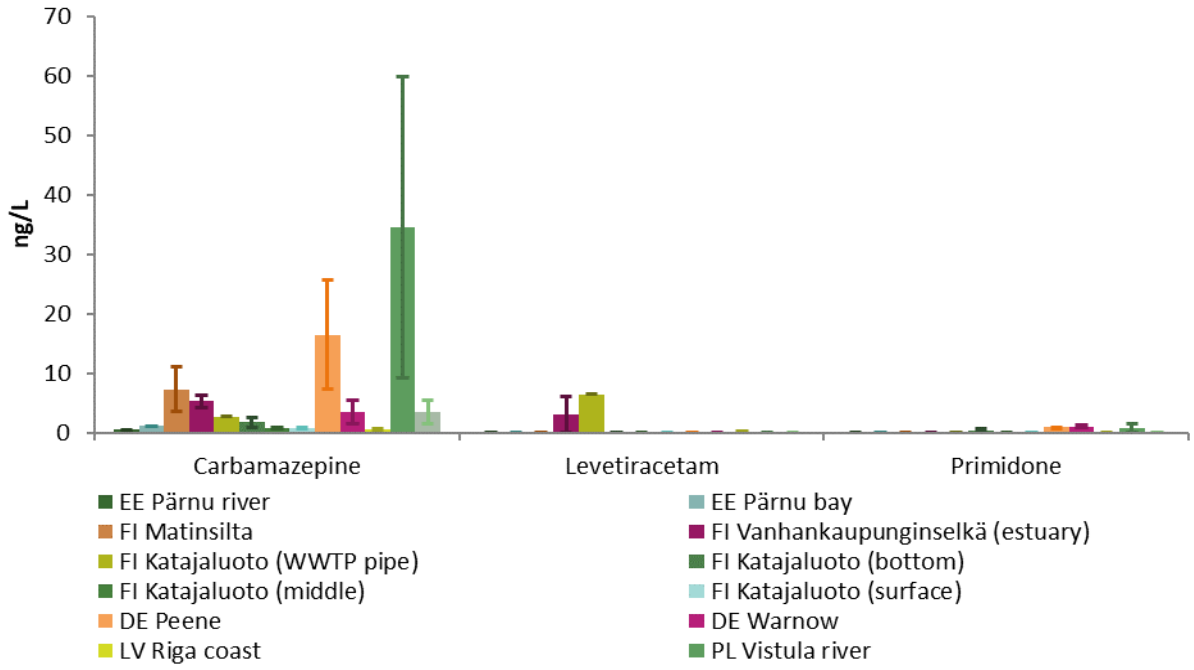


Figure 5.7. Average (wide bar) and minimum and maximum (whiskers) concentrations of antiepileptics in sea waters in the BSR.

Antihypertensives

Four of the five studied antihypertensives were detected in at least one surface water sample, only enalapril was not detected. It should be noted that in coastal waters telmisartan, valsartan, eprosartan, ramipril, and enalapril were analysed only from three samples.

In inland surface waters, DFs for the detected substances varied from 2% (amlodipine, n=55) to 67% (losartan, n=55) and in coastal waters from 27% (candesartan, n=26) to 69% (losartan, n=26). Candesartan and losartan were detected in all countries. Amlodipine was detected only in one Swedish sample.

In inland waters, the concentration of the group of antihypertensives had a 95th percentile of 97 ng/L. Median concentrations of amlodipine, candesartan, enalapril, eprosartan, irbesartan and ramipril were below the LOQs. For losartan, telmisartan and valsartan the median concentrations were 1.1, 7.4 and 10 ng/L, respectively.

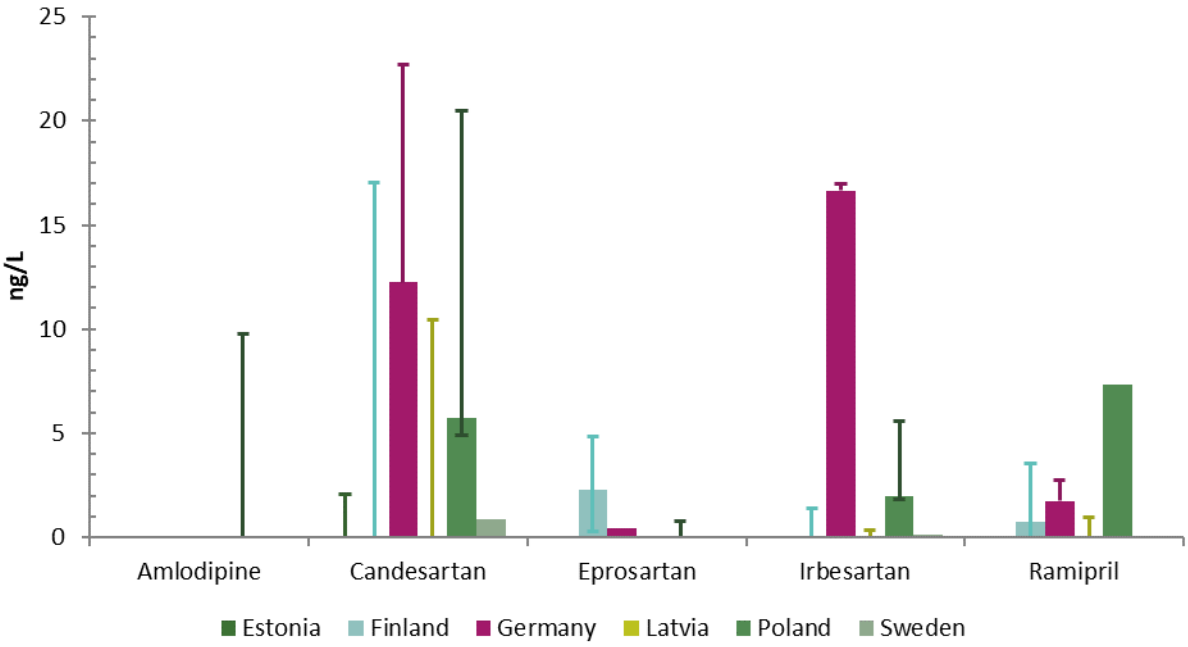


Figure 5.8. Median (wide bar), minimum and maximum (whiskers) concentrations of antihypertensives in inland waters in the BSR.

Concentrations of telmisartan, valsartan and losartan were markedly higher at some sampling sites compared to other antihypertensives (Figure 5.9). Highest measured concentrations of irbesartan (110 ng/L in Germany), telmisartan (2 800 ng/L in Poland) and losartan (200 ng/L in Finland) were 360, 150 and 34 times higher than their quantified median concentrations, respectively. Nevertheless, no PNEC exceedances were detected for any analysed antihypertensive in any sample.

In coastal water, the concentrations of antihypertensives had an overall 95th percentile of 5.0 ng/L (Figure 5.10). The sampling site specific median concentrations were below 7.0 ng/L. The highest concentration (13 ng/L) was measured for candesartan in Bråviken in Sweden.

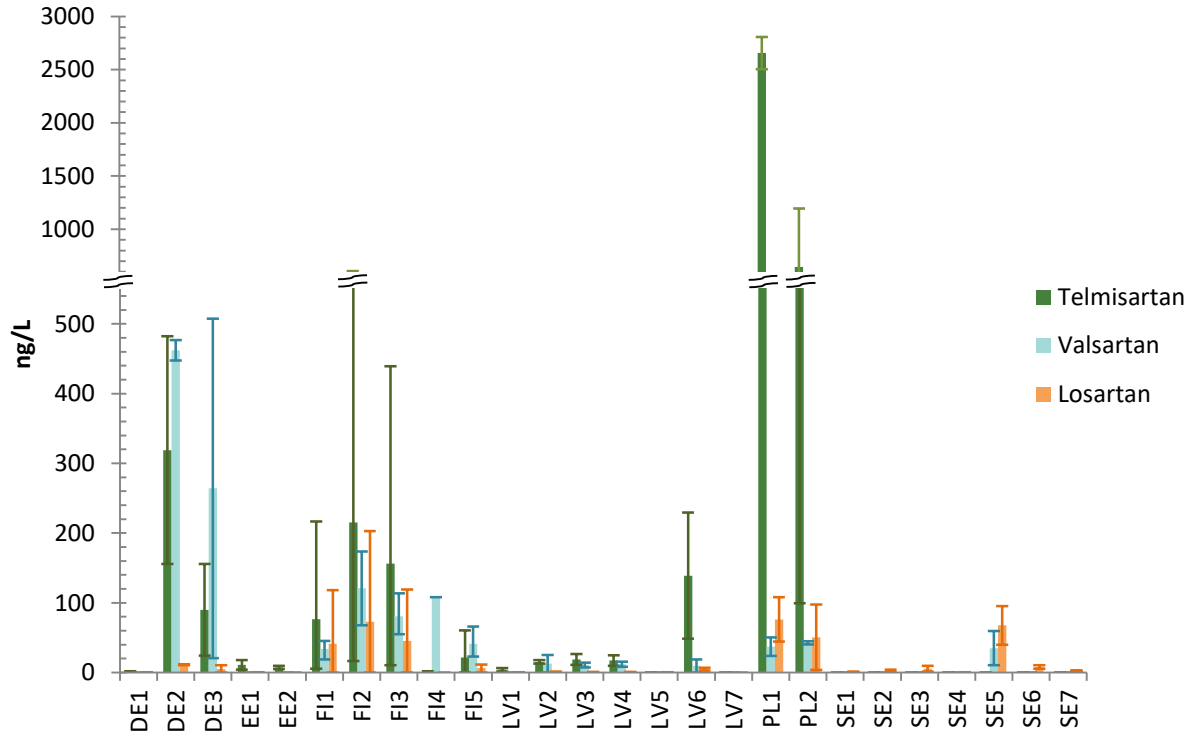


Figure 5.9 Average (wide bar), minimum and maximum (whiskers) concentrations of telmisartan, valsartan and losartan in inland waters in the BSR. Full names of the sampling sites are presented in table 5.2.

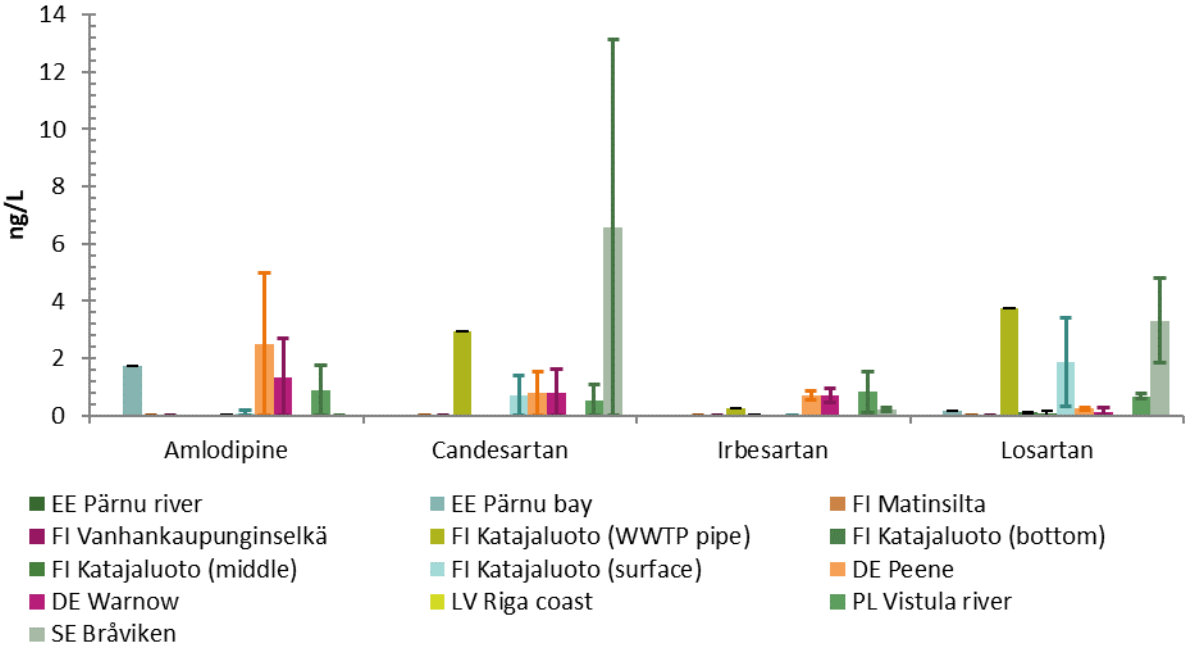


Figure 5.10. Average (wide bar) and minimum and maximum (whiskers) concentrations of antihypertensives in sea waters in the BSR.

Asthma and allergy APIs

All of the studied five asthma and allergy APIs were detected in at least one sample. In inland surface waters, DFs varied from 7% (mometasone furoate, n=55) to 80% (cetirizine, n=55) and in coastal waters from 15% (mometasone furoate and xylometazoline, n=26) to 100% (cetirizine (n=26) and fexofenadine (n=3)). Cetirizine is an antihistamine used for treatment of e.g. hay fever.

In inland waters, the sum concentrations of asthma and allergy APIs had a 95th percentile of 81 ng/L. The highest median concentration (1.8 ng/L) was measured for cetirizine and its country-specific median concentrations ranged from 0.27 ng/L (Estonia) to 170 ng/L (Poland). Remarkably high concentrations of cetirizine were detected in Finland during June 2018 (100–630 ng/L) and in Poland during November 2017 (11–310 ng/L) and July 2018 (110–240 ng/L). Also, in the same samples the concentrations of fexofenadine were remarkably high compared to its median concentrations.

The DFs of fluticasone and mometasone furoate were below 50%, resulting in an overall median concentration of less than the LOQ. Despite its low DF, the highest detected concentration of mometasone furoate (28 ng/L) exceeded its PNEC-value (14 ng/L). This single exceedance was detected in Estonia, upstream from the cities of Türi and Paide during the second sampling campaign (6/2018). In the winter sample of the same site, its concentration was 10 ng/L (0.75 of PNEC).

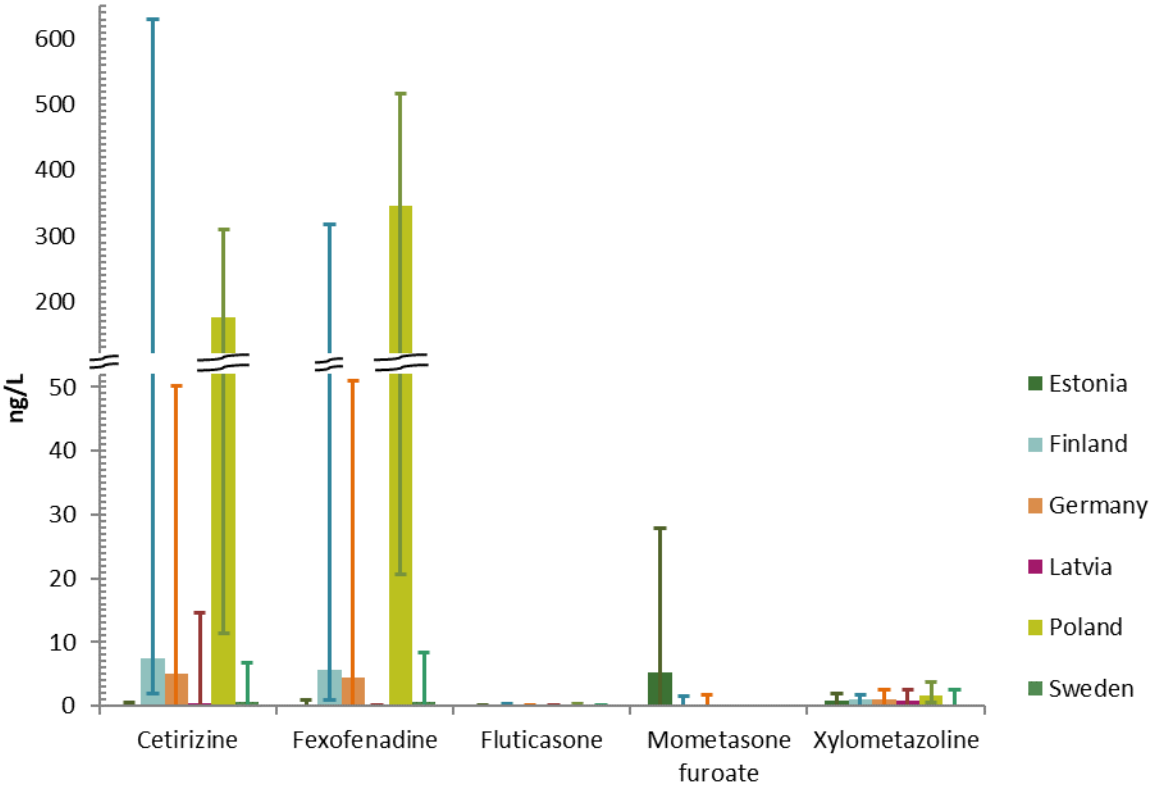


Figure 5.11. Median (wide bar), minimum and maximum (whiskers) concentrations of asthma and allergy APIs in inland waters in the BSR.

In coastal waters the concentrations of the four asthma and allergy APIs had a 95th percentile of 7.9 ng/L. Site specific average concentrations of cetirizine, which was detected in all samples, ranged from 0.03 ng/L (Riga coast, Latvia) to 22 ng/L (Matinsilta estuary, Finland). Fexofenadine concentrations ranged from 0.7 to 3.3 ng/L in the three coastal water samples, where it was analysed. For other compounds, the sampling site specific average concentrations were below 0.82 ng/L.

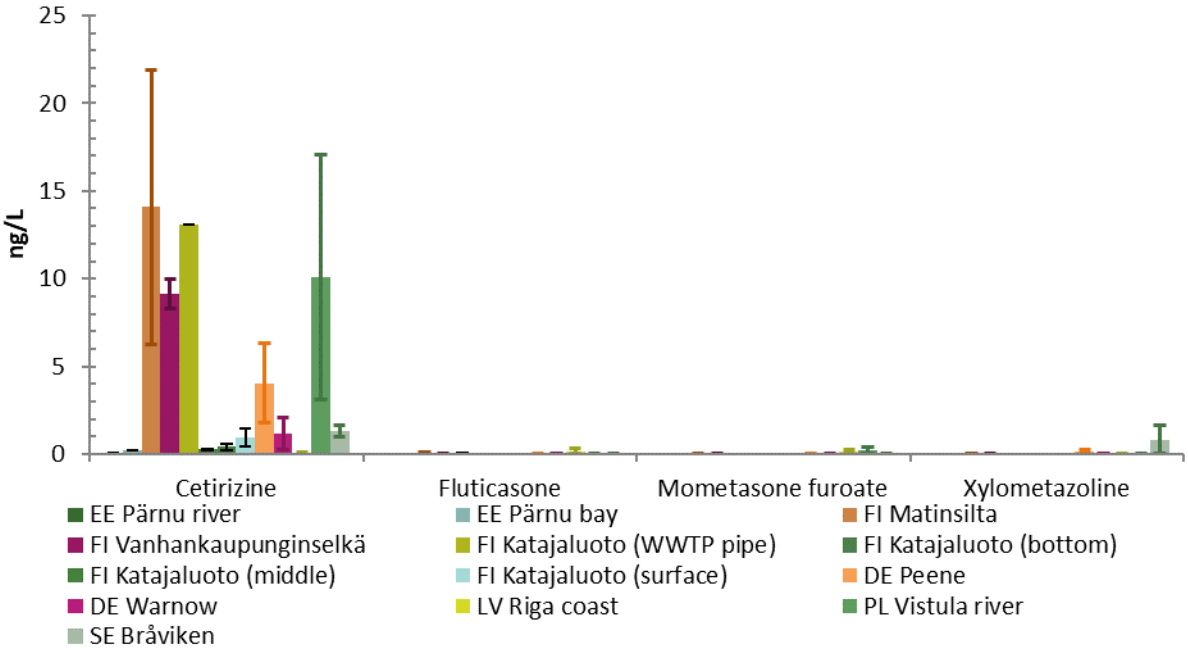


Figure 5.12. Average (wide bar) and minimum and maximum (whiskers) concentrations of asthma and allergy APIs in sea waters in the BSR.

Gastrointestinal and metabolic APIs

All studied gastrointestinal and metabolic APIs were detected in at least one surface water sample. Atorvastatin was analysed only from three coastal samples. In inland waters, mesalazine and simvastatin were analysed only in two Polish samples and it was detected in both samples.
In inland surface waters, overall DFs varied from 24% (bezafibrate) to 87% (metformin) and in coastal waters from 27% (bezafibrate) to 78% (mesalazine). Metformin is used for the treatment of type 2 diabetes and mesalazine in treatment of inflammatory bowel disease. Atorvastatin, bezafibrate, gemfibrozil and simvastatin are used in the treatment for high cholesterol levels.

In inland water samples, the gastrointestinal and metabolic APIs concentration had an overall 95th percentile of 560 ng/L. Country-specific median concentrations of metformin in inland waters varied from 34 ng/L (Latvia) to 260 ng/L (Poland). Metformin and gemfibrozil were the only APIs in this group which were detected in each country.

In Finland and Latvia concentrations above 1 000 ng/L were measured for atorvastatin and metformin and in Sweden for metformin. Metformin exceeded its PNEC value (1350 ng/L) in Latvia (RQ 1.7 in Pupla downstream WWTP site in May), and the concentration was very near the PNEC in Sweden (RQ 0.96 in Dovern in June) and Finland (RQ 0.96 in Vantaanjoki downstream Nurmijärvi WWTP in November).

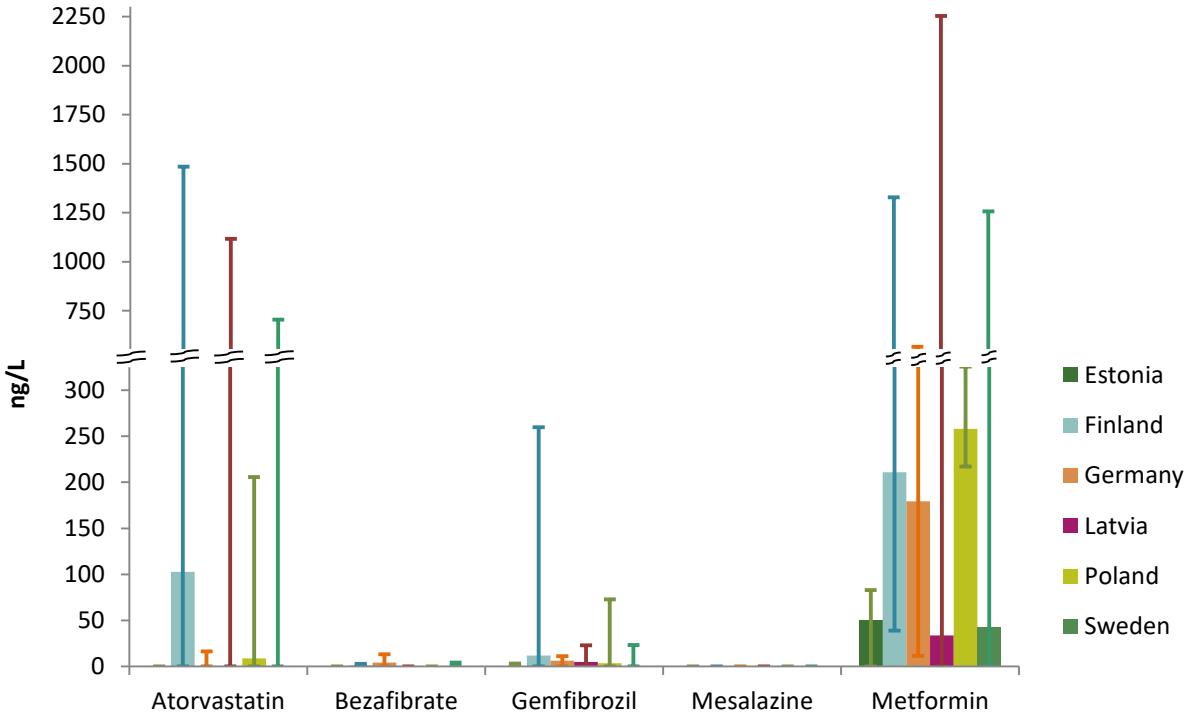


Figure 5.13. Median (wide bar), minimum and maximum (whiskers) concentrations of gastrointestinal and metabolic APIs in inland waters in the BSR.

In coastal waters, the concentrations of the five studied gastrointestinal and metabolic APIs had a 95th percentile of 104 ng/L. Atorvastatin was detected in only one out of three analysed samples, with the quantified concentration reaching 44 ng/L. The highest concentrations were measured for metformin (230 ng/L, Sweden, Bråviken) and mesalazine (190 ng/L, Finland, Vantaanjoki estuary). Sampling site specific average concentrations of metformin ranged from <LOQ (Riga coast, Latvia) to 130 ng/L (Bråviken, Sweden). In case of mesalazine the average concentrations ranged from <LOQ (Bråviken, Sweden) to 160 ng/L (Pärnu river, Estonia) (Figure 5.14).

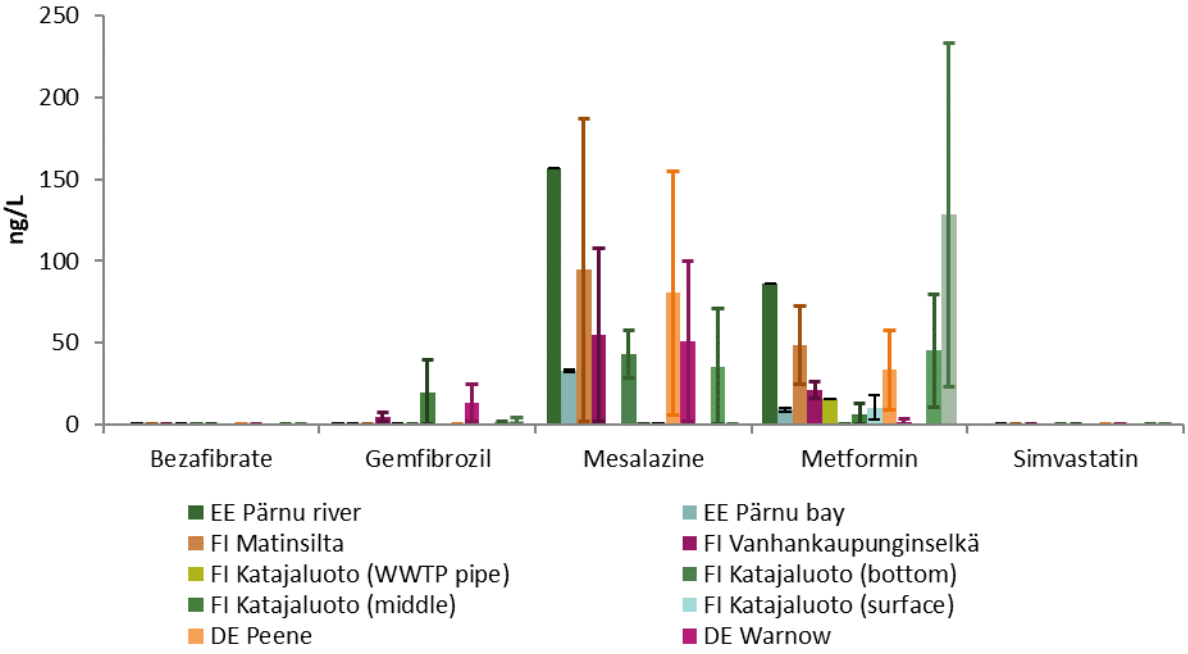


Figure 5.14. Average (wide bar) and minimum and maximum (whiskers) concentrations of gastrointestinal and metabolic

NSAIDs and analgesics

All analysed NSAIDs and analgesics were detected in both inland and coastal waters. All NSAIDs and analgesics were detected in all countries, with an exception of codeine, which was not detected in the Estonian inland water samples. In inland surface waters, DFs varied from 49% (ketoprofen) to 98% (tramadol) and in coastal waters from 19% (ketoprofen) to 96% (tramadol). Tramadol is an opioid used to treat moderate pain. Diclofenac was detected in 87% and 92% of inland and coastal water samples, respectively. Diclofenac is used to treat pain and inflammatory diseases and was listed on the previous EU Water framework directive watch list (2015/495/EY). Median concentrations of NSAIDs and analgesics in inland water ranged from <LOQ (codeine, ketoprofen and oxycodone) to 33 ng/L (diclofenac) (Figures 5.15 and 5.16). The 95th concentration percentile for the group was 360 ng/L. The highest median concentration was measured for diclofenac (33 ng/L), for which country-specific median concentrations ranged from 1.8 ng/L (Sweden) to 1 400 ng/L (Poland). Highest diclofenac concentrations (2 100–2 200 ng/L) were detected in Poland, downstream from the Błonie WWTP.

Diclofenac exceeded its PNEC-value (85 ng/L) in 35% of all inland water samples. PNEC-exceedances were most common in Poland (75% of samples (n=4)) and Finland (62% of samples (n=13)). The PNEC was exceeded occasionally in all Finnish inland sampling sites, and in all samples during the third, low-flow sampling campaign (11/2018). If the detected concentrations are compared to the proposed environmental quality standard (EQS) of 50 ng/L (Loos et al. 2018)), the frequency of exceedance in inland water samples increases to 42%. Similarly, the lowest PNEC-value reported in literature, 20 ng/L (Orias & Perrodin 2013), is exceeded in 58% of the inland water samples, and 15% of coastal samples. Highest national median concentrations were detected in Poland for ketoprofen (7.7 ng/L), naproxen (18 ng/L) and tramadol (430 ng/L), and for codeine and oxycodone in Finland (10 and 2.4 ng/L, respectively).

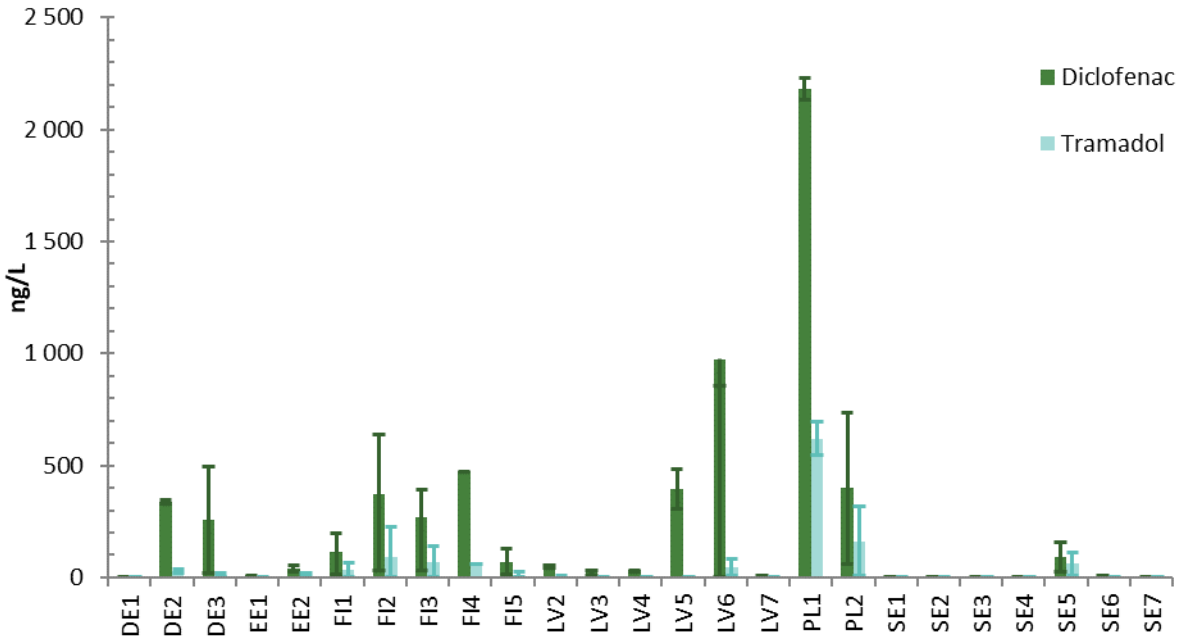


Figure 5.15. Average (bar) and minimum and maximum (whiskers) concentrations of tramadol and diclofenac in inland waters in the BSR. Full names of sampling sites are presented in table 5.2.

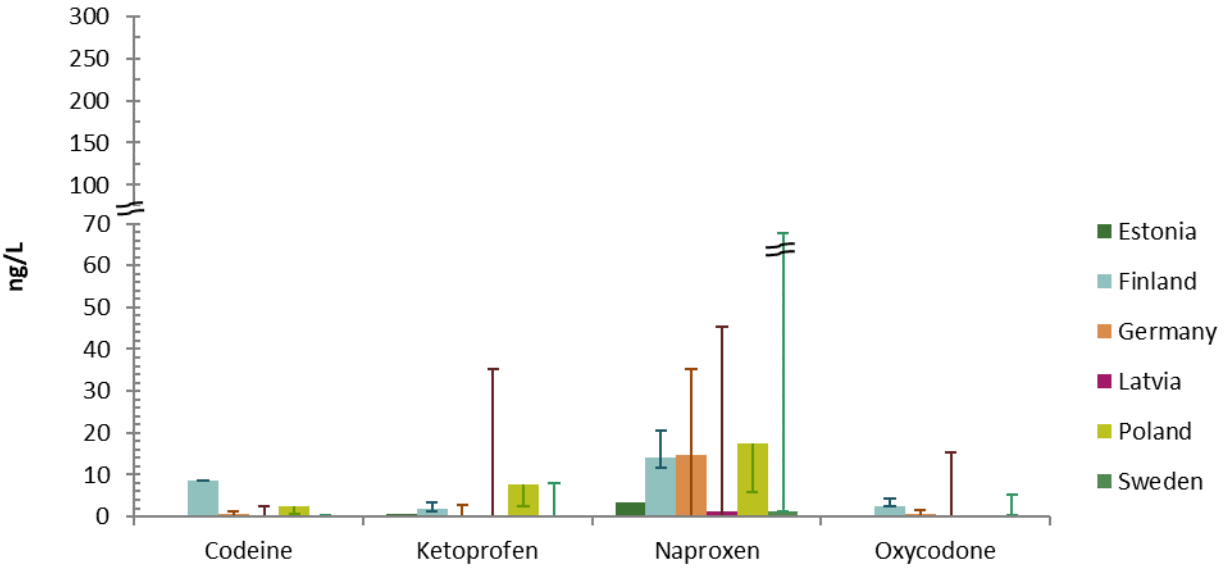


Figure 5.16. Median (wide bar), minimum and maximum (whiskers) concentrations of NSAIDs and analgesics in inland waters in the BSR.

In coastal waters, codeine, diclofenac and tramadol were detected in all countries. Highest median concentrations were measured for diclofenac, for which sampling site specific average concentrations ranged from <LOQ (Pärnu bay, Estonia) to 35 ng/L (Katajaluoto WWTP pipe, Finland). Concentrations of diclofenac in the distance of 1.7 km from the Katajaluoto WWTP pipe ranged from <LOQ to 6.3 ng/L. Ketoprofen was detected only in Riga coast (Latvia), Vistula River estuary (Poland) and Vantaanjoki estuary (Finland).

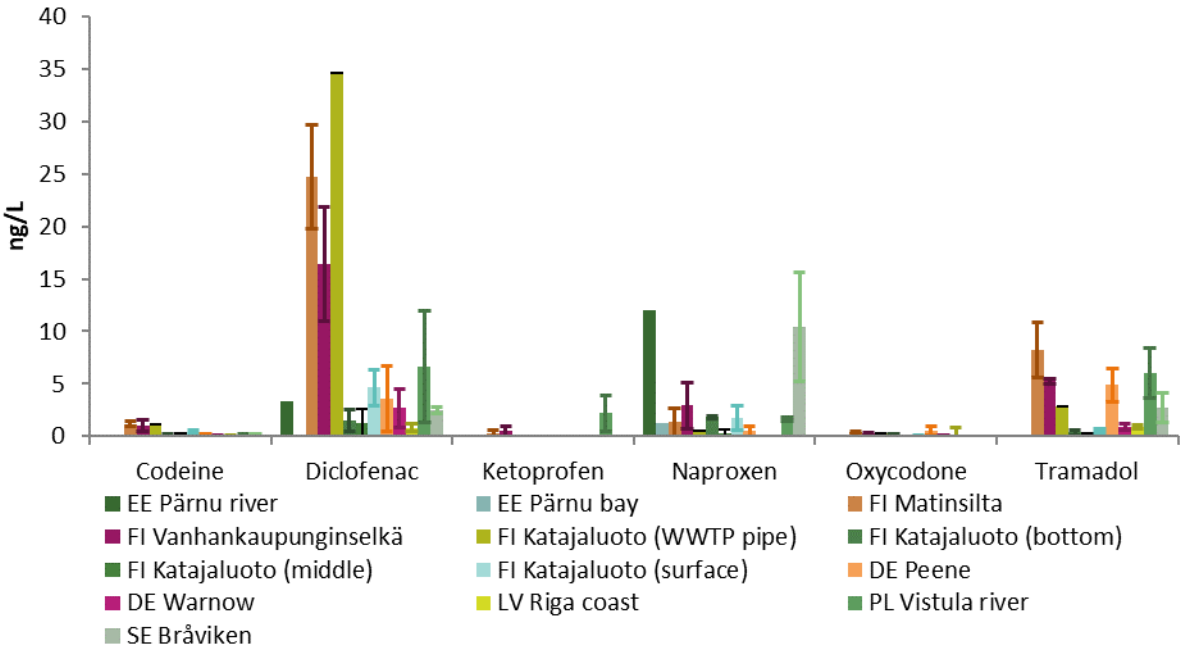


Figure 5.17. Average (wide bar) and minimum and maximum (whiskers) concentrations of NSAIDs and analgesics in sea waters in the BSR.

Cardiovascular APIs

All cardiovascular APIs were detected, but atenolol and warfarin only in inland water samples. In inland surface waters, DFs for the detected APIs varied from 7.3% (atenolol) to 85% (metoprolol) and in coastal waters from 11% (dipyridamole) to 88% (nebivolol).

In inland waters, the median concentrations of cardiovascular APIs varied from <LOQ (atenolol, dipyridamole, sotalol and warfarin) to 4.5 ng/L (metoprolol) (Figure 5.18). Metoprolol and nebivolol were detected in all countries. They were also the only cardiovascular APIs with median concentrations (4.6 ng/L and 0.32 ng/L, respectively) above LOQ. Metoprolol was consistently the cardiovascular API detected in highest median concentrations in inland waters in each country. Metoprolol and nebivolol are beta-blockers used to treat high blood pressure.

The highest concentration (290 ng/L) was measured for metoprolol at a Polish sampling site, located downstream from the Błonie WWTP in the River Rokitnica. Dipyridamole was detected only in two Finnish inland sampling sites, with a maximum average concentration of 5.4 ng/L being detected below the Kalteva WWTP.

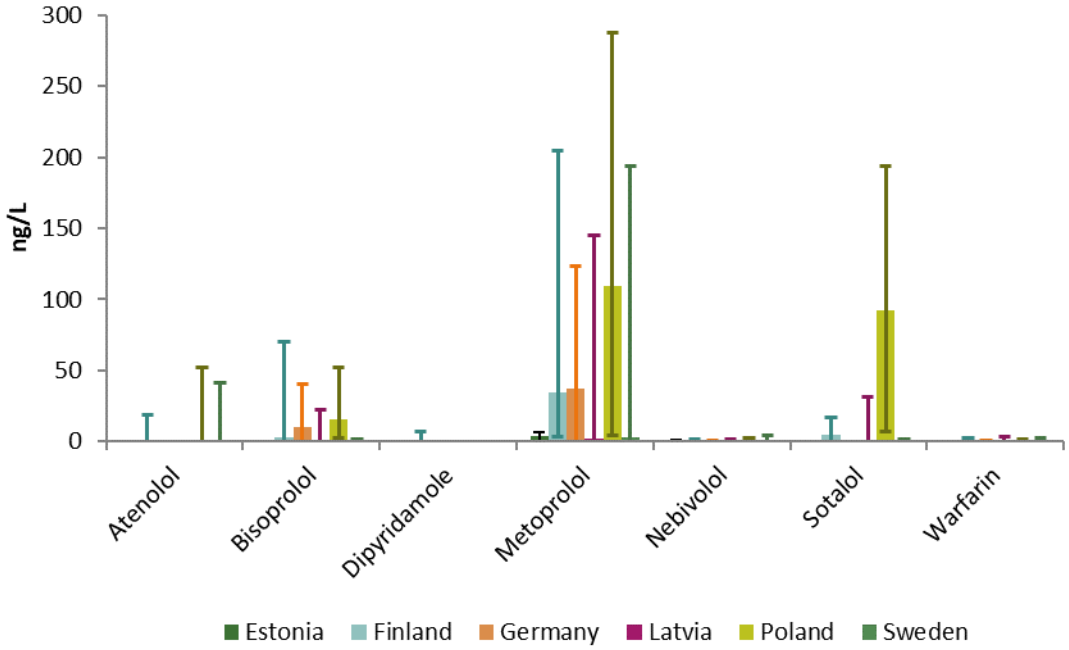


Figure 5.18. Median (wide bar), minimum and maximum (whiskers) concentrations of cardiovascular APIs in inland waters in the BSR.

In coastal waters, the overall 95th concentration percentile for the group was 4.5 ng/L. The API detected in highest median concentrations (0.43 ng/L) was metoprolol. Nebivolol was detected in each of the countries, with highest concentrations (average 4.4 ng/L) being detected in the Peene estuary (Germany).

Dipyridamole was detected only in German and Finnish sampling sites. Previously this substance has been detected in a concentration of 2.8 ng/L in the Baltic Sea water. In this project, the detected concentrations ranged from 0.92 ng/L to 35 ng/L. The highest concentration was detected in Finland, at the location of a WWTP discharge pipe. At a sampling site located approx. 1.7 km away from the discharge pipe, the concentrations for dipyridamole ranged from <LOQ to 2.3 ng/L.

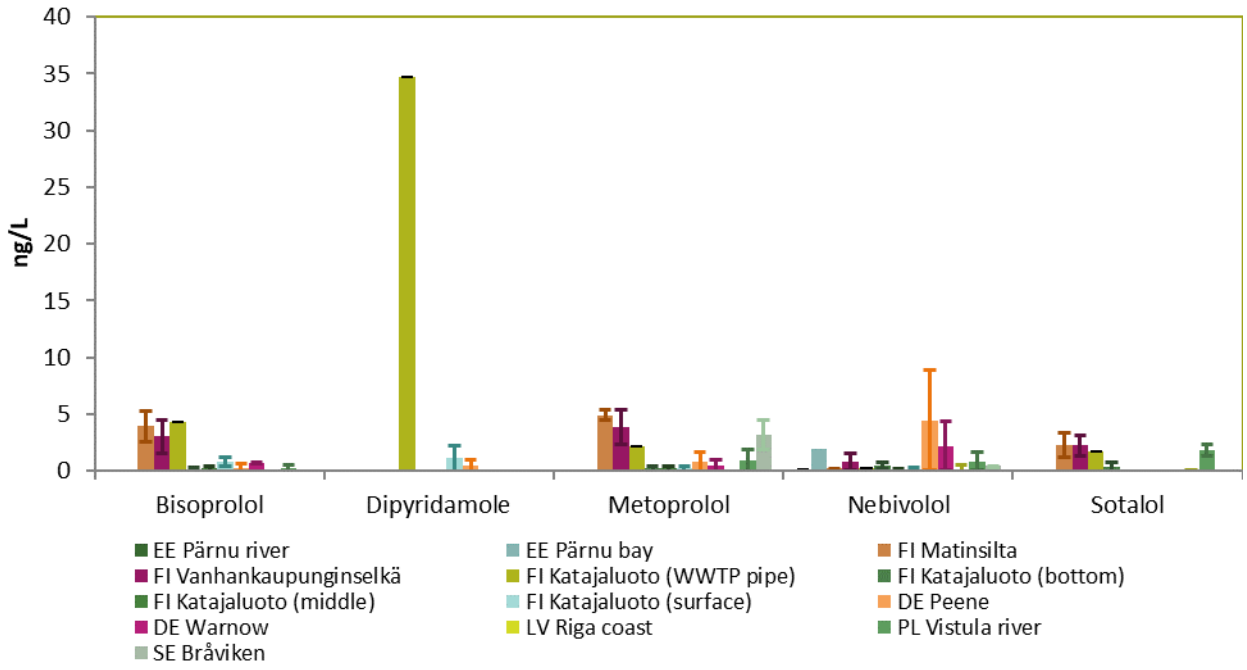


Figure 5.19. Average (wide bar) and minimum and maximum (whiskers) concentrations of cardiovascular APIs in sea waters in the BSR.

Psycopharmaceuticals

All six psychopharmaceuticals studied were detected in inland and coastal waters. In inland surface waters, DFs varied from 20% (quetiapine) to 93% (venlafaxine) and in coastal waters from 42% (sertraline) to 81% (citalopram). Almost all compounds were detected in all countries; quetiapine and temazepam were not detected in Estonia. The median concentrations of psychopharmaceuticals in inland water samples varied from <LOQ (quetiapine) to 2.7 ng/L (venlafaxine) (Figure 5.20). As a group, psychopharmaceutical concentrations had a 95th percentile of 89 ng/L in inland waters. Highest concentrations of oxazepam (290 ng/L), venlafaxine (210 ng/L), temazepam (200 ng/L) and citalopram (59 ng/L) were measured in Finland during June 2019 when the flow rate of the river was low.

In coastal waters, concentrations of psychopharmaceuticals had a 95th percentile of 9.0 ng/L. In general, the concentrations were lower in coastal waters than in inland waters and the maximum concentrations were below 10 ng/L for all psychopharmaceuticals, except oxazepam, which reached a maximum concentration of 17 ng/L (Figure 5.21).

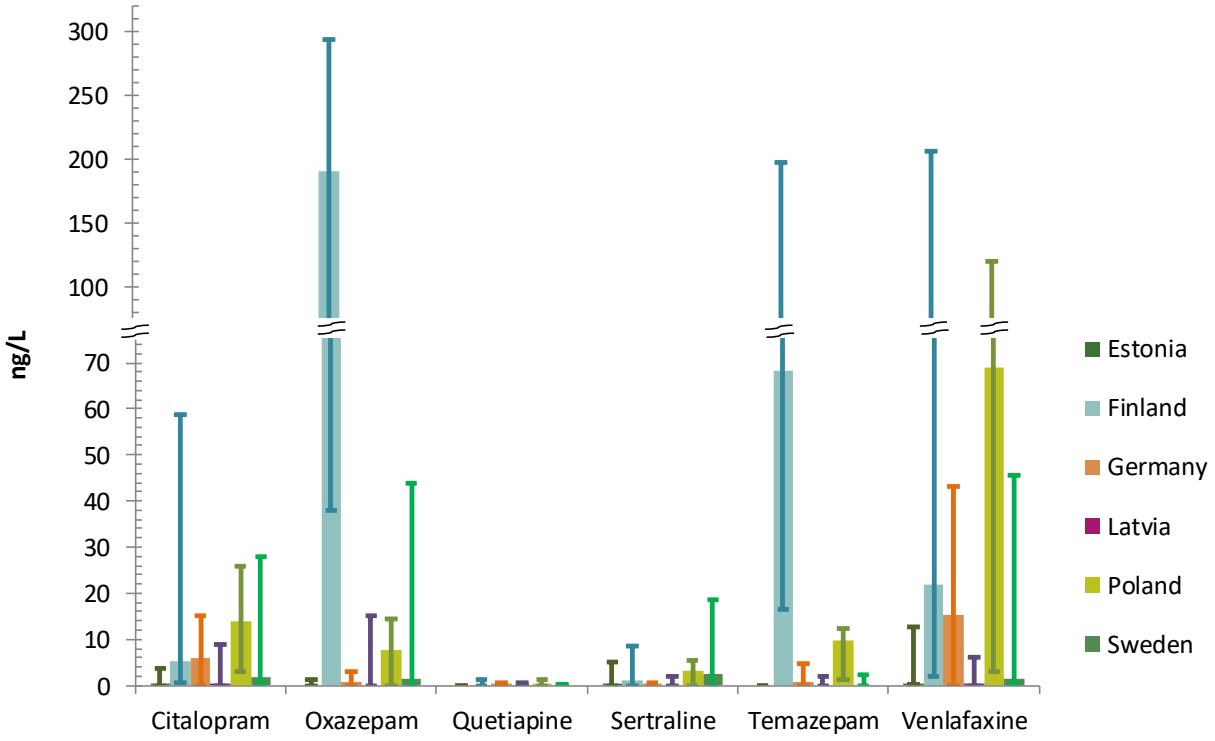


Figure 5.20. Median (wide bar), minimum and maximum (whiskers) concentrations of psychopharmaceuticals in inland waters in the BSR.

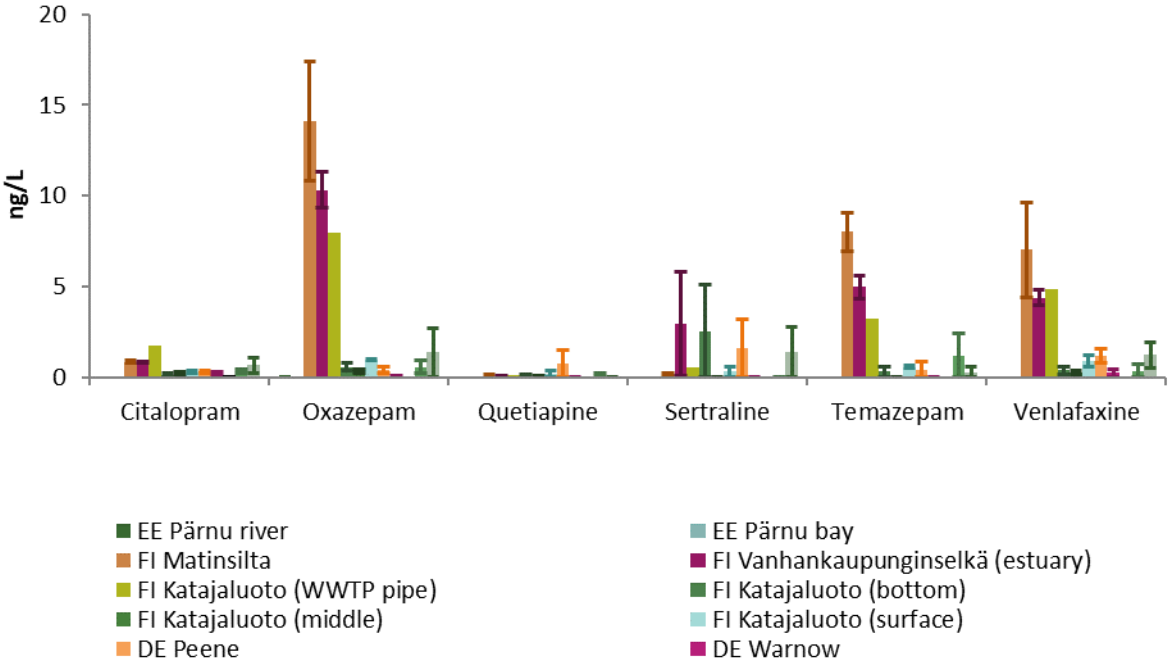


Figure 5.21. Average (wide bar) and minimum and maximum (whiskers) concentrations of psychopharmaceuticals in sea waters in the BSR.

Veterinary APIs

All six studied veterinary APIs were detected in surface waters. In inland surface waters, DFs varied from 2% (toltrazuril) to 69% (emamectin) and in coastal waters from 4% (toltrazuril) to 54% (emamectin and tiamulin). The major application of the most often detected API emamectin is the treatment of sea lice infestations in aquaculture, but it is also used as pesticide against mites and other insect species. It is currently approved as a crop protection chemical in EU but e.g. in Finland and Sweden no products are registered. Tiamulin is an antibiotic used in poultry and pig farming.

In inland waters the median concentrations of veterinary APIs varied from <LOQ (carprofen, fenbendazole, toltrazuril and tylosin) to 0.15 ng/L (emamectin). The case specific median values area given in Figure 5.22. The group concentrations of the six veterinary APIs had a 95th percentile of 4.7 ng/L in inland waters.

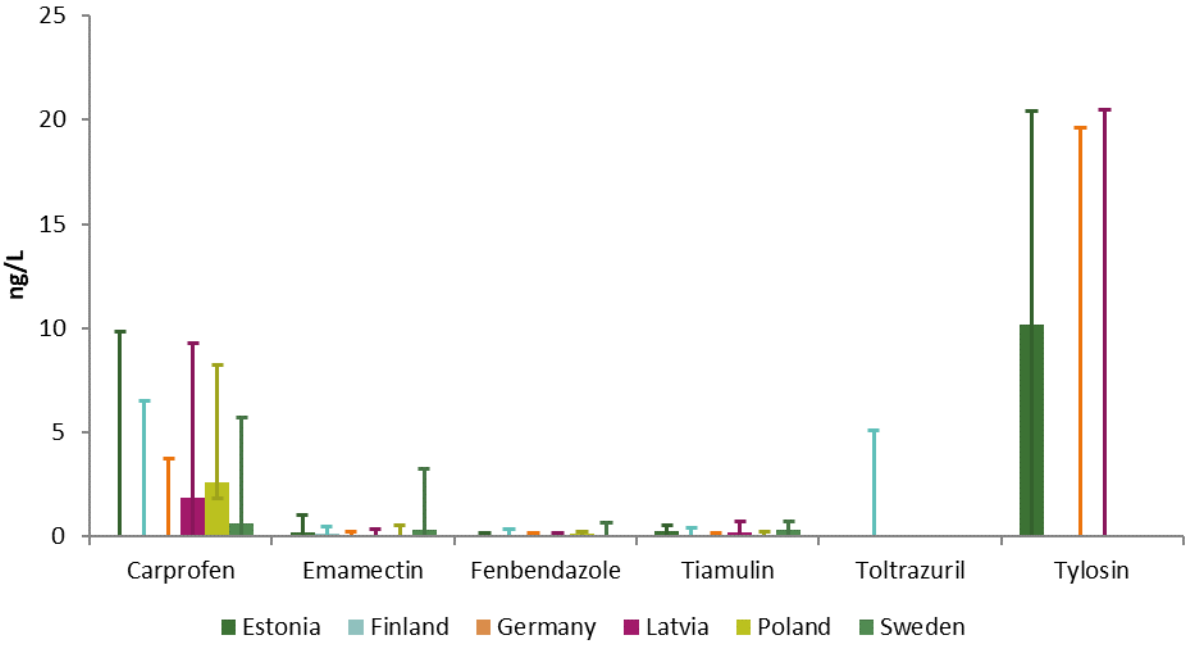


Figure 5.22. Median (wide bar), minimum and maximum (whiskers) concentrations of veterinary APIs in inland waters in the BSR.

In coastal waters, concentrations were at the same level as in inland waters. Tiamulin and emamectin were detected in all countries, reaching the highest sampling site specific median concentrations in Latvia (0.58 ng/L, site LV5) and Sweden (1.8 ng/L, site SE3), respectively.

Toltrazuril was detected only in Finland: in one inland sample taken in November 2018 and one coastal sample taken in March 2018. The detections were temporally and spatially unconnected. The inland water sample with a positive detection was taken from the river Vantaanjoki 68 km upstream from the river mouth (site FI1), while the coastal water sample was taken 1.7 km from the WWTP discharge pipe located near Katajaluoto islet, roughly 10 km off the Helsinki coastline. Both detections were only slightly above the LOQ. To assess whether toltrazuril is widely present at very low concentrations in surface waters, a screening study using a more sensitive analytical method would be required.

Emamectin exceeded its PNEC-value (1 ng/L) in at least one sample in all countries except in Finland. The exceedances were more common in coastal waters than in inland waters. PNEC was exceeded in one Swedish inland water sample, taken upstream of the lake Roxen. Coastal PNEC-exceedances were detected occasionally in Germany, Estonia and Latvia. The highest emamectin concentrations were detected during the second sampling campaign (May 2018) in Germany, when concentrations in the estuaries of rivers Peene and Warnow reached 7.2 ng/L and 4.6 ng/L, respectively.

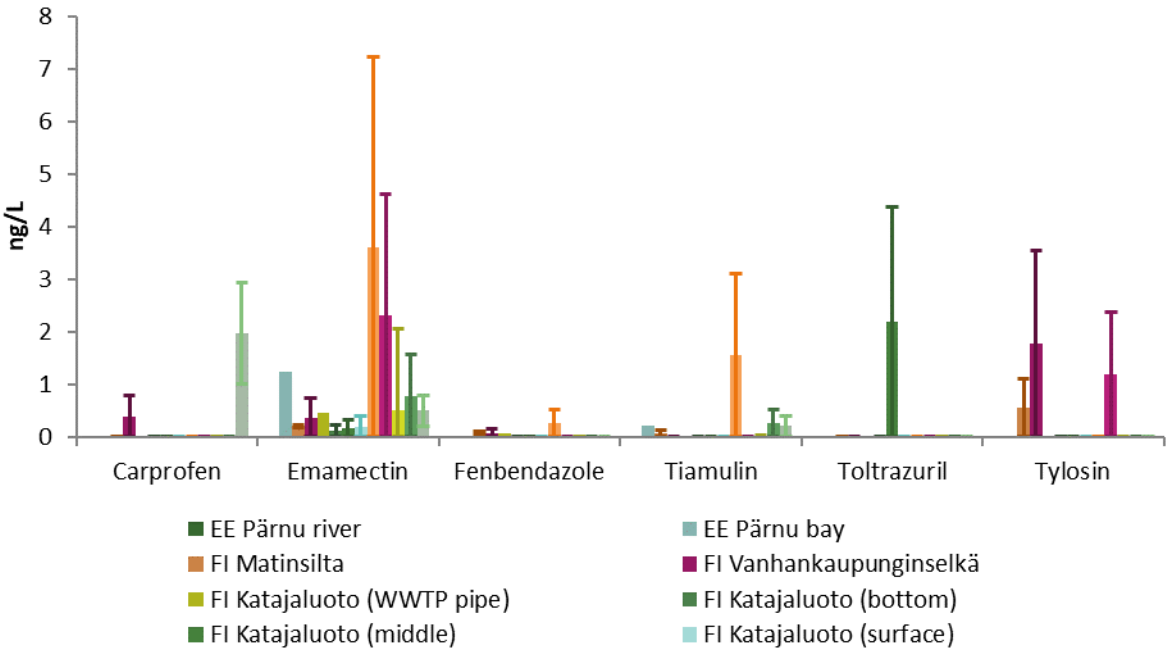


Figure 5.23. Average (wide bar) and minimum and maximum (whiskers) concentrations of vaterinary APIs Baltic Sea water.

Caffeine

Caffeine was detected in 89% of the inland water samples and in 96% of the coastal water samples. The median concentration of caffeine was 32 ng/L in surface waters and 6.0 ng/L in coastal waters. Sampling site specific average surface water concentrations ranged from 1.2 ng/L (Luhtajoki, Finland) to 220 ng/L (Upstream site of the River Rokitnica, Poland) (Figure 5.24). In coastal water samples the sampling site specific average concentrations ranged from <LOQ (Pärnu bay, Estonia) to 77 ng/L (Bråviken, Sweden). The amount of caffeine originating from pharmaceutical use was assumed negligible in comparison to caffeine originating from coffee and other drinks.

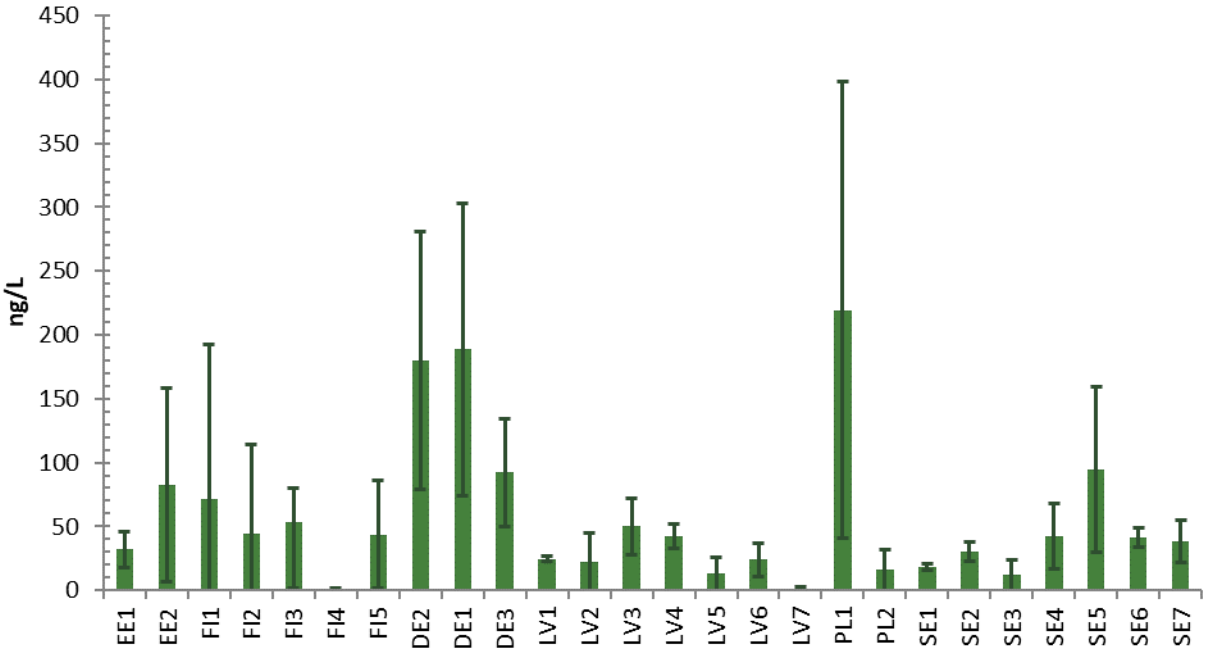


Figure 5.24. Average (wide bar) and range (whiskers) of concentrations of caffeine in the surface waters of the BSR. Full names of sampling sites are prestented in table 5.2.

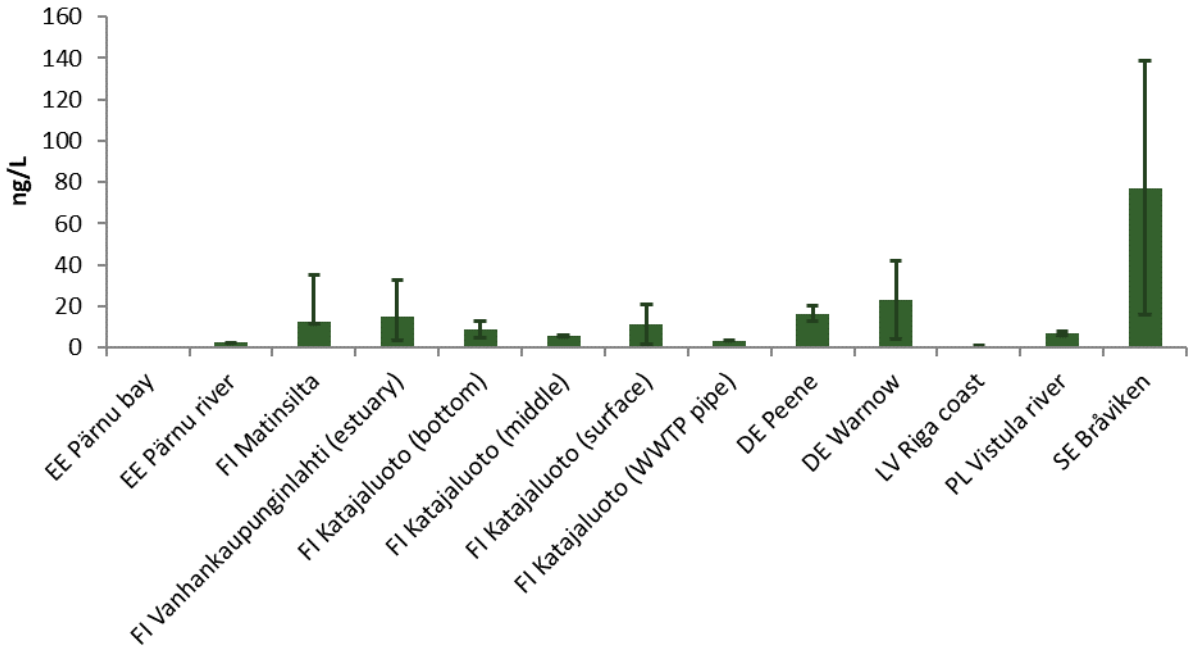


Figure 5.25. Average (wide bar) and minimum and maximum (whiskers) concentrations of caffeine in coastal waters in the BSR.

5.1.2.2 Overview of the API levels in surface waters

Carbamazepine, tramadol and venlafaxine were detected in at least 90% of inland water samples. Corresponding APIs in coastal water samples were carbamazepine, cetirizine, tramadol, caffeine and diclofenac. Although DFs of carbamazepine and tramadol were over 90% in both inland and coastal water samples, their median concentrations were 1.9 and 3.8 times higher in inland surface waters compared to coastal waters, respectively.

In inland waters, the APIs detected in highest median concentrations were gabapentin (88 ng/L), metformin (78 ng/L) and diclofenac (33 ng/L). In coastal waters corresponding APIs were metformin (12 ng/L), caffeine (6.0 ng/L) and diclofenac (2.7 ng/L). Also, gabapentin concentrations were high in coastal waters (34–120 ng/L), but it was analysed in only three samples and therefore the data are not very comprehensive. Ciprofloxacin, sulfadiazine and enalapril were the only compounds which were not detected in any surface water sample.

In inland waters, the mean concentrations of antiepileptics, gastrointestinal and metabolic disease APIs were significantly higher (ANOVA; $p < 0.05$) compared to other analysed API groups except caffeine and NSAIDs and analgesics (Figure 5.26). In coastal waters, the concentrations of gastrointestinal disease APIs and caffeine were significantly higher compared to every other API group (ANOVA; $p < 0.05$). The detection frequencies and concentrations of each API are summarised in Table 5.3.

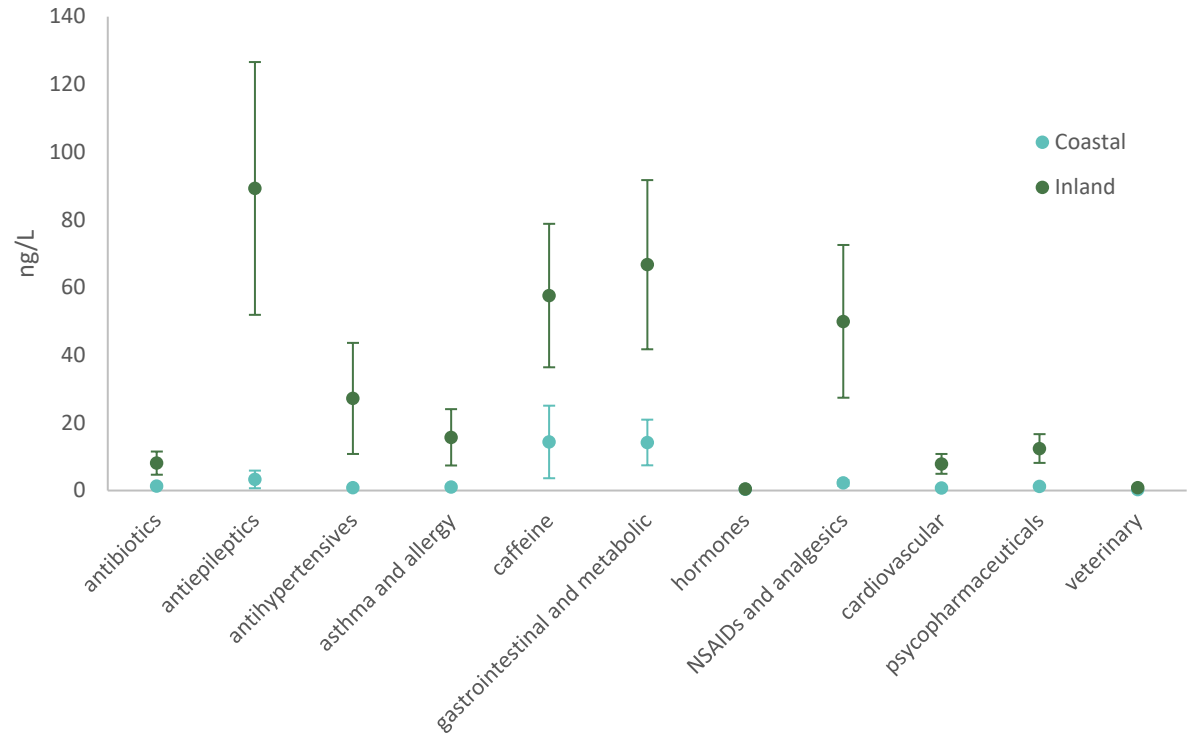


Figure 5.26. Average (plots) and 95% confidence interval (whiskers) concentrations of APIs in surface waters of the BSR.

Table 5.2. Full names of inland water sampling sites.

Code	Site name
DE1	Tollense river, upstream WWTP Neubrandenburg
DE2	Tollense river, downstream WWTP Neubrandenburg
DE3	Warnow river, upstream Rostock
EE1	Pärnu river after river Esna, before city of Paide
EE2	Pärnu river, Jändja
FI1	Vantaa 68,2, upstream WWTP Kalteva
FI2	Vantaa 64,8, downstream WWTP Kalteva
FI3	Vantaa 44,1
FI4	Luhtajoki, downstream of a WWTP
FI5	Vantaa 4,2 (4.2 km from the river mouth)
LV1	Mēmele, 0.5 km below Skaistkalne
LV2	Mūsa river, Latvia-Lithuania border
LV3	Driksa river, upstream Jelgava
LV4	Driksa river, downstream Jelgava
LV5	Pupla river, upstream Olaine
LV6	Pupla river, downstream Olaine
LV7	Lielupe, 0.5 km below Kalnciems
PL1	Rokitnica river, downstream Błonie WWTP
PL2	Rokitnica river, upstream Błonie WWTP
SE1	Vättern
SE2	Boren, downstream Motala WWTP
SE3	Svartån
SE4	Stångån, upstream Linköping WWTP
SE5	Stångån-Roxen, downstream Linköping WWTP
SE6	Dovern
SE7	Glan
SE8	Bråviken (BSE), downstream Norrköping WWTP

Table 5.3. Summary of API detection frequencies (DF) and median and maximum concentrations in surface waters.

Substance	PNEC (CWPharma) (ng/L)	Inland water				Coastal water			
		n	DF (%)	Median (ng/L)	Max (ng/L)	n	DF (%)	Median (ng/L)	Max (ng/L)
Amlodipine	100	55	2	<LOQ	9.8	26	38	<LOQ	7.0
Atenolol	194 000	55	7	<LOQ	52	26	0	<LOQ	<LOQ
Atorvastatin	21 00	53	38	<LOQ	1 500	1	0	<LOQ	<LOQ
Bezafibrate	1 260	55	24	<LOQ	13	26	27	<LOQ	0.59
Bisoprolol	8 000	55	36	<LOQ	70	26	50	0.13	5.3
Caffeine	87 000	55	89	32	400	26	96	6.0	140
Candesartan	421	55	42	<LOQ	19	26	27	<LOQ	13
Carbamazepine	1 280	55	98	3.7	920	26	100	2.0	60
Carprofen	37 270	55	47	<LOQ	9.8	26	12	<LOQ	3.0
Cetirizine	78 620	55	80	1.8	630	26	100	1.2	22
Ciprofloxacin	5.1, (89*)	2	0	<LOQ	<LOQ	23	0	<LOQ	<LOQ
Citalopram	15 400	55	87	2.0	59	26	81	0.25	1.7
Clarithromycin	3.9, (120*)	55	73	3.2	590	26	62	0.080	7.3
Codeine	16 000	38	61	<LOQ	23	25	88	0.18	1.9
Diclofenac	85, (50*)	55	87	33	2 200	26	92	2.7	35
Dipyridamole	2 360	55	9	<LOQ	6.9	26	12	<LOQ	35
Emamectin	1	55	69	0.15	3.2	26	54	0.20	7.2
Enalapril	44 736	53	0	<LOQ	<LOQ	1	0	<LOQ	<LOQ
Eprosartan	100 000	53	34	<LOQ	4.9	1	100	0.24	0.24
Erythromycin	83.5	2	100	<LOQ	0.13	23	48	<LOQ	20
Estrone (E1)	0.008	55	25	<LOQ	10	26	54	0.27	5.4
Fenbendazole	15	55	29	<LOQ	0.63	26	19	<LOQ	0.51
Fexofenadine	200 000	53	70	0.79	520	1	100	2.2	2.2
Fluconazole	15 000	55	71	1.2	280	26	65	0.33	7.4
Fluticasone	550	55	31	<LOQ	0.41	26	38	<LOQ	0.30
Gabapentin	100 000	53	89	82	1 900	1	100	82	82
Gemfibrozil	825	55	62	4.1	260	26	38	<LOQ	40
Irbesartan	100 000	55	47	<LOQ	110	26	62	0.040	1.5
Ketoprofen	2 000	55	49	<LOQ	280	26	19	<LOQ	3.9
Levetiracetam	100 000	55	38	<LOQ	120	26	19	<LOQ	6.5
Lincomycin	1 290	55	44	<LOQ	9.4	26	50	0.020	1.5
Losartan	7 800	55	67	1.1	200	26	69	0.19	7.7
Mesalazine	911 000	2	100	<LOQ	0.12	23	78	2.3	190
Metformin	1 350	55	87	78	2 300	26	69	12	230
Metoprolol	4 380	55	85	4.6	290	26	54	0.43	6.0
Mometasone furoate	14	55	7	<LOQ	28	26	15	<LOQ	0.36
Naproxen	4 980	53	75	3.1	94	22	73	1.1	16
Nebivolol	377	55	65	0.32	4.0	26	88	0.21	8.9
Norethisterone	0.50	55	62	0.26	6.9	22	59	0.040	1.2
Ofloxacin	20.4	55	24	<LOQ	340	25	4	<LOQ	15
Oxazepam	810	38	79	0.45	290	25	76	0.45	17
Oxycodone	3 304 000	38	68	<LOQ	15	25	52	0.040	0.97
Primidone	100 000	55	25	<LOQ	61	26	23	<LOQ	1.5
Progesterone	2 000	55	45	<LOQ	1.4	26	35	<LOQ	0.24
Quetiapine	10 000	55	20	<LOQ	1.2	26	54	0.010	1.5
Ramipril	100 000	53	26	<LOQ	19	1	0	<LOQ	<LOQ
Sertraline	1 070	55	62	0.39	19	26	42	<LOQ	5.8
Simvastatin	22 800	2	100	<LOQ	0.080	23	30	<LOQ	0.14
Sotalol	300 000	55	33	<LOQ	190	26	35	<LOQ	3.4
Sulfadiazine	135	53	0	<LOQ	<LOQ	1	0	<LOQ	<LOQ
Telmisartan	9 880	53	66	6.4	2 800	1	100	1.8	1.8
Temazepam	930	38	53	<LOQ	200	25	48	<LOQ	9.7
Testosterone	1 500	55	35	<LOQ	0.78	26	54	0.060	5.8
Tetra- + doxycycline	1 730/37	55	9	<LOQ	46	26	46	<LOQ	23
Tiamulin	165	55	58	0.11	0.73	26	54	0.010	3.1
Toltrazuril	440	55	2	<LOQ	5.1	26	4	<LOQ	4.4
Tramadol	170 000	55	98	4.4	690	26	96	1.1	11
Trimethoprim	508 000	55	56	0.69	83	26	54	0.10	3.8
Tylosin	34	55	15	<LOQ	20	26	12	<LOQ	3.5
Valsartan	125 000	53	55	8.2	510	1	100	6.7	6.7
Warfarin	67 600	55	16	<LOQ	3.4	26	0	<LOQ	<LOQ
Venlafaxine	3 220	55	93	2.7	210	26	69	0.55	9.6
Xylometazoline	2 030	55	65	1.1	3.8	26	15	<LOQ	1.6

5.1.2.3 Observed concentrations versus PNECs

Eight of the detected 60 APIs exceeded their predicted no-effect concentrations (PNEC) in at least one surface water sample: hormones estrone and norethistrone, antibiotics clatrithromycin, ofloxacin, an analgesic diclofenac, a veterinary medicine emamectin benzoate, an asthma and allergy medicine mometasone furoate and a metabolic desease medicine metformin (see chapter 9). In one sample also the sum concentration of tetracycline and doxycycline exceeded the PNEC of doxycycline but not the PNEC of tetracycline, which is much higher. These are not the same APIs as those observed at the highest concentrations. The number of APIs occurring in concentrations higher than PNEC varied from 0 to 4 per sample (median 1 and average 1.4). In ca. 75% of the samples at least one API exceeded its PNEC. When the natural hormone estrone was excluded, 63% of samples had at least one API exceeding its PNEC. The estimation of the risk caused by estrone is uncertain due to the high LOQ compared to PNEC value and the high variation of PNEC values reported in different sources.

The RQ values of the detected APIs in each sample were summed together in order to estimate the potential mixture effects. The sum RQ values are given in Table 5.4. The sum RQ was dominated by few APIs. However, it must be noted that some APIs that were not analysed in the surface water may pose a risk.

Concentrations and calculated risks varied between the case study areas, sites within the areas (e.g. upstream and downstream) and between the sampling occasions. The flow conditions had marked effects on the variation of concentrations between sampling times. For example, in the Finnish river Vantaanjoki, extreme flow conditions during the samplings resulted in both extremely low and exceptionally high dilution conditions for the treated wastewater. Also, the usage of certain APIs as well as the degradation in WWTPs and surface water varies with seasons. In future screenings and monitoring campaings, it would be beneficial to have more sampling occasions to get information on different flow conditions and seasons, and to overcome the non-representative concentrations in single samples.

The PNEC values have high influence on calculated risk quotients. In this study, the PNECs of estrone and clarithromycin were lower while PNECs of diclofenac, ciprofloxacin and erythromycin were higher than those used under the EU water policy watch list screening (Loos et al. 2018), see Table 5.5. The observed concentrations of estrone and diclofenac were similar for the watch list screening, but the calculated RQ values differed, especially for estrone, due to differences in the PNEC values used in the studies. In this study, the RQ values for estrone would be much smaller using the PNEC value of Loos et al. (2018).

5.1.3 Conclusions

The six case studies gave a good snapshot on the occurrence of the selected APIs in surface waters within Baltic Sea Region: pharmaceuticals are present in rivers, lakes, estuaries and coastal areas close to cities and under other anthropogenic influence. In each water sample, 8–49 APIs were detected, and the sum concentration of the detected APIs varied from 1.8 ng/L to 12 µg/L per sample. Altogether 60 of the analysed 63 APIs were detected in at least one inland or coastal surface water sample.

Eight APIs were detected in concentrations exceeding their PNEC values. These APIs were hormones estrogen and norethisterone, antibiotics clarithromycin and ofloxacin, an analgesic diclofenac, a veterinary medicine emamectin, an asthma and allergy medication momeasone furoate and a metabolic disease medicine metformin. At least one API exceeded its PNEC in 63 of 83 surface water samples. In 8 of 83 samples, there were four APIs present in concentrations higher than PNEC. These results indicate an urgent need to decrease the emissions of pharmaceuticals into the surface waters. The case study screening results highlight the need to monitor pharmaceuticals

and to find ways to decrease their concentrations in the surface waters. The results may be utilized to design future studies and monitoring.

Table 5.4 A summary of the sum risk quotients (sum RQ) and a list of APIs exceeding the PNEC (APIs with RQ>1) in each case study area. In the Swedish and Finnish case studies, the RQ for metformin was very close to 1 and thus presented in brackets. For non-detected concentrations the calculated RQ is marked as ND. Doxycycline RQ was calculated by comparing the sum concentration of tetracycline and doxyxycline to doxycycline PNEC.

	Inland water samples		**Coastal water sampels**	
	Sum RQ	**APIs with RQ>1**	Sum RQ	**APIs with RQ>1**
Estonia	Pärnu river: 2 sites		Pärnu estuary / bay	
	1.2 – 5.2	Norethisterone (ND–2.7) Clarithromycin (ND–1.3) Mometasone furoate (ND–2.0) Emamectin benzoate (ND–1.0)	100 – 215	Estrone (100–213)
Poland	Rokitnica river: 2 sites		Vistula mouth	
	11 – 361	Estrone (ND–350) Clarithromycin (2.1–150) Diclofenac (0.73–26) Ofloxacin (ND–3.0) Norethisterone (ND–1.4)	4.4 – 32	Estrone (ND–31), Norethisterone (ND–2.4), Emamectin benzoate (ND–1.6)
Germany	Tollense river: 2 sites; Warnow upstream		Peene estuary & Warnow river mouth	
	0.03–352	Estrone (ND–340) Norethisterone (ND–14) Clarithromycin (ND–12) Diclofenac (ND–5.8)	0.4 – 680	Estrone (ND–674), Norethisterone (ND–1.7), Emamectin benzoate (ND–7.2)
Latvia	7 river sites		Riga (near WWTP pipe)	
	0.1 – 301	Estrone (ND–300) Norethisterone (ND–1.6) Clarithromycin (ND–27) Diclofenac (ND–13) Metformin (ND–1.7)	0.1 – 2.3	Emamectin benzoate (ND–2.1)
Sweden	Chain of lakes and streams: 7 inland sites		Bråviken	
	0.8 – 20	Ofloxacin (ND–17) Norethisterone (ND–4.2) Emamectin benzoate (ND–3.2) Diclofenac (ND–1.9) Doxycycline (ND-1.3) [Metformin (ND–0.93)]	1.0 – 3,1	Norethisterone (ND–1.1)
Finland	River Vantaanjoki: 4 sites & a tributary site		Estuary of river Vantaa: 2 sites	
	0.9 – 1283	Estrone (ND–1260) Clarithromycin (0.49–26) Diclofenac (0.19–7.5) Norethistrone (ND–2.8) [Metformin (0.03–0.98)]	1.5 – 580	Estrone (ND–64)
Finland			Helsinki coast, about 7 km offshore	
			66 0.28 – 126	estrone (RQ 64) at the WWTP pipe outlet estrone (ND–127) a mile from the pipe

Table 5.5 Comparison of the inland surface water concentrations of the case studies with the results of the EU wide watch list screening. To improve the comparability of the studies, the presented results were calculated by treating <LOQ results as LOQ/2.

	This study						**Watch list screening (Loos et al. 2018)**					
API	PNEC (ng/L)	n	DF (%)	Median (ng/L)	95th percentile	Max (ng/L)	PNEC (ng/L)	n	DF (%)	Median (ng/L)	95th percentile	Max (ng/L)
Estrone (E1)	0.008	55	25	0.35	7.2	10	3.6	1358	55	2.5	5.7	99
Diclofenac	85	55	87	33	1300	2200	50	17748	69	40	460	7100
Clarithromycin	3.9	55	73	3.2	101	590	120	7443	59	15	130	1600
Erythromycin	83.5	2	100	0.12	-	0.13	20	6313	8.4	10	50	1100

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5.2 Environmental levels of APIs in river and estuary sediments

5.2.1 Methods

Sediment sampling was performed in Bråviken estuary (SE), Pärnu river (EST), Pärnu bay (EST) and the Gulf of Riga (LV). All sediment samples were frozen at -20° C after sampling and sent to SYKE for chemical analyses of 75 APIs and dry matter content. Sampling dates and raw data are presented in Annex 4.

In Sweden, sediment samples were taken from Bråviken estuary in December 2017 and in June 2018. At each visit, six sediment samples were taken using a core sampler and the upper 5 cm of these subsamples were integrated into one sample for analysis. The sampling location is located outside the city of Norrköping approx. 7,5 km downstream of the discharge of treated wastewater from the WWTP in Norrköping. The depth of the sampling location was 12 m.

Estonian sediment samples were taken from Pärnu river in December 2017 and in Pärnu bay in June 2018. The original plan was to take samples from the bay at both sampling time points, but due to bad weather conditions in December 2017, it was not possible to take sea samples and instead the samples were taken from the mouth of Pärnu river. For the December sample, five subsamples were taken in Pärnu river and the upper 10 cm of sediment from each was integrated into one sample for analysis. For the June sample, ten subsamples were taken from the middle of Pärnu bay and the upper 5 cm were then integrated into one sample for analysis.

In Latvia, the Gulf of Riga was sampled one nautical mile (~1.85 km) from the shore in December 2017 and May 2018. The depth of the station was 12 m and located near an outlet of a wastewater treatment plant pipe. At both sampling timepoints, three sediment subsamples were taken using a Van-Veen grab sampler and the upper 5 cm of the subsamples were integrated into one sample for analysis.

5.2.2 Results and discussion

5.2.2.1 Observed occurrence and concentration levels of APIs

Sediments from three Baltic Sea Estuaries in Sweden (SE), Latvia (LV) and Estonia (EST), and an Estonian river, were analysed for 63-65 APIs. The number of detected compounds varied from 13 to 41 per sample. Altogether 47 out of 65 analysed APIs were detected in at least one sample. All measured concentrations are presented in Annex 4. Substances that were detected above LOQ in at least one of the studied sediment samples are presented in figure 5.27-5.29. Five APIs were found in all sediment samples: caffeine, metformin, oxazepam, risperidone and tramadol. The APIs found in the highest concentrations were the NSAID and analgesic paracetamol in the sediments of Bråviken estuary and the asthma and allergy medication xylometazoline in Riga coast and in Pärnu bay.

The concentrations of APIs were generally higher in the sediments from the mouth of Pärnu river than in Pärnu bay, probably due to higher dilution of APIs in coastal waters. The exceptions were xylometazoline, hydrochlorothiazide and the sum of tetracycline and doxycycline that were instead higher in the sediments of Pärnu bay than in Pärnu river. Since the bay and the river were sampled at different times of year, other explanations for the observed differences are seasonal variations in consumption of APIs and temperature dependent degradation rates, but further studies are needed to elucidate this.

Sediment sampling in Bråviken estuary, Sweden. Photo: Sabina Hoppe, CAB.

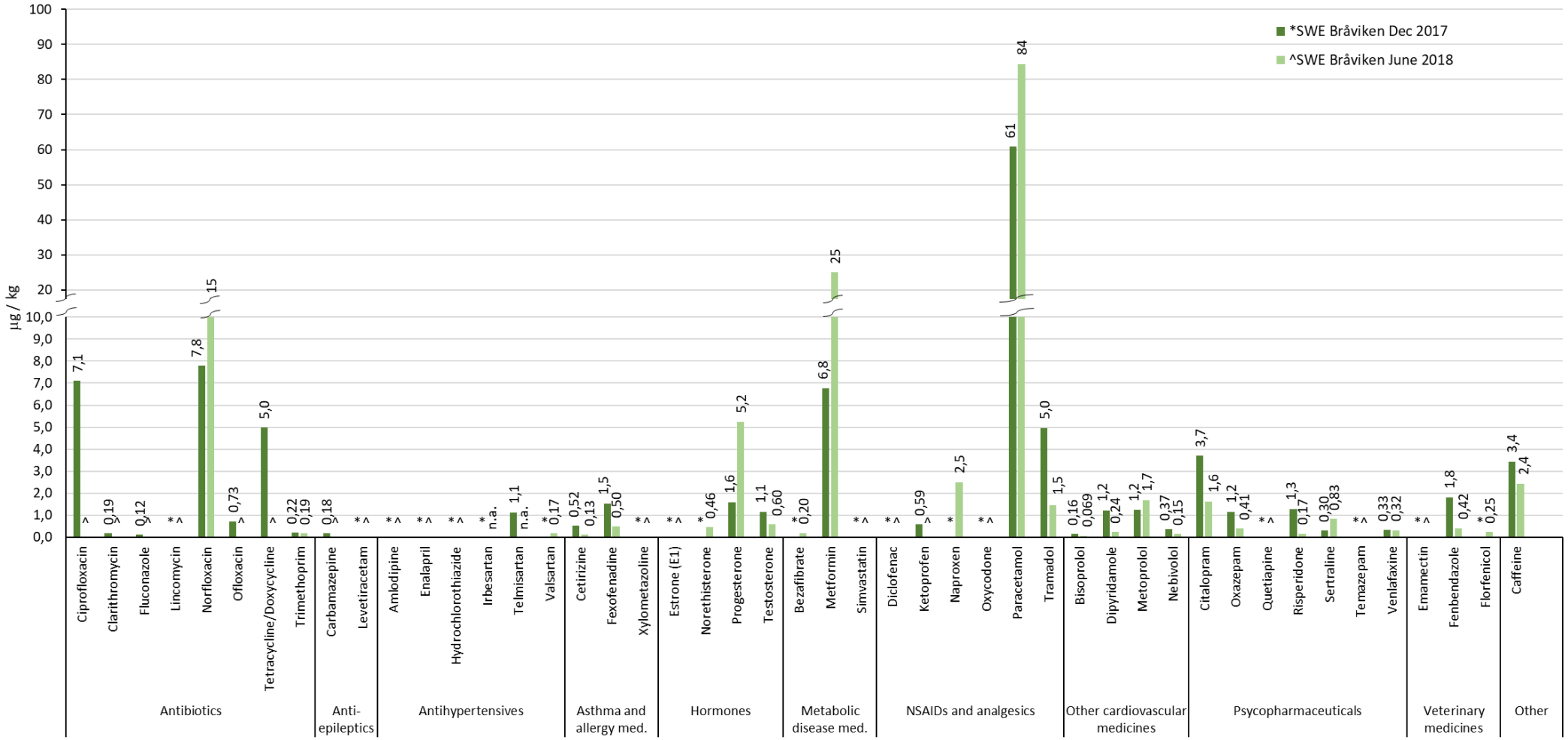

Figure 5.27. APIs in sediments of the Bråviken estuary (SE) in December 2017 and June 2018. API below LOQ are marked with "*" for samples taken in December 2017 and "^" for samples taken in June 2018. Substances above LOQ in at least one of the sediment samples from the Baltic Sea Estuaries are included.

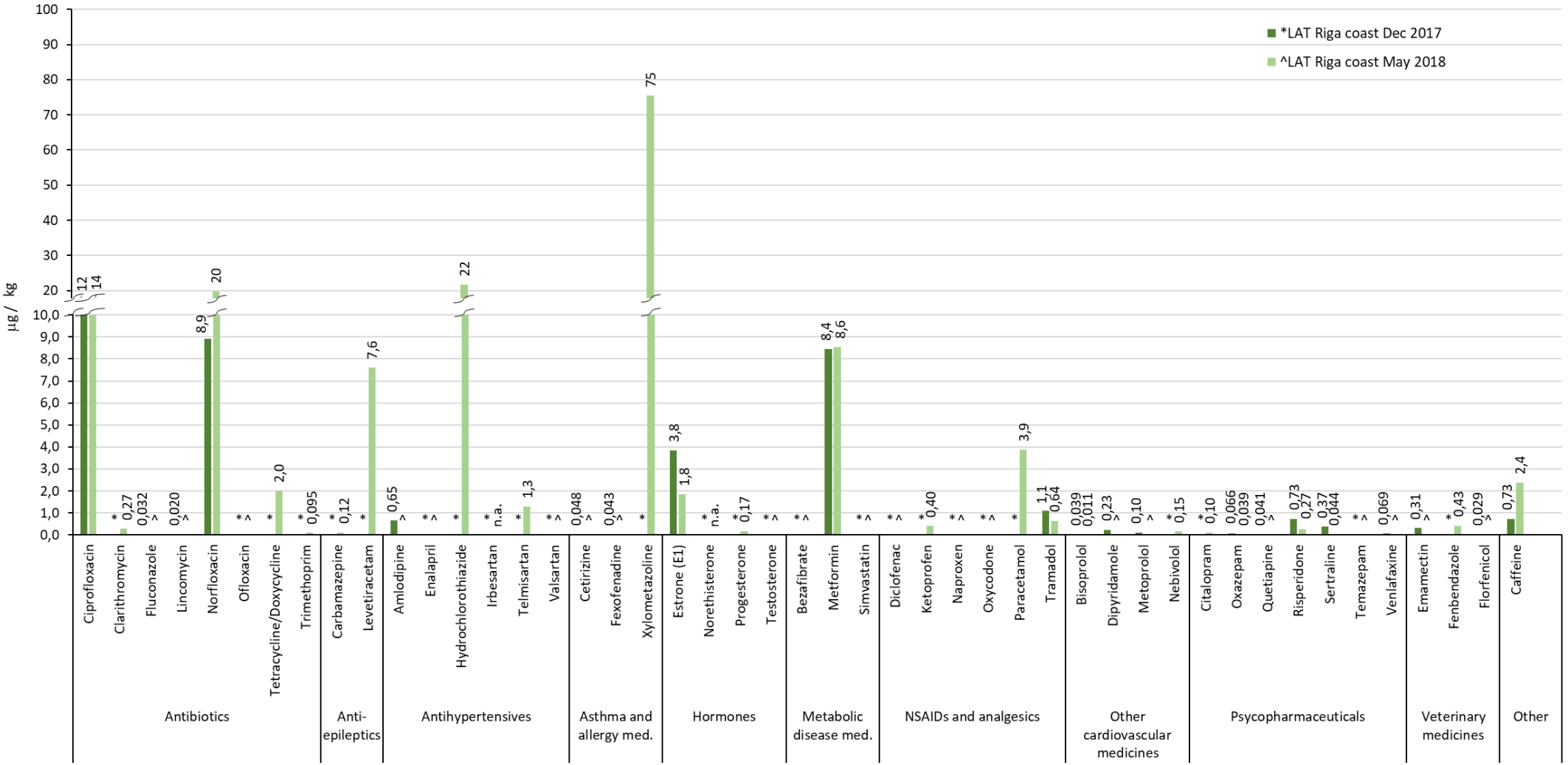

Figure 5.28. APIs in sediments from the Riga coast (LV) in December 2017 and May 2018. API below LOQ are marked with "*" for samples taken in December 2017 and "^" for samples taken in May 2018. Substances above LOQ in at least one of the sediment samples from the Baltic Sea Estuaries are included.

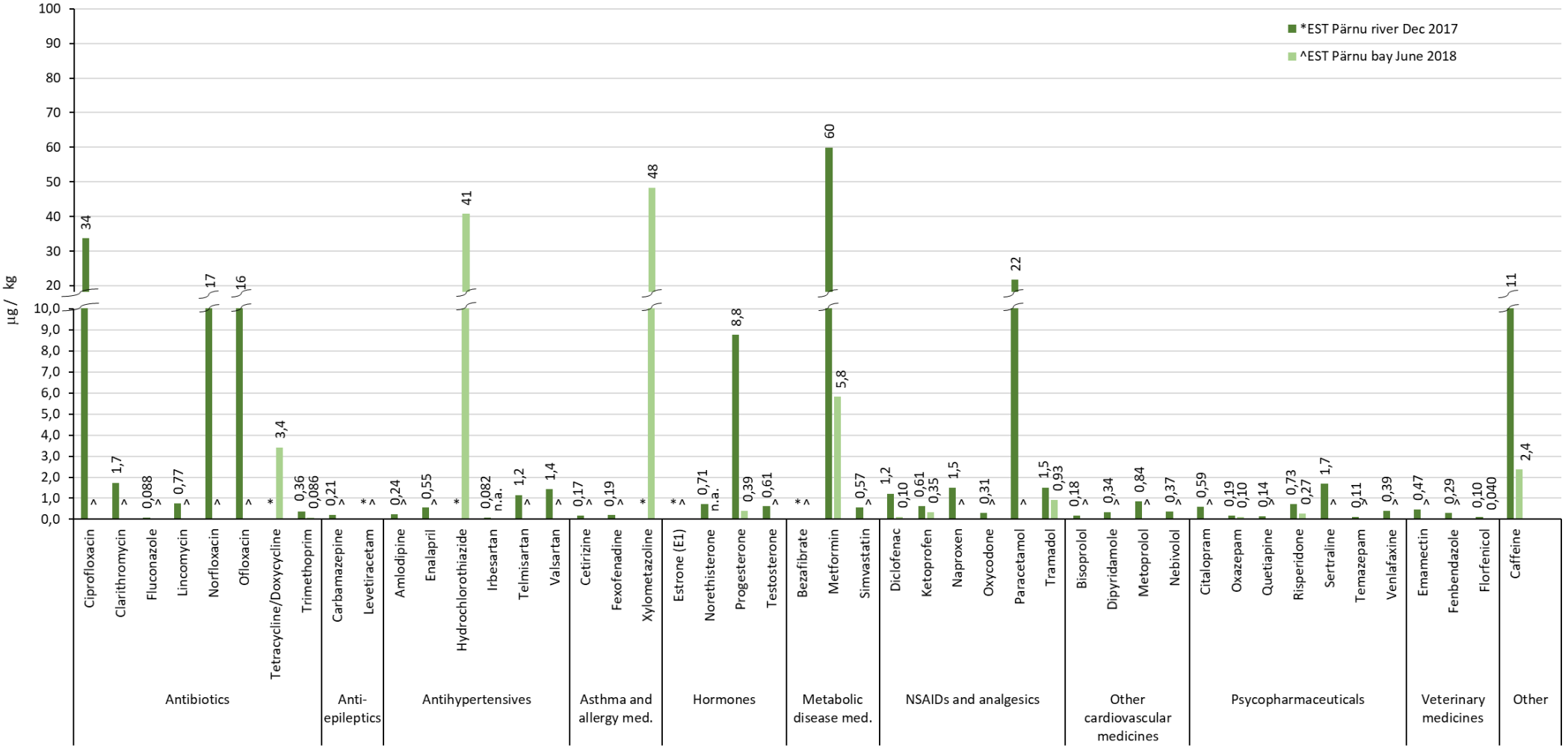

Figure 5.29. APIs in Estonian sediments from Pärnu river (December 2017) and Pärny bay (June 2018). API below LOQ are marked with "*" for samples taken in December 2017 and "^" for samples taken in June 2018. Substances above LOQ in at least one of the sediment samples from the Baltic Sea Estuaries are included.

5.2.2.2 Observed concentrations versus PNECs

The measured environmental concentrations of APIs were compared with the predicted no effect concentrations (PNECs) derived from chapter 9 (Table 5.6). Ten of the detected 47 APIs exceeded their PNECs (Table 5.6-5.7):

- hormones estrone and norethistrone,
- antibiotics clarithromycin, ciprofloxacin, ofloxacin, and the sum of tetracycline and doxycycline,
- NSAID and analgesic diclofenac and paracetamol,
- a veterinary medicine emamectin benzoate, and
- a metabolic disease medicine metformin.

Also, eight of these APIs were found at problematic levels in some surface water samples (chapter 5.1), while paracetamol and ciprofloxacin exceeded the PNECs in sediments only.

The number of APIs occurring in concentrations higher than PNECs were: 2 in Pärnu bay, 8 in Pärnu river, 4-6 in Riga coast and 3-5 in Bråviken. Sediment samples collected in chapter 7, that were close to fish farms, also contained 2-5 APIs that exceeded the PNECs. Hence, all ten collected sediment samples within the CWPharma-project contained at least two APIs at levels that pose an environmental risk.

For eight APIs, the environmental risk cannot be excluded because the LOQs were higher than the PNECs (Annex 20). These compounds were erythromycin, estriol, ivermectin, mometasone, sulfamethoxazole and tylosin. Also, the LOQs for estrone, norethisterone, and the sum concentration of tetracycline and doxycycline were higher than the PNEC in some of the analysed samples. The low LOQs of the other measured APIs allowed reliable risk estimations of these compounds.

The RQ values of the detected APIs in each sample were summed together in order to estimate the potential mixture effects. The sum RQ values varied from 96 in Pärnu bay to 19 215 in Riga's coast (Table 5.7). The sum RQ was dominated by a few APIs, especially estrone in sediments from Riga's coast. When excluding estrone, the sum RQ values varied between 8,9 and 248. The risk quotient values indicate that both single APIs and the mixture of APIs may pose environmental risks to organisms in the sediments. In addition, several other APIs that are not covered in the present study may also contribute to the combined ecological risk. The concentration levels are further described by API groups.

Hormones

At least one of the five analysed hormones was found in each sediment sample. The most frequently detected hormone was progesterone which was detected in 83 % of the samples (n=6). Concentrations of hormones varied between below LOQ up to 8.8 µg/kg d.w. Estriol was not detected in any of the sediment samples, but the LOQ was higher than the PNEC and risk cannot be excluded. Progesterone and norethisterone were found in the highest concentrations in Bråviken bay (5.2 µg/kg d.w. and 0.46 µg/kg d.w., respectively) and in Pärnu river (8.8 µg/kg d.w. and 0.71 µg/kg d.w., respectively), while estrone was found in the highest concentration in Riga coast (4 µg/kg d.w.). The LOQs for estrone and norethisterone were higher than the PNEC in some of the analysed samples. The obtained concentrations of estrone in Latvia and norethisterone in Sweden and Estonia were much higher than their PNECs. Risk Quotients (RQs) were 9 200 – 19 200 for estrone and 105 – 161 for norethisterone. The estrone detected in the environment is likely naturally excreted from humans and animals, while norethisterone may also derive from medicinal usage (Chapter 4). Testosterone was detected in sediments from Bråviken and Pärnu river in concentrations below the PNEC.

Table 5.6. Summary of the PNEC, API detection frequencies (DF) and concentration ranges in the sediments. Bold numbers indicate exceedance of PNEC and an environmental risk. LOQ* means that that limit of quantification was higher than the PNEC and that risk cannot be excluded.

API	PNEC µg/kg d.w.	DF (%)	Bråviken bay (n=2) µg/kg d.w.	Riga coast (n=2) µg/kg d.w.	Pärnu bay (n=1) µg/kg d.w.	Pärnu river (n=1) µg/kg d.w.
Atenolol	363	0	<LOQ	<LOQ	<LOQ	<LOQ
Amlodipine	0.81	33	<LOQ	<LOQ - 0.65	<LOQ	0.24
Bezafibrate	4.1	17	<LOQ - 0.20	<LOQ	<LOQ	<LOQ
Bisoprolol	31	83	0.069 - 0.16	0.011 - 0.039	<LOQ	0.18
Caffeine	1 470	100	2.4 - 3.4	0.73 - 2.36	2.4	11
Carbamazepine	10	50	<LOQ - 0.18	<LOQ - 0.12	<LOQ	0.21
Cetirizine	403	67	0.13 - 0.52	<LOQ - 0.05	<LOQ	0.17
Ciprofloxacin	6.7	67	<LOQ - 7.1	**12 - 14**	<LOQ	**34**
Citalopram	317	67	1.6 - 3.7	<LOQ - 0.10	<LOQ	0.59
Clarithromycin	0.41	50	<LOQ - 0.19	<LOQ - 0.27	<LOQ	**1.7**
Codeine	28	0	<LOQ	<LOQ	<LOQ	<LOQ
Diclofenac	0.47	33	<LOQ	<LOQ	0.10	**1.2**
Dipyridamole	5.1	67	0.24 - 1.2	<LOQ - 0.23	<LOQ	0.34
Emamectin	0.31	33	<LOQ	<LOQ - 0.31	<LOQ	**0.47**
Enalapril	46	17	<LOQ	<LOQ	<LOQ	0.55
Eprosartan	4 020	0	<LOQ	<LOQ	<LOQ	<LOQ
Erythromycin	1.2	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Estriol (E3)	0.0038	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Estrone (E1)	0.00020	33	<LOQ*	1.8 - 3.8	<LOQ*	<LOQ*
Fenbendazole	18	67	0.42 - 1.8	<LOQ - 0.43	<LOQ	0.29
Fexofenadine	19 000	67	0.50 - 1.5	<LOQ - 0.043	<LOQ	0.19
Florfenicol	48	67	<LOQ - 0.25	<LOQ - 0.029	0.040	0.10
Fluconazole	17 300	50	<LOQ - 0.12	<LOQ - 0.032	<LOQ	0.088
Fluticasone	3.6	0	<LOQ	<LOQ	<LOQ	<LOQ
Gemfibrozil	13	0	<LOQ	<LOQ	<LOQ	<LOQ
Hydrochlorothiazide	1040	33	<LOQ	<LOQ - 22	41	<LOQ
Irbesartan	198 000	33	<LOQ	<LOQ	N/A	0.082
Ivermectin	0.0077	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Ketoprofen	14	67	<LOQ - 0.59	<LOQ - 0.40	0.35	0.61
Levetiracetam	89	17	<LOQ	<LOQ - 7.6	<LOQ	<LOQ
Lincomycin	1.6	33	<LOQ	<LOQ - 0.02	<LOQ	0.77
Metformin	1.6	100	**6.8 - 25**	**8.4 - 8.6**	**5.8**	**60**
Metoprolol	9.2	67	1.2 - 1.7	<LOQ - 0.10	<LOQ	0.84
Mometasone	0.05	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Naproxen	34	33	<LOQ - 2.5	<LOQ	<LOQ	1.5
Nebivolol	4.0	67	0.15 - 0.37	<LOQ - 0.15	<LOQ	0.37
Norethisterone	0.0044	40	<LOQ* - 0.46	<LOQ*	N/A	0.71
Norfloxacin	637	83	7.8 - 15	8.9 - 19	<LOQ	17
Ofloxacin	0.93	33	<LOQ - 0.73	<LOQ	<LOQ	**16**
Olanzepine	9.8	0	<LOQ	<LOQ	<LOQ	<LOQ
Oxazepam	3.3	100	0.41 - 1.2	0.04 - 0.07	0.10	0.19
Oxycodone	4 320	17	<LOQ	<LOQ	<LOQ	0.31
Paracetamol	1.3	67	**61-84**	<LOQ - 3.9	<LOQ	**22**
Primidone	142	0	<LOQ	<LOQ	<LOQ	<LOQ
Progesterone	123	83	1.6 - 5.2	<LOQ - 0.17	0.39	8.8
Quetiapine	12	33	<LOQ	<LOQ - 0.04	<LOQ	0.14
Ramipril	810	0	<LOQ	<LOQ	<LOQ	<LOQ
Risperidone	216	100	0.17 - 1.3	0.27 - 0.73	0.27	0.73
Sertraline	344	83	0.30 - 0.83	0.044 - 0.37	<LOQ	1.7
Simvastatin	3 870	17	<LOQ	<LOQ	<LOQ	0.57
Sotalol	326	0	<LOQ	<LOQ	<LOQ	<LOQ
Sulfamethoxazole	0.11	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Telmisartan	41	60	1.1	<LOQ - 1.28	<LOQ	1.2
Temazepam	15	17	<LOQ	<LOQ	<LOQ	0.11
Testosterone	21	50	0.60 - 1.1	<LOQ	<LOQ	0.61

API	PNEC µg/kg d.w.	DF (%)	Bråviken bay (n=2) µg/kg d.w.	Riga coast (n=2) µg/kg d.w.	Pärnu bay (n=1) µg/kg d.w.	Pärnu river (n=1) µg/kg d.w.
Tetracycline/ Doxycycline	1.43/0.037	50	<LOQ* - 5.0	<LOQ* - 2.0	**3.4**	<LOQ*
Tiamulin	129	0	<LOQ	<LOQ	<LOQ	<LOQ
Toltrazuril	44	0	<LOQ	<LOQ	<LOQ	<LOQ
Tramadol	2 410	100	1.5 - 5.0	0.64 - 1.1	0.93	1.5
Trimethoprim	1 220	83	0.19 - 0.22	<LOQ - 0.09	0.086	0.36
Tylosin	0.097	0	<LOQ*	<LOQ*	<LOQ*	<LOQ*
Valsartan	776	33	<LOQ - 0.17	<LOQ	<LOQ	1.4
Warfarin	98	0	<LOQ	<LOQ	<LOQ	<LOQ
Venlafaxine	16	67	0.32 - 0.33	<LOQ - 0.07	<LOQ	0.39
Xylometazoline	2 970	33	<LOQ	<LOQ - 75	48	<LOQ

Antibiotics

Antibiotics were found in all sediment samples. The most frequently detected of the ten analysed antibiotics were trimethoprim (DF 83 %) and norfloxacin (DF 83 %) followed by ciprofloxacin (DF 67 %). Clarithromycin, fluconazole, and tetracycline/doxycycline were detected in three out of six sediment samples. Erythromycin and sulfamethoxazole were not detected in any of the sediment samples. However, the LOQs for erythromycin and sulfamethoxazole were higher than their PNECs which means that the environmental risk of those compounds cannot be excluded. Also, the LOQs for the sum concentration of tetracycline and doxycycline was higher than the PNEC in three of the analysed samples. The highest concentration of an antibiotic (34 µg/kg d.w.) was measured for ciprofloxacin in the sediments from the mouth of Pärnu river. In Pärnu river ofloxacin and clarithromycin were also detected in the highest concentrations (16 µg/kg d.w. and 1.7 µg/kg d.w., respectively). Norfloxacin was found in concentrations up to 20 µg/kg d.w. in Riga coast. The concentration of norfloxacin in sediments collected from Bråviken and Riga coast in May/June was about twice as high as in sediments collected in December. The sum concentration of doxycycline and tetracycline was up to 5.0 µg/kg d.w. in Bråviken.

The sediment risk assessment revealed that the levels of ciprofloxacin, clarithromycin and the sum concentration of doxycycline and tetracycline may pose environmental risks in many of the Baltic Sea estuaries. The highest risk quotient (RQ of 135) was found for the sum concentration of doxycycline and tetracycline in sediments of Bråviken sampled in December. The concentrations of ciprofloxacin and clarithromycin in Pärnu river were 4-5 times higher than their PNECs. Also, the concentration of ofloxacin exceeded PNEC in Pärnu river (RQ of 7). Lincomycin was detected in sediments from Pärnu river and one sample from Riga coast, but in concentrations below the PNEC.

Antiepileptics

The concentrations of the three analysed antiepileptics were below their PNECs. The highest concentration of antiepileptics (7,6 µg/kg d.w.) was measured for levetiracetam in the sediments from Riga coast sampled in May. Carbamazepine is a commonly detected API in surface waters (DF 98 %) but was only detected in half of the sediment samples (up to 0,21 µg/kg d.w., n=6). Primidone was not detected in any of the sediment samples.

Antihypertensives

Six of the eight studied antihypertensives were detected in at least one sediment sample. Eprosartan and ramipril were not detected in any of the sediment samples. The most frequently detected antihypertensive was telmisartan which was detected in three out of five analysed sediment samples. The highest concentration of antihypertensives was measured for hydrochlorothiazide in sediments from Riga coast and Pärnu bay collected in May-June (22 µg/kg d.w. and 41 µg/kg d.w., respectively). The levels of hydrochlorothiazide and other analysed antihypertensives in the

sediments were below their PNECs, and do not pose an environmental risk. The concentration of hydrochlorothiazide was below LOQ in the sediment from Bråviken.

Asthma and allergy APIs

At least one of the five analysed asthma and allergy APIs was found in each sediment sample. The most frequently detected asthma and allergy APIs were cetirizine and fexofenadine which were detected in four of the six analysed sediment samples. Mometasone and fluticasone xylometazoline were not detected in any of the sediment samples. The highest concentration of antihypertensives was measured for hydrochlorothiazide in the spring samples collected in Riga coast (75 µg/kg d.w.) and in Pärnu bay (48 µg/kg d.w.). Xylometazoline is used to treat e.g. allergies and sinus irritation. This API was not found sediments from Bråviken or in the winter samples from Riga coast or Pärnu river. The levels of xylometazoline and the other analysed asthma and allergy APIs do not exceed their PNECs. However, the LOQ for mometazone was higher than the PNEC which means that the environmental risk of this compounds cannot be excluded.

Metabolic disease medications

The metabolic disease medication metformin was found in all sediment samples, in concentrations ranging from 5.8 to 60 µg/kg d.w. Metformin is slowly degraded in the environment and the calculations of risk quotients indicate that the levels of metformin pose an environmental risk in all the studied sediments (RQs of 3,6-16). Gemfibrozil was not detected in any of the sediment samples, and bezafibrate and simvastatin were only detected in one out of six analysed sediment samples (DF 16 %) and the concentrations were well below the PNECs.

NSAIDs and analgesics

The analysed NSAIDs and analgesics were detected in at least one sediment sample, with an exception of codeine which was not detected at all. The most frequently detected NSAIDs and analgesic was tramadol which was detected in all sediment samples, followed by ketoprofen and paracetamol (DF 67 %). The concentrations of tramadol varied between 0,93 to 5,0 µg/kg d.w. and were below the PNEC. Also, the concentrations of ketoprofen, naproxen and oxycodone were below their PNECs. The API found in the highest concentration was paracetamol in the sediments of Bråviken estuary (SE): 61 µg/kg d.w. in December and 84 µg/kg d.w. in June. The presence of paracetamol in the sediments is surprising given that this API is biodegradable (99% degradation in 5 days according to fass.se) and highly removed in wastewater treatment plants (Chapter 6 and fass.se). However, this study suggest that parts of the conjugated paracetamol may be converted back into free paracetamol in the sediment compartment. In addition, the high consumption of paracetamol (chapter 4) results in a continuous release of this API in such an amount that it is accumulated in the sediments of the Baltic Sea. The calculations of risk quotients indicate that the levels of paracetamol in the sediments pose an environmental risk in Bråviken estuary, Pärnu river and some other coastal areas described in Chapter 7. Diclofenac was only detected in the Estonian samples, in concentrations up to 1,2 µg/kg d.w. The concentration of diclofenac in the sediment of Pärnu river was three times above the PNEC.

Cardiovascular APIs

The cardiovascular APIs atenolol, sotalol and warfarin were not detected in the collected sediments. Bisoprolol was detected in five out of six analysed sediment samples, followed by dipyridamole, metoprolol and nebivolol (DF 67 %). The highest concentration of cardiovascular APIs was measured for metoprolol in sediments from Bråviken (1,2 – 1,7 µg/kg d.w.). None of the seven analysed cardiovascular APIs was found in concentrations above their PNECs.

Psycopharmaceuticals

Oxazepam and risperidone were found in all sediment samples, in concentrations up to 1,3 µg/kg d.w. Sertraline was detected in five out of six analysed sediment samples, followed by citalopram and venlafaxin (DF 67 %). The highest concentration of psychopharmaceuticals was measured for citalopram in the sediments from Bråviken sampled in December (3,7 µg/kg d.w.). Olanzepine was

not detected in any of the sediment samples. Quetiapine was found in Pärnu river and in one sediment sample from Riga coast. Temazepame was only detected in sediments of Pänu river. The concentrations of the eight analysed psycopharmaceuticals were all below their PNECs.

Veterinary APIs

The most frequently detected veterinary APIs were fenbendazole and florfenicol which were detected in four out of six analysed sediment samples. The highest concentration of veterinary APIs was measured for fenbendazole in sediments from Bråviken. The concentration of emamectin in the sediment collected from Pärnu river (0,47 µg/kg d.w.) exceeded the PNEC (RQ of 1,5). Also, the concentration of emamectin in one Latvian sediment sample may be environmentally risky (RQ of 1,0). Ivermectin, tiamulin, toltrazuril and tylosin were not detected in the sediments. However, the LOQ for tylosin was higher than the PNECs and the environmental risk of this compounds cannot be excluded.

Caffeine

Caffeine was detected in all sediment samples in concentrations between 0,73 to 11 µg/kg d.w. The concentration of caffeine was higher in Pärnu river than in the Baltic Sea estuaries. Caffeine is mainly originating from coffee and other drinks and not from pharmaceutical use. The measured concentrations were below the PNEC.

Table 5.7 A summary of the sum risk quotients (sum RQ) and a list of detected APIs exceeding the PNEC (APIs with RQ>1) in sediments collected from Baltic Sea Estuaries and Pärnu river.

	Sum RQ	**APIs with RQ>1**	**Sum RQ**	**APIs with RQ>1**
Estonia	Pärnu bay (June)		Pärnu river (December)	
	96	Metformin (RQ=3,6) Tetracycline/Doxycycline (RQ=92)	248	Ciprofloxacin (RQ=5,1) Clarithromycin (RQ=4,2) Diclofenac (RQ=2,6) Emamectin (RQ=1,5) Metformin (RQ=37) Norethisterone (RQ=161) Ofloxacin (RQ=17) Paracetamol (RQ=17)
Latvia	Riga coast (May)		Riga coast (December)	
	9 271 (65 excl. estrone)	Ciprofloxacin (RQ=2,1) Estrone (E1) (RQ=9 206) Metformin (RQ=5,3) Paracetamol (RQ=3,1) Tetracycline/Doxycycline (RQ=54)	19 215 (8,9 excl. estrone)	Ciprofloxacin (RQ=1,8) Estrone (E1) (RQ=19 206) Metformin (RQ=5,2)
Sweden	Bråviken estuary (June)		Bråviken estuary (December)	
	188	Metformin (RQ=16) Norethisterone (RQ=105) Paracetamol (RQ=67)	191	Ciprofloxacin (RQ=1,1) Metformin (RQ=4,2) Paracetamol (RQ=48) Tetracycline/Doxycycline (RQ=135)

5.2.3 Conclusions

Analyses of sediments in three Baltic Sea Estuaries in Sweden, Latvia and Estonia showed the presence of 47 out of 65 analysed APIs, representing all the studied API groups. Five APIs were found in all sediment samples: metformin, caffeine, tramadol, oxazepam and risperidone. The two APIs found in the highest concentrations were paracetamol (up to 84 µg/kg d.w.) in the sediments of Bråviken estuary, and xylometazoline in the sediments of Riga coast (up to 75 µg/kg d.w.) and

in Pärnu bay (48 µg/kg d.w.). The concentrations of the antibiotics norfloxacin and ciprofloxacin were up to 20 µg/kg d.w and 34 µg/kg d.w, respectively. Hormones were detected in all sediment samples, ranging from below LOQ to 8.8 µg/kg d.w. Depending on the characteristics of each API even a low level in the sediment may pose a risk to sediment dwelling organisms.

All ten collected sediment samples within the CWPharma-project contained levels of at least two APIs that pose an environmental risk. The APIs that most frequently exceeded their PNECs were ciprofloxacin (antibiotic), metformin (metabolic disease medication) and paracetamol (NSAID and analgesic). In some sediment samples, risks were also observed for diclofenac (NSAID and analgesic), emamectin (veterinary medicine), estrone and norethisterone (hormones), and clarithromycin, ofloxacin and the sum concentration of doxycycline and tetracycline (antibiotics). In addition, several other APIs contributed to the combined ecological risk, although their concentrations did not exceed the predicted no effect concentration (PNEC). Further studies of API levels in sediments and their effect are needed to elucidate the impact of APIs on benthic fauna. The results from the present study indicate an urgent need to implement reduction measures to decrease API levels and for monitoring of pharmaceuticals in sediments.

6 APIs in wastewater and sludge

6.1 Concentrations of APIs in influents, effluents and sludge from municipal wastewater treatment plants

6.1.1 Methods

Wastewater samples were taken as integrated, flow-proportional 24-hour samples in Estonia, Finland, Poland and Sweden, except the effluent of WWTP1 in Latvia. The wastewater treatment plant sludge was taken as integrated samples (Estonia), integrated time samples (Latvia – WWTP 1) or grab samples (Finland, Sweden, Latvia – WWTP 2). Influent, effluent and sludge samples were frozen (temperature -18–20 °C), and in such way transported to the Laboratory of SYKE in Helsinki. Time between sampling and freezing was less than four hours.
75 APIs were analysed in the influent and effluent samples, and 31 APIs in sludge samples. Also, the dry matter contents of the sludge samples were determined.
Influent and effluent samples were taken from 16 wastewater treatment plants two or three times:

- 3 in Estonia: Paide, Pärnu, Türi (December 2017 and June 2018);
- 2 in Finland: Kalteva (Hyvinkää) and Viikki (Helsinki) (December 2017, August 2018 and November 2018);
- 4 in Germany: Greifswald (February 2018, June 2018 and December 2018), Neubrandenburg (February 2018 and June 2018), Rostock (March 2018, June 2018 and November 2018) and Wismar (February 2018 and June 2018);
- 3 in Latvia: WWTP1, WWTP2 and WWTP3 (November/December 2017 and May 2018);
- 1 in Poland: Błonie (November 2017 and July 2018);
- 3 in Sweden: Linköping, Motala, Norrköping (December 2017 and June 2018).

Sludge samples were taken in 12 wastewater treatment plants one to three times:

- 2 in Estonia: Paide and Pärnu (December 2017 and June 2018);
- 2 in Finland: Kalteva (June 2018) and Viikki (December 2017 and August 2018);
- 2 in Germany: Greifswald (February 2018, June 2018 and December 2018) and Rostock (June 2018 and November 2018);
- 2 in Latvia: WWTP1 and WWTP2 (November/December 2017 and May/June 2018);
- 1 in Poland: Błonie (November 2017 and July 2018);
- 3 in Sweden: Linköping, Motala and Norrköping (December 2017 and June 2018).

Different types of sludge were sampled in the case studies. Dewatered sludge was sampled in Estonia, Latvia, Sweden/Norrköping and Sweden/Motala, and dewatered digested sludge in Poland and Finland/Viikki. In Sweden/Linköping samples were taken from both dewatered and dewatered digested sludge. The sludge sample from Finland/Kalteva was taken from raw sludge, before it was dewatered in a centrifuge.

Calculations of removal efficiency of APIs were performed on selected APIs, that in one season were measured in both influent and effluent. Some data were excluded from efficiency calculations based on the following criteria:
1) concentrations of influent or effluent are not available (not analysed, N/A);
2) concentrations of influent are < LOQ;
3) data of landfill stations;
4) concentration of the influent < 5 * $LOQ_{effluent}$;
5) samples that melted during the delivery to the laboratory.

Removal rates were calculated for each sampling occasion, by comparing the effluent and influent concentrations. During calculations, values lower than LOQ were defined as the LOQ concentration. This resulted in a conservative estimate of the removal efficiency.
Formulas for calculations are as follows:

1) Residual in effluent: $Conc._{effl.}$ *100 / $conc._{infl.}$
2) Treatment efficiency: 100 - residual in effluent

The API analysis in various samples (influent, effluent and sewage sludge) from different countries (Latvia, Estonia, Finland, Sweden and Germany) allowed a simple statistical analysis regarding the fate of APIs during the wastewater treatment process. The aim of this analysis was to provide an estimation of the mass balances, i.e. the distribution of APIs between effluent and sludge. The API amount in influent versus the API sum amount in effluent and sludge represents the disappearance during the treatment process due to decomposition or transformation into different compounds. The amount of each API in influent, effluent and sludge was calculated based on the measured concentrations. The API mass in each influent and effluent sample was calculated using the annual wastewater flow rates, and API mass in sludge using the annual amount of produced sewage sludge (in terms of dry solids). Only the APIs that were detected in influent and in effluent and/or sludge during one sampling round were selected for the mass balance calculations. Some data were excluded from the analysis based on the following criteria:

1) The amount of API in sludge and/or effluent was higher than in influent;
2) The concentration of the API was below LOQ or N/A in all three matrixes or at least in the influent.
3) The samples had melted during the transport to the analysing laboratory.

The following formulas were used for calculating the mass balance (C = concentration and V = volume):

1) API amount in influent (kg): $C._{infl.} * V_{infl.}$
2) API amount in effluent (kg): $C_{effl.} * V_{effl.}$
3) API amount in sludge (kg): $C_{sludge} * Amount_{sludge}$
4) API remaining in effluent (%): 100% * API amount in effluent / API amount in influent
5) API remaining in sludge (%): 100% * API amount in sludge / API amount in influent
6) API lost (%): 100% – API remaining in effluent – API remaining in sludge

6.1.2 Results and discussion

6.1.2.1 Concentrations of APIs in wastewater influents and effluents

The following overview includes all the wastewater influent and effluent results of the CWPharma case studies, except those below LOQ and the results with remark “not available” (where there was some interference for the compound, mostly due to matrix, and therefore the result could not be recorded or reported). Detection frequencies (DF) are presented to highlight the most commonly detected APIs. The API concentrations are presented as micrograms per one litre of sample (µg/L). Average concentrations were calculated and can be seen in charts below. Values below LOQ are replaced with LOQ values (the same as in calculations of efficiency – chapter 6.1.2.2. If all samples for a specific API were below LOQ in both influent and effluent, the API is not shown in the charts. If the API concentration was <LOQ for one matrix – influent or effluent – the average concentration was set as 0 and marked with “ * ”. All the measured concentrations in wastewater influents and effluents are presented in Annex 5 and Annex 6.

Antibiotics

Influent

In influents, we detected nine out of eleven APIs from the antibiotics group (figure 6.1 and 6.2): clarithromycin, erythromycin, fluconazole, lincomycin, norfloxacin, ofloxacin, sulfamethoxazole,

tetracycline+doxycycline (SUM) and trimethoprim. The most frequently detected APIs were trimethoprim (DF 100%), sulfamethoxazole (DF 94%) and fluconazole (DF 91%). Ciprofloxacin and sulfadiazine were not detected in any influent sample. Lincomycin was detected only in one sample in Poland. The highest measured concentration of each API was:

- Ciprofloxacin – not detected, all samples <3.1 µg/L;
- Clarithromycin – 1.9 µg/L in Estonia, Paide in December 2017;
- Erythromycin – 19 µg/L in Estonia, Paide in June 2018;
- Fluconazole – 0.44 µg/L in Poland, Błonie WWTP in November 2017;
- Lincomycin – 0.022 µg/L in Poland, Błonie WWTP in July 2018;
- Norfloxacin – 13 µg/L in Latvia, WWTP 1 in November 2017;
- Ofloxacin – 3.8 µg/L in Germany, Neubrandenburg in June 2018;
- Sulfadiazine – not detected, all samples <0.59 µg/L;
- Sulfamethoxazole – 0.94 µg/L in Latvia, WWTP 2 in December 2017;
- Tetracycline+doxycycline (SUM) – 2.5 µg/L in Finland, Kalteva in December 2017;
- Trimethoprim – 1.4 µg/L in Finland, Viikki in August 2018.

Effluent

In effluents, we detected nine out of eleven APIs of the antibiotics group: clarithromycin, erythromycin, fluconazole, lincomycin, norfloxacin, ofloxacin, sulfamethoxazole, tetracycline+doxycycline (SUM) and trimethoprim. The most detected APIs were clarithromycin (DF 94%), erythromycin (DF 94%), trimethoprim (DF 93%) and fluconazole (DF 91%). Ciprofloxacin and sulfadiazine were not detected in any effluent sample.

The highest measured concentrations of the APIs were:

- Ciprofloxacin – not detected, all samples <1.6 µg/L;
- Clarithromycin – 2.2 µg/L in Estonia, Paide in December 2017;
- Erythromycin – 8.3 µg/L in Germany, Neubrandenburg in February 2018;
- Fluconazole – 0.51 µg/L in Germany, Greifswald in June 2018;
- Lincomycin – 0.063 µg/L in Latvia, WWTP 2 in May 2018;
- Norfloxacin – 19 µg/L in Estonia, Türi in June 2018;
- Ofloxacin – 0.74 µg/L in Germany, Greifswald in February 2018;
- Sulfadiazine – not detected, all samples <0.30 µg/L;
- Sulfamethoxazole – 0.27 µg/L in Finland, Viikki in August 2018;
- Tetracycline+doxycycline (SUM) – 0.55 µg/L in Estonia, Paide in June 2018;
- Trimethoprim – 0.47 µg/L in Finland, Kalteva in November 2018.

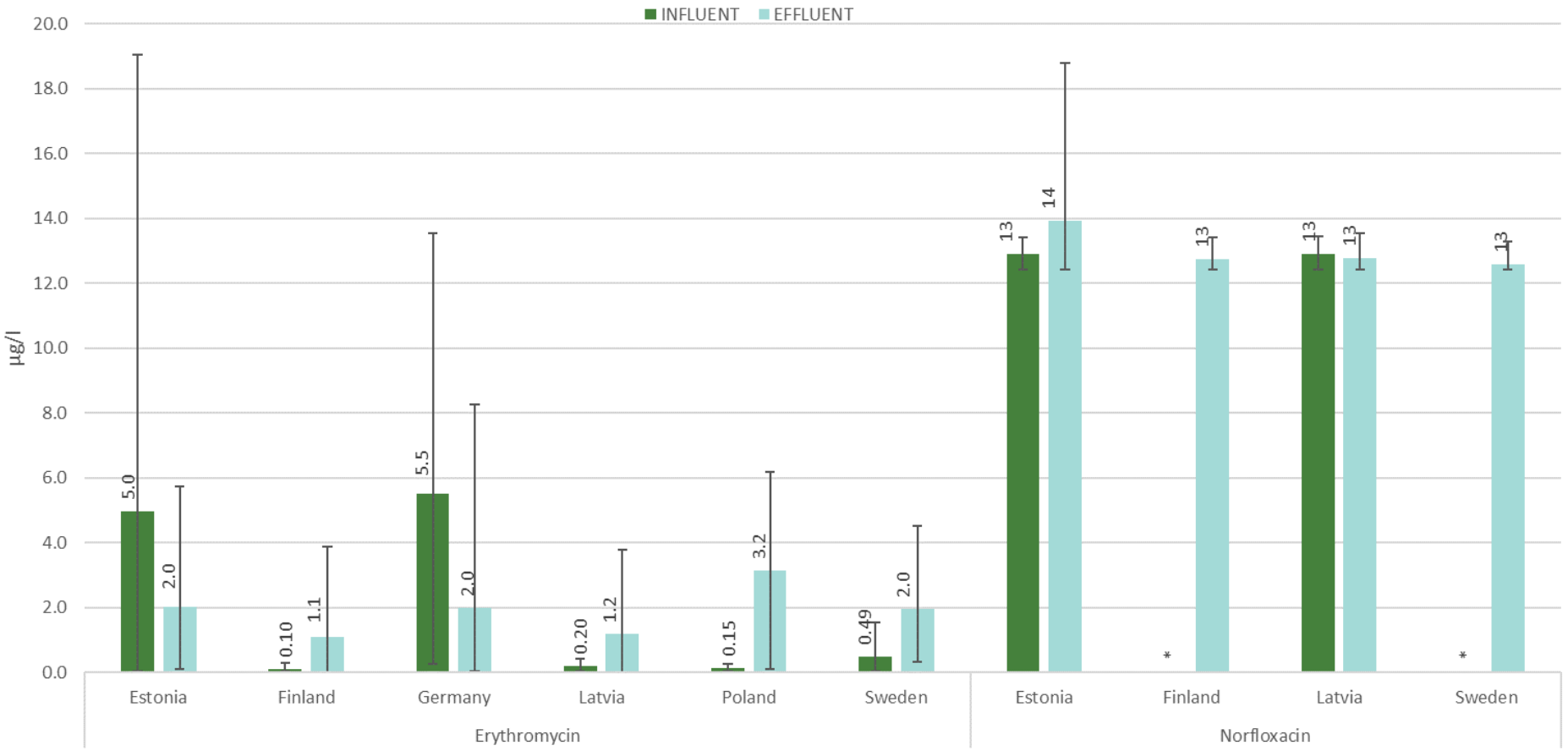

Figure 6.1. Average concentrations of 1st part of API of antibiotics group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

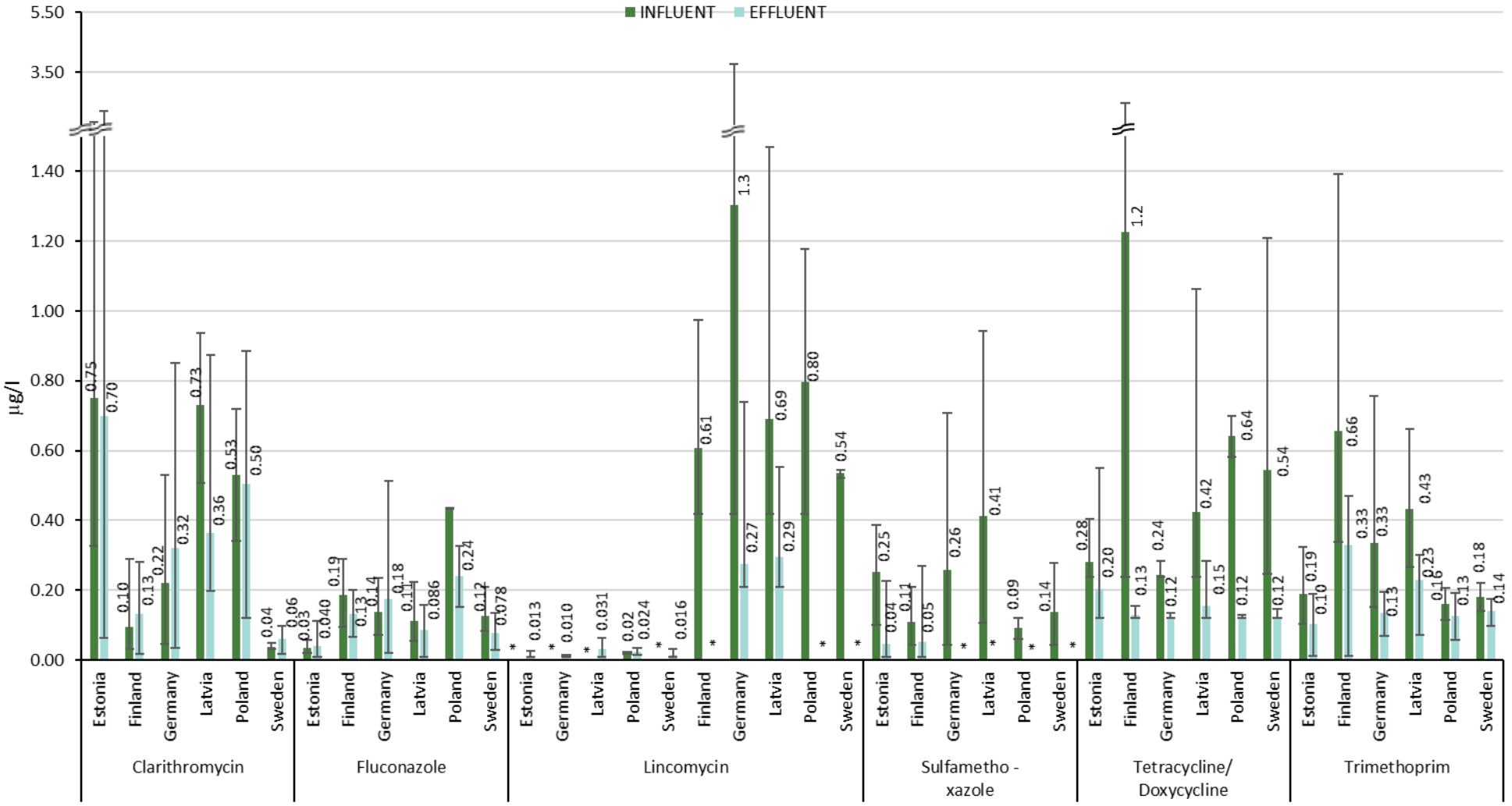

Figure 6.2. Average concentrations of 2nd part of API of antibiotics group in WWTP influent and effluent. Error bars represent the range of average concentrations in all WWTP per country. * - all samples <LOQ.

Antiepileptics

Influents
All the studied APIs of the antiepileptics group were detected in WWTP influents (figure 6.3): carbamazepine, gabapentin, levetiracetam and primidone. The most frequently detected APIs were gabapentin (DF 100%) and levetiracetam (DF 97%). The highest concentrations of all the antiepileptics we obtained in the German influents.
The highest concentration of each API was:

- Carbamazepine – 3.5 µg/L in Germany, Neubrandenburg in February 2018;
- Gabapentin – 95 µg/L in Germany, Neubrandenburg in February 2018;
- Levetiracetam – 27 µg/L in Germany, Greifswald in June 2018;
- Primidone – 0.75 µg/L in Germany, Neubrandenburg in February 2018.

Effluents
Each of the four antiepileptics were detected also in the WWTP effluents: carbamazepine, gabapentin, levetiracetam and primidone. The most frequently detected APIs were carbamazepine (DF 97%) and gabapentin (DF 82%).
The maximum concentration of each antiepileptic was:

- Carbamazepine – 2.5 µg/L in Estonia, Paide in June 2018;
- Gabapentin – 14 µg/L in Sweden, Motala in June 2018;
- Levetiracetam – 1.2 µg/L in Sweden, Motala in December 2017;
- Primidone – 0.93 µg/L in Germany, Neubrandenburg in February 2018.

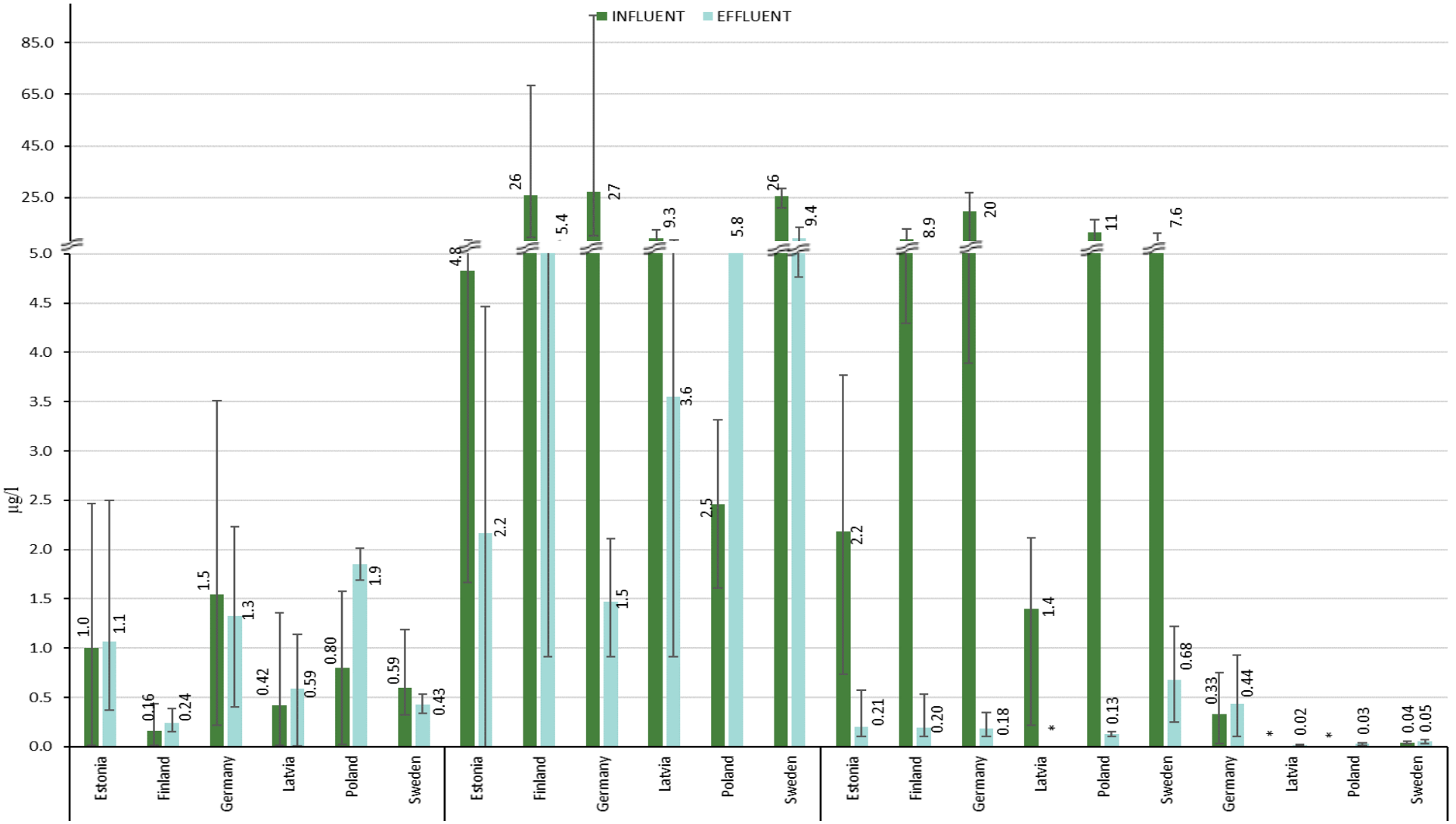

Figure 6.3. Average concentrations of API of antiepileptics group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Antihypertensives

Influent

In influents, we detected nine out of ten antihypertensives: amlodipine, enalapril, eprosartan, hydrochlorothiazide, irbesartan, losartan, ramipril, telmisartan, valsartan and venlafaxine (figure 6.4 and 6.5). The most frequently detected APIs were valsartan (DF 97%) and hydrochlorothiazide (DF 94%). Candesartan was not detected in any influent sample.

The highest measured concentrations of each antihypertensive were:

- Amlodipine – 0.45 µg/L in Germany, Rostock in June 2018;
- Candesartan – not detected, all samples <0.77 µg/L;
- Enalapril – 0.24 µg/L in two countries: Germany (Neubrandenburg, in February 2018) and Sweden (Norrköping, in December 2017)
- Eprosartan – 1.0 µg/L in Germany, Neubrandenburg in February 2018
- Hydrochlorothiazide – 21 µg/L in Estonia, Türi in June 2018;
- Irbesartan – 4.7 µg/L in Germany, Neubrandenburg in June 2018;
- Losartan – 3.6 µg/L in Sweden, Motala in June 2018;
- Ramipril – 0.17 µg/L in Germany, Neubrandenburg in Febraury 2018;
- Telmisartan – 13 µg/L in Germany, Greifswald in February 2018;
- Valsartan – 54 µg/L in Germany, Neubrandenburg in February 2018.

Effluent

In the WWTP effluent, we detected eight out of ten antihypertensives: candesartan, eprosartan, hydrochlorothiazide, irbesartan, losartan, ramipril, telmisartan and valsartan. The most often detected APIs were hydrochlorothiazide (DF 97%), telmisartan and valsartan (DF 88%).

The highest obtained concentrations were:

- Amlodipine –not detected, all samples <0.11 µg/L;
- Candesartan – 0.041 µg/L in Germany, Wismar in June 2018;
- Enalapril – not detected, all samples<0.083 µg/L;
- Eprosartan – 0.23 µg/L in Germany, Neubrandenburg in February 2018;
- Hydrochlorothiazide – 19 µg/L in Germany, Rostock in June 2018;
- Irbesartan – 0.0018 µg/L in Germany, Neubrandenburg in June 2018;
- Losartan – 4.2 µg/L in Sweden, Motala in June 2018;
- Ramipril – 0.29 µg/L in Germany, Greifswald in June 2018;
- Telmisartan – 4.7 µg/L in Poland, Błonie WWTP in July 2018
- Valsartan – 21 µg/L Germany, Neubrandenburg in February 2018.

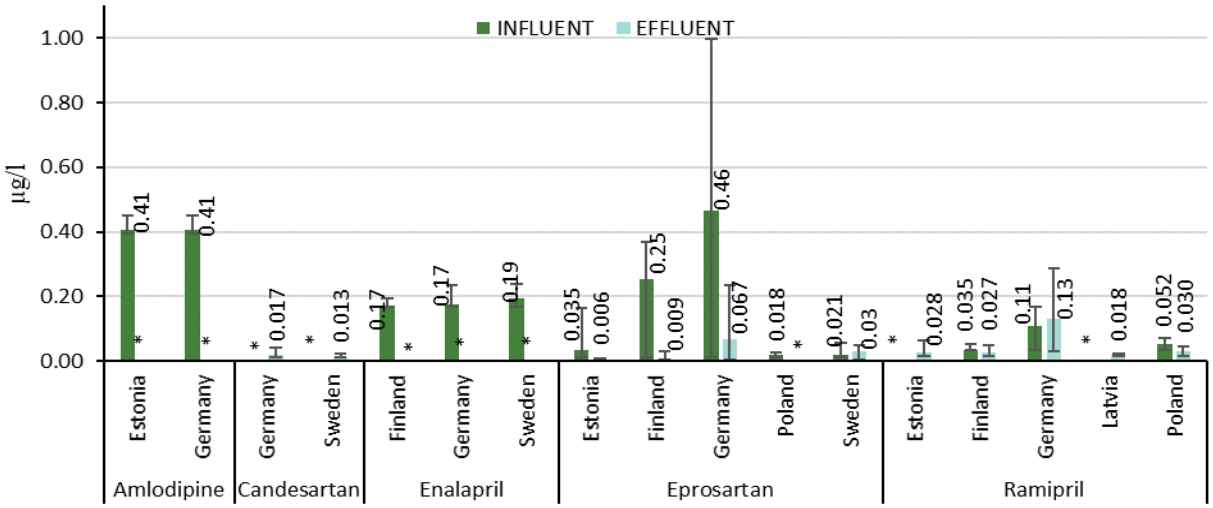

Figure 6.4. Average concentrations of the 1st part of antihypertensives in WWTP influent and effluent. Error bars represent the range of the average concentrations in each WWTP per country. * - all samples <LOQ.

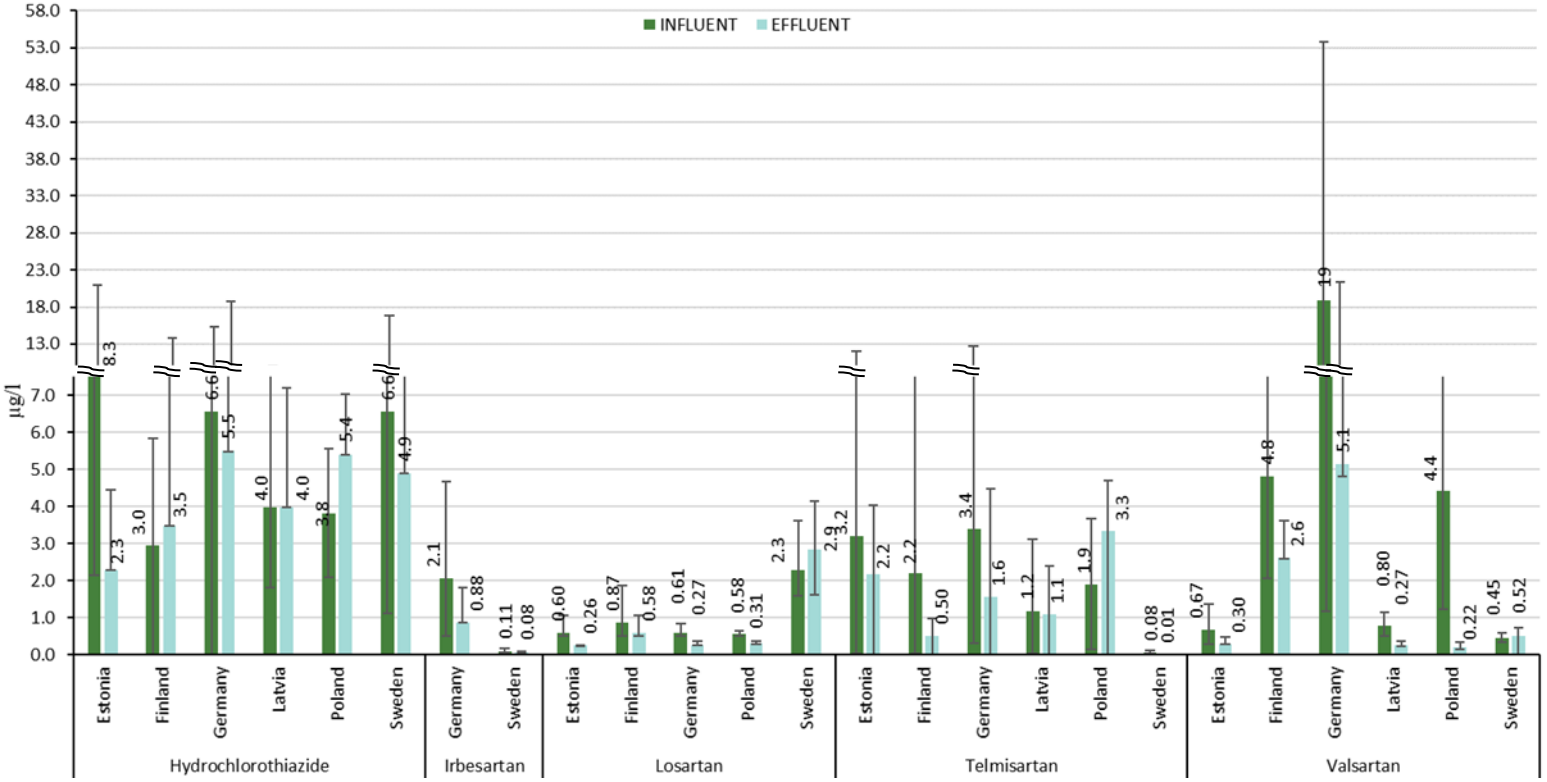

Figure 6.5. Average concentrations of the 2nd part of antihypertensives in WWTP influent and effluent. Error bars represent the range of the average concentrations in each WWTP per country. * - all samples <LOQ.

Asthma and allergy medications

Influents

Two out of five APIs from the asthma and allergy medication group were detected in influents: fluticasone and xylometazoline (figure 6.6). Both were detected only in few samples - xylometazoline in two German samples (DF 6%), and fluticasone in one Estonian influent (DF 3%). Cetirizine, fexofenidine and mometasone furoate were not detected in any influent sample. The highest measured concentrations were:

- Cetirizine – not detected, all samples <3.2 µg/L**;**
- Fexofenadine – not detected, all samples <4.3 µg/L;
- Fluticasone – 0.61 µg/L in Estonia, Pärnu in June 2018;
- Mometasone furoate **–** not detected, all samples <0.83 µg/L;
- Xylometazoline 0.061 µg/L in Germany, Neubrandenburg in June 2018.

Effluents

In effluent three out of five APIs from asthma and allergy medicaments group were detected: cetirizine and xylometazoline. The most detected API in this group was xylometazoline (DF 38%). Cetirizine was detected only once in Finland, and fexofenadine was detected once in Poland. Fluticasone and mometasone furoate were below LOQ in all effluent samples. The highest measured concentrations were:

- Cetirizine – 1.3 µg/L in Finland, Kalteva in June 2018;
- Fexofenadine – 1.8 µg/L in Poland, Błonie in July 2018;
- Fluticasone – not detected, all samples <0.15 µg/L);
- Mometasone furoate – not detected, all samples <0.15 µg/L;
- Xylometazoline – 0.099 µg/L in Germany, Neubrandenburg in February 2018.

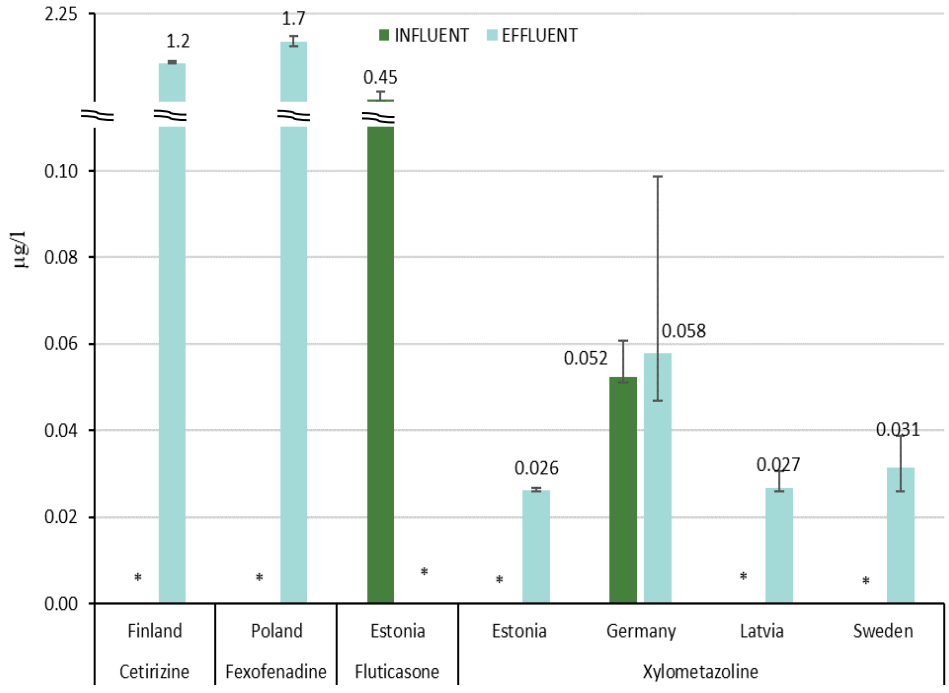

Figure 6.6. The average concentrations of the APIs of the asthma and allergy medications group in WWTP influent and effluent. Error bars represent the range of the average concentrations in each WWTP of each country. * - all samples <LOQ.

Gastrointestinal disease medications

Influent

One API out of three gastrointestinal medications was detected in influents (figure 6.7): mesalazine (DF 92%). The other gastrointestinal medicines, pantoprazole and omeprazole+esomeprazole, had much higher LOQs, and were not detected in any influent sample. The UBA database (UBA 2019) contains only one positive detection of pantoprazole (0.13 µg/L) from China, while most European data points are <0.001 µg/L.

The highest measured concentrations were:

- Mesalazine – 18 µg/L in Germany, Neubrandenburg in June 2018;
- Omeprazole+esomeprazole – not detected, all samples <8.4 µg/L;
- Pantoprazole – below LOQ value (0.76 µg/L).

Effluent

In the effluent, we detected only mesalazine from the gastrointestinal medications group. The concentrations of mezalazine were above LOQ in 50% of the samples. Pantoprazole and omeprazole+esomeprazole were not detected in the effluent samples taken from any of the countries.

The highest measured concentrations for each API were:

- Mesalazine – 0.94 µg/L in Germany, Neubrandenburg in February 2018;
- Omeprazole+esomeprazole – not detected, all samples <8.4 µg/L;
- Pantoprazole – not detected, all samples <0.76 µg/L.

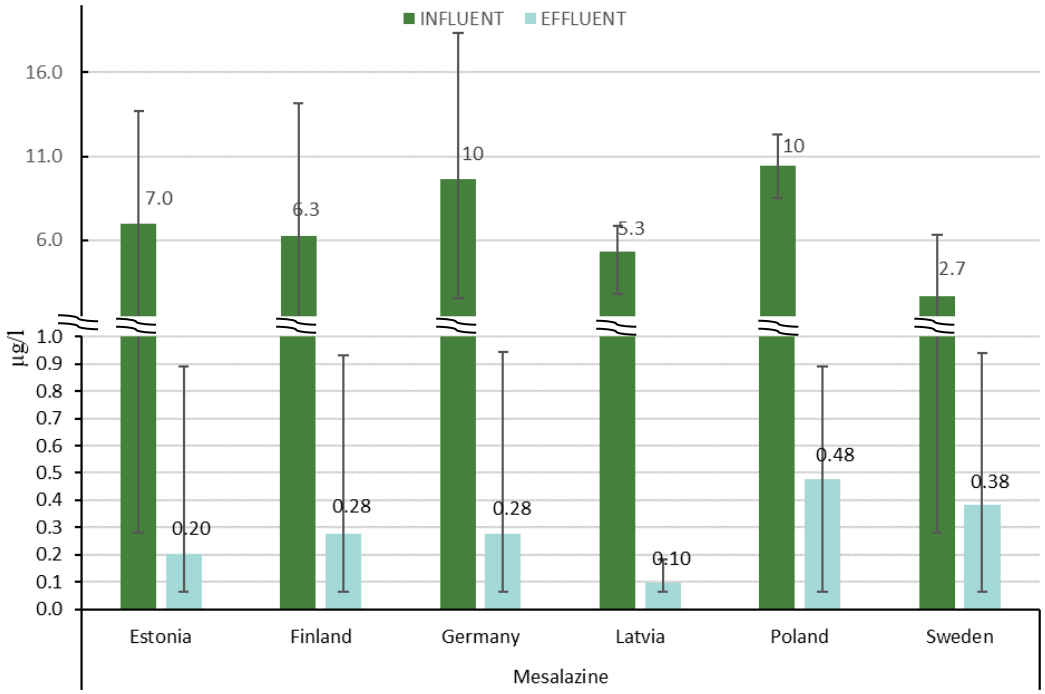

Figure 6.7. Average concentrations of API of gastrointestinal disease medications group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Hormones

Influent

All five analysed hormones were detected in the influent samples: estriol, estrone, norethisterone, progesterone and testosterone (figure 6.8). The most frequently detected APIs were estrone (DF 67%) and norethisterone (DF 61%).

The highest concentrations for each API were:

- Estriol – 0.25 µg/L in Finland, Viikki in August 2018;

- Estrone – 12 µg/L in Sweden, Norrköping in June 2018;
- Norethisterone - 2.8 µg/L in Germany, Greifswald in February 2018;
- Progesterone – 88 µg/L in Poland, Błonie WWTP in July 2018;
- Testosterone – 0.20 µg/L in Germany, Neubrandenburg in February 2018.

Effluent

In the WWTP effluent, four out of five hormones were detected in at least one sample: estrone, norethisterone, progesterone and testosterone. The most frequently detected hormone was estrone (DF 24%). Testosterone was detected only in one sample from Latvia. Estriol was not detected in any effluent sample.

The highest concentrations for each API were:

- Estriol – not detected, all samples <8.4 µg/L;
- Estrone – 11 µg/L in Latvia, WWTP 3 in December 2017;
- Norethisterone – 0.11 µg/L in Latvia, WWTP 3 in May 2018;
- Progesterone – 0.029 µg/L in Latvia, WWTP 3 in December 2017;
- Testosterone – 0.032 µg/L in WWTP 3 in May 2018.

All the highest effluent concentrations for hormones were observed in Latvia, WWTP 3. The maximum concentration of estrone was 192 times higher than the second highest value, which was 0.055 µg/L (Finland, Viikinmäki November 2018). As caffeine concentration was also very high in the Latvian effluent sample (at the same level as the highest influent concentration), it might indicate some trouble with the WWTP process, as these biologically degradable compounds were not removed at all.

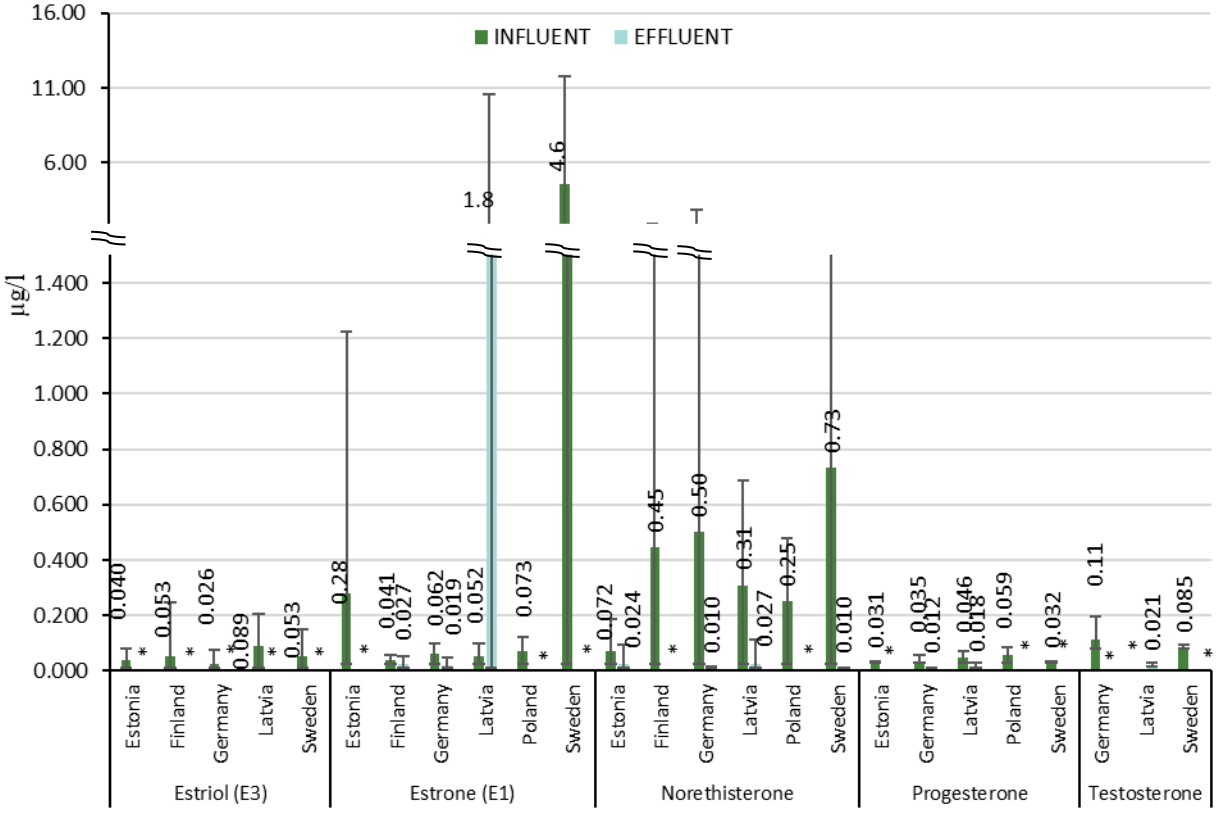

Figure 6.8. Average concentrations of API of hormones group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Metabolic disease medications

Influent

In influents, we detected five out of six APIs used for metabolic diseases: allopurinol, bezafibrate, gemfibrozil, metformin and simvastatin (figure 6.9). Metformin was detected in all samples (DF 100%), and bezafibrate in 55% of the samples. Atorvastatin was not detected in any of the influent samples, probably due to the high LOQ. The highest concentrations of the APIs were:
Allopurinol – 160 µg/L in Finland, Kalteva, in November 2018;
Atorvastatin – not detected, all samples <10 µg/L;
Bezafibrate – 1.4 µg/L in Germany, Wismar, in February 2018;
Gemfibrozil – 0.78 µg/L in Germany, Rostock, in June 2018;
Metformin – 480 µg/L in Germany, Neubrandenburg, in February 2018;
Simvastatin – 0.098 µg/L in Estonia, Paide, in June 2018.

Effluent

In the effluents we detected five out of six APIs of the metabolic disease medications group: allopurinol, atorvastatin, bezafibrate, metformin and simvastatin. The most frequently detected API was bezafibrate (DF 53%). Gemfibrozil was not detected in any of the effluent samples.
The highest concentrations of the APIs were:
Allopurinol – 7.3 µg/L in Latvia, WWTP 3 in December 2017;
Atorvastatin – 17 µg/L in Latvia, WWTP 2 in December 2017;
Bezafibrate – 0.39 µg/L in Germany, Neubrandenburg in February 2018;
Gemfibrozil – not detected, all samples <0.10 µg/L;
Metformin – 2.6 µg/L in Finland, Kalteva in December 2017;
Simvastatin – 0.0077 µg/L in Finland, Kalteva in December 2017.
The highest detected concentration of allopurinol in Latvia is 17 times higher than the second highest value: 0.43 µg/L in Germany. In the Latvian effluent, other biologically degradable APIs were also detected in exceptionally high concentrations, indicating problems in the WWTP process during the sampling.

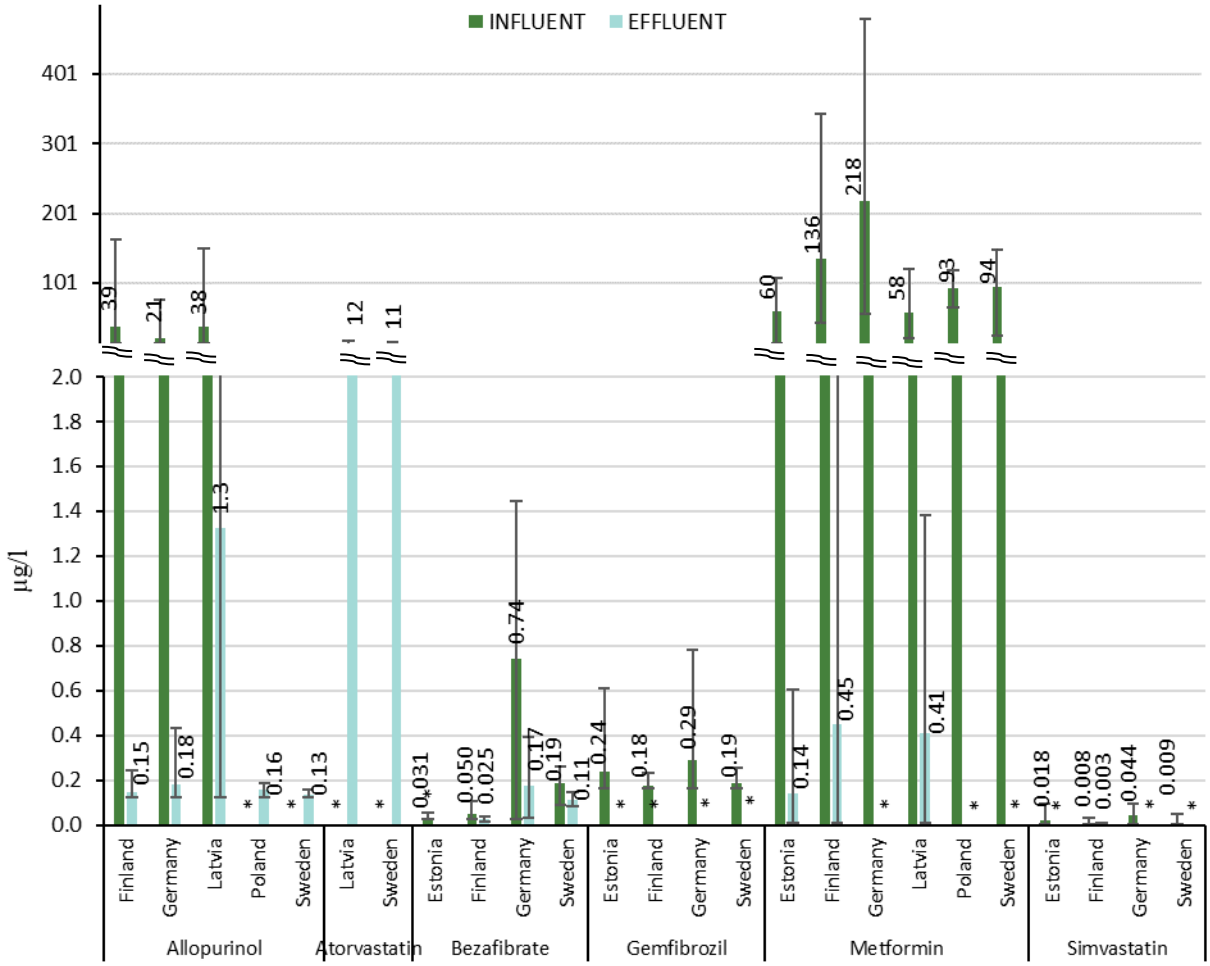

Figure 6.9. Average concentrations of API of metabolic disease medications group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

NSAIDs and analgesics

Influent

In influents, we detected seven out of eight NSAIDs and analgesics APIs**:** codeine, diclofenac, ibuprofen, ketoprofen, naproxen, paracetamol and tramadol (figure 6.10). Diclofenac, ketoprofen and naproxen were detected in all influent samples. Oxycodone was not detected in any influent sample.

The highest concentrations of the APIs were:

- Codeine – 4.5 µg/L in Finland, Kalteva in November 2018;
- Diclofenac – 16 µg/L in Germany, Neubrandenburg in February 2018;
- Ibuprofen – 8.0 µg/L in Finland, Kalteva in December 2017;
- Ketoprofen – 2.8 µg/L in Poland, Błonie in November 2017;
- Naproxen – 12 µg/L in Estonia, Türi in June 2018;
- Oxycodone – not detected, all samples <0.26 µg/L;
- Paracetamol - 1000 µg/L in Sweden, Linköping in December 2017;
- Tramadol – 1.4 µg/L in Sweden, Motala in June 2018.

Effluent

In the effluents we also detected seven out of eight APIs of the NSAIDs and analgesics group: codeine, diclofenac, ibuprofen, ketoprofen, naproxen, paracetamol and tramadol. Diclofenac was detected in all effluent samples. Naproxen and tramadol also had high DFs (97%). Oxycodone was not detected in any of the effluent samples.

Ibuprofen was not analysed in surface water but it was detected in 40% of effluent wastewater samples at concentrations ranging from 3.7 to 44 µg/L. In order not to exceed the surface water PNEC value (0.12 ng/L), the effluent emissions would require a dilution factor of more than 31 000 in the receiving waterbody.

The highest concentration of each API was:

- Codeine – 0.66 µg/L in Finland, Viikki in November 2018;
- Diclofenac – 38 µg/L in Estonia, Paide in June 2018;
- Ibuprofen – 44 µg/L in Latvia, WWTP 2 in December 2017;
- Ketoprofen – 0.37 µg/L in Estonia, Pärnu in December 2017;
- Naproxen – 1.3 µg/L in Sweden, Linköping in December 2017;
- Oxycodone –not detected, all samples <0.12 µg/L;
- Paracetamol - 5.4 µg/L in Finland, Kalteva in December 2017;
- Tramadol – 1.5 µg/L in Sweden, Motala in June 2018.

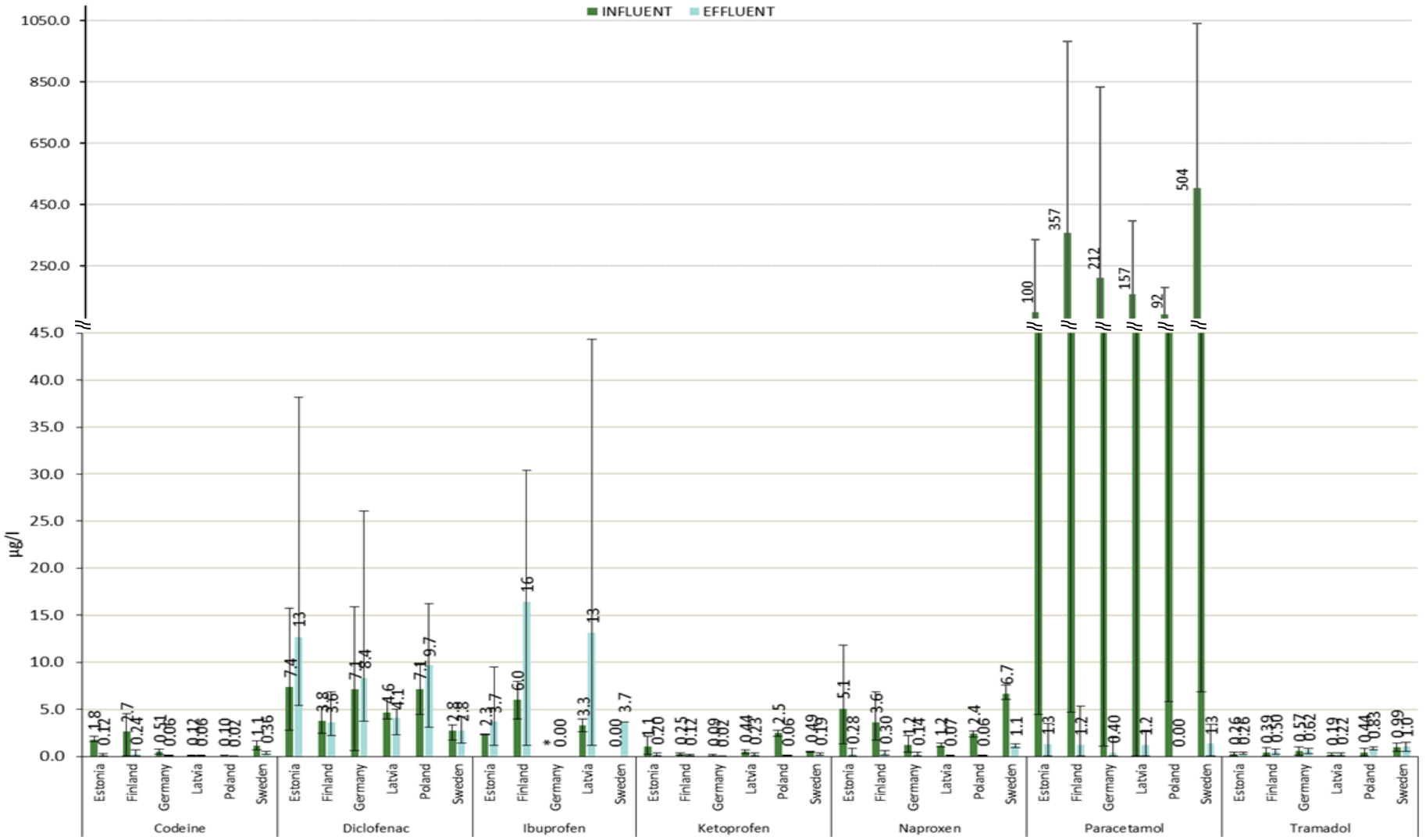

Figure 6.10. Average concentrations of API of NSAIDs and analgesics group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country.

Other - caffeine

Influent

Caffeine was detected in 93% of samples (figure 6.11).
The highest concentration – 24 µg/L – was observed in Germany, Neubrandenburg in June 2018.

Effluent

Caffeine was detected in 15% of the effluent samples.
The highest concentration – 32 µg/L – was observed in Latvia, WWTP 3 in December 2017. The second highest concentration was ten times less: 3.3 µg/L in Germany (Neubrandenburg, February 2018).

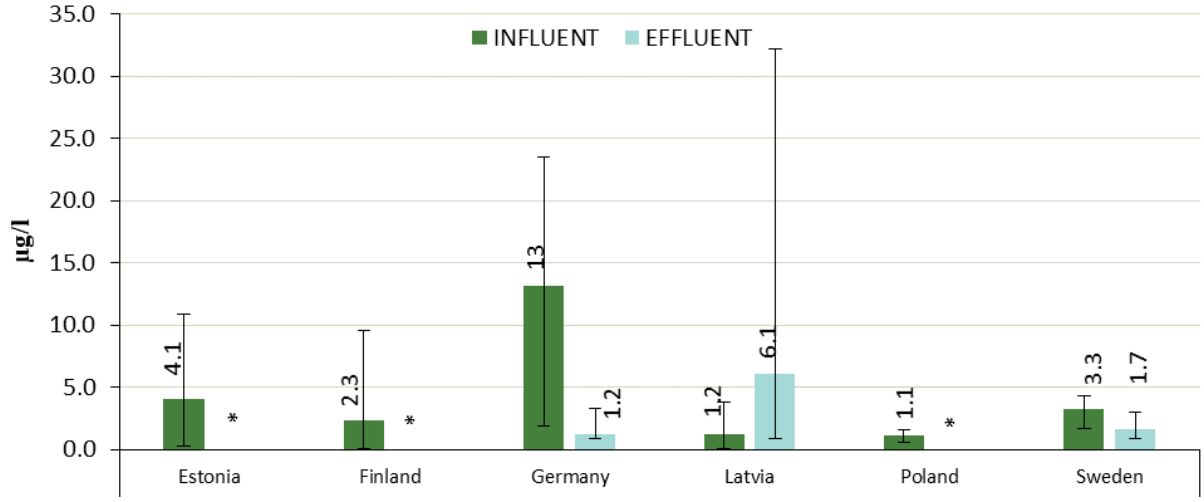

Figure 6.11. Average concentrations of API of caffeine in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Other cardiovascular medicines

Influent

In influents, we detected all seven APIs of the other cardiovascular medicines group: atenolol, bisoprolol, dipyridamole, metoprolol, nebivolol, sotalol and warfarin (figure 6.12). The most frequently detected APIs were metoprolol (DF 79%), sotalol (DF 78%) and bisoprolol (DF 69%).
The highest concentrations were:

- Atenolol – 2.6 µg/L in Sweden, Motala in December 2017;
- Bisoprolol – 1.8 µg/L in Germany, Neubrandenburg in June 2018;
- Dipyridamole – 5 µg/L in Finland, Kalteva in June 2018;
- Metoprolol – 4 µg/L in Germany, Wismar in June 2018;
- Nebivolol – 1.5 µg/L in Estonia, Pärnu in June 2018;
- Sotalol – 0.27 µg/L in Poland, Błonie in July 2018;
- Warfarin – 0.027 µg/L in Finland, Viikki in August 2018.

Effluent

In the effluents we also detected all seven APIs of the other cardiovascular medicines group: atenolol, bisoprolol, dipyridamole, metoprolol, nebivolol, sotalol and warfarin. The most frequently detected APIs were metoprolol (DF 100%), sotalol (DF 97%) and bisoprolol (DF 68%). Nebivolol was detected only once in Estonia. The highest concentrations were:

- Atenolol – 0.54 µg/L in Sweden, Norrköping in December 2017;
- Bisoprolol – 1.4 µg/L in Germany, Neubrandenburg in February 2018;
- Dipyridamole – 0.81 µg/L in Finland, Viikki in December 2017;
- Metoprolol – 7.3 µg/L in Estonia, Türi in June 2018;
- Nebivolol – 0.034 µg/L in Estonia, Paide in June 2018;
- Sotalol – 0.24 µg/L in Latvia, WWTP 2 in May 2018;
- Warfarin – 0.020 µg/L in Finland, Viikki in August 2018.

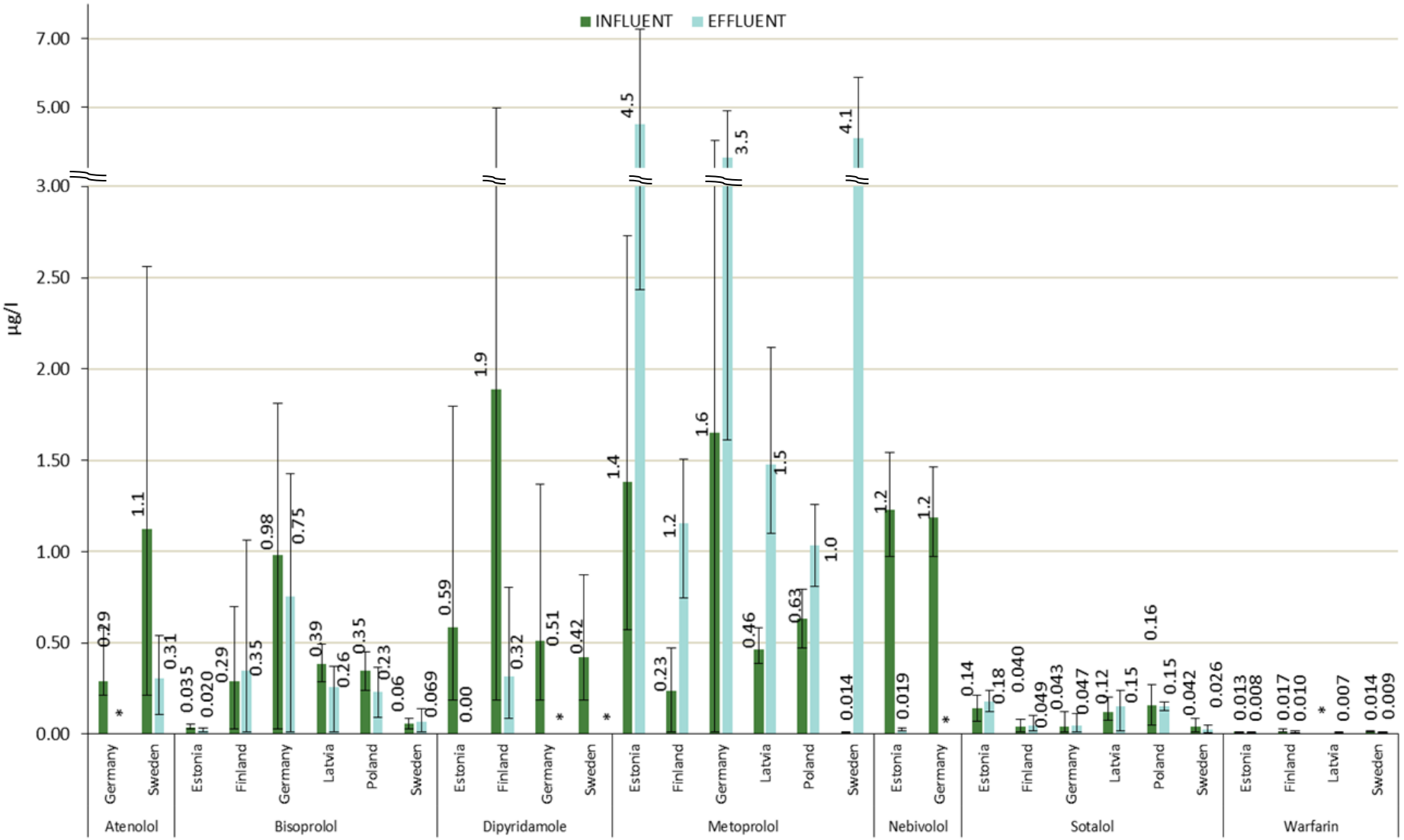

Figure 6.12. Average concentrations of API of other cardiovascular medicines group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Psychopharmaceuticals

Influents

In the influents, we detected seven out of eight studied psychopharmaceuticals: citalopram, olanzapine, oxazepam, quetiapine, sertraline, temazepam and venlafaxine (figure 6.13). Most frequently detected APIs were oxazepam (DF 96%), venlafaxine (DF 91%), citalopram (DF 89%), temazepam (DF 67%) and sertraline (DF 67%). Risperidone was not detected in any of the influent samples.

The highest concentration of each API was:

- Citalopram – 0.81 µg/L in Germany, Neubrandenburg in June 2018;
- Olanzapine – 2.4 µg/L in Poland, Błonie in July 2018;
- Oxazepam – 3.1 µg/L in Finland, Kalteva in November 2018;
- Quetiapine – 0.69 ng/L in Estonia, Türi in June 2018;
- Risperidone – not detected, all samples <0.80 µg/L;
- Sertraline – 0.93 µg/L in Finland, Kalteva in June 2018;
- Temazepam – 2.4 µg/L in November 2018;
- Venlafaxine – 1.5 µg/L in Germany, Neubrandenburg in June 2018.

Effluents

In the WWTP effluent, we detected seven out of eight psychopharmaceuticals: citalopram, olanzapine, oxazepam, risperidone, sertraline, temazepam and venlafaxine. The detection frequency of oxazepam was 100%. Citalopram, venlafaxine and temazepam also had high DFs, 97%, 97% and 88%, respectively. Quetiapine was not detected in any of the effluent samples.

The highest concentrations were:

- Citalopram – 0.35 µg/L in Germany, Neubrandenburg in June 2018;
- Olanzapine – 0.43 µg/L in Germany, Wismar in June 2018;
- Oxazepam – 2.7 µg/L in Finland, Kalteva in November 2018;
- Quetiapine – not detected, all samples <0.010 µg/L;
- Risperidone – 0.012 µg/L in Germany, Wismar in June 2018;
- Sertraline – 0.15 µg/L in Sweden, Motala in December 2017;
- Temazepam – 1.8 µg/L in November 2018;
- Venlafaxine – 0.96 µg/L Germany, Rostock in November 2018.

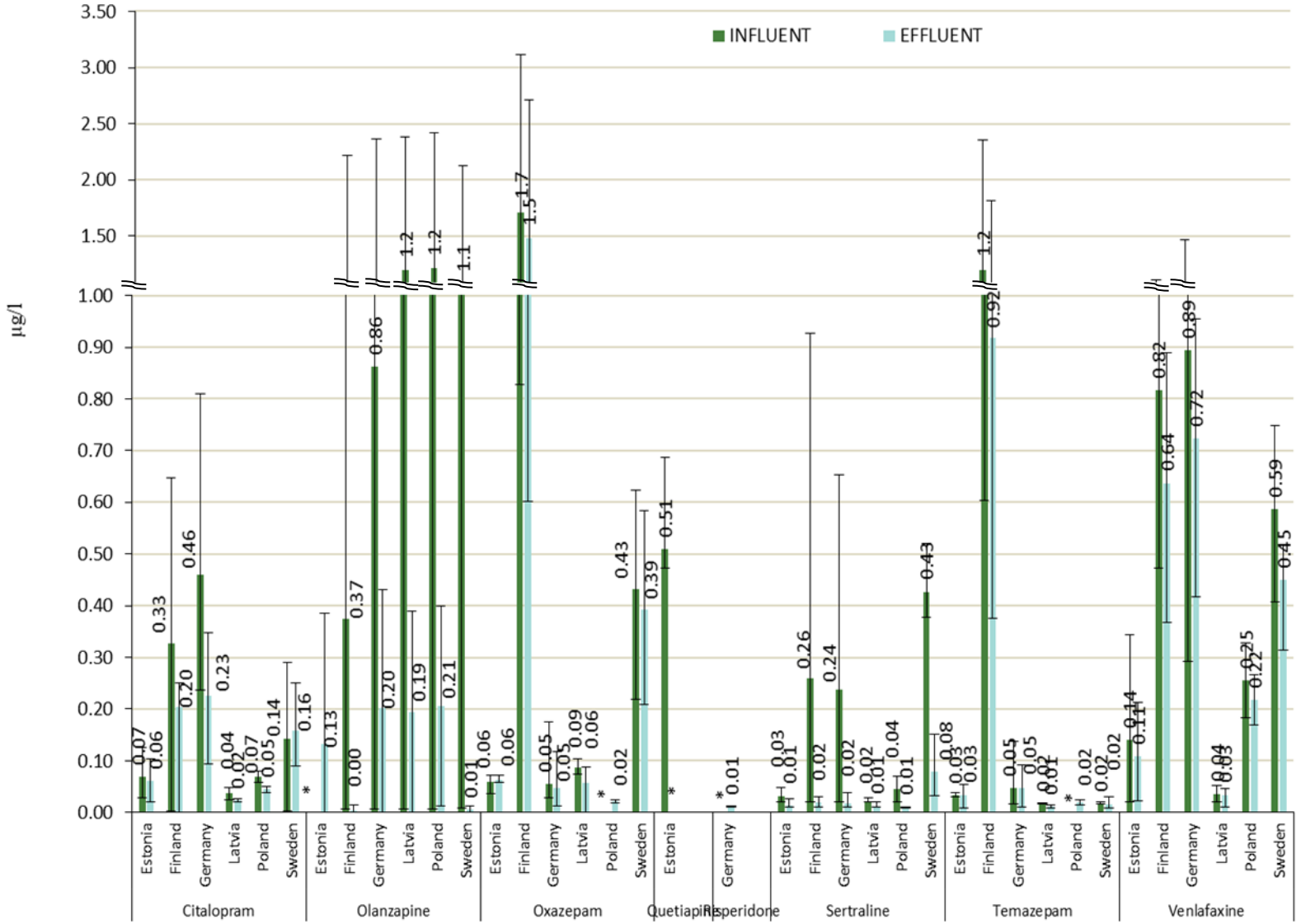

Figure 6.13. Average concentrations of API of psychopharmaceuticals group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

Veterinary medicines

Influents
Two of the eight veterinary APIs were detected in the wastewater influent samples: carprofen and fenbendazole (figure 6.14**)**. The most often detected API was carprofen (DF 31%). Fenbendazole was detected only once in a German influent. Emamectin, florfenicol, tiamulin, toltrazuril and tylosin were not detected in any of the influent samples. The highest concentration for each detected veterinary API was:

- Carprofen – 0.084 µg/L Germany, Neubrandenburg in February 2018;
- Emamectin –not detected, all samples <0.029 µg/L;
- Fenbendazole – 0.036 µg/L in Germany, Neubrandenburg in February 2018;
- Florfenicol – not detected, all samples <0.064 µg/L;
- Tiamulin – not detected, all samples <0.038 µg/L;
- Toltrazuril –not detected, all samples <9 µg/L;
- Tylosin –not detected, all samples <0.32 µg/L.

Effluents
In the wastewater effluent, four of the seven studied veterinary APIs were detected: carprofen, emamectin, fenbendazole and tylosin. Most frequently detected API was tylosin (DF 50%). Fenbendazole was detected only once in Germany. Florfenicol, tiamulin and toltrazuril were not detected in any effluent sample.
The highest concentration of each API was:

- Carprofen – 0.010 µg/L in Germany, Neubrandenburg in February 2018;
- Emamectin – 0.039 µg/L in Estonia, Paide in June 2018;
- Fenbendazole – 0.015 µg/L in Germany, Wismar in June 2018;
- Florfenicol –not detected, all samples <0.032 µg/L;
- Tiamulin – not detected, all samples <0.019 µg/L;
- Toltrazuril – not detected, all samples <9 µg/L;
- Tylosin – 0.35 µg/L in Germany, Greifswald in June 2018.

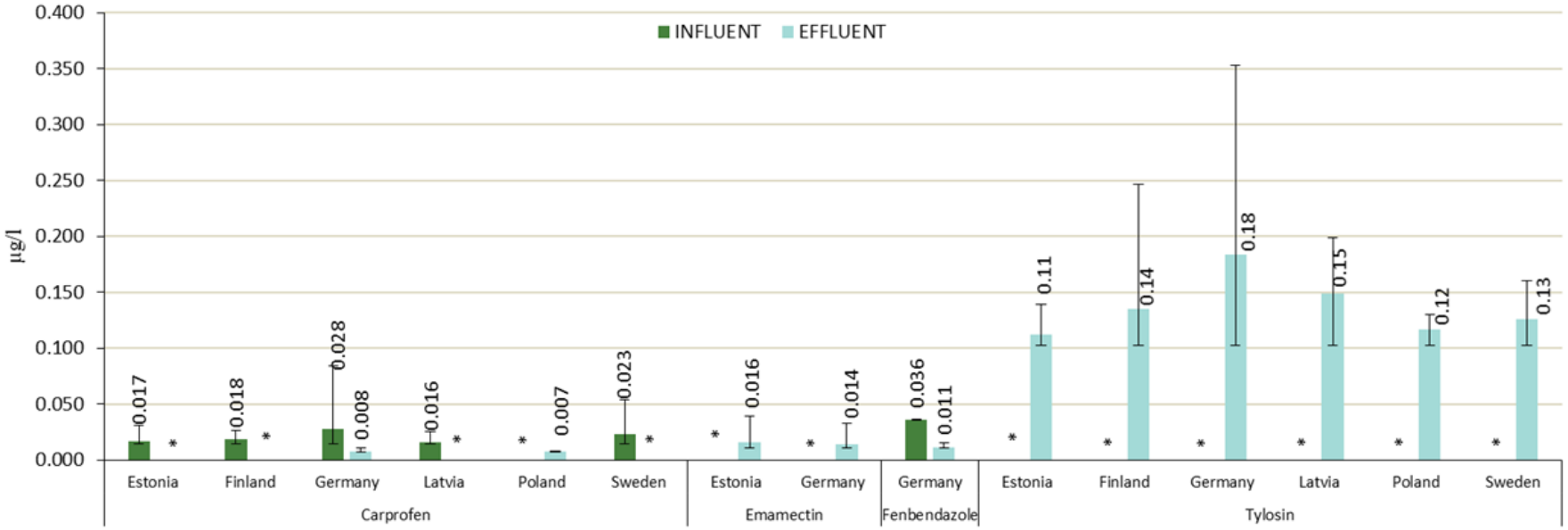

Figure 6.14. Average concentrations of API of veterinary medicines group in influent and effluent. Error bars represent range of average concentrations in all WWTP per country. * - all samples <LOQ.

6.1.2.2 Efficiency of wastewater treatment plants - influent and effluent data

The API removal efficiencies of the studied wastewater treatment plants are summarized in Annex 7. Site-specific average removal rates were calculated for each WWTP and API. These values are presented in table 6.1. Previous data about the API removal efficiency are mainly in range of CWPharma project results or the ranges of the results overlap. There are also differencies in the results, for example the removal efficiency of metoprolol was negative in CWPharma, whereas in the literature 3–83% removal rates have been reported. CWPharma project results show some negative efficiency rates. The negative efficiency rates could be explained by the process where some pharmaceutical ingredients become metabolised as conjugates in our body, but further along in the process, in the presence of microorganisms in the wastewater treatment plant, the conjugates may revert back to the original compounds (Birziņš, 2018; Pereira et al., 2020). Table 6.2 summarises the studied wastewater treatment plants, their capacity in PE and treatment methods.

Table 6.1. The average removal efficiencies at the CWPharma case study WWTPs and comparison with literature.

Compound	Removal efficiency*, % (CWPharma)	Number of data points (CWPharma)	Removal efficiency, % (literature)
Atenolol	60–82	4	51 (Fick et al. 2011) 20–97 (Gros et al. 2010) <0–85 (Luo et al. 2014) 8 (Miege et al. 2009) -5 (Äystö et al. 2020)
Allopurinol	99–100	4	N/A
Bezafibrate	8–82	8	23–99 (Gros et al. 2010) 9–71 (Luo et al. 2014) 68 (Miege et al. 2009)
Bisoprolol	-54–79	13	39 (Fick et al. 2011) 23 (Magnér et al. 2016) 32 (Äystö et al. 2020)
Caffeine	90–92	5	89–100% (Al Qarni et al. 2016) 50–100 (Luo et al. 2014) 100 (Äystö et al. 2020)
Carbamazepine	-364–98	21	13–28 (Al Qarni et al. 2016) 52 (Fernández-López et al. 2016) -3 (Fick et al. 2011) 9 (Miehe, 2010) <0–62 (Luo et al. 2014) 9 (Miege et al. 2009) <10 (Radjenovic et al. 2007) 0–20 (Tambosi et al. 2010) -7 (Äystö et al. 2020)
Carprofen	87–88	2	N/A
Citalopram	-29–59	25	11 (Fick et al. 2011) 39 (Äystö et al. 2020)
Clarithromycin	-23–64	18	54 (Fick et al. 2011) 45 (Miege et al. 2009)
Codeine	47–99	19	68 (Fick et al. 2011) 42 (Kasprzyk-Hordern et al. 2009)
Diclofenac	-154–33	29	74 (Fernández-López et al. 2016) 28 (Fick et al. 2011) 30–100 (Gros et al. 2010) <0–81 (Luo et al. 2014) 32 (Miege et al. 2009) 55 (Papageorgiou et al. 2016 17 (Äystö et al. 2020)
Dipyridamole	41–97	9	>99 (Fick et al. 2011)
Eprosartan	16–98	12	46 (Fick et al. 2011)
Erythromycin	-165–99	16	43 (Fick et al. 2011) <0–83 (Luo et al. 2014) 67 (Miege et al. 2009)
Estrone (E1)	60–100	11	76±46 (Chang et al. 2011) 82 (Esperanza et al. 2007) 75–91 (Luo et al. 2014) -28 (Mailler et al. 2015) 76–98 (Miehe, 2010) 95 (Äystö et al. 2020)
Fluconazole	-60–84	21	33 (Fick et al. 2011)
Gabapentin	41–100	18	84 (Kasprzyk-Hordern et al. 2009)
Gemfibrozil	84	1	30–99 (Gros et al. 2010) 0–17 (Luo et al. 2014)
Hydrochlorothiazide	-333–94	27	32 (Gros et al. 2010) 13 (Äystö et al. 2020)
Ibuprofen	86	1	>99 (Carmona et al. 2014) 71 (Fick et al. 2011) 65–100 (Gros et al. 2010) 72–100 (Luo et al. 2014) 74 (Miege et al. 2009) 95–99 (Miehe 2010) 100 (Äystö et al. 2020)
Irbesartan	-138–98	4	NA
Ketoprofen	-2–99	24	36 (Fick et al. 2011) 40–100 (Gros et al. 2010) 11–100 (Luo et al. 2014)

			23–58 (Miehe 2010) 54 (Äystö et al. 2020)
Levetiracetam	60–100	25	NA
Losartan	-34–69	8	82 (UNESCO & HELCOM 2017)
Mesalazine	68–99	26	NA
Metformin	98–100	29	>61 (Fick et al. 2011)
Metoprolol	-318 – -72	19	31 (Fick et al. 2011) 3–56 (Luo et al., 2014) 5.9 (Magnér et al. 2016) 10 (Miege et al. 2009) >10 (Radjenovic et al. 2007) 83 (Tambosi et al. 2010) 31 (Äystö et al. 2020)
Naproxen	64–100	25	>90 (Carmona et al. 2014) 84 (Fernández-López et al. 2016 72 (Fick et al. 2011) 60–100 (Gros et al. 2010) 43–99 (Luo et al. 2014) 69 (Magnér et al. 2016) 45–86 (Miehe 2010) 91 (Äystö et al. 2020)
Nebivolol	98–99	4	NA
Norethisterone	-18–99	16	73 (UNESCO & HELCOM 2017)
Ofloxacin	83–90	2	>7 (Fick et al. 2011) 20–99 (Gros et al. 2010) -157–4 (Leung et al. 2012) 24 (Radjenovic et al. 2007) 77 (Tambosi et al. 2010)
Olanzapine	83–99	12	38–99 (Kosma et al. 2019)
Oxazepam	-23–98	16	-6 (Fick et al. 2011)
Paracetamol	60–100	27	100 (Fick et al. 2011)
Primidone	-24 – -13	3	NA
Progesterone	59–86	3	97±1.7 (Chang et al. 2011) >95 (Esperanza et al. 2007) 97 (Äystö et al. 2020)
Quetiapine	83	1	29–92 (Kosma et al. 2019)
Ramipril	-60 – -1	3	NA
Sertraline	61–96	11	71 (Fick et al. 2011) >70 (Kosma et al. 2019)
Simvastatin	95–98	5	NA
Sotalol	-136–55	21	11 (Schrap et al. 2003) -35 (Äystö et al. 2020)
Sulfamethoxazole	-31–98	24	73 (Fick et al. 2011) 30–92 (Gros et al. 2010) 4–89 (Luo et al. 2014) 59 (Miege et al. 2009) 41–48 (Miehe 2010) 91 (Äystö et al. 2020)
Telmisartan	-1049–96	17	58 (Fick et al. 2011)
Temazepam	-74–34	7	NA
Testosterone	80–91	4	96±7.9 (Chang et al. 2011) >95 (Esperanza et al. 2007)
Tetracycline+doxycycline (SUM)	83–90	7	Tetracycline >96 (Fick et al. 2011) Tetracycline 40–89 (Gros et al. 2010) Tetracycline 44–90 (Leung et al. 2012) Tetracycline 94 (Äystö et al. 2020) Doxycycline 96 (Äystö et al. 2020)
Tramadol	-49–90	20	-3 (Fick et al. 2011)
Trimethoprim	9–73	25	39 (Fick et al. 2011) 4–45 (Leung et al. 2012) <0–82 (Luo et al. 2014) 16 (Miege et al. 2009) 6 (Äystö et al. 2020)
Valsartan	10–99	16	NA
Venlafaxine	-91–63	18	21 (Fick et al. 2011)

*A range of the average removal efficiencies at the studied WWTPs. The average removal efficiencies of all WWTPs are presented in Annex7.

Table 6.2. The size and treatment process of the studied wastewater treatment plants.

Country	WWTP	Capacity in PE	Main treatment process
Estonia	Paide	35 000 PE	SBR (with bio-N removal + chemical P-removal)
	Pärnu	125 000 PE	AAO (AS with bio-P and bio-N removal + chemical P-removal)
	Türi	8050 PE	AAO (AS with bio-P and bio-N removal + chemical P-removal)
Finland	Kalteva	40 700 PE	AS (2 parallel lines)
	Viikki	1 320 000 PE	AS (9 parallel lines)
Germany	Greifswald	60 400 PE	AS with anaerobic and aerobic zones, nitrification and denitrification
	Neubrandenburg	67 150 PE	SBR
	Rostock	237 316 PE	AS with anaerobic and aerobic zones, nitrification and denitrification
	Wismar	79 000 PE	AS with anaerobic and aerobic zones, nitrification and denitrification
Latvia	WWTP 1	87 756 PE (2017) 89 149 PE (2018)	AS with anaerobic and aerobic zones, nitrification and denitrification
	WWTP 2	656 296 PE (2017) 703 797 PE (2018)	AS, aeration, nitrification and denitrification
	WWTP 3	14 014 PE (2017) 13 832 PE (2018)	AS, denitrification
Poland	Błonie	29 509 PE	AS
Sweden	Linköping	216 000 PE (2018)	Primary clarifiers, AS, nitrification and denitrification intermittent aerated, ozonation (not running at the time of sampling), MBBR, tertiary sedimentation
	Motala	30 180 PE (2018)	AS with anaerobic and aerobic zones, nitrification and denitrification
	Norrköping	157 800 PE (2018)	Primary pre-treatment with $FeCl_3$ (sedimentation), AS, nitrification and denitrification, sedimentation, secondary treatment with $FeCl_3$ (sedimentation)

AAO = anaerobic-anoxic-oxic process; AS = activated sludge process; MBBR = moving bed biofilm reactor; SBR = sequencing batch reactor process.

6.1.2.3 Concentrations of APIs in WWTP sludge

This chapter presents the API concentrations in the sludge of the CWPharma case study WWTPs. The results with remark "not available" are not included; there was some interference for the compound, mostly due to matrix, and therefore the result could not be recorded or reported. The concentrations are presented as micrograms per kilogram (µg/kg) of dry sludge (i.e. per dry weight). All measured concentrations in WWTP sludge are presented in Annex 8.

Antibiotics

In sludge, we detected all four of the analysed antibiotics: fluconazole, lincomycin, ofloxacin and trimethoprim (figure 6.15). Most frequently detected API was fluconazole (DF 89%). The highest observed API concentrations were:

- Fluconazole – 34 µg/kg in Poland, Błonie WWTP in November 2017;
- Lincomycin – 2.2 µg/kg in Germany, WWTP Greifswald in June 2018;
- Ofloxacin – 8600 µg/kg in Finland, Kalteva in June 2018;
- Trimethoprim – 41 µg/kg in Estonia, Pärnu, in December 2017.

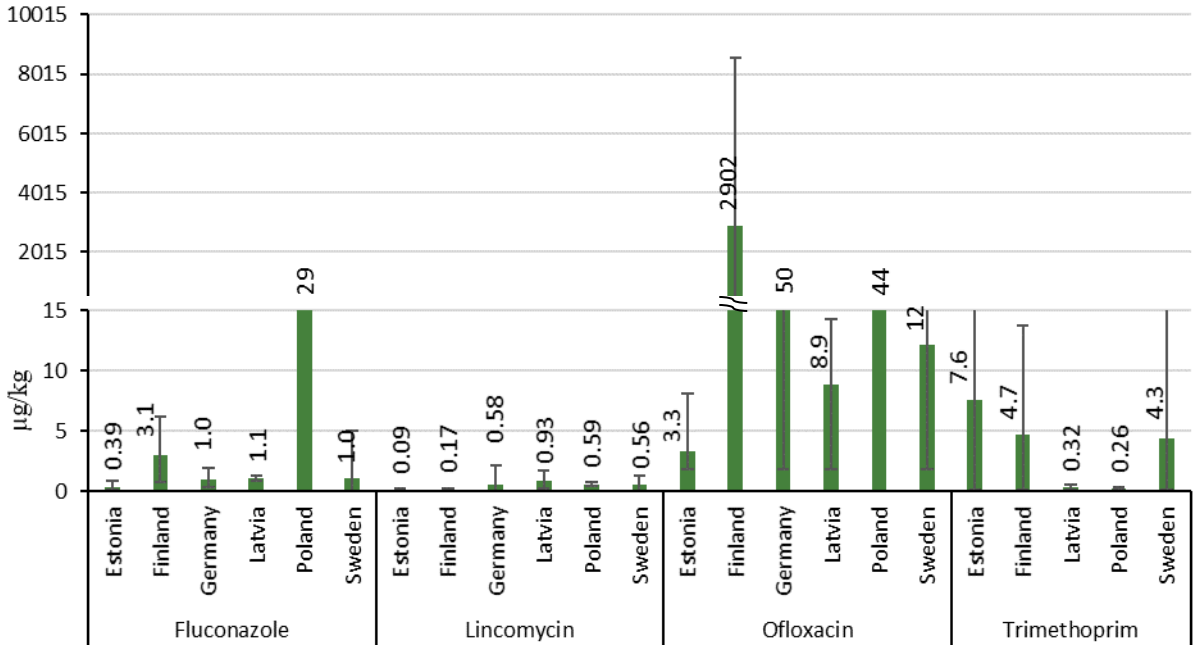

Figure 6.15. Average concentrations of antibiotics in sludge. Error bars represent the range of average concentrations in each country.

Antiepileptics

All four antiepileptic APIs were detected in sludge: carbamazepine, gabapentin, levetiracetam and primidone (figure 6.16). Carbamazepine was detected in all samples.
The highest observed API concentrations were:

- Carbamazepine – 600 µg/kg Poland, Błonie WWTP in November 2017;
- Gabapentin – 51 µg/kg in Estonia, Pärnu, in December 2017;
- Levetiracetam – 31 µg/kg in Finland, Kalteva in June 2018;
- Primidone – 5.1 µg/kg in Sweden, Linköping in June 2018.

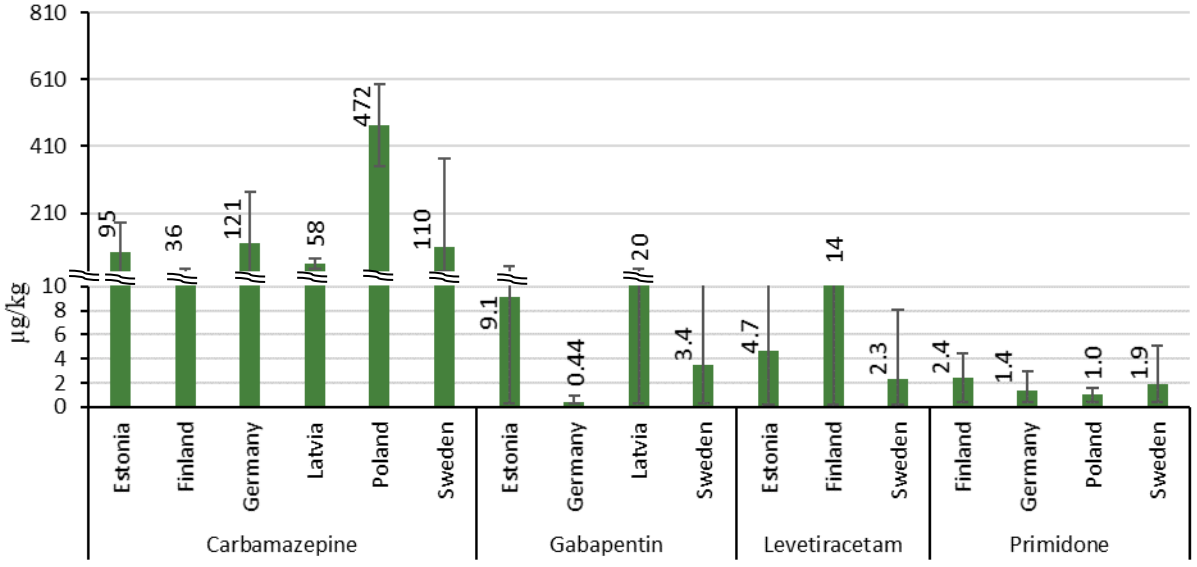

Figure 6.16. Average concentrations of the antiepileptics in sludge. Error bars represent the range of the average concentrations in each country.

Antihypertensives

Three out of the four studied antihypertensive APIs were detected in sludge: enalapril, irbesartan and telmisartan (figure 6.17). Irbesartan was also frequently detected (DF 93%). Ramipril was not detected in any of the sludge samples. The highest observed API concentrations were:

- Enalapril – 1.4 µg/kg in Estonia, Pärnu, in December 2017;
- Irbesartan – 51 µg/kg in Germany, WWTP Greiswald in February 2018;
- Ramipril –not detected, all samples <0.46 µg/kg;
- Telmisartan – 8700 µg/kg in Estonia, Paide in December 2017.

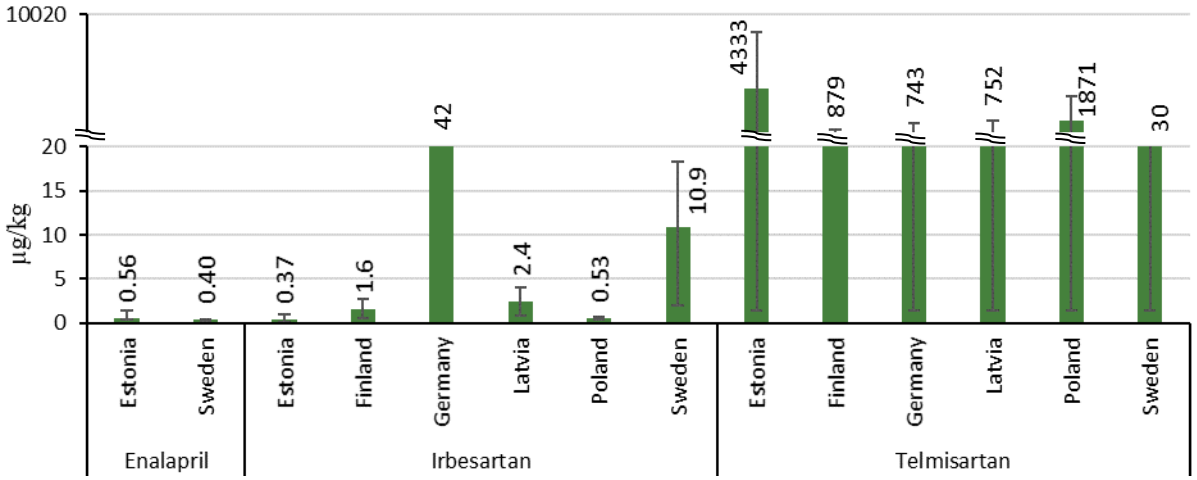

Figure 6.17. Average concentrations of the antihypertensive APIs in sludge. Error bars represent the range of the average concentrations in each country.

Metabolic disease medications

From the metabolic disease medications group only metformin was measured in sludge. It was detected in all samples (figure 6.18). The highest observed concentration of metformin was 510 µg/kg in Estonia, Pärnu, in June 2018.

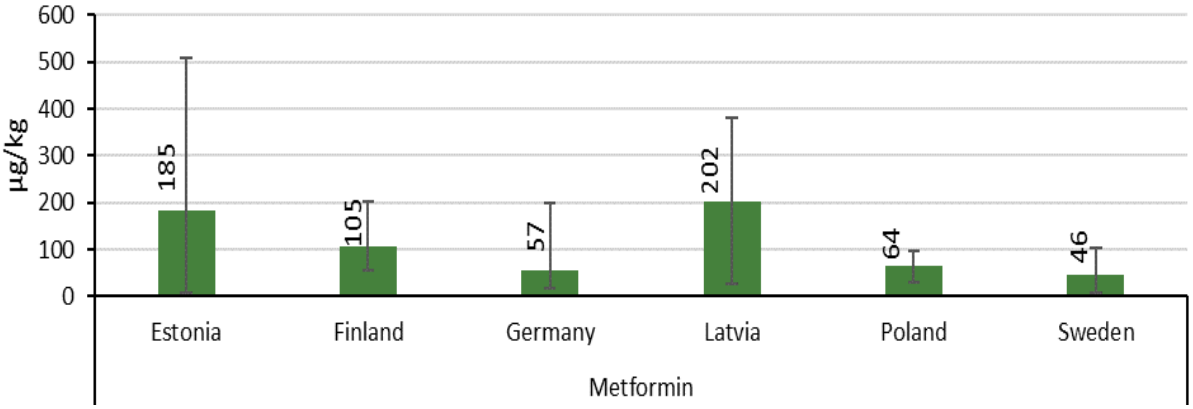

Figure 6.18. Average concentrations of metformin in sludge. Error bars represent the range of the average concentrations in each country.

NSAIDs and analgesics in sludge

All six APIs of the NSAIDs and analgesics group were detected in sludge: codeine, diclofenac, ketoprofen, naproxen, oxycodone and tramadol (figure 6.19.). Diclofenac was detected in all samples. Other frequently detected APIs were tramadol (DF 93%), oxycodone (DF 79%) and naproxen (DF 71%). The highest observed concentrations were:

- Codeine – 43 µg/kg in Finland, Kalteva in June 2018;
- Diclofenac – 960 µg/kg in Poland, Błonie WWTP in July 2018;
- Ketoprofen – 79 µg/kg in Poland, Błonie WWTP in November 2017;

- Naproxen – 42 µg/kg in Finland, Kalteva in June 2018;
- Oxycodone – 100 µg/kg in Estonia, Pärnu in June 2018;
- Tramadol – 71 µg/kg in Poland, Błonie WWTP in November 2017.

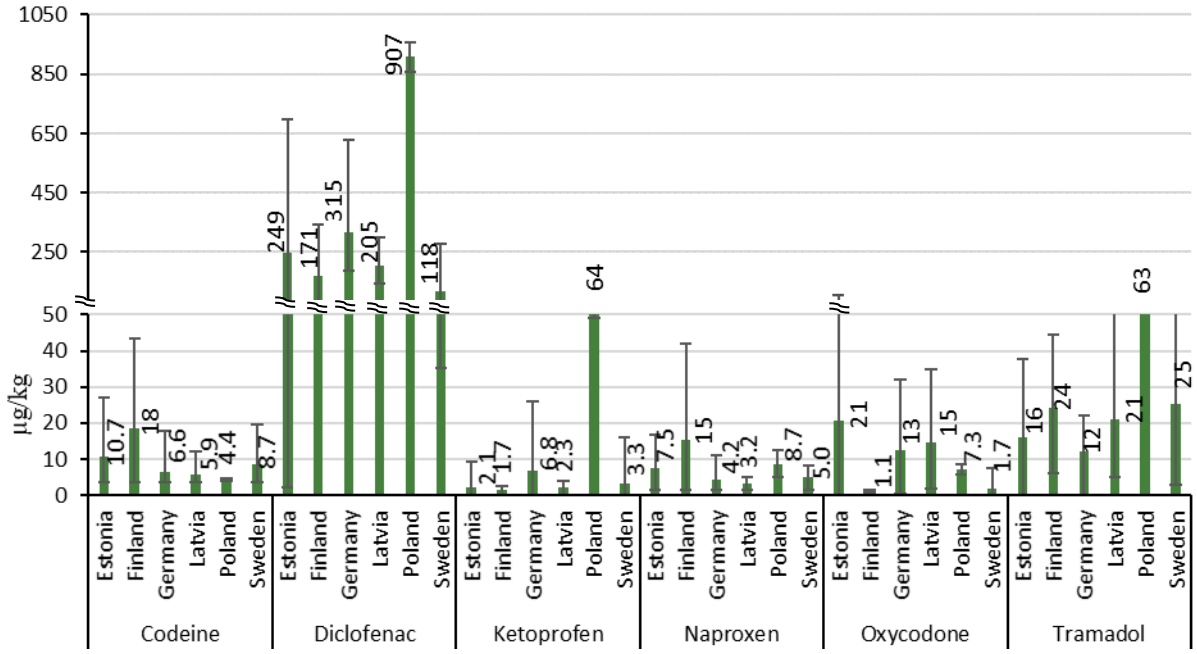

Figure 6.19. Average concentrations of the APIs of NSAIDs and analgesics group in sludge. Error bars represent the range of the average concentrations in each country.

Other APIs

Caffeine was detected in all sludge samples (figure 6.20.). The highest observed concentration was 160 µg/kg in Estonia, Pärnu in June 2018.

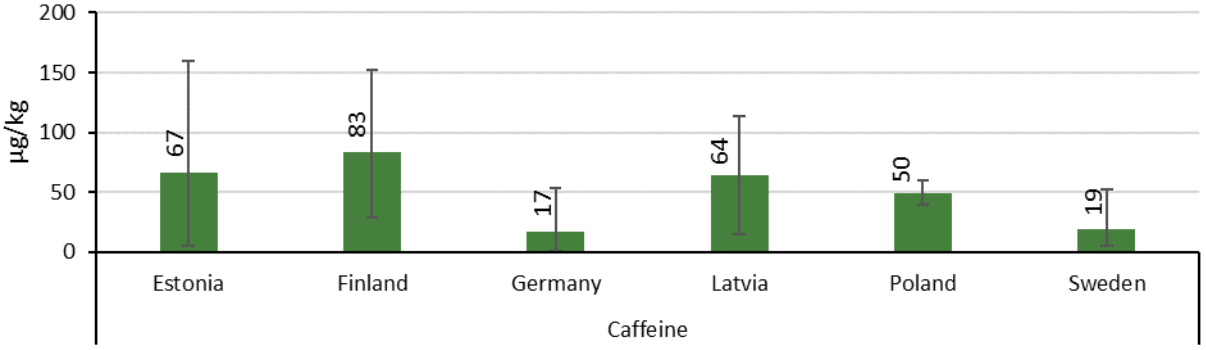

Figure 6.20. Average concentrations of caffeine in sludge. Error bars represent the range of the average concentrations in each country.

Other cardiovascular medicines

Two APIs, bisoprolol and metoprolol, from the other cardiovascular medicines group were measured in sludge. Metoprolol was detected in all sludge samples, and bisoprolol in 93% of the samples (figure 6.21).

The highest observed concentrations were:

- Bisoprolol – 120 µg/kg in Germany, Rostock, in November 2018;
- Metoprolol – 410 µg/kg in Sweden, Linköping (digested sludge) in December 2017.

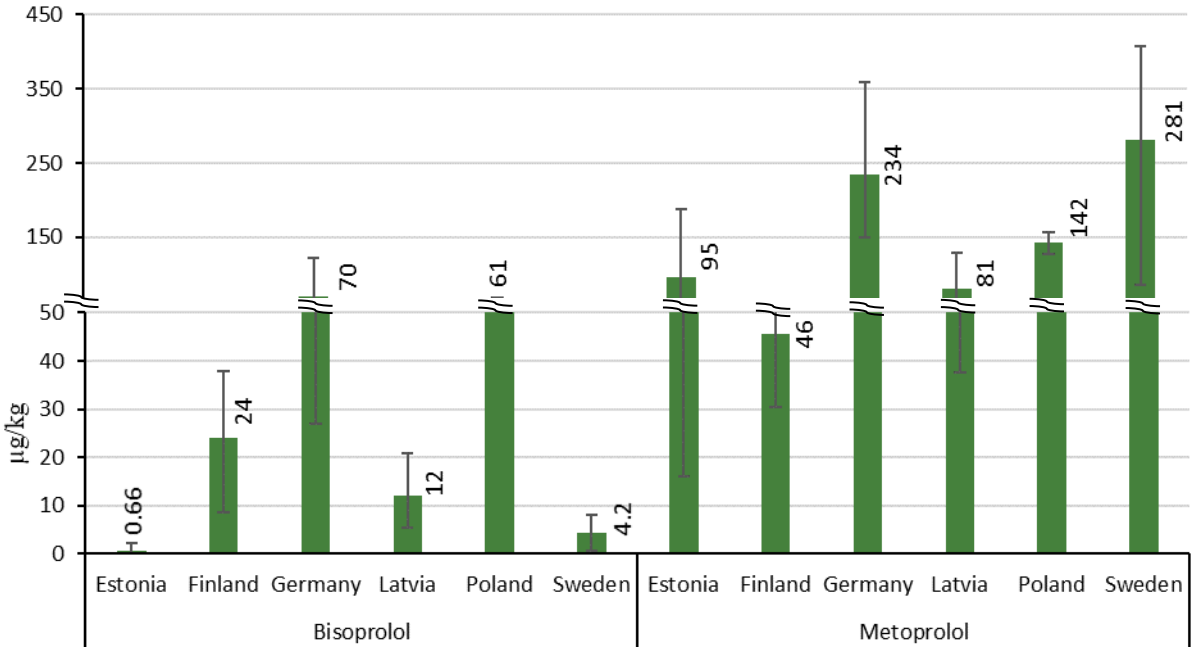

Figure 6.21. Average concentrations of the APIs of other cardiovascular medicines group in sludge. Error bars represent the range of the average concentrations in each country.

Psychopharmaceuticals

All seven psychopharmaceuticals were detected in sludge: citalopram, olanzapine, oxazepam, risperidone, sertraline, temazepam and venlafaxine (figure 6.22.). Citalopram, sertraline and venlafaxine were detected in all samples (DF 100%). Oxazepam and temazepam were also frequently detected (DF 96%).

The highest observed concentrations were:

- Citalopram – 510 µg/kg in Finland, Viikki in August 2018;
- Olanzapine – 180 µg/kg in Poland, Błonie WWTP in July 2018;
- Oxazepam – 140 µg/kg in Finland, Viikki in August 2018;
- Risperidone – 8.4 µg/kg in Poland, Błonie WWTP in November 2017;
- Sertraline – 1400 µg/kg in Sweden, Linköping in December 2017;
- Temazepam – 310 µg/kg in Finland, Viikki in August 2018;
- Venlafaxine – 135 µg/kg in Sweden, Motala in December 2017.

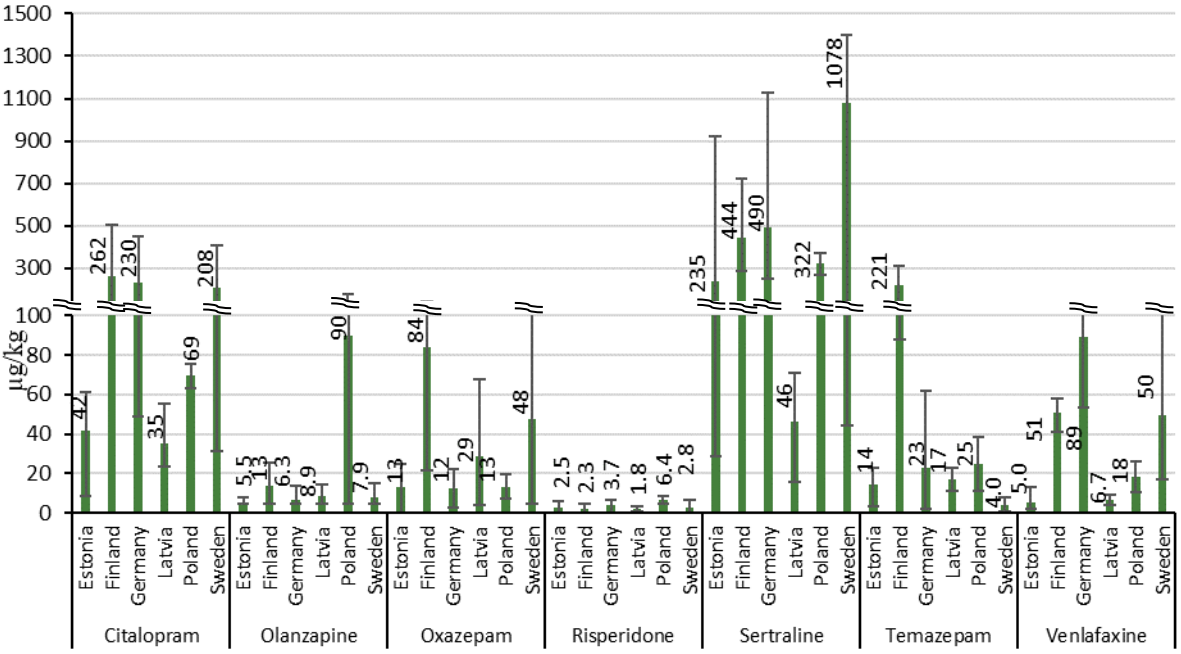

Figure 6.22. Average concentrations of psychopharmaceuticals in sludge. Error bars represent the range of the average concentrations in each country.

Veterinary medicines

Two veterinary APIs were measured in the sludge samples. Tylosin was not detected in any sample, and totrazuril was detected only in one sample from Poland

The highest observed concentrations were:

- Toltrazuril – 31 µg/kg in Poland, Błonie WWTP in July 2018;
- Tylosin – not detected, all samples <53 µg/kg.

However, lincomycin, which is included in the antibiotics group in this report but only known to be used for humans in Latvia, was detected in several sludge samples.

6.1.2.4 Mass balance of the APIs - influent, effluent, sludge

The distribution of each API between the influent, effluent and sludge was studied. The percentages are the median results of the calculations and therefore the masses are not balanced. Criteria for sample selection did not fully match the criteria in the wastewater treatment plant efficiency calculations, which may produce some inconsistencies in the results (Chapter 6.1.2.2). **Negative efficiency values** (Table 6.1) **were not** included in the **mass balance** calculations (Table 6.3) because mass balance could not be calculated if API's concentration was higher in effluent than in influent. Therefore, there are certain inconsistencies between the calculated efficiency and mass balance (Table 6.4) which needs to be considered when interpreting the results.

The following factors impact the accuracy of the results, i.e. are source of errors and uncertainties:

1) small number of measurements with usable results;
2) the annual load of the APIs relies on only a couple of measurements and the total annual amount of wastewater treated and discharged;
3) the influent, effluent and sludge were sampled at the same time, disregarding the water and sludge retention times at the plant;
4) Due to data availability and consistency, we had to use the annual wastewater flow rates and sludge production instead of the data of the sampling days.

The results of this estimation are summarized in table 6.3. Due to operating with different number of samples with different results, percentage values of distribution of APIs between various matrices (effluent, sludge and, presumably, desintegration or disappearance during the process of treatment of waste water) show only approximate trends, and therefore do not always sum up to exactly 100%.

Table 6.3. API distribution between effluent and sludge at the case study wastewater treatment plants. Only the API concentrations with effluent concentration less than influent concentration were included in the calculations.

API	API remaining in effluent, % from incoming load		API remaining in sludge, % from incoming load		API disappearing during the treatment process, % from incoming load*		Number of data points
	Average	Median	Average	Median	Average	Median	
Bisoprolol	61	67	2.6	1.3	40	34	18
Caffeine	23	17	2.6	0.11	79	87	17
Carbamazepine	64	72	3.7	2.0	32	24	17
Citalopram	61	60	24	16	32	32	18
Codeine	23	23	0.39	0.28	78	78	17
Diclofenac	76	83	2.5	0.82	23	16	22
Enalapril	38	35	0.065	0.045	62	65	5
Fluconazole	44	34	0.34	0.25	56	65	18
Gabapentin	28	20	0.038	0.002	74	84	16
Irbesartan	57	61	1.2	0.75	40	31	13
Ketoprofen	39	36	1.4	0.099	60	64	17
Levetiracetam	11	5.0	0.04	0.004	89	95	14
Lincomycin	-	-	0.35	0.38	-	-	5
Metformin	3	0.008	0.11	0.011	97	100	19
Metoprolol	3	2.6	3.0	1.4	94	96	6
Naproxen	7	43	0.12	0.059	93	96	18
Ofloxacin	36	24	0.87	0.12	70	74	13
Olanzapine	7.6	2.8	9.3	0.32	86	89	13
Oxazepam	59	66	5.7	4.0	34	29	16
Oxycodone	-	-	2.0	0.18	-	-	4
Primidone	91	91	0.31	0.16	6.9	6.9	6
Ramipril	81	81	0.28	0.25	19	19	4
Risperidone	2.6	2.6	0.10	0.052	99	99	10
Sertraline	9.3	5.3	62	61	39	34	14
Telmisartan	16	6.4	16.	7.6	76	87	14
Temazepam	68	61	11	7.7	27	26	15
Tramadol	84	89	2.9	0.84	22	9.8	20
Trimethoprim	58	58	0.51	0.022	41	38	18
Tylosin	45	44	-	-	-	-	5
Venlafaxine	76	81	3.8	2.8	22	16	19

*calculated as the sum of the API mass in effluent and sludge versus the API mass in influent.

The partitioning of APIs at WWTP as median rates (in %) from incoming load:
Bisoprolol mostly remained in the effluent (67%) and partly disappeared during treatment (34%). Only 1.3% concentrated in sludge. The mass balance results for sludge were consistent between the samples and WWTPs, but the effluent data were more dispersed. Results correspond well with the data from Magnér et al. (2016), where residual amount of bisoprolol was 77% in effluent and 1.4% in sludge. Results correspond also with Fick et al. (2011) and Äystö et al. (2020), where 61% and 68% of bisoprolol remained in effluent, respectively.
Caffeine disappeared during treatment, mostly more than 87%. A small proportion, typically lower than 17%, remained in the effluent, while concentration in sludge was negligible (0.11%). The amount concentrating in sludge was fairly similar at all WWTPs but partitioning in effluent varied a lot. The calculated removal rates were generally consistent with other research, such as Al Qarni et al. (2016), Luo et al. (2014) and Äystö et al. (2020), where the removal rates for caffeine were 89–100%, 50–100% and 100%, respectively.

Carbamazepine mostly remained in the effluent (72%) and 24% disappeared during treatment. A small amount ended up in sludge (2.0%). The accuracy of sludge results was good, but the effluent data were scattered. These results were in accordance with the removal rates obtained by most of the other studies (Radjenovic et al. 2007 (<10%), Miege et al. 2009 (9%), Miehe 2010 (9%), Tambosi et al. 2010 (0–20%), Al Qarni et al. 2016 (13–28%), Fick et al. 2011 (-3%), Äystö et al. 2020 (-7%)). Fernández-López et al. (2016) and Luo et al. (2014) obtained higher removal rates for carbamazepine in their research: 52% and up to 62%, respectively. The proportion of carbamazepine remaining in sludge was roughly in line with 0.94% obtained by Magnér et al. (2016).

Citalopram tended to remain in the effluent (60%) rather than disappeared during the treatment (32%). 16% accumulated in sludge. However, there was a lot of variation in the mass balance results. The median removal rate was in line with Fick et al. 2011 and Äystö et al. 2020 where the amount of citalopram remaining in effluent was 89% and 61%, respectively. Results differed from other research, where 31.8% remained in effluent and 8.6% in sludge (Magnér et al. 2016).

Codeine tended to disappear during the treatment (78%). 23% of codeine remained in effluent. Codeine did not concentrate in sludge (0.28%). The mass balance calculations were fairly consistent and did not vary much. The calculated removal efficiency was a little bit higher than in other studies, where removal efficiency was 42% (Kasprzyk-Hordern et al., 2009) or 68% (Fick et al., 2011).

Diclofenac remained strongly in the effluent (83%). 16% disappeared during treatment and concentration in sludge was negligible (0.82%). Partitioning in sludge was consistent and the proportion remaining in effluent was also fairly accurate. The results corresponded well with the 17% removal rate obtained by Äystö et al. (2020), 28% removal rate obtained by Fick et al. (2011), 32% removal rate obtained by Miege et al. (2009), and the very low partitioning into sludge (0.37%) obtained by Magnér et al. (2016). Higher removal rates have also been obtained in the literature (Fernández-López et al. 2016, Gros et al. 2010 and Luo et al. 2014, see Table 6.1).

Enalapril mostly disappeared during treatment (65% or more) rather than remaining in effluent (35% or less). Concentration in sludge was negligible (0.045%). However, there were very few data points to calculate the mass balance and the results varied, and we did not find any literature data to verify our results.

Fluconazole mostly disappeared during treatment (65%) while 34% remained in effluent. Concentration in sludge was negligible (0.25%). The removal rate in this study was higher than the 33% obtained by Fick et al. (2011). The difference is likely caused by the exclusion of the negative removal rates in the mass balance calculations and the high variation in the effluent/influent data (the removal efficiencies of this study are presented in Chapter 6.1.2.2).

Gabapentin mostly disappeared during treatment (84% or more) rather than remaining in effluent (20%). Very small amounts remained in sludge (0.002% or less). Despite the scattered results, the proportion remaining in the effluent was in line with the 84% removal rate obtained by Kasprzyk-Hordern et al. (2009).

Irbesartan partly remained in effluent (61% with a trend to be less), partly disappeared in the treatment (31% with a trend to be higher). Concentration in sludge was negligible (0.75%). There was a lot of variation in the effluent/influent data, and we did not find any literature reference.

Ketoprofen mostly disappeared during treatment (64% or more) and partly remained in effluent (36%). Concentration in sludge was negligible (0.099%). The amount concentrating in sludge corresponds with 0.014% obtained by Magnér et al. (2016). However, the residual amount of ketoprofen in effluent varied a lot in this study and in the literature, where it ranges from 0% to 97% (Table 6.1).

Levetiracetam dissapeared almost totally during treatment (95% or more). 5.0% or less remained in effluent and concentration in a sludge was negligible (0.004% or less). The data were very consistent and thus the mass balance results were considered reliable, although we did not find any literature data to verify our results.

Lincomycin concentrations were often higher in effluents than in influent (only one sample above LOQ) and it was detected only occasionally in the WWTP samples. Based on the available results more than 0.38% of lincomycin concentrated in sludge, but other values could not be calculated.

Lincomycin is used mainly in veterinary medicine and thus not assumed very relevant API at the WWTPs.

Metformin disappeared almost completely during the treatment (100%) and a negligible amount remained in effluent (0.008% and less) or sludge (0.011%). The calculated mass balance was very consistent and there was almost no dispersion between the WWTPs. These results matched well with Fick et al. 2011, where removal rate was >61%.

Metoprolol seemed to largely disappear during treatment (96% or more) while less than 2.6% remained in effluent, when the negative removal rates were excluded in the calculations (i.e. most data points of this study). In contrast, the average removal rates at the WWTPs, calculated in Chapter 6.1.2.2, were negative as shown in Table 6.1. Most of the removal rates presented in the literature were also a lot lower (3–56%, see table 6.1), but a higher rate has been reported (83% by Tambiosi et al. 2010). 1.4% of metoprolol partitioned in sludge, which is in agreement with the 1.3% reported by Magnér et al. (2016).

Naproxen mostly disappeared during treatment (96% or more) while only 4.3% or less remained in effluent. Concentration in sludge was negligible (0.059%). The mass balances did not vary much between the WWTPs, and the removal rate is in line with other studies (43–100%, Table 6.1).

Ofloxacin tended to disappear during treatment (74% or more). 24% or less remained in effluent. Concentration in sludge was negligible (0.12%). The removal rates varied a lot between different studies, ranging from -157% to 99% (Table 6.1). Consequently, the removal rates of this study were much higher than the 24% obtained by Radjenovic et al. (2007), up to 4% by Leung et al. (2012), and >7% by Fick et al. (2011), but they were accordance with 77% removal rate of Tambosi et al. (2010) and up to 99% of Gros et al. (2010).

Olanzapine largely disappeared during treatment (89%) and a small fraction remained in effluent (2.8%). Only 0.32% concentrated in sludge. The fraction remaining in effluent was within the range of Kosma et al. (2019), where the removal rate of olanzepine was 38–99%.

Oxazepam remained largely in effuent (66%) and 4.0% partitioned in sludge. 29% of the incoming oxazepam disappeared during treatment. The proportion remaining in effluent is affected by the exclusion of negative removal rates in the mass balance calculations, and the removal rates calculated in Chapter 6.1.2.2 range from -23% to 96% (Table 6.1). Fick et al. (2011) have also obtained a negative removal rate for oxazepam (-6%). Also, the retention in sludge was higher than the 0.87% reported by Magnér et al. (2016).

Oxycodone was not detected in any influent or effluent sample. However, the partitioning in sludge was estimated to be >0.18% based on the LOQ in the influent.

Primidone remained in the effluent (91%) and only 6.9% disappeared during treatment. 0.16% or less partitioned in sludge. The calculations were based on very few effluent results, but the sludge data were more comprehensive. We did not find any literature data on the fate of primidone at WWTPs.

Ramipril concentrations were often higher in effluent than in influent. Even if the negative removal was excluded in the mass balance calculations, the results indicated that ramipril passes through the treatment (81% remains in effluent while 19% disappeared during the treatment. Only a fraction, 0.25%, ended up in sludge. We did not find any literature data on the fate of ramipril at WWTP.

Risperidone was not detected in any influent sample and it was above LOQ in only one effluent, but it was detected in most sludge samples. When the influent and effluent LOQs were used for estimating the mass balance, the much higher value for influents than effluents resulted in <99% disappearance during the treatment and >2.6% remaining in effluent. At least 0.052% partitioned in sludge. The mass balance calculated by Magnér et al. (2016) was considered more reliable: 15% of risperidone partitioned in effluent and 0.47% in sludge.

Sertraline tended to remain in sludge (61%). Also, considerable amounts disappeared during the treatment (34%) and only a small part (5.3%) remained in the effluents. Accuracy of the effluent data were good, but the sludge data were quite dispersed. Results are consistent with Magnér et al. (2016), where 3.4% of sertraline partitioned in effluent and 15% in sludge. Kosma et al. (2019) and Fick et al. (2011) have reported over 70% removal rates for sertraline.

Telmisartan mainly disappeared during treatment (87%) and the remaining amount was distributed almost equally between sludge (7.6%) and effluent (6.4%). Except a couple of outlier samples, the overall accuracy of results was fair for both effluent and sludge. The removal rate was higher than reported previously (58% by Fick et al. 2011).
Temazepam mostly remained in effluent (61%). 26% of temazepam disappeared during the treatment, while 7.7% partitioned in sludge. The accuracy of the sludge results was good, but the effluent results were more dispersed.
Tramadol mainly remained in effluent (89%) and only 9.8% disappeared during the treatment. Concentration in sludge was negligible (0.84%). Good accuracy for sludge data, but effluent data were more dispersed. Fick et al. (2011) have reported even higher tendency to stay in effluent and a removal rate of -3%.
Trimethoprim partly remained in effluent (58%) and partly disappeared during the treatment (at least 38%). Concentration in sludge was negligible (0.022% and less). Data accuracy for sludge was good, while the effluent results were highly dispersed. The literature presents very varying removal rates for trimethoprim. The share of trimethoprim remaining in effluent is rather well in line with some of the reported removal rates (Fick et al., 2011; Leung et al., 2012; Luo et al., 2014). However, some studies present significantly lower removal rates for trimethoprim: 16% by Miege et al. (2009), and 6% by Äystö et al. (2020).
Tylosin was not detected in any influent or sludge sample but was detected in several effluents, and thus the partitioning calculations are highly uncertain. Based on the LOQ in influent, 44% of tylosin would have remained in effluent.
Venlafaxine mainly remained in effluent (81%) while 16% disappeared during the treatment. 2.8% concentrated in sludge. The sludge results were fairly accurate, but the effluent results were dispersed. The percentage of venlafaxine remaining in effluent was similar to Fick et al. (2011), where 21% removal rate was reported.

To summarize, APIs tending to **remain in the effluent** (≥50% from the incoming load) are:

- Primidone
- Tramadol
- Ramipril
- Diclofenac
- Venlafaxine
- Temazepam
- Carbamazepine
- Bisoprolol
- Citalopram
- Oxazepam
- Trimethoprim
- Irbesartan

APIs tending to concentrate in **sewage sludge** were sertraline, citalopram, telmisartan and temazepam. APIs which **disappear during the treatment process**, probably due to decomposition or transformation into another compounds are risperidone, metformin, metoprolol and naproxen. More than 50% disappearance was also observed for levetiracetam, olanzapine, caffeine, codeine, telmisartan, gabapentin, ofloxacin, enalapril, ketoprofen and fluconazole (Table 6.3).

The calculated balances are summarized as graphs in Annex 9. The results are also compiled in Table 6.4 and compared with WWTP efficiency (effluent vs. influent, table 6.1). The removal rates obtained with balance and efficiency calculations are summarized in table 6.4. The second column of table 6.4 shows the value of API remaining in effluent, average % from incoming load (value from table 6.3). In the third column there are the adjusted efficiency values (from table 6.1.), but taking out negative efficiency values, where concentrations in effluent were higher than in influent. After comparing these two values, it can be concluded that the values in columns 2 and 3 (API

remaining in effluent) match well, with up to 23% difference. The fourth column presents the removal rate (effluent vs. influent) based on balance calculations (calculated from column 3). The efficiencies from Table 6.1 were added for comparison in column 5. The APIs for which the calculated removal rates differed significantly are highlighted with grey background: carbamazepine, diclofenac, irbesartan, metoprolol, ramipril and telmisartan. The differences in balance and removal rate results were caused by the different input data, as described in section 6.1.1.

Table 6.4. Comparison of the average API amount remaining in effluent estimated with balance-based calculations and efficiency-based calculations.

API	API remaining in effluent, % from incoming load	API remaining in effluent, average %, recalculated from Table 6.1 and Annex 7.*	Average rate of API removal (staying in sludge or being decomposited), recalculated from Table 6.1 and Annex 7.*	Average efficiency in Table 6.1, calculated from influent and effluent data**
Bisoprolol	61	61	39	15
Caffeine	23	10	90	91
Carbamazepine	64	58	42	-9
Citalopram	61	64	36	25
Codeine	23	20	80	80
Diclofenac	76	79	21	-16
Enalapril	38	-	-	-
Fluconazole	44	51	49	22
Gabapentin	28	30	70	69
Irbesartan	57	47	53	-3
Ketoprofen	39	36	64	60
Levetiracetam	11	8	92	92
Lincomycin	-	-	-	-
Metformin	3	0.7	99	99
Metoprolol	3	-	-	-225
Naproxen	7	10	90	89
Ofloxacin	36	13	87	87
Olanzapine	7.6	8	92	91
Oxazepam	59	73	27	19
Oxycodone	-	-	-	-
Primidone	91	-	-	-18
Ramipril	81	78	22	-31
Risperidone	2.6	-	-	-
Sertraline	9.3	13	87	85
Telmisartan	16	30	70	-41
Temazepam	68	72	28	8
Tramadol	84	80	20	5
Trimethoprim	58	62	38	37
Tylosin	45	-	-	-
Venlafaxine	76	76	24	12

- Values cannot be calculated

* Amount of API that remains in effluent (recalculations from efficiency data based on influent and effluent data, but taking out negative efficiency values to go together with balance methodology)

** Including all the samples corresponding to criteria described in chapter 6.1.1.

Very different average removal rates (positive vs. negative) depending on calculation method: balance calculations include only effluent concentrations that were smaller than the respective influent concentrations, while the efficiency values include also effluent concentrations higher than influent concentrations.

6.1.3 Conclusions

Influent

The APIs that were detected in at least 90% of the **influent** samples were caffeine, codeine, diclofenac, fluconazole, gabapentin, hydrochlorothiazide, ketoprofen, levetiracetam, mesalazine, metformin, naproxen, oxazepam, paracetamol, sulfamethoxazole, trimethoprim, valsartan and venlafaxine. Paracetamol was the most abundant API in influents. The three highest paracetamol concentrations were 1000 µg/L in Linköping and Norrköping (SE) and 980 µg/L in Kalteva (FI). Altogether 59 out of 75 APIs, representing all 12 studied API groups, were detected in the influents.

Six APIs were found in all influent samples: diclofenac, gabapentin, ketoprofen, metformin, naproxen and trimethoprim. The following APIs were not detected in the influents, because of relatively high LOQs or as they are used in veterinary medicine: ciprofloxacin, esomeprazole, sulfadiazine, candesartan, cetirizine, fexofenadine, mometasone furoate, pantoprazole, atorvastatin, oxycodone, risperidone, emamectin, florfenicol, tiamulin, toltrazuril and tylosin.

Effluent

Fifteen APIs were detected in at least 90% of the **effluent** samples: carbamazepine, citalopram, clarithromycin, diclofenac, erythromycin, fluconazole, hydrochlorothiazide, ketoprofen, metoprolol, naproxen, oxazepam, sotalol, tramadol, trimethoprim and venlafaxine. The APIs with the highest detected concentrations were ibuprofen (44 µg/L WWTP 2, LV), diclofenac (38 µg/L Paide, EE) and caffeine (32 µg/L WWTP 3, LV).

60 out of 75 analysed APIs were detected in effluents, representing all 12 studied API groups. Three APIs were found in all effluent samples: diclofenac, metoprolol and oxazepam. The following APIs were not detected in any effluent sample, mainly due to relatively high LOQ: ciprofloxacin, esomeprazole, sulfadiazine, amlodipine, enalapril, fluticasone, mometasone furoate, pantoprazole, estriol, gemfibrozil, oxycodone and quetiapine. Also, the veterinary medicines florfenicol, tiamulin and toltrazuril were not detected in any WWTP effluent.

Sludge

The APIs that were detected in at least 90% of the **sludge** samples were carbamazepine, irbesartan, venlafaxine, metformin, diclofenac, tramadol, caffeine, bisoprolol, metoprolol, citalopram, oxazepam, sertraline and temazepam. The APIs with the highest detected concentrations were telmisartan, with maximum concentrations of 8700 µg/kg d.w. in Paide (EE) and 7100 µg/kg d.w. in Pärnu (EE), and ofloxacin, up to 8600 µg/kg d.w. in Kalteva (FI). 29 out of 31 analysed APIs were detected in sludge, representing all the nine studied API groups.

Eight APIs were found in all sludge samples: diclofenac, carbamazepine, venlafaxine, metformin, caffeine, metoprolol, citalopram and sertraline. The most often detected groups were metabolic disease medications (detected.e. metformin, DF 100%), other cardiovascular medications (average DF 96%) and caffeine (DF 100%). Ramipril and tylosin were not above LOQ in any sludge sample.

Removal efficiency – influent and effluent data

Three APIs had negative efficiency values in all WWTPs: metoprolol, primidone and ramipril. The PNEC values of these APIs are relatively high and were not exceeded in the surface waters of CWPharma case studies. 28 APIs, 56% of the APIs we calculated the WWTP efficiencies, had positive efficiency values in all WWTPs. Only nine out of 50 APIs had negative or zero average efficiency rate: carbamazepine, diclofenac, hydrochlorthiazide, irbesartan, metoprolol, sotalol, telmisartan, primidone and ramipril. Out of these nine APIs, only diclofenac exceeded the PNEC in the surface waters of the CWPharma case studies. The average efficiency varied between several WWTPs for 19 APIs – it was either positive or negative and there was no clear coherence between treatment efficiency and wastewater treatment technology.

Balance of APIs - influent, effluent, sludge data

While all the effluent concentrations that were higher than the respective influent concentrations were excluded from the balance calculations, out of 30 APIs included in the balance calculations, 14 APIs were lost by more than 50% during the treatment (probably decomposed or transformed into different compounds). 12 APIs tended to remain in the effluent. Only one API (setraline) concentrated in sludge, while only a small or negligible percentage of other APIs concentrated in sludge. For three APIs (lincomycin, oxycodone and tylosin) there were not enough data to calculate the balance, because their concentrations were below LOQ in most samples.

The calculated partitioning of APIs at WWTPs was at least partially consistent with the literature. Our results for bisoprolol, caffeine, risperidone, sertraline, gabapentin, metformin and venlafaxine were well in line with the findings in other studies. Also, our results for citalopram, carbamazepine, ketoprofen (consistent rate of API concentrated in sludge, but not in effluent), metoprolol (results in different research are controversial), codeine, naproxen, olanzapine, sertraline and trimethoprim are mostly consistent with the literature. However, our results for citalopram (regarding rate in effluent), ketoprofen (regarding rate in effluent), oxazepam (sludge only), diclofenac, fluconazole, ofloxacin and telmisartan were controversial to the results of other research. The differences can be at least partly explained by the high dispersion of the API concentrations in effluents and sludge, and the low number of samples per WWTP in our study. In fact, only a few APIs had relatively consistent concentrations in both effluent and sludge: levetiracetam, metformin, metoprolol, naproxen, olanzapine, primidone and risperidone. Also, several factors cause uncertainty for the presented WWTP removal and balance results. First and foremost, the annual load of the APIs relies on only a couple of measurements per WWTP and the total annual amount of treated and discharged wastewater and produced sludge.

6.2 Concentrations of APIs at landfill WWTP

6.2.1 Method

Landfill samples were collected at the Metsä-Tuomela waste treatment plant in Finland three times during 2018: in March, June and November. The plant receives and treats municipal waste from the Riihimäki town with approx. 28 000 inhabitants. The plant also receives and stores recyclable and hazardous materials and processes end of life vehicles and contaminated soils. The area of the landfill site is 5.5 ha. The waste treatment plant has its own WWTP which treats leachates from the landfill area. The treatment method used in the WWTP is a biological nitrogen removal process. Also, the runoff waters from a nearby composting field are conducted to the WWTP. The composted material includes sewage sludge collected from municipal WWTPs. The WWTP treats approximately 25 000 m^3 of wastewater per year (ca. 70 m^3/d). Treated wastewater is released into a nearby ditch.

Nowadays, pharmaceutical waste is not disposed of to the landfill. It is possible that pharmaceutical wastes have been put in the landfill in the past, but there is no information about this. Probably at least some pharmaceuticals have ended up in landfills among the municipal waste. However, the runoff from the composting field may be a more potent source of pharmaceuticals to the WWTP than the landfill leachates. Wastewater samples were collected at the WWTP from both untreated and treated wastewater. Influent samples were taken as grab samples. Effluent samples were taken as 24-hour composite samples to a big plastic container and transferred to smaller plastic bottles. Samples were kept cold during transportation to SYKE laboratory and stored frozen at the laboratory.

6.2.2 Results and discussion

The following overview describes the API concentrations in the landfill WWTP influent and effluent. The concentrations of the APIs that were detected in at least one influent or effluent sample are presented in figures. All raw data are presented in Annex 10.

Antiepileptics

Influent

All four analyzed antiepilectic APIs were detected in the landfill WWTP influent: carbamazepine, gabapentin, levetiracetam and primidone (figure 6.23). Three of them - carbamazepine, gabapentin and levetiracetam - were detected in all influent samples.

The highest observed concentrations were:

- Carbamazepine – 0.25 µg/L (in March 2018);
- Gabapentin – 7.0 µg/L (in June 2018);
- Levetiracetam – 1.0 µg/L (in March 2018);
- Primidone – 0.081 µg/L (in June 2018).

Effluent

Two out of four measured antiepilectics, carbamazepine and primidone, were detected in all landfill WWTP effluent samples. Gabapentin and levetiracetam were not detected.

The highest observed concentrations were:

- Carbamazepine – 0.22 µg/L (in June 2018);
- Gabapentin – not detected, all samples <0.91 µg/L;
- Levetiracetam – not detected, all samples <0.11 µg/L;
- Primidone – 0.073 µg/L (in June 2018).

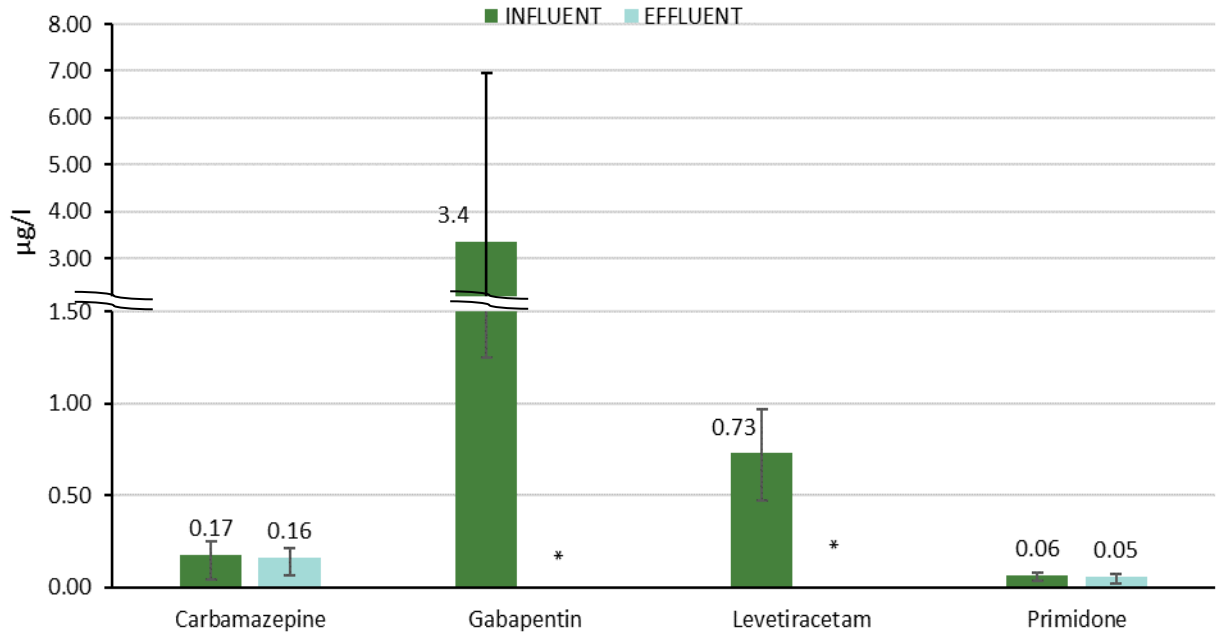

Figure 6.23. Average concentrations of antiepileptics in landfill WWTP influents and effluents. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Antibiotics

Influent

Only two out of eleven studied antibiotics were detected in landfill WWTP influent: erythromycin and fluconazole (figure 6.24). Fluconazole was detected in all three samples and erythromycin in one sample.

The highest observed concentrations were:

- Ciprofloxacin – not detected, all samples <3.1 µg/L;
- Clarithromycin – not detected, all samples <0.031 µg/L;
- Erythromycin – 2.5 µg/L (in March 2018);
- Fluconazole – 0.077 µg/L (in June 2018);
- Lincomycin – not detected, all samples <0.018 µg/L;
- Norfloxacin – not detected, all samples <12 µg/L;
- Ofloxacin – not detected, all samples <0.42 µg/L;
- Sulfadiazine – not detected, all samples <0.59 µg/L;
- Sulfamethoxazole – not detected, all samples <0.042 µg/L;
- Tetracycline+doxycycline (SUM) – not detected, all samples <0.24 µg/L;
- Trimethoprim – not detected, all samples <0.022 µg/L.

Effluent

Only three out of eleven studied antibiotics were detected in landfill WWTP effluent: erythromycin, fluconazole and lincomycin. Fluconazole was detected in all three samples. Erythromycin was detected in two out of three samples and lincomycin in one sample.

The highest observed concentrations were:

- Ciprofloxacin – not detected, all samples <1.6 µg/L;
- Clarithromycin – not detected, all samples <0.016 µg/L;
- Erythromycin – 1.8 µg/L (in March 2018);
- Fluconazole –0.029 µg/L (in June 2018);
- Lincomycin – 0.013 µg/L (in March 2018);
- Norfloxacin – not detected, all samples <1.2 µg/L;
- Ofloxacin – not detected, all samples <0.21 µg/L;
- Sulfadiazine – not detected, all samples <0.3 µg/L;

- Sulfamethoxazole – not detected, all samples <0.009 µg/L;
- Tetracycline+doxycycline (SUM) – not detected, all samples <0.12 µg/L;
- Trimethoprim – not detected, all samples <0.011 µg/L.

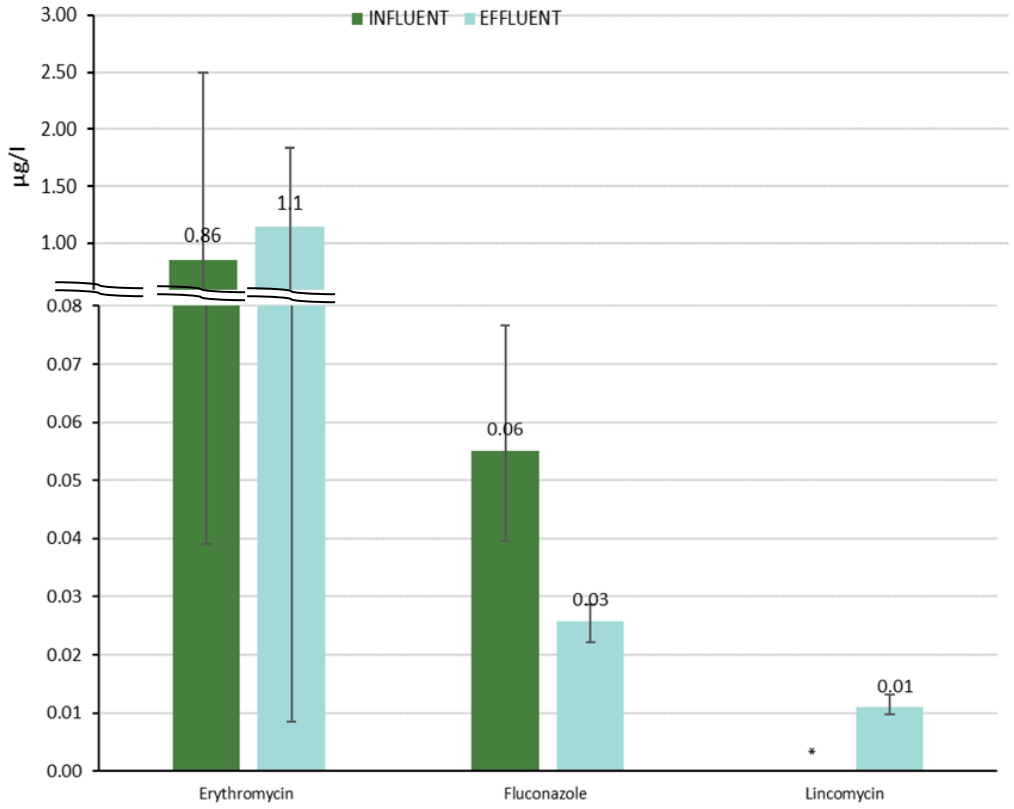

Figure 6.24. Average concentrations of antibiotics at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Antihypertensives

Influent

Three out of ten antihypertensives were detected in landfill WWTP influent: eprosartan, hydrochlorothiazide and telmisartan (figure 6.25). Erposartan and hydrochlorothiazide were detected in two out of three samples, and telmisartan in one sample.

The highest observed concentrations were:

- Amlodipine – not detected, all samples <0.40 µg/L;
- Candesartan – not detected, all samples <0.77 µg/L;
- Enalapril – not detected, all samples <0.17 µg/L;
- Eprosartan – 0.030 µg/L (in June 2018);
- Hydrochlorothiazide – 79 µg/L (in June 2018);
- Irbesartan – not detected, all samples <0.053 µg/L;
- Losartan – not detected, all samples <0.51 µg/L;
- Ramipril – not detected, all samples <0.032 µg/L;
- Telmisartan – 0.077 µg/L (in June 2018);
- Valsartan - not detected, all samples <0.30 µg/L.

Effluent
Only one out of ten studied antihypertensives was detected in landfill effluent: hydrochlorothiazide. It was detected in two out of three samples.
The highest observed concentrations were:

- Amlodipine – not detected, all samples <0.11 µg/L;
- Candesartan - not detected, all samples <0.011 µg/L;
- Enalapril - not detected, all samples <0.083 µg/L;
- Eprosartan – not detected, all samples <0.005 µg/L;
- Hydrochlorothiazide –4.4 µg/L (in March 2018);
- Irbesartan – not detected, all samples <0.070 µg/L;
- Losartan – not detected, all samples <0.25 µg/L;
- Ramipril – not detected, all samples <0.016 µg/L;
- Telmisartan – not detected, all samples <0.011 µg/L;
- Valsartan – not detected, all samples <0.15 µg/L.

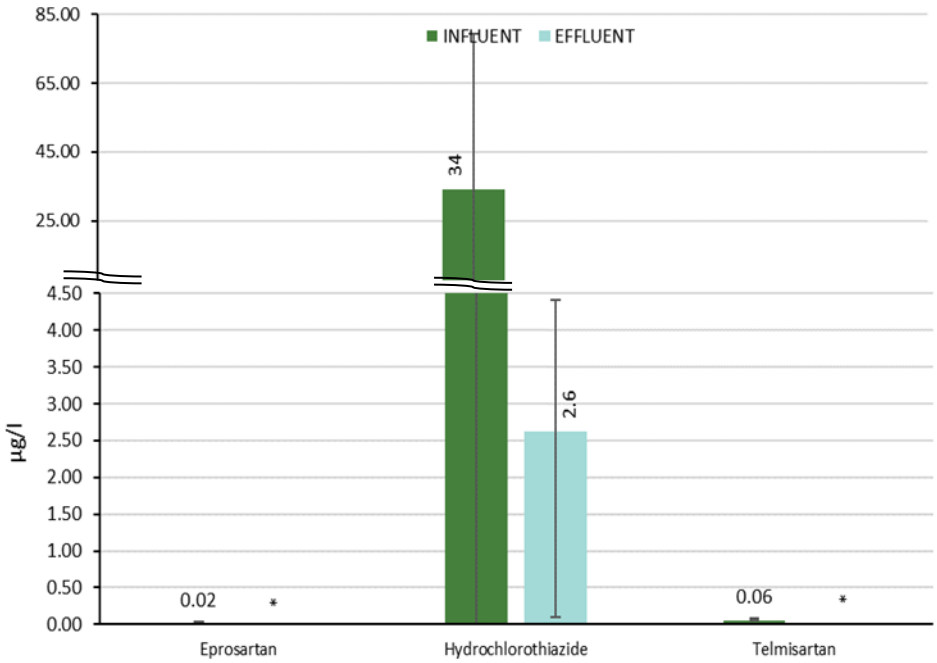

Figure 6.25. Average concentrations of antihypertensives in landfill WWTP influents and effluents. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Asthma and allergy medications

Influent
None of the five studied asthma and allergy APIs were detected in landfill WWTP influent:

- Cetirizine – not detected, all samples <3.2 µg/L;
- Fexofenadine – not detected, all samples <4.3 µg/L;
- Fluticasone – not detected, all samples <0.42 µg/L;
- Mometasone furoate – not detected, all samples <0.83 µg/L;
- Xylometazoline – not detected, all samples <0.051 µg/L.

Effluent
The five asthma and allergy APIs were not detected in landfill WWTP effluent:

- Cetirizine – not detected, all samples <1.2 µg/L;
- Fexofenadine – not detected, all samples <1.6 µg/L;
- Fluticasone – not detected, all samples <0.15 µg/L;
- Mometasone furoate – not detected, all samples <0.027 µg/L;
- Xylometazoline – not detected, all samples <0.026 µg/L.

Gastrointestinal disease medications

Influent

One of the three measured APIs, mesalazine, was detected in two out of three landfill WWTP influent samples (figure 6.26.).

The highest observed concertations were:

- Mesalazine – 3.3 µg/L (in June 2018);
- Omeprazole+esomeprazole (SUM) – not detected, all samples <8.4 µg/L;
- Pantoprazole – not detected, all samples <0.76 µg/L.

Effluent

Mesalazine was the only gastrointestinal disease medicine detected in landfill effluent. It was detected in two out of three samples.

The highest observed concetrations were:

- Mesalazine – 0.95 µg/L (in March 2018);
- Omeprazole+esomeprazole (SUM) – not detected, all samples < 8.4 µg/L;
- Pantoprazole – not detected, all samples <0.76 µg/L.

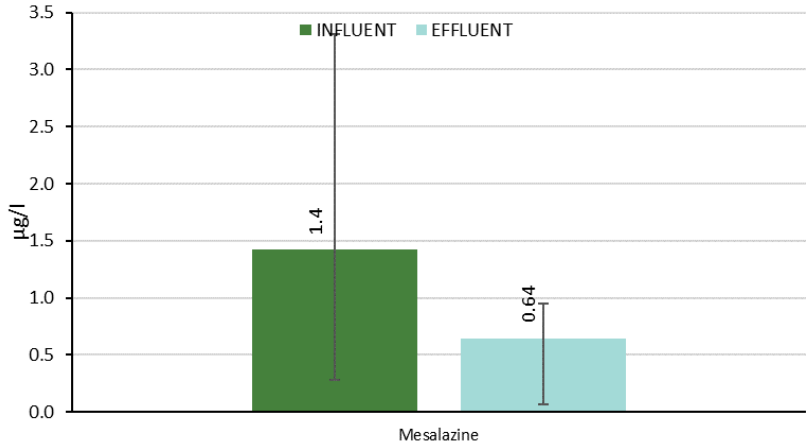

Figure 6.26. Average concentrations gastrointestinal disease medications group APIs at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Hormones

Influent

Two out of the five measured hormones were detected in landfill WWTP influent: estriol and estrone (figure 6.27). Both were detected in only one sample.

The highest observed concentrations were:

- Estriol – 0.084 µg/L (in March 2018);
- Estrone – 0.057 µg/L (in March 2018)
- Norethisterone – not detected, all samples <0.024 µg/L;
- Progesterone – not detected, all samples <0.031 µg/L;
- Testosterone – not detected, all samples <0.081 µg/L.

Effluent

Out of five measured hormones, only estrone was detected in one landfill WWTP effluent sample.

The highest observed concentrations were:

- Estriol – not detected, all samples <8.4 µg/L;
- Estrone – 0.65 µg/L (in November 2018);
- Norethisterone – not detected, all samples <0.010 µg/L;
- Progesterone – not detected, all samples <0.012 µg/L;
- Testosterone – not detected, all samples <0.018 µg/L.

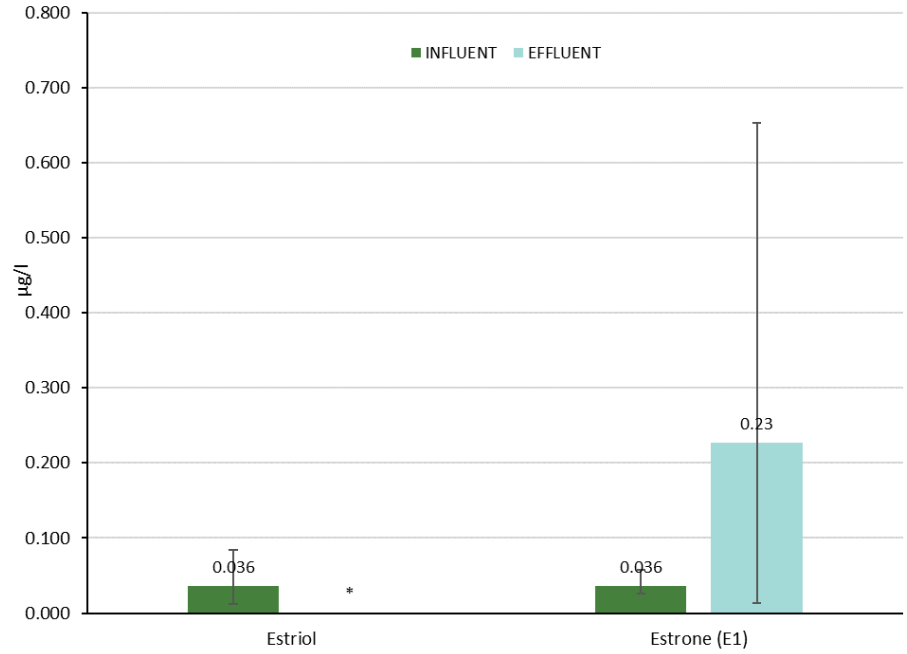

Figure 6.27. Average concentrations of hormones at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Metabolic disease medications

Influent

Two out of six measured metabolic disease medications were detected in landfill WWTP influent: gemfibrozil and metformin (figure 6.28). Both were detected in two out of three samples.

The highest observed concentrations were:

- Allopurinol – not detected, all samples <14 µg/L;
- Atorvastatin – not detected, all samples <10 µg/L;
- Bezafibrate – not detected, all samples <27 µg/L;
- Gemfibrozil – 0.35 µg/L (in June 2018);
- Merformin – 2.6 µg/L (in June 2018)
- Simvastatin – not detected, all samples <0.001 µg/L.

Effluent

The metabolic disease medications were not detected in landfill WWTP effluent:

- Allopurinol – not detected, all samples <0.12 µg/L;
- Atorvastatin – not detected, all samples <10 µg/L;
- Bezafibrate – not detected, all samples <0.013 µg/L;
- Gemfibrozil – not detected, all samples <0.10 µg/L;
- Merformin – not detected, all samples <0.008 µg/L;
- Simvastatin – not detected, all samples <0.002 µg/L.

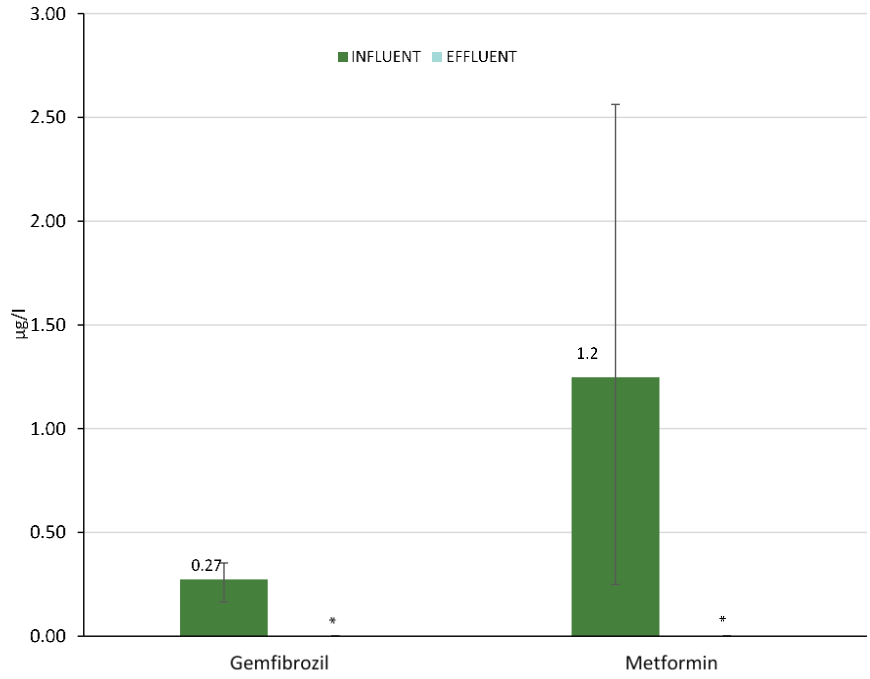

Figure 6.28. Average concentrations of API of metabolic disease medications group in landfill WWTP influents and effluents. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

NSAIDs and analgesics

Influent

Five out of seven APIs of the NSAIDs and analgesics group were detected in landfill WWTP influent: diclofenac, ketoprofen, naproxen, paracetamol and tramadol (figure 6.29). Three of them were detected in all three samples: diclofenac, ketoprofen and naproxen. Codeine and oxycodone were below LOQ in all samples.

The highest observed concentrations were:

- Codeine – not detected, all samples <0.042 µg/L;
- Diclofenac –0.30 µg/L (in November 2018);
- Ketoprofen – 1.7 µg/L (in March 2018);
- Naproxen – 0.23 µg/L (in June 2018);
- Oxycodone – not detected, all samples <0.26 µg/L;
- Paracetamol – 74 µg/L (in June 2018);
- Tramadol – 0.084 µg/L (in June 2018).

Effluent

Four out of seven analysed NSAIDs and analgesics were detected in landfill WWTP effluent: diclofenac, ketoprofen, naproxen and tramadol. Diclofenac was detected in all samples, while codeine, oxycodone and paracetamol remained below LOQ.

The highest observed concentrations were:

- Codeine – not detected, all samples <0.011 µg/L;
- Diclofenac – 0.41 µg/L (in March 2018);
- Ketoprofen – 0.013 µg/L (in March 2018);
- Naproxen – 0.016 µg/L (in November 2018);
- Oxycodone – not detected, all samples <0.12 µg/L;
- Paracetamol – not detected, all samples < 0.077 µg/L;
- Tramadol – 0.071 µg/L (in March 2018).

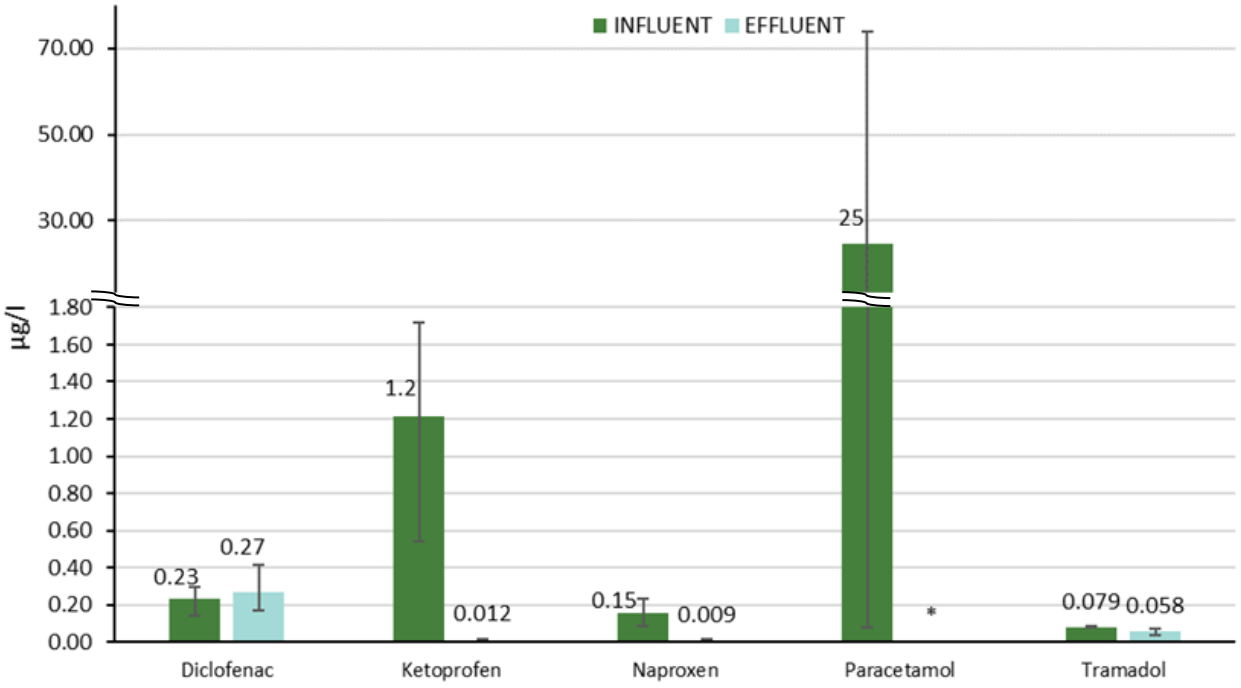

Figure 6.29. Average concentrations of NSAIDs and analgesics at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Caffeine

Influent

Caffeine was detected in one influent sample in March 2018 and the concentration was 0.021 µg/L.

Effluent

Caffeine was detected in one effluent sample with a concentration of 8.8 µg/L (June 2018).

Other cardiovascular medicines

Influent

Four out of seven APIs of the other cardiovascular medicines group were detected in landfill influent: dipyridamole, metoprolol, nebivolol and warfarin (figure 6.30). Nebivolol was detected in all samples, metoprolol on two samples and dipyridamole and warfarin in one sample. The highest observed concentrations were:

- Atenolol – not detected, all samples <0.21 µg/L;
- Bisoprolol – not detected, all samples <0.030 µg/L;
- Dipyridamole – 0.57 µg/L (in March 2018);
- Metoprolol – 0.029 µg/L (in March 2018);
- Nebivolol – 1.4 µg/L (in March 2018);
- Sotalol – not detected, all samples <0.015 µg/L;
- Warfarin – 0.023 µg/L (in March 2018).

Effluent

Two out of seven APIs were detected in landfill WWTP effluent: bisoprolol and metoprolol. Both were detected in only one sample. The highest observed concentrations were:

- Atenolol – not detected, all samples <0.11µg/L;
- Bisoprolol – 0.031 µg/L (in November 2018);
- Dipyridamole – not detected, all samples <0.087 µg/L;

- Metoprolol – 0.043 µg/L (in March 2018);
- Nebivolol – not detected, all samples <0.016 µg/L;
- Sotalol – not detected, all samples <0.008 µg/L;
- Warfarin – not detected, all samples <0.006 µg/L.

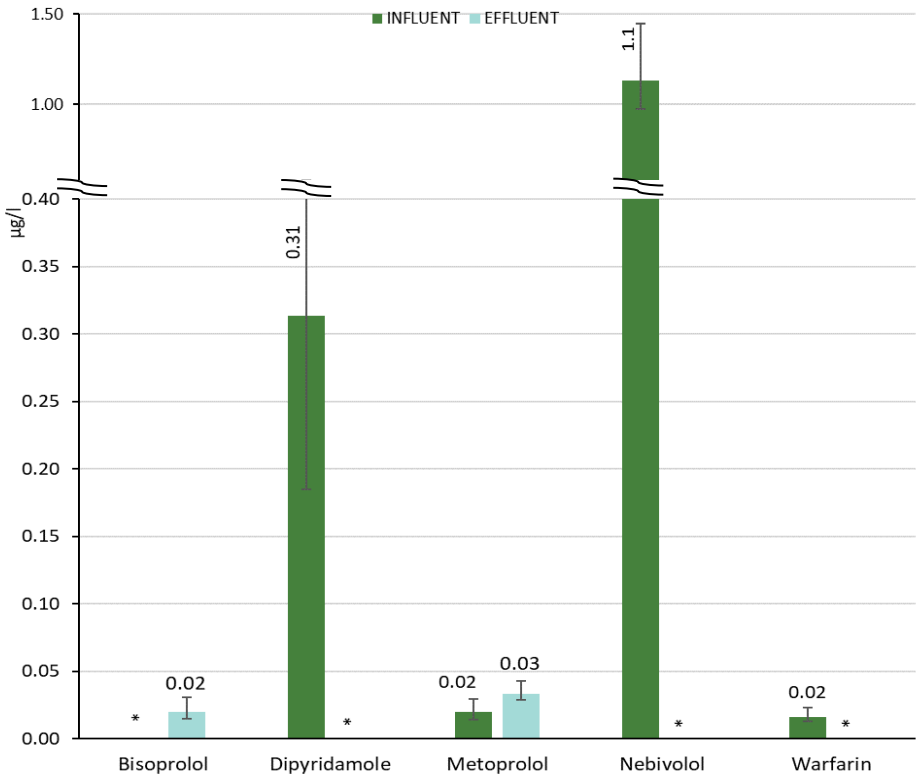

Figure 6.30. Average concentrations of the API of other cardiovascular medicines group in landfill WWTP influents and effluents. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Psychopharmaceuticals

Influents

Two out of eight psychopharmaceuticals were detected in landfill influents: citalopram and olanzapine (figure 6.32.). Citalopram was detected in two out of three samples, and olanzepine in one sample.

The highest observed concentrations were:

- Citalopram – 0.009 µg/L (in June 2018);
- Olanzapine – 2.1 µg/L (in June 2018);
- Oxazepam – not detected, all samples <0.023 µg/L;
- Quetiapine – not detected, all samples <0.47 µg/L;
- Risperidone – not detected, all samples <0.80 µg/L;
- Sertraline – not detected, all samples <0.020 µg/L;
- Temazepam – not detected, all samples <0.017 µg/L;
- Venlafaxine – not detected, all samples <0.020 µg/L.

Effluents

Four out of eight psychopharmaceuticals were detected in landfill WWTP effluent: citalopram, olanzapine, oxazepam and venlafaxine (figure 6.32). Citalopram, olanzepine were detected in two samples, and oxazepam and venlafaxine in one sample.

The highest observed concentrations were:

- Citalopram – 0.004 µg/L (in June 2018);

- Olanzapine – 0.015 µg/L (in June 2018);
- Oxazepam – 0.004 µg/L (in March 2018);
- Quetiapine – not detected, all samples <0.12 µg/L;
- Risperidone – not detected, all samples <0.010 µg/L;
- Sertraline – not detected, all samples <0.010 µg/L;
- Temazepam – not detected, all samples <0.008 µg/L;
- Venlafaxine – 0.007 µg/L (in June 2018).

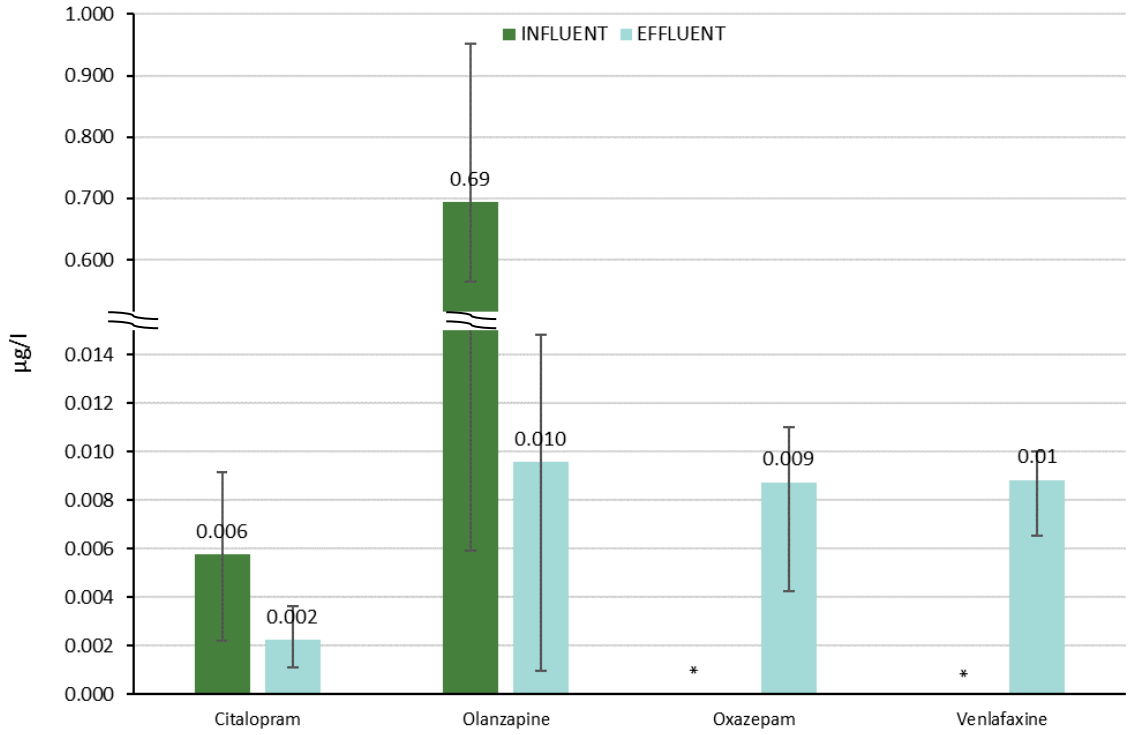

Figure 6.32. Average concentrations of psychopharmaceuticals at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

Veterinary medicines

Influents

None of the eight studied veterinary APIs was detected in landfill WWTP influent:

- Carprofen – not detected, all samples <0.014 µg/L;
- Emamectin – not detected, all samples <0.029 µg/L;
- Fenbendazole – not detected, all samples <0.036 µg/L;
- Florfenicol – not detected, all samples <0.064 µg/L;
- Tiamulin – not detected, all samples <0.038 µg/L;
- Toltrazuril – not detected, all samples <0.009 µg/L;
- Tylosin – not detected, all samples <0.32 µg/L.

Effluents

Two out of eight veterinary APIs were detected in landfill WWTP effluent: carprofen and emamectin (figure 6.33). Both were detected in one sample.

The highest observed concentrations were:

- Carprofen – 0.093 µg/L (in November 2018);
- Emamectin – 0.017 µg/L (in June 2018);
- Fenbendazole – not detected, all samples <0.011 µg/L;
- Florfenicol – not detected, all samples <0.032 µg/L;
- Tiamulin – not detected, all samples <0.019 µg/L;

- Toltrazuril – not detected, all samples <9.0 µg/L;
- Tylosin – not detected, all samples <0.10 µg/L.

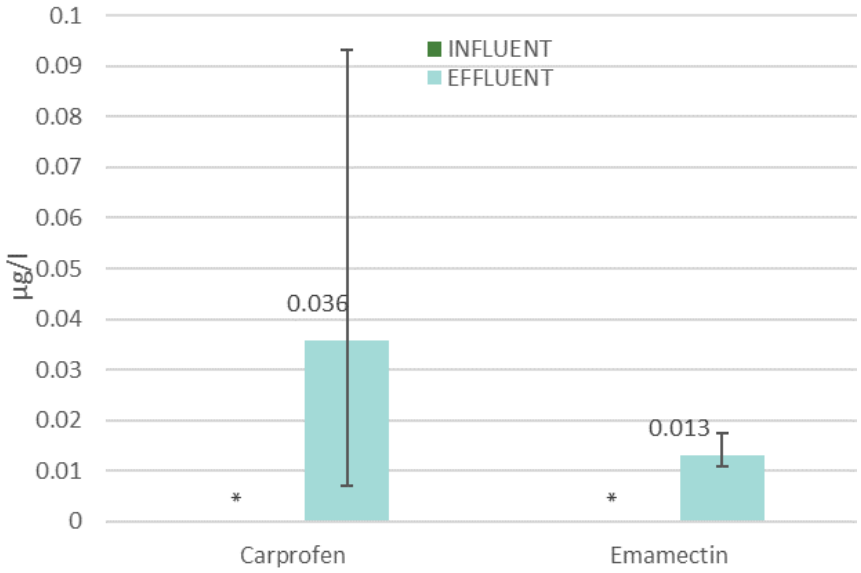

Figure 6.33. Average concentrations of veterinary APIs at landfill WWTP. Error bars represent the concentration range (LOQ–maximum value) detected in the samples. * - all samples <LOQ.

6.2.3 Conclusions

APIs that were detected in all three samples in landfill WWTP **influent** were fluconazole, carbamazepine, gabapentin, levetiracetam, diclofenac, ketoprofen and naproxen. The most abundant APIs in landfill WWTP influent were hydrochlorothiazide (up to 79 µg/L), paracetamol (up to 74 µg/L) and gabapentin (up to 7.0 µg/L) and their maximum concentrations were detected in June 2018. Altogether 26 out of 74 analysed APIs were detected in at least one influent sample, representing ten API groups. Only asthma and allergy and veterinary APIs were not detected. APIs that were found in all **effluent** samples were diclofenac, carbamazepine, fluconazole and primidone.

The highest detected concentrations in landfill WWTP effluent were for caffeine (8.8 µg/L in June 2018), hydrochlorothiazide (4.4 µg/L in March 2018) and erythromycin (1.8 µg/L in March 2018). 21 out of 74 analysed APIs were detected in at least one effluent sample, representing ten out of twelve API groups. Only APIs of asthma and allergy medications and metabolic disease medications were not detected.

The concentrations of certain APIs in landfill WWTP influent and effluent were rather high. However, the total API load from the landfill WWTP was low compared to municipal WWTPs in the Vantaanjoki case study area, because the flow rate at the landfill WWTP was only 24 000 m^3/a, corresponding a water volume produced by approximately 300 persons. Because we only studied the API emissions at one landfill WWTP, further studies are needed to assess the relevance of landfills as a source of APIs.

6.3 Concentrations of APIs in wastewaters from hospitals

6.3.1 Methods

General

Effluents from hospitals were collected in Linköping (SE), Norrköping (SE), Pärnu (EST) and Wismar (DE). Time proportional 24-h sampling was performed using automatic samplers. The composite samples were frozen in -20 °C after sampling and sent to SYKE for chemical analyses of 57–74 APIs. Sampling dates and raw data are presented in µg/L (Annex 11) and g/day (Annex 12). The water flow (m^3/day) was recorded at both the hospitals and the connected WWTPs. The load of APIs (g/day) originating from the hospitals was compared to the load of APIs in the connected WWTP influents. No manufacturing facilities were connected to the WWTPs in Linköping, Norrköping, Pärnu and Wismar. Therefore, the API load to the WWTPs from other sources than hospitals and households was expected to be negligible.

Sweden

The composite samples from the hospitals in Linköping and Norrköping consisted of individual samples (40 mL and 72 mL, respectively) sampled every 10 minutes during 24 h. The total water flows of the hospital effluents were 577 m^3/day in Norrköping hospital and 195 m^3/day in Linköping hospital on the sampling days. The water flow was 40 043 m³/day at Linköping WWTP (June 15, 2018) and 38 650 m³/day at Norrköping WWTP (June 7, 2018). The University Hospital in Linköping has 6 150 employees and about 600 care places. The hospital in Norrköping has 2 402 employees and about 300 care places. During 2019, the hospital in Linköping received 342 956 patient visits, and the hospital in Norrköping received 160 137 patient visits.

Estonia

The composite samples from Pärnu hospital consisted of individual samples (50 mL, sampled every 15 minutes for 24 hours). The total daily (24 h) water flows of the effluents of Pärnu hospital were estimated as approx. 83 m³/day, based on the water consumption of about 2000–3000 m^3/month. The volume of the influent to Pärnu WWTP was 39 375 m³/day in December 2017 and 10 759 m³/day in June 2018. The hospital in Pärnu has about 1300 employees and receives 15000 patient visits each year.

Germany

The composite samples from Wismar hospital consisted of individual samples (60 mL sampled every 30 minutes for 24 hours). The total daily (24 h) water flows of the effluents of Wismar hospital were 84.6 m³ in February and 75.2 m³ in June. The influent flow to Wismar WWTP was 9 902 m³/day in February 2018 and 10 297 m³/day in June 2018. The Wismar hospital has about 960 employees and treats around 40 000 patients per year.

6.3.2 Results and discussion

6.3.2.1 Concentrations of APIs in hospital effluents

Effluents from hospitals in Pärnu (EST), Wismar (DE), Linköping (SE) and Norrköping (SE) were analyzed for 57–74 APIs (table 6.5). All raw data are presented in Annex 11. Overall, 55 APIs were quantified in at least one of the hospital effluents, while 20 APIs were below the limit of quantification (LOQ) in all effluents. 19–39 APIs were detected in each hospital effluent and the detection frequencies were 33–53% (table 6.5).

The sum of the quantified APIs varied between 75 and 1220 µg/L in the hospital effluents. The concentrations of APIs in the hospital effluents from Pärnu, Linköping and Norrköping were about two to six times higher than the concentrations in the influents of the connected WWTPs. On the contrary, the API concentrations in the Wismar hospital effluents were lower than the concentrations in the influents of Wismar WWTP (Table 6.5). The highest total concentration of APIs in hospital effluents, as well as WWTPs influents, were found in winter samples from Pärnu and Wismar.

Table 6.5. The table shows the number of APIs analysed in hospital wastewater effluents and the influents of the connected WWTPs, the number of APIs above LOQ in hospital effluents, and the detection frequencies (DF) in hospital effluents. The table also shows the sum of the quantified APIs in the effluents of hospitals and in the influents of the connected WWTPs as well as the ratio between hospitals and WWTPs (API sum concentration in hospital effluent divided with sum concentration in WWTP influent).

	Number of analysed APIs	Number of APIs above LOQ in hospital effluents	DF in hospital effluents (%)	Sum of APIs in hospital effluents (µg/L)	Sum of APIs in WWTP influents (µg/L)	Hospital effluent vs. WWTP influent
Pärnu hospital, Dec 2017	71	30	42	1 220	198	6.2
Pärnu hospital, June 2018	74	39	53	415	152	2.7
Wismar hospital, Feb 2018	73	33	45	975	1 209	0.81
Wismar hospital, June 2018	74	27	36	75	310	0.24
Linköping hospital, June 2018	57	19	33	93	53	1.8
Norrköping hospital, June 2018	57	22	39	225	99	2.3

Substances detected in at least one of the hospital effluents are presented in figure 6.34–6.36. About 30–50% of the detected APIs were found in concentrations below 1 µg/L, and 75–90% of the detected APIs were found in concentrations below 10 µg/L. APIs found in concentrations above 100 µg/L were gabapentin in Pärnu hospital effluent, and metformin and paracetamol in Pärnu and Wismar hospital effluents sampled in winter. In June, the concentration of metformin was also above 100 µg/L in the effluents of the hospitals in Pärnu and Norrköping.

Six APIs were found in all hospital effluents: metformin (3.8–170 µg/L), mesalazine (0.66–14 µg/L), hydrochlorothiazide (1.9–16 µg/L), diclofenac (0.25–9.6 µg/L), carbamazepine (0.038–2.3 µg/L) and bisoprolol (0.038–0.82 µg/L). APIs detected in all analysed effluents (DF 100%, but not analysed in all samples) were caffeine (0.97–27 µg/L), trimethoprim (0.49–11 µg/L), sulfamethoxazole (0.31–11 µg/L), ibuprofen (2.8 µg/L), venlafaxine (0.077–0.48 µg/L), sertraline (0.10–0.52 µg/L) and ramipril (0.037–0.11 µg/L).

Samples in Pärnu and Wismar were taken in winter (December or February) and in summer (June), enabling seasonal comparisons. In Pärnu and Wismar hospital effluents, the concentrations of citalopram and venlafaxine (both psycopharmaceuticals), clarithromycin (antibiotic) and diclofenac (anti-inflammatory medicine) were higher in winter than in summer. Concentrations of nine APIs were higher in all the effluents sampled in summer than in winter: erythromycin, sulfamethoxazole and trimethoprim (antibiotics), hydrochlorothiazide (antihypertensive), mesalazine (gastrointestinal disease medication), estriol (hormone), dipyridamole, metoprolol and nebivolol (both cardiovascular medicines). Most APIs (39 out of 74) were found in Pärnu hospital effluent in June (Table 6.5).

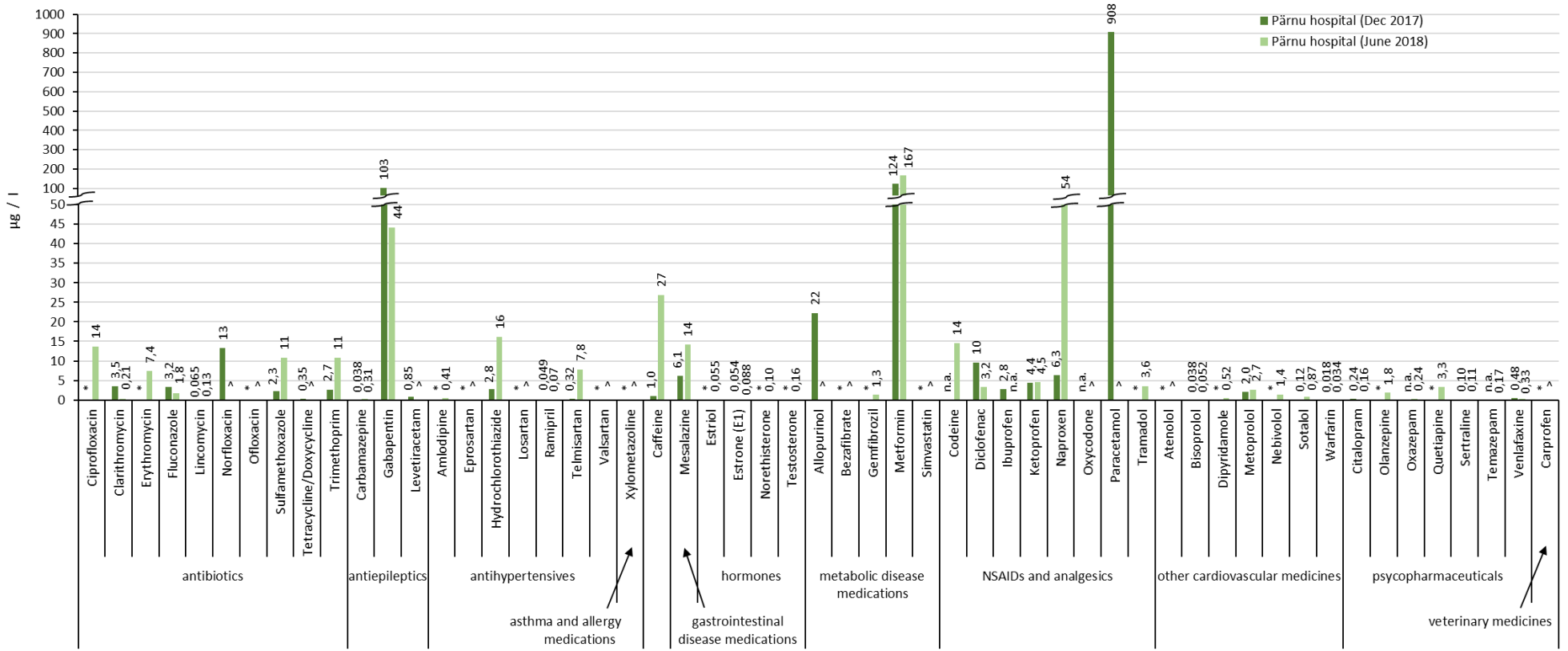

Figure 6.34. APIs in the Pärnu hospital effluent sampled in December 2017 and June 2018. APIs below LOQ are marked with "*" for the sample taken in December 2017 and "^" for the sample taken in June 2018.

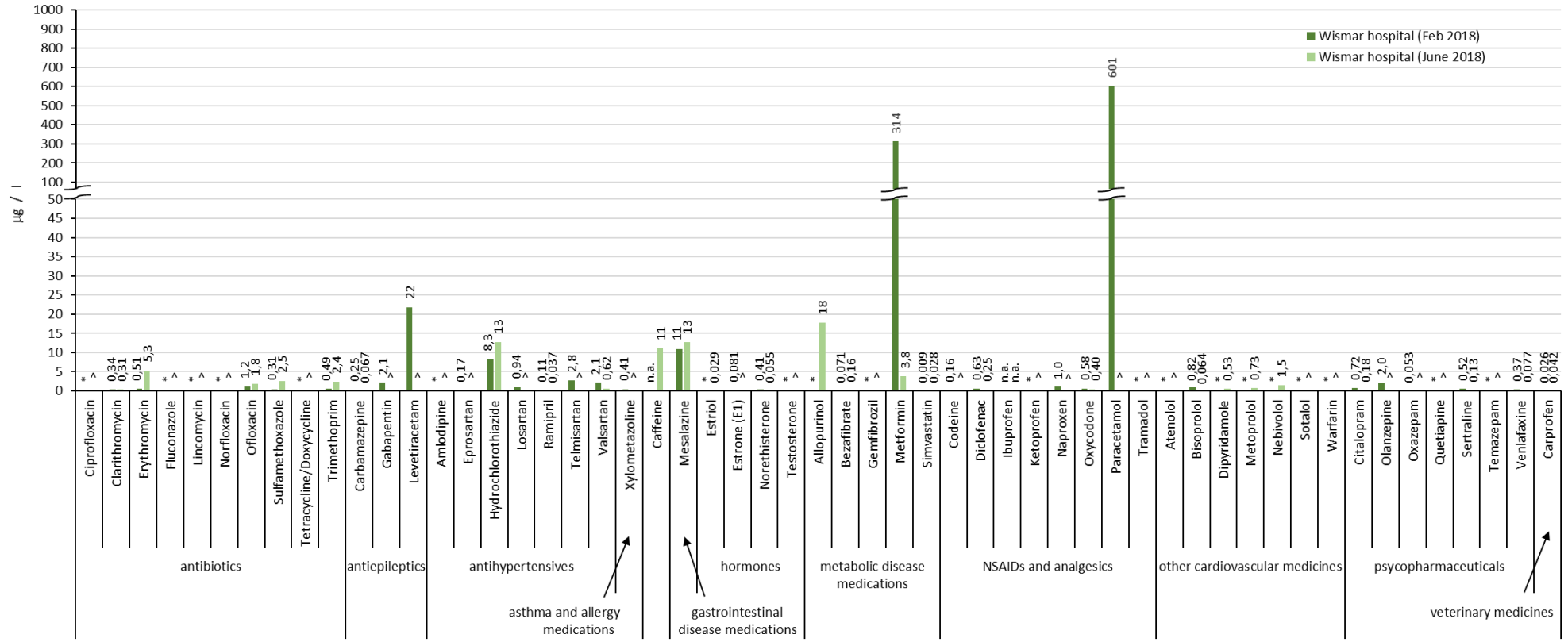

Figure 6.35. APIs in Wismar hospital effluent sampled in February 2018 and June 2018. APIs below LOQ are marked with "*" for the sample taken in February 2018 and "^" for the sample taken in June 2018.

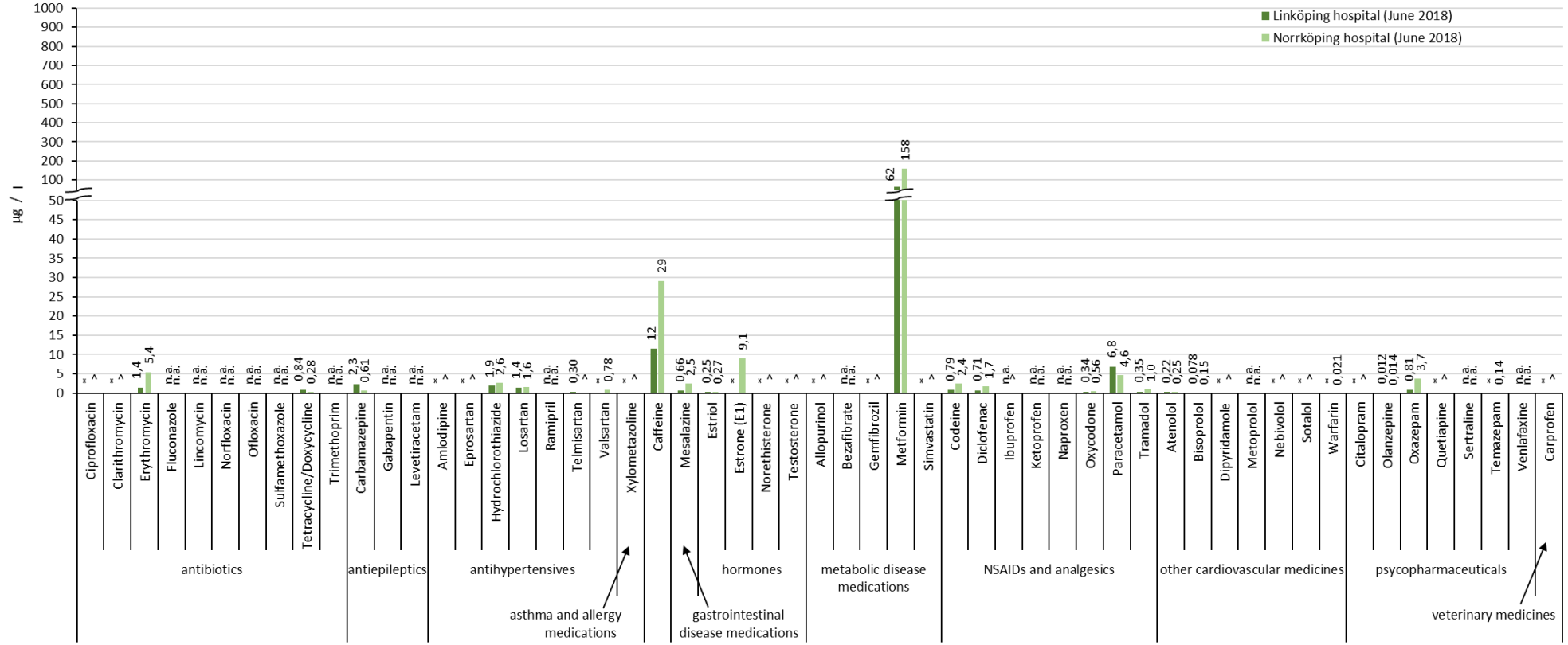

Figure 6.36. APIs in the effluents from hospitals in Linköping and Norrköping sampled in June 2018. APIs below LOQ are marked with "*" for the Linköping hospital effluent and "^" for the Norrköping hospital effluent.

6.3.2.2 API load from hospitals

The load of APIs discharging from each hospital was compared to the load of APIs in the connected WWTP influents. The total load of the detected APIs in hospital effluents was at maximum 3.2% of the overall API load (Table 6.6). The comparatively low percentage of APIs in g/day from the hospitals is due to the low water flows from the hospitals compared to the total influent flows of the connected WWTPs.

Table 6.6. Sum of the quantified APIs (g/day) in hospitals effluents and in the connected WWTP influents, and % of APIs from hospitals compared to the overall load. Included are also data on water flow in hospital effluents and WWTPs influents.

	Hospital effluents: Sum of APIs (g/day)	WWTP influents: Sum of APIs (g/day)	APIs from hospital (%)	Water flow from hospital (%)	Hospital effluent (m^3/day)	WWTP influent (m^3/day)
Pärnu hospital, Dec 2017	101	7 754	1.3	0.21	83	39 375
Pärnu hospital, June 2018	34	1 529	2.3	0.77	83	10 759
Wismar hospital, Feb 2018	82	11 941	0.69	0.85	85	9 902
Wismar hospital, June 2018	5.7	2 686	0.21	0.73	75	10 297
Linköping hospital, June 2018	54	1 665	3.2	1.4	577	40 043
Norrköping hospital, June 2018	44	3 809	1.1	0.50	195	38 650

Hospitals are significant sources of those APIs that are used to treat patients in hospitals. Table 6.7 presents the APIs for which the hospitals constitute ≥1% of the total load in the WWTP influents. Effluents from Pärnu hospital contained the highest number of APIs above 1 % compared to the overall load from the connected WWTP influents. More than 5% of the antibiotics fluconazole and trimethoprim detected in Pärnu WWTP influent came from Pärnu hospital (Table 6.7), although the water flow was less than 1% (Table 6.6). Pärnu hospital discharges about one third of the total load of trimethoprim and an antihypertensive telmisartan (table 6.7 and Annex 12). The hospital in Linköping discharges 5% of oxazepam (a psycopharmaceutical) and about 10% of caffeine and carbamazepine (an antiepileptic).

Several APIs were only detected in the effluents of hospitals and not found in the WWTP influents (Annex 12). One example is oxycodone, an analgesic opioid medication, which was found in the effluents from hospitals in Wismar, Linköping and Norrköping but not in the influents of the connected WWTPs. Hence, these APIs were diluted below LOQ and/or degraded on the way to the WWTP.

Table 6.7. Percentage of APIs in hospitals effluents compared to WWTP influents. Only APIs ≥1% in hospital effluents are shown.

	1–5% from hospitals	5–10% from hospitals	10–35% from hospitals
Pärnu hospital, Dec 2017	Clarithromycin, sulfamethoxazole, metformin, naproxen, ketoprofen, paracetamol, venlafaxine	Trimethoprim, gabapentin	Fluconazole, citalopram+escitalopram (SUM)
Pärnu hospital, June 2018	Erythromycin, gabapentin, hydrochlorothiazide, metformin, ketoprofen, metoprolol, sotalol, warfarin, citalopram+escitalopram (SUM), oxazepam, sertraline, temazepam	Caffeine, codeine, naproxen, tramadol	Fluconazole, sulfamethoxazole, trimethoprim, telmisartan
Wismar hospital, Feb 2018	Ofloxacin, sulfamethoxazole, trimethoprim, levetiracetam, hydrochlorothiazide, mesalazine, citalopram+escitalopram (SUM), oxazepam, sertraline	None	None
Wismar hospital, June 2018	Clarithromycin, sulfamethoxazole, trimethoprim, hydrochlorothiazide	None	None
Linköping hospital, June 2018	Erythromycin, tetracycline+doxycycline (SUM), hydrochlorothiazide, estriol, metformin, codeine, paracetamol, bisoprolol, olanzapine	Oxazepam, caffeine	Carbamazepine
Norrköping hospital, June 2018	Erythromycin, hydrochlorothiazide, metformin, codeine, bisoprolol, caffeine, oxazepam	None	None

6.3.3 Conclusions

The concentrations of APIs differ between hospitals. The differences may be due to the number of patients and specialties in treatment methods at the four hospitals. The degree of dilution and degradation of APIs in the effluents from the hospitals may also be different depending on e.g. the pipeline system and sampling location. The highest total concentration as well as load of the quantified APIs were found in the effluents of Pärnu hospital sampled in December (1220 µg/L and 101 g/day).

Thirteen APIs were found in all the hospital effluent samples where they were analysed: metformin, caffeine, hydrochlorothiazide, mesalazine, trimethoprim, sulfamethoxazole, diclofenac, carbamazepine, ibuprofen, bisoprolol, sertraline, venlafaxine and ramipril. Most of the detected APIs were present in concentrations below 10 µg/L. APIs with concentrations above 100 µg/L were gabapentin, metformin and paracetamol.

Some consistent seasonal differences were found in the effluents from hospitals in Pärnu and Wismar, sampled both during winter and summer. However, more samples should be analyzed to make conclusions about seasonal variations in the load of APIs from hospitals. Several APIs that were detected in the hospital effluents were not found in the WWTP influents, e.g. oxycodone, an analgesic opioid medication. Hence, these APIs were diluted and/or degraded on the way to the WWTP.

The total concentration of the quantified APIs (µg/L) was generally higher in the effluents of hospitals than in the influents of the connected WWTPs. Because of the comparatively low water flows from the hospitals, the total load of the quantified APIs (g/day) in the effluents from hospitals were only 0.2–3.2% of the overall API load. Hence, hospitals have less contribution to the total load of APIs to the WWTPs compare to the households. It is therefore more cost-efficient to install advanced treatment technologies at the WWTPs than at the hospitals. However, the hospitals may be significant sources of some APIs that are predominantly used at hospitals.

Sampling of hospital effluents by using automatic samplers. Photo: Helene Ek Henning, CAB.

6.4 Concentrations of APIs in the wastewater of pharmaceutical manufacturing plant

6.4.1 Methods

APIs were determined in the effluent of a Latvian pharmaceutical manufacturing plant. The plant has its own biological WWTP with a moving layer biofilm reactor process. The samples were taken from the WWTP effluent in December 2017 and May 2018. The average discharge of the WWTP is 200–500 m^3/day. The effluents of the WWTP are released to the municipal wastewater treatment plant.

6.4.2 Results and discussion

6.4.2.1 Concentrations of APIs in effluents from API manufacturer

Of the 74 APIs analysed in manufacturing plant effluents, 23 were detected in at least one of the two samples (Annex 13). Six of them – hydrochlorothiazide, telmisartan, estrone, diclofenac, paracetamol and warfarin – were detected in both samples (Figure 6.37).

The **antibiotics** detected in the samples were sulfadiazine and tetracycline+doxycycline (SUM), which were above LOQ in May, and clarithromycine detected slightly above LOQ in December. The highest concentration of an antibiotic was obtained for sulfadiazine (0.58 µg/L, May). Three APIs of the **antihypertensive medication** group were detected in the samples: hydrochlorothiazide, telmisartan and valsartan. Hydrochlorothiazide was the most abundant antihypertensive in both samples with concentration of 6.9 µg/L in May and 1.2 µg/L in December.

Xylometazoline was the only **asthma and allergy** API that was detected in the manufacturing effluents (0.028 µg/L, May). Three **hormones**, estrone, norethisterone and testosterone, were detected in the May samples with a maximum concentration of 0.031 µg/L (testosterone), while estrone was the only detected hormone in December sample (5.5 µg/L). Allopurinol was the only detected API of the **metabolic disease medications** group. It was detected only in December with a concentration of 4.8 µg/L.

Four APIs from the group **NSAIDs and analgesics** were detected in May (diclofenac, ketoprofen, naproxen and paracetamol), while three APIs were detected in December (diclofenac, paracetamol and tramadol). With the concentration of 16 µg/L in December, paracetamol was the most abundant of all the analysed APIs in the manufacturing plant effluents. Also, **psychopharmaceuticals** were detected more often in the sample taken in May than December. Olanzapine and venlafaxine had the highest concentrations, 0.39 µg/L and 0.25 µg/L in May.

Warfarin was the only detected API of the **other cardiovascular medicines** group. It was detected in both samples with a concentration of up to 2.0 µg/L (May). **Caffeine** was above LOQ only in December when the concentration reached 8.8 µg/L.

The pharmaceutical company manufactures over 90 final dosage form (FDF) pharmaceutical products, including solid form products, solutions for injections, ointments and syrups. According to permits of polluting activities, their largest production is for tegafur (5 t), meldonium (150 t), oxytocin (0.07 t), zopiclone (3.15 t), ursodeoxycholic acid (20 t) and xylazine (1.5 t). These APIs were not analysed within the project. From the 74 APIs measured in manufacturer wastewaters only ten were listed as products of the manufacturer. Some of the produced APIs like atenolol, ibuprofen and simvastatin were not detected in the wastewaters, while paracetamol was found at the highest concentration (Table 6.7).

Table 6.7. APIs detected in the manufacturer wastewaters and their dosage and product forms produced by the manufacturer. N/A = not analysed due to matrix interferences.

API	API group	Concentration, µg/L		Dosage and product form produced by the manufacturer
		Sampling time 07.12.2017.	Sampling time 28.05.2018.	
Atenolol	other cardiovascular medicines	<LOQ	<LOQ	50 mg /100 mg film-coated tablets
Diclofenac	NSAIDs and analgesics	0.042	0.022	20 mg/g ointment
Ibuprofen	NSAIDs and analgesics	<LOQ	N/A	*not specified*
Ketoprofen	NSAIDs and analgesics	0.86	N/A	2.5% gel
Paracetamol	NSAIDs and analgesics	4.5	16	500 mg tablets
Risperidone	psychopharmaceuticals	<LOQ	0.072	2 mg, 4 mg film-coated tablets
Simvastatin	metabolic disease medications	<LOQ	<LOQ	2 mg, 4 mg film-coated tablets
Sulfadiazine	antibiotics	0.58	<LOQ	10 mg/g ointment
Venlafaxine	psychopharmaceuticals	0.25	N/A	37.5 mg / 75 mg tablets
Warfarin	other cardiovascular medicines	2.0	0.068	2.5 mg / 3 mg / 5 mg tablets

6.4.2.2 API loads from API manufacturer

The load of APIs discharging from API manufacturer was compared to the load of APIs in the connected WWTP influents. The total load of the detected APIs in API manufacturer effluents was at maximum 5 % of the overall API load in WWTP influent (Table 6.8). The load was calculated from annual wastewater amount data – for the years 2017 and 2018. The comparatively low percentage of APIs in t/year from the API manufacturer is due to the low water flows from the API manufacturer compared to the total influent flows of the connected WWTP.

Table 6.8. Sum of the quantified APIs (t/year) in API manufacturer effluents and in the connected WWTP influents, and % of APIs from API manufacturer compared to the overall load. Included are also data on wastewater flow in API manufacturer effluents and WWTPs influents.

	API manu-facturer effluents: Sum of APIs (t/year)	WWTP influents: Sum of APIs (t/year)	APIs from API manufacturer (average %)	Water flow from API manu-facturer (%)	API manu-facturer effluent (thousand. m^3/year)	WWTP influent (thousand m^3/year)
Dec 2017	0.003	21	5	0.17	87	52 002
May 2018	0.002	0.86	0.21	0.22	104	47 541

6.4.3. Conclusions

23 out of the 74 analysed APIs were detected in the manufacturer wastewaters, representing nine studied API groups. Only six APIs – hydrochlorothiazide, telmisartan, estrone, diclofenac, paracetamol and warfarin – were detected in both December and May samples. Ten of the APIs measured in manufacturer wastewaters were included in the manufactured products. The three APIs found in the highest concentrations were paracetamol (up to 16 µg/L), caffeine (up to 8 µg/L) and hydrochlorothiazide (up to 6.9 µg/L).

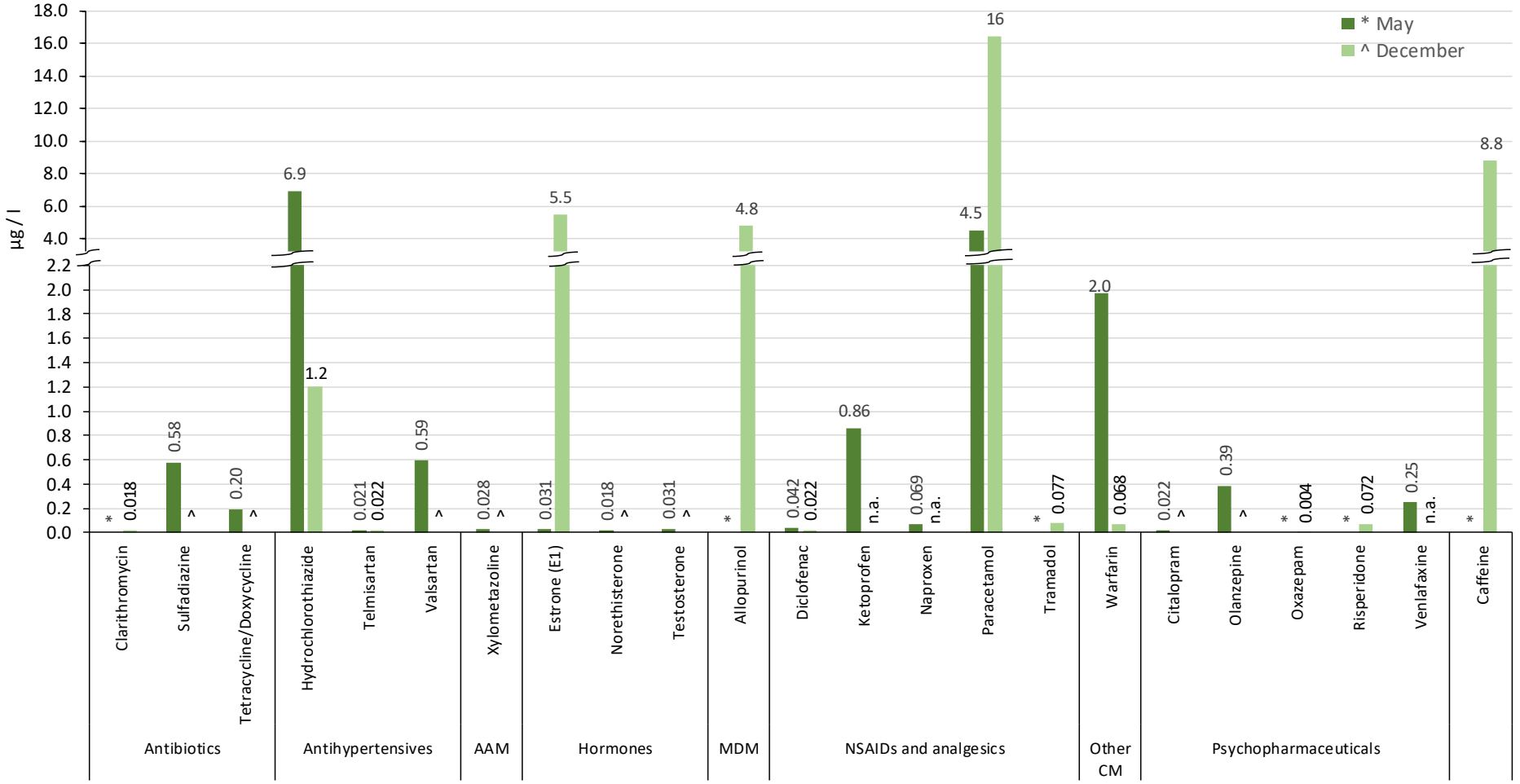

Fig.6.37. APIs in the manufacturer effluents. Abbreviations: AAM - asthma and allergy medications; MDM - metabolic disease medications; Other CM - other cardiovascular medicines. APIs with measured concentration below detection limit are marked in the chart with "*" (May) and "^" (December). APIs which could not be analysed due to matrix interferences are marked in the chart with "n.a.".

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7 APIs in surface water and sediments near fish, poultry and pig farms

7.1 Fish farms

7.1.1 Methods

7.1.1.1 Description of the fish farms

APIs were analysed from samples taken in two fish farms located in Estonia and Finland. Samples were taken from surface water and sediments. An overview of the fish farms is shown in table 7.1.

Table 7.1. Description of the fish farms, applied pharmaceuticals and the performed sampling. The bolded pharmaceuticals were measured in the project.

Fish farm	Location	Cultivated species	APIs applied	Sampling, water	Sampling, sediment
Estonian	River	Rainbow trout	Florfenicol - antibiotic	1 site 1 depth in 6.12.2017 & 6.06.2018	1 site in 6.12.2017
Finnish	Archipelago Sea	Whitefish	Sulfadiazine - antibiotic, **Trimethoprim** - antibiotic, **Emamectin*** - anti-lice medicine	3 sites with 2 depths in 21.8.2018 & 18.9.2018	3 sites in 17.9.2018

*Used on nearby fish farms for rainbow trout which are stored in studied fish farm and processed in nearby building from where treated process wastewater are discharged to sea near studied fish farm.

The Estonian fish farm was located at the very beginning of Pärnu river (distance between discharge and the river is app. 250 m, figure 7.1). The river water on the fish farm site can be influenced by village wastewater and storm waters, as the farm is located alongside the village (400 inhabitants), and a cattle farm (1 300 animals). The cultivated species was Rainbow trout (*Oncorhynchus mykiss*).

The Finnish fish farm is located in the Finnish Archipelago Sea. The site is one of several fish farming sites scattered in the archipelago area. The selected site is located in an approx. 350 m wide east-west strait between two islands, as presented in Figure 7.2. A small wastewater treatment plant processing the wastewaters from the fish processing plant and ten apartments is located in the same strait. The cultivated species during sampling was whitefish (*Coregonus lavaretus*).

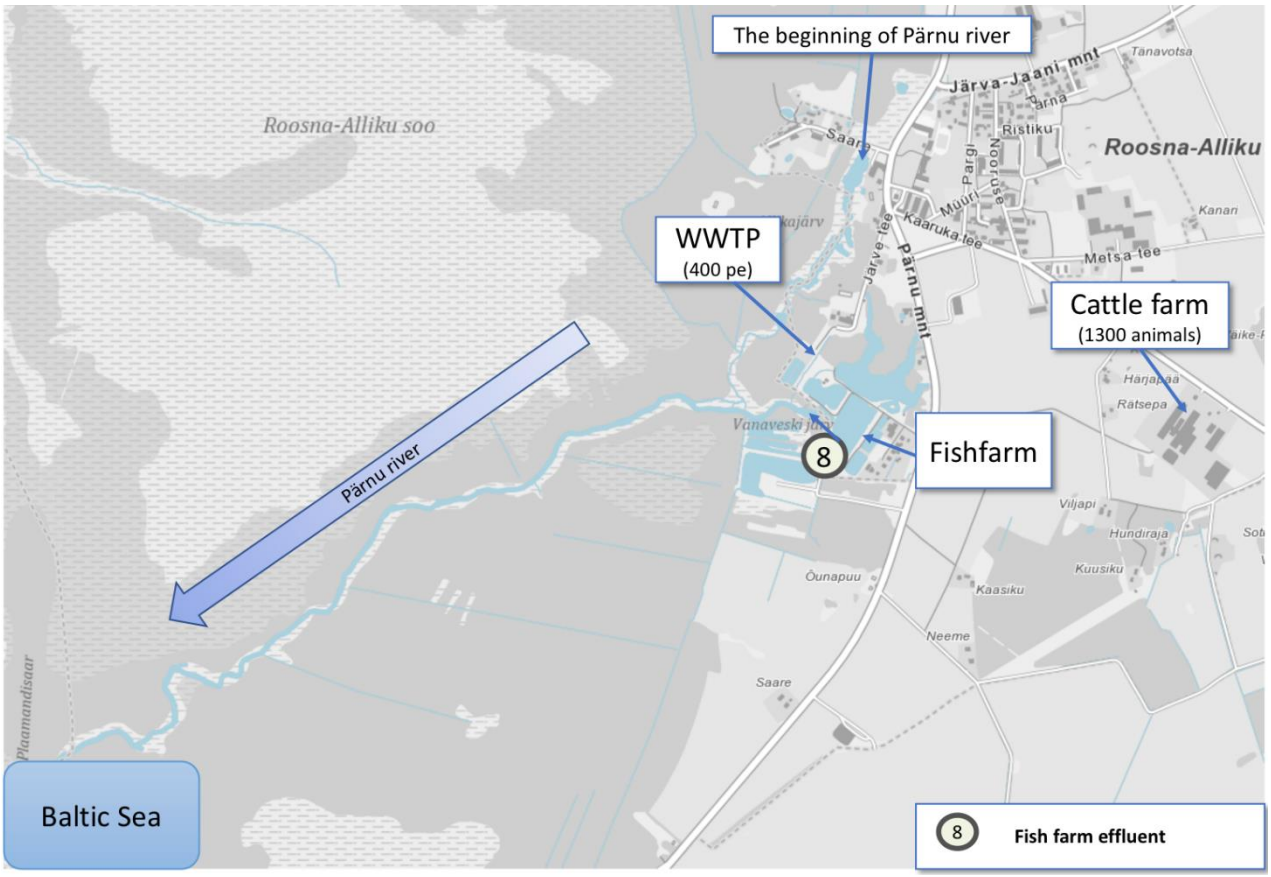

Figure 7.1. Schematic location of the Estonian fish farm and other nearby API sources.

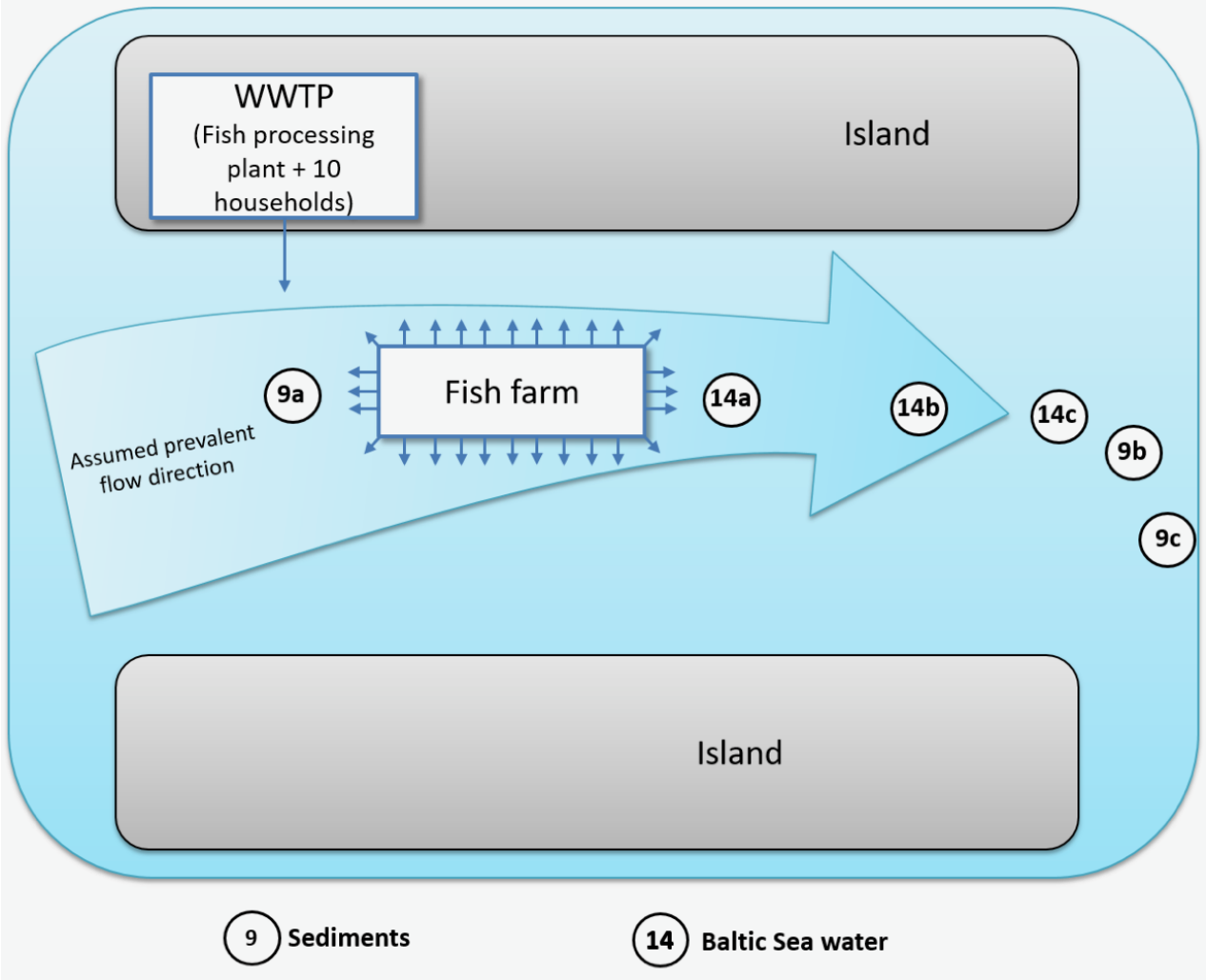

Figure 7.2. Scematic location of the Finnish fish farm sampling points.

7.1.1.2 Sampling on the fish farms

Water sampling was carried out twice and sediment sampling once. For Finnish samples the interval between two sampling campaigns was three weeks (August and September 2018). In Estonia, seasonal variability was in focus and samples were taken in winter (December 2017) and summer (June 2018).

At the Finnish site, both water and sediment samples were taken at three sampling sites. Schematic overview is shown in figure 7.2. Water sampling sites were located 0 m (14a), 150 m (14b) and 400 m (14c) from the fish farm. Sediment sampling sites were located approx. 0 m (9a), 650 m (9b) and 950 m (9c) from the fish farm. Water samples were taken from two depths (1 m below the water surface and 1 m above the bottom) using a 2 L Limnos water sampler. Sediment samples were taken using a slicing Limnos corer (figure 7.3). Each sediment sample was taken from the 3–4 cm top layer. To reach the minimum sample volume of 1 L, sediment samples needed to be aggregated from several points. Water depth at the sampling points ranged from 4.9 to 8.7 m. Due to rough weather and bottom type and morphology, water and sediment samples could not be taken from the same points. Sampling points were selected based on information on prevailing wind direction (from west to east) and local knowledge.

Figure 7.3. Slicing Limnos corer. Photo: Lauri Äystö, SYKE.

In the Estonian site the water and sediment samples were taken from the same location (figure 7.1). Water samples were taken from 0.2 m below water surface (depth of the water around 0.4 m) as composite samples and sediment samples as grab samples from transect 10 x 10 m.

7.1.2 Results and discussion

7.1.2.1 Concentrations of the APIs applied on site

Although the fish farm sampling was a part of the project, the APIs analysed were not chosen as fish farm specific. The list of APIs was analysed based on consumption data and analytical capacity. Fortunately, we still had two APIs in our measurement scope that were applied on site: trimethoprim and emamectin. Unfortunately, two other APIs that were known to be used in the studied fish farms (florfenicol and sulfadiazine) were not analysed in the project.

The last time antibiotics were applied at the Estonian fish farm before the sampling was more than a year before the first sampling (in the summer 2016). Applied API was florfenicol, an antibiotic in group of amphenicols[7]. Florfenicol was not analysed in the project. Infectious Haematopoietic Necrosis disease was found in the farm in October 2018 and the farm was closed.

In the Finnish farm, the fish started showing symptoms of disease in late summer 2018. Therefore, a veterinarian ordered a 10-day course of antibiotics to be administered. The active substances in the pharmaceutical product were trimethoprim and sulfadiazine. The administered amounts of active substances at the site during a 10-day course in August 2018 were 1.6 kg of trimethoprim and 7.9 kg of sulfadiazine. A course of antibiotics (sulfadiazine and trimethoprim) was ongoing during the first sampling round in August. Previous medication had been given around noon the previous day (~24 h before sampling). The course of antibiotics (sulfadiazine, trimethoprim) was ended 25 days before the second sampling.

In addition, rainbow trout farmed in other sites close to the Finnish fish farm were given fodder containing emamectin benzoate to remove lices (*Argulus foliaceus*) during the summer 2018, and the medication was continuing during the samplings. For Estonian fish farm, there was no data about fodder used during the sampling time.

The concentrations of trimethoprim and emamectin for both countries are presented in figures 7.4, 7.5 and 7.6. Those were the two APIs that were used at the Finnish fish farm. Concentrations of trimethoprim in water were clearly higher during the first sampling round, as expected as the medication was still ongoing. Trimethoprim concentration in water was higher in the Finnish fish farm area during the usage compared to other coastal areas sampled in CWPharma. PNEC[8] value proposed for trimethoprim is 60 µg/L. All the measured concentrations were lower than the PNEC (figure 7.4). The temporal comparison for sediment was not possible as the sediment samples were taken only once.

Figure 7.6 shows the concentrations of emamectin in the fish farm water samples. All the measured concentrations were lower than the PNEC of emamectin benzoate (1 ng/L, chapter 9). In the sediment, emamectin was detected in Estonia (0.34 µg/kg d.w) but not in Finland (<0.24 µg/kg d.w.). RQ of emamectin in Estonian sediment is 1.12 and shows a risk to the environment (chapter 9). For comparison, emamectin was detected in all surface water samples analysed in the project. The concentrations were often higher than in the fish farms.

[7] http://www.aquaflor-usa.com/pdfs/Aquaflor_Product_Bulletin_FINAL.pdf
[8] https://circabc.europa.eu/sd/a/7fe29322-946a-4ead-b3b9-e3b156d0c318/Monitoring-based%20Exercise%20Report_FINAL%20DRAFT_25nov2016.pdf

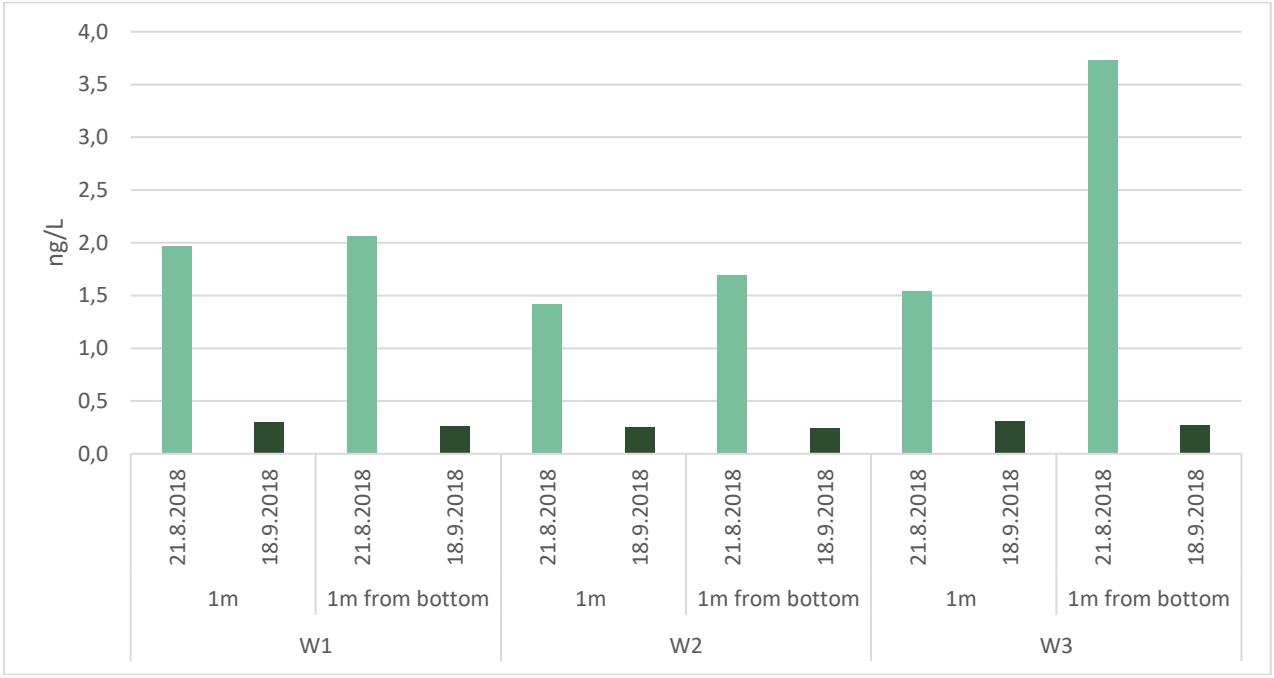

Figure 7.4. Trimethoprim in Finnish fish farm water sites 14a, 14b and 14c. Trimethoprim was applied to fish 24 h before the August sampling (light green bars) and last treatment before September sampling (dark green bars) was 25 days before.

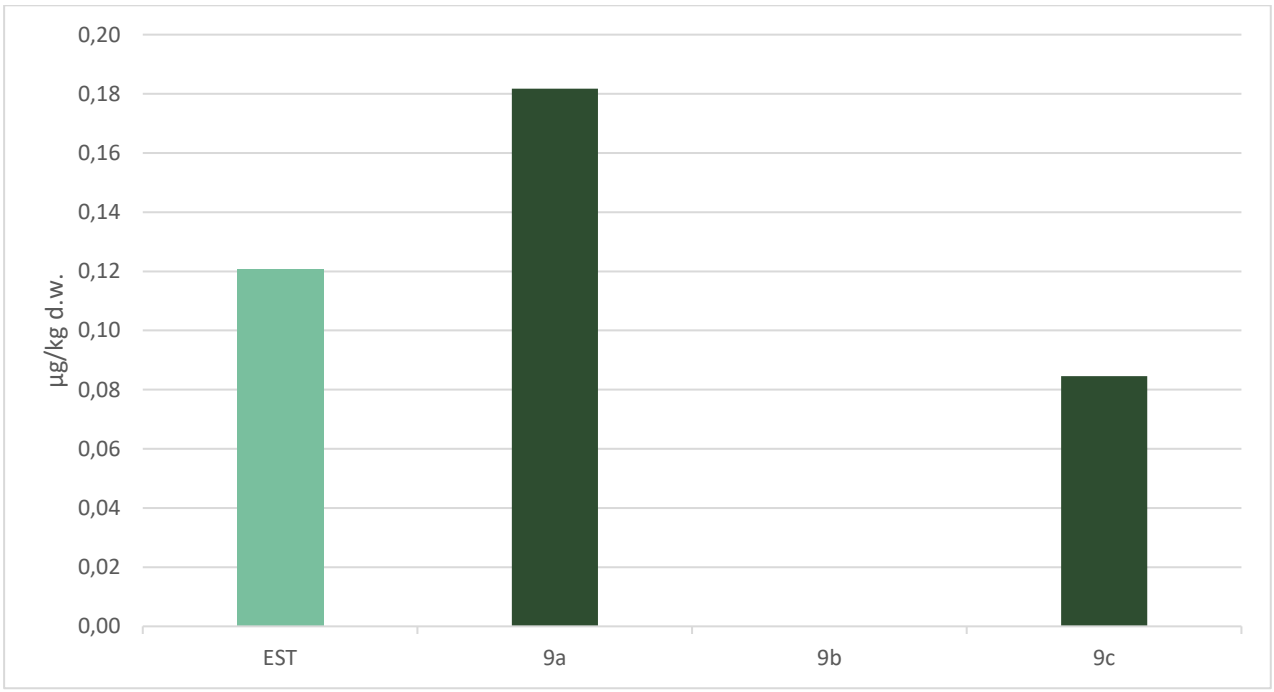

Figure 7.5. Trimethoprim in the sediments of the Estonian (EST) and Finnish (9a, 9b and 9c) fish farms (µg/kg d.w.).

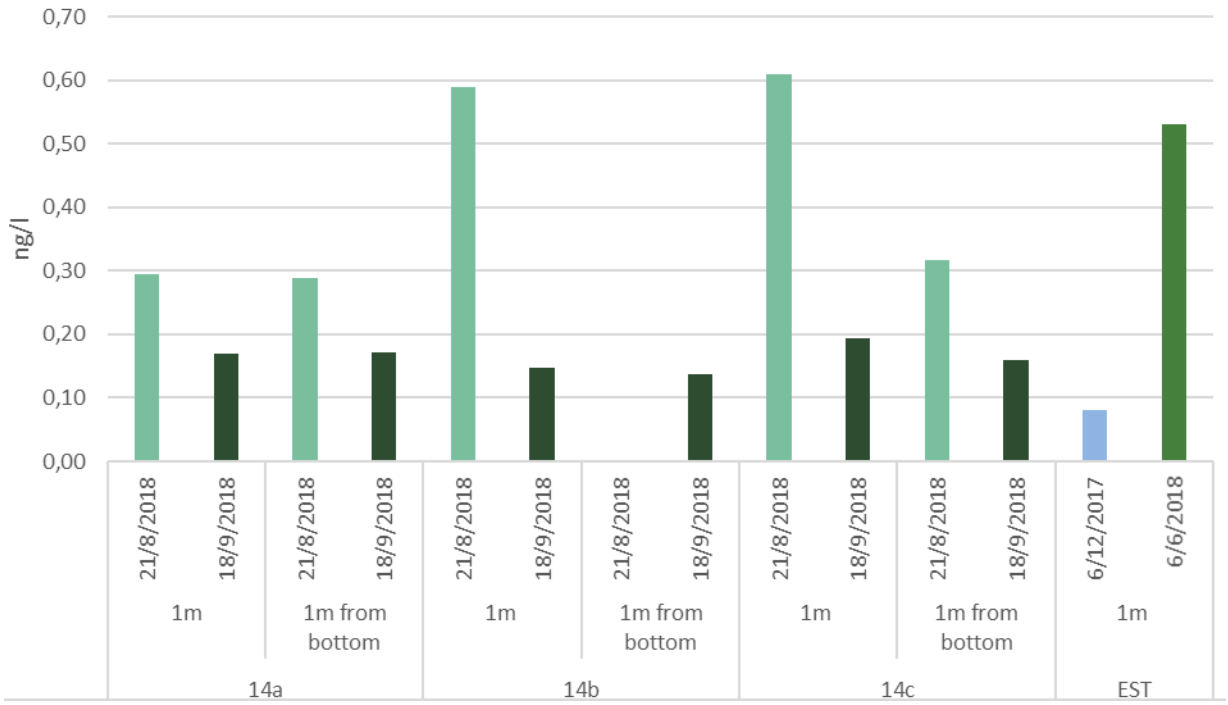

Figure 7.6. Emamectin concentrations in water samples (1m from the surface and 1m fromt the bottom) in the Finnish (14a, 14b and 14c) and Estonian (EST) fish farm sites.

7.1.2.2 Results of the other APIs measured in fish farm samples

On the fish farms, 41 out of 64 measured APIs were detected in sediment and 32 out of 53 in water. All raw data of API concentrations in sediments and water are presented in Annex 14 and Annex 15. Five APIs were detected in all sediment samples: fenbendazole, fexofenadine, progesterone, risperidone and tramadol (Figure 7.7). Highest concentration in sediment was detected for paracetamol: 520 µg/kg d.w. on the Finnish farm. Results of sediment samples from Estonian and Finnish fish farms are shown in figure 7.8.

Two substances were detected in all the water samples, carbamazepine and caffeine. High concentrations of caffeine show influence from other urban sources, confirming that all detected APIs are not only emissions from fish farming. The concentrations of APIs found in water are shown in figures 7.9–7.12. Mesalazine was detected in highest concentration, 71 ng/L, at Estonian fish farm (Figure 7.9). Mesalazine is a human medicine used to treat inflammatory bowel disease.

On the Estonian fish farm, 27 APIs were detected in sediment and 22 APIs in water. API concentrations in the Estonian fish farm water are shown in figure 7.9. On the Finnish fish farm, 34 APIs were detected in sediment samples and 27 APIs in water samples. APIs detected in Finnish fish farm water samples are shown in figures 7.10, 7.11 and 7.12. There was a slight difference between water samples taken near the bottom (1 m above the bottom) and those taken near the surface (1 m below) at the Finnish sampling site. Six more APIs were detected from near bottom water samples than from surface layer (candesartan, mometasone, progesterone, citalopram, oxazepam and dipyridamole). On the other hand, fluconazole was only detected in one surface water sample.

In the Finnish sampling site, the pharmaceutical concentrations were higher during the first sampling round. This was expected for the substances used at the site, since active medication with antibiotic containing trimethoprim was ongoing during the first sampling round but had ended 25 days before the second sampling. However, the differences in concentrations applied to other substances as well.

The occurrence of several substances not used in the fish farming site is likely explained by the wastewater emissions of ten households from a nearby island and other diffuse emissions from the scattered dwellings from nearby summer cottages and permanent residential buildings.

During the first sampling round in Finland, the API sum concentrations were the highest at the second closest sampling site (14b) but this was not the case during the second sampling, when the API sum concentrations were quite equal at all three sites (14a-14c). This may be explained by different weather and wind conditions during the sampling rounds which affect the water currents and emissions from different sources to be differently directed. Secondly, September is already off-season in the cottages, leading to less inhabitants and emissions from scattered dwellings in the area. Altogether these issues may have caused the lower water concentrations in September compared to August.

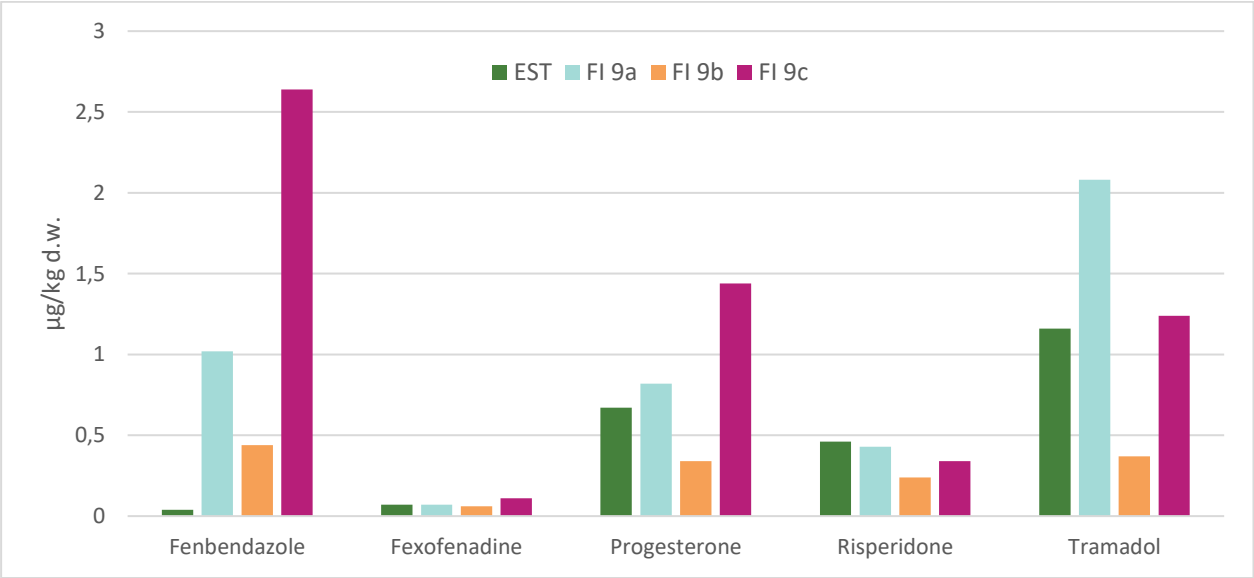

Figure 7.7. APIs detected in all fish farm sediment samples (µg/kg dw).

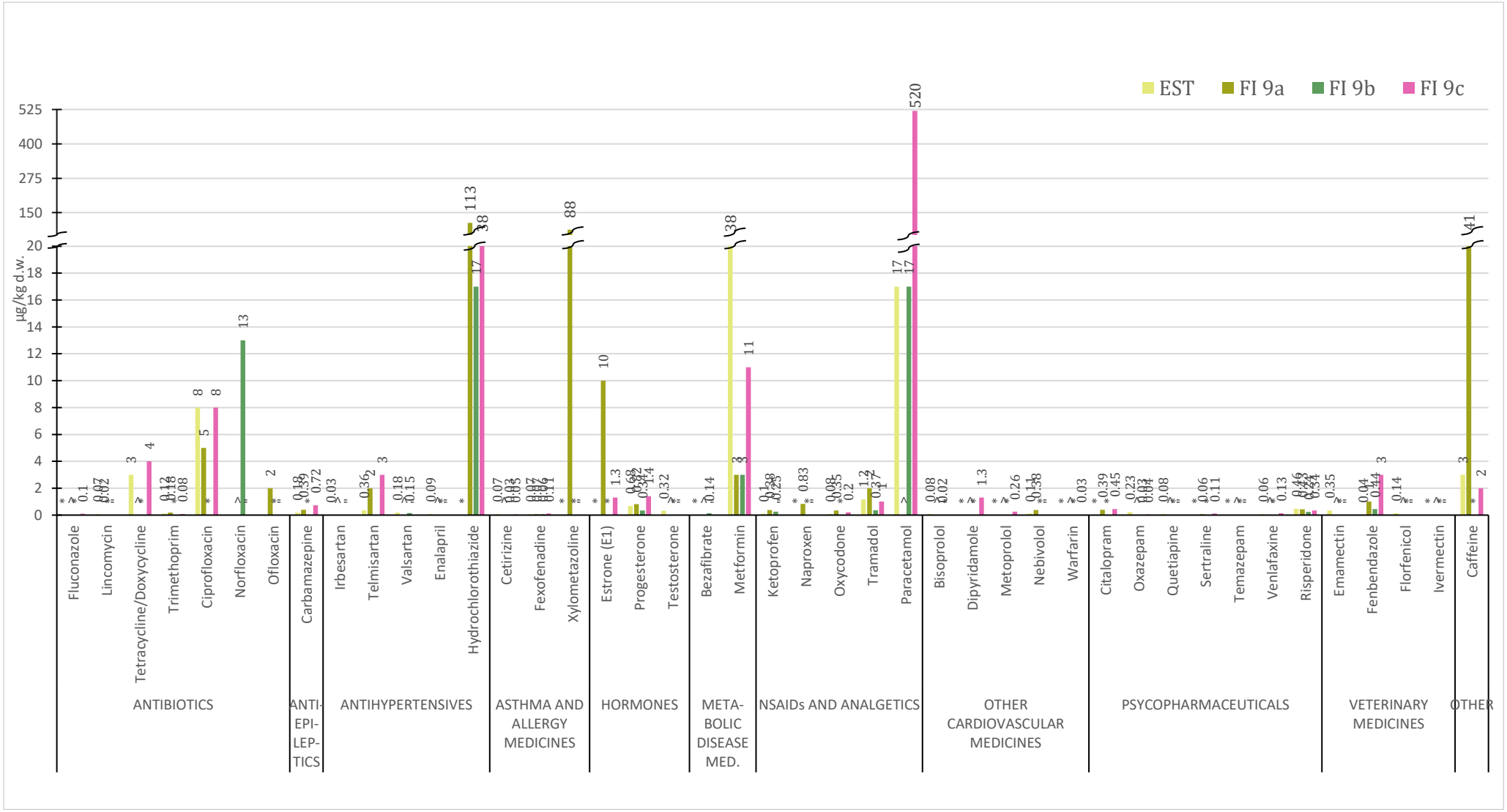

Figure 7.8. APIs detected in Estonian and Finnish sediments from the vicinity of fish farms.

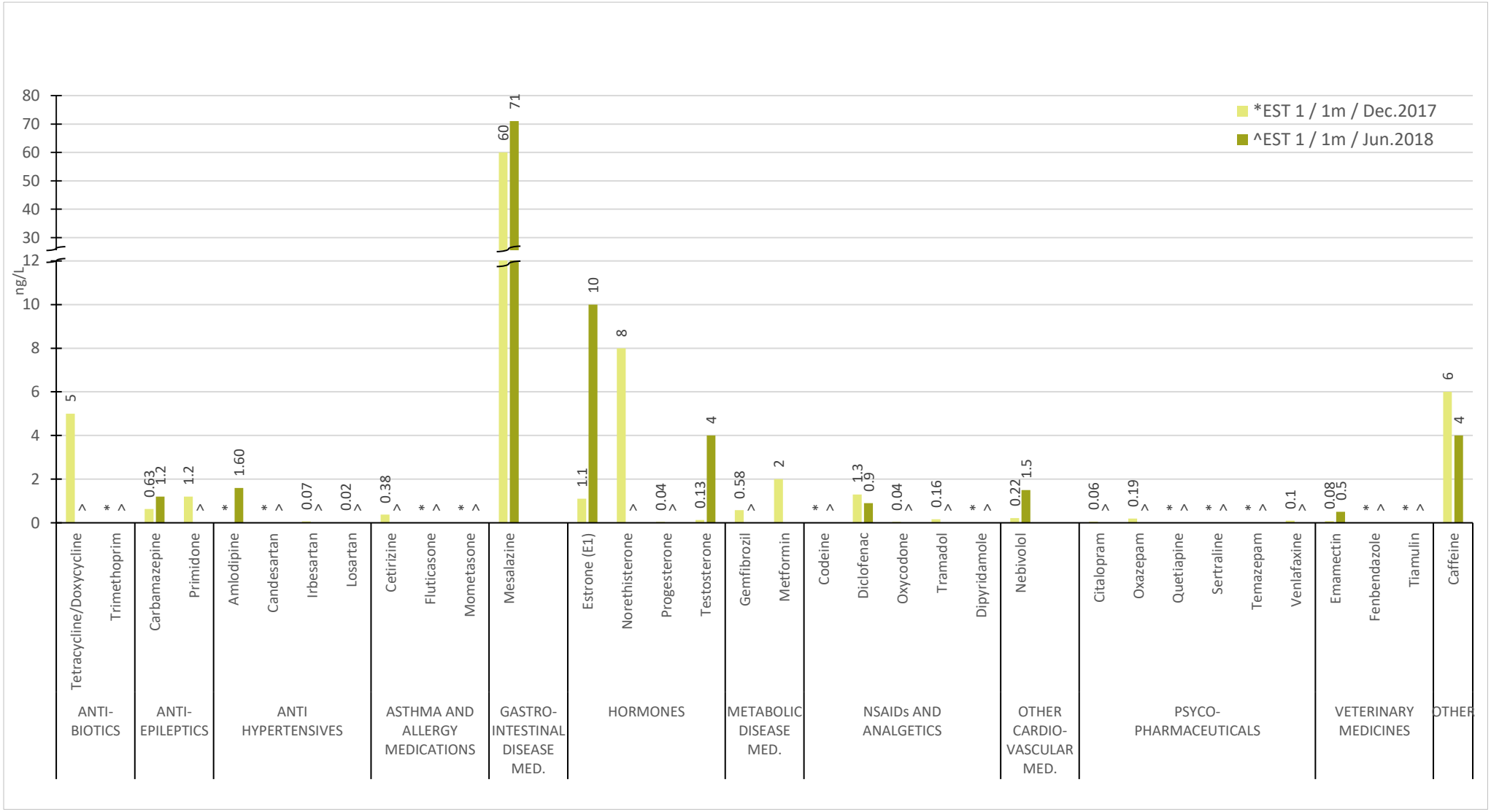

Figure 7.9. APIs detected in surface water at Estonian fish farm. Samples were taken 1 m below surface (marked as 1m).

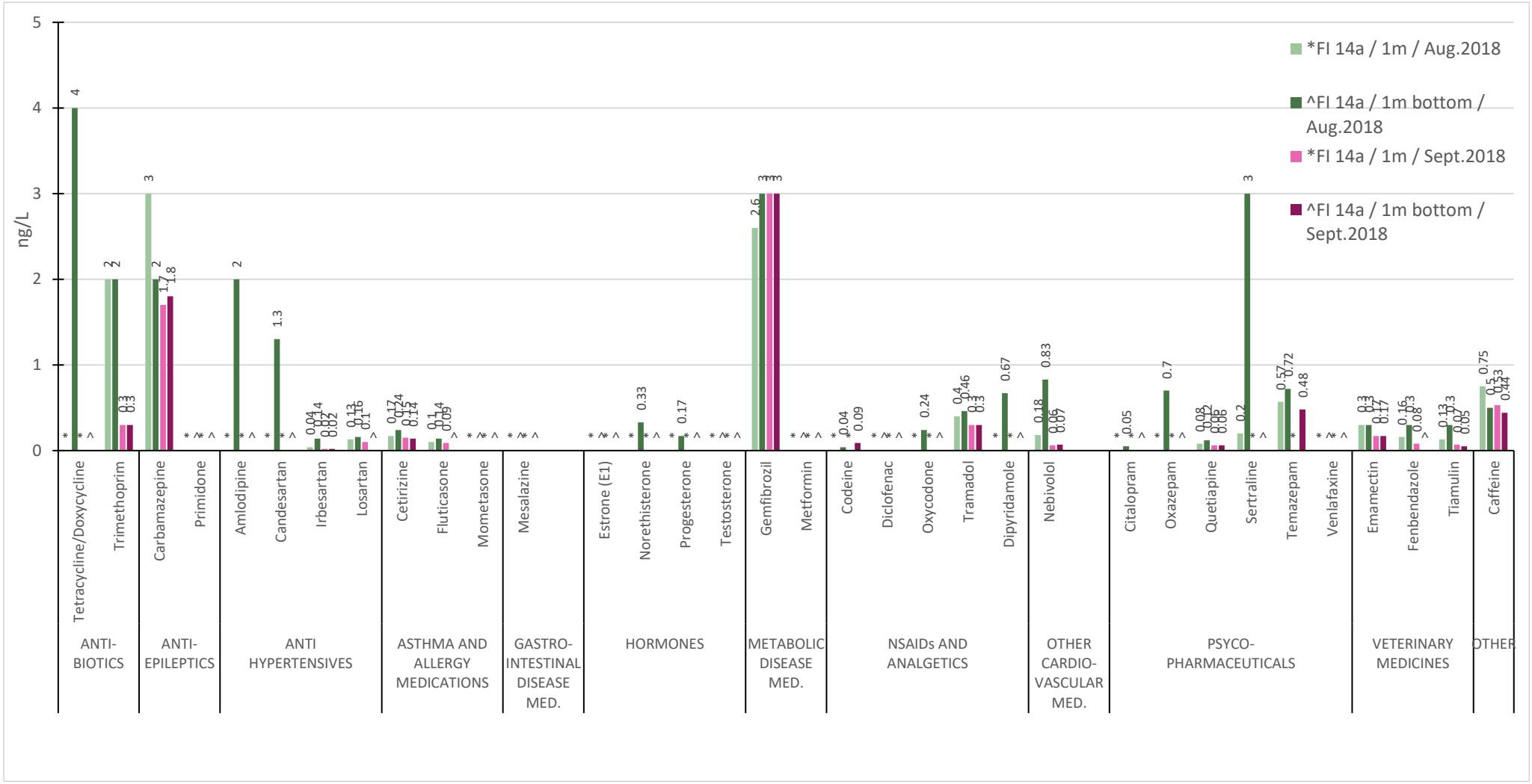

Figure 7.10. APIs detected in surface water at Finnish site 14a located 0 m from the fish farm. Samples were taken from two depths, 1 m below surface and 1 m above bottom (marked as 1m and 1m bottom).

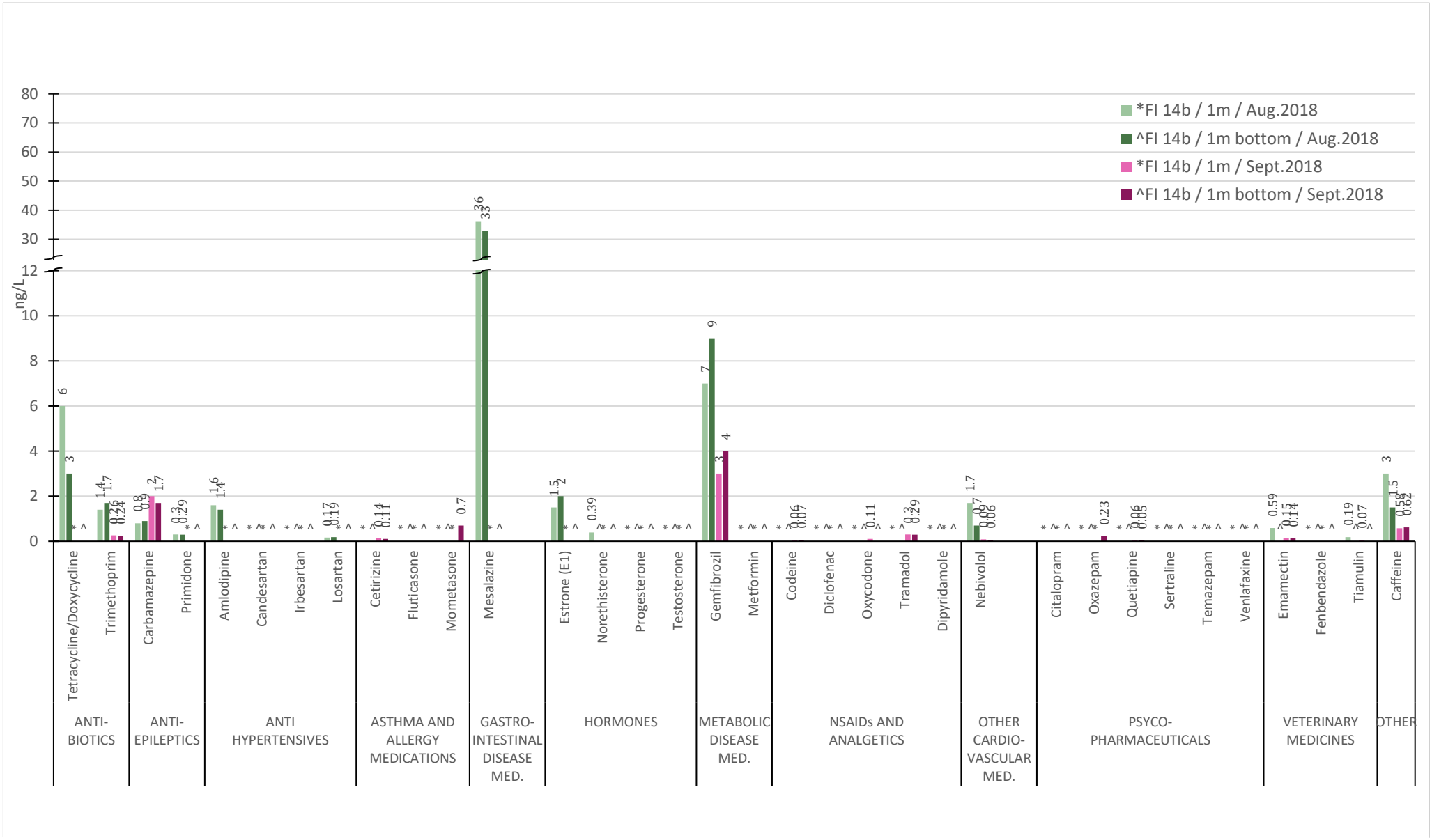

Figure 7.11. APIs detected in surface water at Finnish site 14b located 150 m from the fish farm. Samples were taken from two depths, 1 m below surface and 1 m above bottom (marked as 1m and 1m bottom).

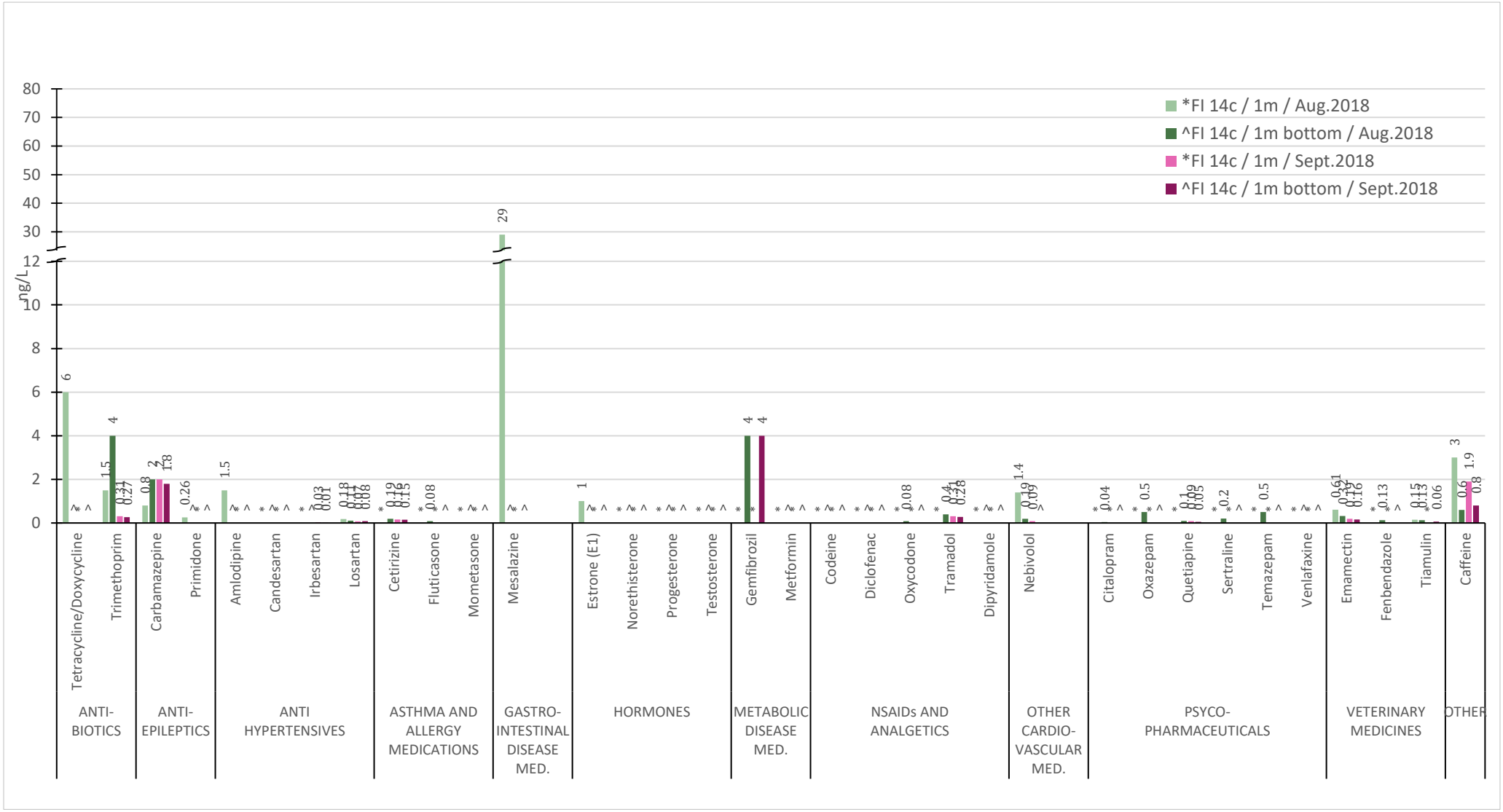

Figure 7.12. APIs detected in the surface water of Finnish site 14c located 400 m from the fish farm. Samples were taken from two depths, 1 m below surface and 1 m above bottom (marked as 1m and 1m bottom).

7.1.3 Conclusions

Water and sediments at two fish farms in Estonia and Finland were analysed for APIs (53 in water and 64 in sediment). Two of the analysed APIs, trimethoprim and emamectin, were known to be used at the Finnish fish farm, and none of them at the Estonian fish farm. Trimethoprim concentrations were 1.4 – 3.7 ng/L in water and 0.08 – 0.18 µg/kg d.w. in sediment of the Finnish fish farm. In the Estonian fish farm, trimethoprim was not detected (<0.17 ng/L) in the water, whereas the concentration in sediment was 0.12 µg/kg d.w. Emamectin was detected only in the Estonian fish farm samples at concentrations 0.08 – 0.6 ng/L in water and 0.34 µg/kg d.w. in sediment. Trimethoprim and emamectin concentrations of the fish farm samples do not pose environmental risks (lower than PNEC).

Our study showed the human impact is comprehensive. In natural waters it is difficult to find a place were only fish farm impact could be studied. In our case study farms the influence from other activities was evident, although we tried to minimize the influence when selecting the sites. The water and sediments at the fish farms also contained other APIs, indicating influences from other sources (e.g. WWTPs and private sewers). In total, 41 APIs were detected in fish farm sediments and 32 in water. Two APIs were detected in all the water samples near the fish farms: carbamazepine and caffeine. The highest concentration in water samples was detected for mesalazine (71 ng/L). Five APIs were detected in all sediment samples near fish farms: fenbendazole, fexofenadine, progesterone, risperidone and tramadol. The highest concentration in sediment was detected for paracetamol (520 µg/kg d.w.). The overall concentrations and the number of detected APIs were lower or consistent with other surface water samples of the project.

7.2 Pig and poultry farms

7.2.1 Methods

The concentrations of 55–59 APIs were analysed in the water of a watercourse near one pig and one poultry farm in Latvia. Sampling was done according ISO standard (LVS EN ISO 5667-6:2017) with horizontal water sampler. Surface water samplings were performed in a drainage ditch 300 m from the pig farm at 29 November 2017 and 22 May 2018, in Vegerupe river 600 m from the poultry farm at 28 November 2017 and 25 May 2018. The samples were taken with horizontal bathometer 0.5 m from the water surface. Four subsamples were taken for one integrated surface water sample. The samples were collected in polyethylene bottles and kept frozen until delivery to SYKE laboratory for analyses.

7.2.2 Results and discussion

The results of field measurements and observed weather conditions at sampling times are presented in Table 7.2. APIs from each group were detected in the surface water near the pig and poultry farms (Table 7.3). Raw results are presented in Annex 16. 24 APIs were detected in at least one sample taken in November, and 14 APIs in May (Table 7.4 and Figure 7.13). While many API concentrations were quantified in the range of 10 to 590 ng/L, only estrone concentration in a single water sample (1.3 ng/L) exceed its PNEC value 0.008 ng/L. Four APIs were detected in all samples:

- Caffeine (2.2 – 590 ng/L),
- Diclofenac (NSAID and analgesic) (0.89 – 7.7 ng/L),
- Metoprolol (other cardiovascular medicine) (0.24 – 5.0 ng/L),
- Tiamulin (veterinary medicine) (1.3 – 18 ng/L).

In November 2017 the highest quantified concentrations in water were detected for caffeine 94 ng/L and gabapentin 25 ng/L near the poultry farm and caffeine 140 ng/L and tylosin 23 ng/L near the pig farm. Tylosin is an antibiotic used in veterinary medicine and its presence in water near farms is expected. In May 2018, the highest quantified concentrations in water were detected for caffeine 590 ng/L near the pig farm and metformin 190 ng/L near the poultry farm. There is a wide range of caffeine sources in water since this substance is used not only in the pharmaceutical industry but also in the food and beverage industry. Likewise, it is difficult to identify the source of metformin since metformin is now widely prescribed as an anti-diabetic drug and is among the most abundant pharmaceuticals being introduced into the environment.

Eight APIs were found only in the November samples: cetirizine, citalopram, emamectin, nebivolol, progesterone, tramadol, tylosin and xylometazoline. In November, all veterinary pharmaceuticals (six in total) were detected: five near the pig farm and four near the poultry farm. In May, three of the six veterenary APIs were quantified in water near the pig farm, and one near the poultry farm. Two APIs fexofenadine (asthma and allergy medication) and toltrazuril (veterinary medicine) were quantified only in water samples near the pig farm in November and May.

In Latvia, autumn 2017 was remarkable with heavy rains – precipitation was second highest in the observation history. We cannot exlude that due to heavy rain and extremely high water the drainage water from households, small family farms, pastures and allotments as well as soil leaching and release of substances from agricultural fields can be additional sources of some pharmaceuticals in the surface waters besides wastewaters from large pig and poultry farms.

In contrary to autumn 2017, the following spring was relatively dry and warm. Therefore, the end of May 2018 was considered a low-flow period. The concentration of some APIs in water were lower in May, which may be due to reduced soil leaching and vegetation. At the same time the concentration of some APIs increased. Different physical (temperature and sunlight radiation), chemical (oxygen presence) and biological conditions can affect substance solubility in water,

adsorption on suspended particles and degradation. For example, an increase in water temperature increases the solubility of the substances and reduces sorption to particles. Also, substances can be taken up by algae and waterweed. On the other hand, the water supply to watercourses from more distant sources was limited due to reduced amount of drainage waters in this dry and warm spring. According to this we assume that the sources of water pollution with specific APIs used by humans (i.e., caffeine and metformin) were located directly at watercourses and the discharged wastewaters were not as diluted by drainage waters as in the rainy autumn.

Table 7.2. Observations and field measurements at the sampling sites near pig and poultry farm.

Observation month	Weather condition	Water temperature, °C	Conductivity, µS cm^{-1}	pH	O_2, mg L^{-1} /Saturation %
	Sapling site near pig farm				
November 2017	Air temperature +3°C, cloudy, slow wind, without precipitation	5.6	668	7.79	10.3/82
May 2018	Air temperature +24°C, sunny, slow wind, without precipitation	14.0	818	8.29	17.8/173
	Sapling site near poultry farm				
November 2017	Air temperature +2°C, strong wind, rainy (long rain)	3.1	621	7.70	11.5/85
May 2018	Air temperature +24°C, sunny, no wind, without precipitation	15.9	836	7.25	7.1/72

Table 7.3. APIs analyzed in the surface water near pig and poultry farms, and the number of detected APIs above LOQ.

API group	APIs measured in water / detected APIs in bold	Number of detected APIs in water samples
ANTIBIOTICS	**Clarithromycin**, fluconazole, lincomycin, ofloxacin, sulfadiazine, trimethoprim, tetracycline+doxycycline (SUM)	1 / 7
ANTIEPILEPTICS	**Carbamazepine, gabapentin**, levetiracetam, primidone	2 / 4
ANTI-HYPERTENSIVES	Amlodipine, candesartan, enalapril, eprosartan, irbesartan, **losartan**, ramipril, telmisartan, valsartan	1 / 9
ASTHMA AND ALLERGY MEDICATIONS	**Cetirizine, fexofenadine,** fluticasone, mometasone furoate**, xylometazoline**	3 / 6
HORMONES	**Estrone (E1),** norethisterone, **progesterone,** testosterone	2 /4
METABOLIC DISEASE MEDICATIONS	Atorvastatin, bezafibrate, **gemfibrozil, metformin**	2 / 4
NSAIDs AND ANALGETICS[1]	Codeine**, diclofenac, ketoprofen, naproxen,** oxycodone**, tramadol**	4 / 6
OTHER CARDIOVASCULAR MEDICINES	Atenolol, bisoprolol, dipyridamole, **metoprolol**, **nebivolol**, sotalol, warfarin	2 / 7
PSYCOPHARMA-CEUTICALS[2]	**Citalopram,** oxazepam, quetiapine, sertraline, temazepam, **venlafaxine**	2 / 6
VETERINARY MEDICINES	**Carprofen, emamectin, fenbendazole, tiamulin, toltrazuril, tylosin**	6 / 6
OTHER	**Caffeine**	1 / 1

1. Codeine and oxycodone were not analysed in samples collected in November 2017.
2. Oxazepam and temazepam were not analysed in samples collected in November 2017.

Table 7.4. APIs detected in surface waters near pig and poultry farms in concentration levels ≤1 ng/L, 1 – 10 ng/L, 10 – 100 ng/L, > 100 ng/L.

Sampling time	APIs found in range LOQ – 1 ng/L	APIs found in range 1 – 10 ng/L	APIs found in range 10 – 100 ng/L	APIs conc. above 100 ng/L
November 2017	Carbamazepine, Cetirizine, Citalopram, Emamectin, Fenbendazole, Losartan, Metoprolol, Nebivolol, Progesterone, Tramadol, Venlafaxine	Carprofen, Clarithromycin, Diclofenac, Fexofenadine, Gemfibrozil, Ketoprofen, Toltrazuril, Xylometazoline	Gabapentin, Metformin, Tiamulin, Tylosin	Caffeine
May 2018	Carprofen, Clarithromycin, Venlafaxine	Carbamazepine, Diclofenac, Estrone (E1), Fexofenadine, Metoprolol, Tiamulin, Toltrazuril	Gabapentin, Naproxen	Caffeine, Metformin

7.2.3 Conclusions

The number of quantified APIs in each sample varied between 7 and 21, and detection rates were 24 – 44%. In total, 26 APIs were detected in at least one water sample, and four of them were quantified in all soil samples (caffeine, diclofenac, metoprolol, tiamulin). Concentrations below 1 ng/L were found for 11 APIs in November and 3 APIs in May, concentrations up to 10 ng/L for 19 and 10 APIs in November and May respectively. The highest quantified concentrations in water were detected for caffeine (94 ng/L) and gabapentin (25 ng/L) near the poultry farm and caffeine (140 ng/L) and tylosin (23 ng/L) near the pig farm. In May 2018 the highest quantified concentrations in water were detected for caffeine (590 ng/L) near the pig farm and metformin (190 ng/L) near the poultry farm. Within the November sampling round, all veterinary medications were quantified, at least in one sample though several APIs for human use also were found in the same samples. During the high precipitation in Latvia in autumn 2017 there could have been several sources of APIs in the watercourse – households, small family farms, soil leaching and release of substances from agricultural fields, pastures, allotments and other point sources in river drainage area. Within the sampling round in May 2018, the concentrations of caffeine and metformin were much higher than concentrations in November. Our assumption is that due to the dry and warm spring, both vegetation and drainage waters have been reduced and wastewaters from direct API sources discharged in watercourses were not as diluted by drainage waters.

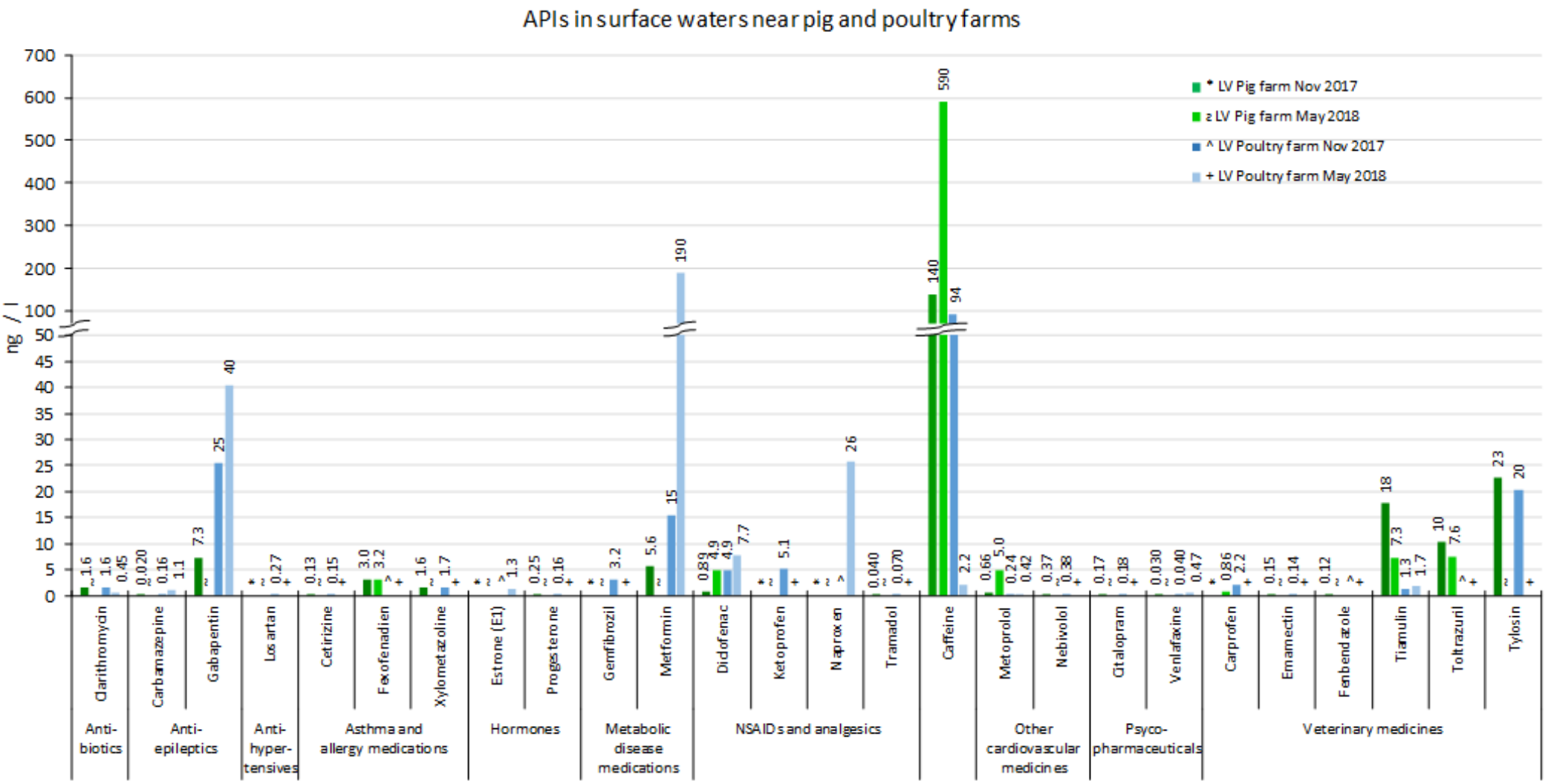

Figure 7.13. API in surface waters near pig and poultry farms in Latvia in November 2017 and May 2018; API below detection limit in November 2017 are marked with "*" for pig farm and "^" for poultry farm, API below detection limit in May 2018 are marked with "ƨ" for pig farm and "+" for poultry farm.

7.3 APIs in soil fertilized with sludge or manure

7.3.1 Method

Estonia
Soil samples were taken according to ISO 5667-12 by Auger sampler (30 cm depth, 7 subsamples) on 17 October 2018. During sampling, weather was sunny, without precipitation, no wind. Before sampling, the weather was sunny and without precipitation for 6 days.

Soil structure of the site EST1 was granular, silty loam gleysols (LkG). Organic carbon content was 22 – 40%, and dry matter 78%. The field with subsurface drainage was used for pasture. Cow manure (50 t/ha) was applied on the field most recently one month before sampling (18 September 2018). Pharmaceuticals used at the farm were antibioticstetracycline, trimethoprim, erythromycin and tylosin tartrate.

Soil structure of the site EST2 was granular, clay loam gleysols (Gi). The organic carbon content was 20 – 25%, and dry matter 80%. The field without subsurface drainage was used for growing winter cereal. Dairy cattle manure was applied on the field most recently five weeks before sampling (12 September 2018). Pharmaceuticals used at the farm were antibiotics tetracycline, sulfamethoxazole and lincomycin hydrochloride, NSAID and analgesic ketoprofen, and hormone progesterone.

Germany
Soil samples were taken by shovel (25 cm depth, 6 subsamples) on 24 May 2018. Weather conditions during sampling were sunny, without precipitation, and with slow wind. Soil structure was prismatic silty sand, dry matter 94%. Organic carbon content was not determined. The field without subsurface drainage was used for agriculture. For agriculture rape production 7 tons/ha of sewage sludge of a WWTP was applied on field before sowing.

Latvia
Soil samples were taken according to ISO 5667-12 by Auger sampler (15 cm depth) on 12 June 2018. Samples were taken from 10 points along a 1 km row. Weather conditions during sampling were sunny, without precipitation, and with slow wind. In the week before sampling, small precipitation was observed on the 5^{th} and 11^{th} of June (0.2 and 1.7 mm in Dobele and 0.4 and 0.5 mm in Kalnciems - towns between which the soil sampling place was located). Sampling day was sunny. Soil structure was blocky with more clay and 84% of dry matter. Organic carbon content was not determined. The field without subsurface drainage was used for agriculture, and manure had been applied on this field.

Sweden
Soil samples were taken by a small shovel (app. 5 cm depth, 6 subsamples) on 29 June 2018. Weather condition during sampling was sunny, without precipitation and no wind. Weather before sampling was seven sunny days without precipitation. The fields SWE1 and SWE2 with subsurface drainage were used for agriculture. Sewage sludge from WWTPs was applied on both fields two years prior to sampling. Soil structure of SWE2 was light clay soil with 96% dry matter. Soil structure of SWE1 was dry clay soil with 93% dry matter. Organic carbon content was not determined.

7.3.2 Results and discussion

Soils from six fields in Estonia (EST), Germany (GER), Latvia (LV) and Sweden (SE) were analyzed for 63-64 APIs. The detection rates are presented in Table 7.5 and the APIs detected in Table 7.6. All raw data are presented in Annex 17. Substances detected in at least one of the soil samples are presented in Figure 7.14–7.17.

Five APIs were detected in all soil samples:

- Trimethoprim (antibiotic): 0.059–0.25 µg/kg d.w.
- Paracetamol (NSAID and analgesic): 1.4–28 µg/kg d.w.
- Tramadol (NSAID and analgesic): 0.31–1.5 µg/kg d.w.
- Risperidone (psychopharmaceutical): 0.079–0.40 µg/kg d.w.
- Fenbendazole (veterinary medicine): 0.40–1.7 µg/kg d.w.

The highest concentration of these five APIs were all detected in soil from the field in Latvia. 29 - 28 APIs were not found in any of the soil samples (i.e. below LOQ). The other 35 quantified APIs (above LOQ) were detected in 1–5 soil samples.

Table 7.5. The number of analyzed APIs in soil samples, number of APIs above LOQ and the detection rates in the soil samples from Estonia (EST1 and EST2), Germany, Latvia and Sweden (SWE1 and SWE2). The number of APIs found in concentrations below 1 µg/kg d.w. and below 10 µg/kg d.w. in soil samples and detection rate for APIs below 10 µg/kg d.w. in soil samples.

	Number of analysed APIs	Number of APIs above LOQ in soil samples	Detection rate in soil samples (%)	APIs conc. below 1 µg/kg d.w.	APIs conc. below 10 µg/kg d.w.	Detection rate below 10 µg/kg d.w. (%)
Estonia (EST1), October 2018	64	16	25	14	16	100
Estonia (EST2), October 2018	63	18	28	15	16	89
Germany, May 2018	64	20	31	13	18	90
Latvia, June 2018	63	25	40	18	22	89
Sweden (SWE1), June 2018	63	16	25	12	15	94
Sweden, (SWE2), June 2018	63	19	30	15	16	84

Antibiotics

Norfloxacin was quantified in four soil samples from Estonia (EST2), Latvia, and Sweden (SWE1 and SWE2) in concentrations up to 18 µg/kg d.w. The highest concentration was detected in the soil sample from Latvia. Norfloxacin is a synthetic, broad-spectrum fluorinated antibiotic. It was approved for medical use in 1983, today it is extensively used both in human and veterinary medicine. At the same time the concentration of antibiotics such as ciprofloxacin, fluconazole and ofloxacin were below LOQ in all soil samples except in the sample from Germany (Figure 7.3.2.). Ciprofloxacin concentration in this sample exceeded the PNEC value in soil 1.3 times and ofloxacin by 1.8 times. The removal of fluorinated antibiotics by biological treatment is ineffective and their accumulation in the environment is causing an increasing concern (Amorim et al., 2014). If released to soil, fluorinated antibiotics are expected to be immobile, but these compounds may be susceptible to direct photolysis by sunlight. Relatively high concentration of fluorinated antibiotics detected in soil samples analysed within our research confirm the concern.

Trimethoprim was found in all soil samples in concentrations up to 0.25 µg/kg d.w. Trimethoprim is an old antibiotic and has been used since the 1960s. It is a hydrophilic substance with moderate to low adsorption constants to organic carbon, activated sludge and soil, and has been regularly

detected in the environment. After ingestion about 40%–75% of a dose is excreted in 24 h and up to 60% of the excreted amount is the unchanged form of trimethoprim (Straub, 2013). According to the status report by HELCOM and UNESCO (2017) trimethoprim is a stable pharmaceutical and it is fairly resistant to degradation during wastewater treatment in WWTP –sorption to sludge is only 45%. The half-life of trimethoprim in aquatic environment ranges from 57 to 100 days and it can be affected by nitrifying conditions (Straub, 2013). In our research, trimethoprim was known to be used on one farm in Estonia, and we can expect that the WWTP sludge applied on fields in Germany and Sweden also contained trimethoprim. In fact, as trimethoprim has been used for more than 60 years, fertilization with sludge or manure in the past can be the reason of current findings of this pharmaceutical in all the soil samples of this study. In contrary to this assumption, some other old and "popular" antibiotics – erythromycin, sulfamethoxazole (usually used in combination with trimethoprim), tetracycline or doxycycline, were below LOQ in all soil samples. Different degradation rates of the substances could result in removal of antibiotics from soil, but there is no research data to confirm this assumption. Also, the antibiotics clarithromycin and lincomycin, tetracycline+doxycycline (SUM) were below LOQ in all samples.

Antiepileptics

The concentrations of the antiepileptics carbamazepine, levetiracetam and primidone were below LOQ in all soil samples.

Antihypertensives

Hydrochlorothiazide was quantified in four soil samples from Estonia (EST2), Germany, Latvia, and Sweden (SWE2) in concentrations up to 110 μg/kg d.w. The highest concentration was detected in a soil sample from Latvia, but this concentration did not exceed the PNEC value for soil. Hydrochlorothiazide concentrations in soil samples were relatively high in comparison with concentrations of all analyzed APIs. Hydrochlorothiazide is globally the most frequently used and relatively safe diuretic to treat hypertension and has been used clinically for more than half a century. After ingestion, it undergoes a little metabolism and at least 61% of the oral dose is eliminated by the kidney unchanged, via urine (O'Grady et al., 1999). Current treatment technologies are unable to eliminate it from the wastewater and it can be considered as a concern for the aquatic environment (Monteil et al., 2019). Due to the low biodegradation hydrochlorothiazide can be persistent pollutant in environment. At the same time, it is sensitive to UV/VIS light (Gumieniczek et al., 2018). We assume that hydrochlorothiazide could be exposed to the photodegradation process and could be reduced in soil.

Telmisartan was analysed only in two soil samples from Estonia (EST1) and Germany, observed values were 0.65 μg/kg d.w. and 0.28 μg/kg d.w., respectively. For other samples results of telmisartan are not available (N/A). Valsartan concentration above LOQ was detected only in two soil samples from Latvia and Sweden (SWE1), respectively 0.21 μg/kg d.w. and 0.17 μg/kg d.w. The concentrations of amlodipine, enalapril, eprosartan, ramipril were below LOQ in all soil samples.

Asthma and allergy medications

Cetirizine was quantified in four soil samples from Estonia (EST2), Latvia, and Sweden (SWE1 and SWE2) in concentrations up to 0.098 μg/kg d.w. The highest concentration of cetirizine was detected in soil sample from Latvia. Fexofenadine was quantified in five soil samples from Estonia (EST2), Latvia, Germany and Sweden (SWE1 and SWE2) in concentrations up to 0.18 μg/kg d.w. and the highest concentration was detected in a soil sample from Latvia. Xylometazoline concentrations above LOQ were detected only in two soil samples from Estonia (EST1) and Germany, 2.3 μg/kg d.w. and 7.2 μg/kg d.w. respectively. The concentrations of fluticasone and mometasone furoate were below LOQ in all samples.

Hormones

Quantifiable values of progesterone concentration were detected only in two soil samples from Estonia (EST1) and Latvia, respectively 0.30 μg/kg d.w. and 0.22 μg/kg d.w. Only in one soil sample from Germany was estrone (E1) detected above LOQ (16 μg/kg d.w.). Due to high estrone (E1) bioconcentration in aquatic organisms its PNEC concentration in water and soil is rather low. The PNEC value for estrone in the German soil sample was exceeded up to 160 000 times. The concentrations of hormones such as estriol (E3) and testosterone were below LOQ. Hormone norethisterone was analysed only in soil samples from Estonia (EST2), Latvia and Sweden (SWE 1 and SWE 2) but its concentration was below LOQ.

Metabolic disease medications

Bezafibrate was quantified in four soil samples from Estonia (EST2), Latvia, and Sweden (SWE1 and SWE2). Quantified concentrations reached 0.18 μg/kg d.w. and the highest concentration was detected in two soil samples from Estonia (EST2) and Sweden (SWE2). Metformin was quantified in five soil samples from Estonia (EST2), Germany, Latvia, and Sweden (SWE1 and SWE2) in concentrations up to 3.1 μg/kg d.w. The highest concentration was detected in a soil sample from Germany. Relatively high concentrations of metformin were found in soil samples from Germany and Sweden where sludge from WWTP was applied on the field and these concentrations exceeded PNEC values for soil 10 and 4.8 times, respectively. Metformin is now widely prescribed as an anti-diabetic drug and is among the most abundant pharmaceuticals being introduced into the environment. Metformin is found in the wastewater and surface waters around the world, often due to incomplete metabolism in humans and subsequent excretion. Most of the metformin is removed during sewage treatment and may be anaerobically degraded during sludge digestion. Also, in the environment it is transformed very slowly by photodegradation in surface waters and anaerobically degraded in soils or in sediments (Straub et al., 2019). At the time metformin demonstrated a high uptake by rape (*Brassica napus* cv. Sheik and *Brassica rapa* cv. Valo), (Eggen and Lillo, 2012). The concentrations of two metabolic disease medications – gemfibrozil and simvastatin – were below of LOQ in all samples.

NSAIDs and analgesics

Quantifiable values of ketoprofen were found in five soil samples from Estonia (EST1 and EST2), Germany and Sweden (SWE1 and SWE2). The highest quantified concentration reached 0.97 μg/kg d.w. in Estonia (EST2). All detected concentrations of ketoprofen exceeded PNEC values in soil 10 – 26 times. Oxycodone was quantified in four soil samples from Estonia (EST1 and EST2), Germany and Latvia in concentrations up to 0.45 μg/kg d.w. The highest concentration was detected in a soil sample from Latvia. Diclofenac concentrations were below LOQ in all soil samples, except in one sample from Estonia (0.43 μg/kg d.w., EST2), which exceeded the PNEC value for soil 2.0 times. Codeine and naproxen were not detected in any soil sample.

Paracetamol was found in all soil samples and in relatively high concentrations, up to 27 μg/kg d.w. All detected concentrations of paracetamol exceeded PNEC values for soil up to 110 times. It is one of the most commonly used medication to treat pain and fever worldwide (Kasciuškevičiūtė et al., 2018). In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours as a mixture of metabolites and approximately 4% as unchanged paracetamol (Forrest et al., 1982). According to HELCOM state report (BSAP No. 149) the calculated removal rate of paracetamol in WWTP was more than 70%. The history of paracetamol commercial production and use started in 1950s-1960s with rapid growth in production and consumption in 1980s. Therefore, we assume that the presence of paracetamol in all soil samples is the result of extensive use of this analgesic in the past and present.

Tramadol was also found in all soil samples, but concentrations did not exceed the PNEC value for soil. The commercial production of tramadol started in 1977 in Germany. Tramadol is used primarily to treat mild to severe pain. For humans, approximately 30% of the dose is excreted in the

urine as unchanged drug, whereas 60% of the dose is excreted as metabolites (NIH; DailyMed). Calculated removal rate of tramadol in WWTP is approximately 3%, so due to the low biodegradation this compound can be considered as a concern for the aquatic environment (BSAP No.149). Tramadol bioaccumulates in the roots and leaves of spinach from fields fertilized with sewage sludge (Kodešová et al., 2019). It has also been shown that tramadol and its metabolites can accumulate in the roots of the Cameroonian medicinal plant, *Nauclea latifolia*, near cattle pastures (Kusari et al., 2014). Our assumption is that due to the high solubility in water and high bioaccumulation rate in plant roots tramadol may remain in soil longer. This could be the reason of tramadol findings in all soil samples which have been analyzed during this project.

Other cardiovascular medicines

Bisoprolol was quantified in four soil samples from Estonia (EST2), Latvia, and Sweden (SWE1 and SWE2) in concentrations up to 0.049 μg/kg d.w. The highest concentration was observed in soil sample from Latvia. Metoprolol concentrations above LOQ were detected in three soil samples from Estonia (EST1), Latvia and Sweden (SWE1). The highest concentration 0.16 μg/kg d.w. of metoprolol was detected in a soil sample from Sweden (SWE1). Measurements of nebivolol concentrations showed that values above LOQ were detected in four soil samples from Estonia (EST2), Germany, Latvia and Sweden (SWE2). The highest quantified concentration reached 0.41 μg/kg d.w. and was detected in a soil sample from Latvia. Warfarin concentration detections above LOQ were observed in two soil samples from Estonia (EST1) and Latvia, respectively 0.018 μg/kg d.w. and 0.048 μg/kg d.w. Concentration values of three other cardiovascular medicines – atenolol, dipyridamole, sotalol were below LOQ.

Psychopharmaceuticals

Oxazepam was quantified in four soil samples from Estonia (EST1), Germany, Latvia, and Sweden (SWE2) in concentrations up to 0.42 μg/kg d.w. The highest concentration was observed in soil sample from Latvia. Concentration values of sertraline above LOQ were found in three soil samples from Estonia (EST1 and EST2) and Sweden (SWE2), the highest observed concentration reached 0.10 μg/kg d.w. and was detected in a soil sample from Estonia (EST2). Temazepam was quantified in three soil samples from Latvia and Sweden (SWE1 and SWE2) in concentrations up to 0.36 μg/kg d.w. The highest concentration was detected in a soil sample from Latvia. Venlafaxine was observed in four soil samples from Estonia (EST1), Germany, Latvia and Sweden (SWE2). The highest observed concentration reached 0.20 μg/kg d.w. and was detected in soil sample from Latvia. At the same time citalopram was detected above LOQ only in one soil sample from Latvia (0.19 μg/kg d.w.). The concentrations of other two psychopharmaceuticals – olanzapine and quetiapine were below LOQ in all samples.

It was described before that risperidone was quantified in all soil samples in concentrations up to 0.40 μg/kg d.w. It is a relatively new medication, first approved for commercial production in 1993 in United States. Risperidone is used for humans as well as animals (cats and dogs) for the same purpose – as a nervous system agent. Calculated removal rate of risperidone in WWTP is approximately 7%, so due to the low biodegradation this compound can be considered as a concern for the aquatic environment (HELCOM and UNESCO 2017). Risperidone is extensively metabolized in the liver by hydroxylation to its main pharmacoactive metabolite, 9-hydroxyrisperidone (Asimakopoulos and Kannan, 2016) but information about its excretion is quite poor as well as information about bioavailability and accumulation in plants from the fields fertilized with sludge or manure. Therefore, it is difficult to explain risperidone's presence in all the soil samples and further understanding of the environmental fate and impacts of this compound is needed.

Table 7.6. APIs found in soil samples above LOQ and ranged by results ≤1 µg/kg d.w., 1 – 10 µg/kg d.w., 10 – 100 µg/kg d.w.

Sampling site	APIs found in range LOQ – 1 µg/kg d.w.	APIs found in range 1 – 10 µg/kg d.w.	APIs found in range 10 – 100 µg/kg d.w.	APIs conc. above 100 µg/kg d.w.
Estonia (EST1), October 2018	Fenbendazole, Fexofenadine, Florfenicol, Ketoprofen, Metoprolol, Oxazepam, Oxycodone, Progesterone, Risperidone, Sertraline, Telmisartan, Tramadol, Trimethoprim, Warfarin, Venlafaxine	Paracetamol, Xylometazoline		
Estonia (EST2), October 2018	Bisoprolol, Cetirizine, Diclofenac, Fenbendazole, Fexofenadine, Bezafibrate, Florfenicol, Ketoprofen, Metformin, Nebivolol, Oxycodone, Risperidone, Sertraline, Tramadol, Trimethoprim	Paracetamol	Hydrochlorothiazide, Norfloxacin	
Germany, May 2018	Caffeine, Fenbendazole, Fexofenadine, Fluconazole, Ketoprofen, Nebivolol, Ofloxacin, Oxazepam, Oxycodone, Risperidone, Telmisartan, Tramadol, Trimethoprim, Venlafaxine	Ciprofloxacin, Metformin, Paracetamol, Xylometazoline	Estrone (E1), Hydrochlorothiazide	
Latvia, June 2018	Bezafibrate, Cetirizine, Citalopram, Fexofenadine, Metformin, Florfenicol, Ivermectin, Nebivolol, Oxazepam, Oxycodone, Progesterone, Risperidone, Temazepam, Trimethoprim, Valsartan, Venlafaxine, Warfarin	Caffeine, Fenbendazole, Tiamulin, Tramadol	Norfloxacin, Paracetamol	Hydrochlorothiazide
Sweden (SWE1), June 2018	Bezafibrate, Bisoprolol, Cetirizine. Fenbendazole, Fexofenadine, Ketoprofen, Metoprolol, Risperidone, Temazepam, Tramadol, Trimethoprim, Valsartan	Caffeine, Metformin, Paracetamol,	Norfloxacin	
Sweden, (SWE2), June 2018	Bezafibrate, Bisoprolol, Cetirizine, Fenbendazole, Fexofenadine, Ketoprofen, Metformin, Nebivolol, Oxazepam, Risperidone, Sertraline, Temazepam, Tramadol, Trimethoprim, Venlafaxine	Caffeine, Paracetamol	Hydrochlorothiazide, Ivermectin, Norfloxacin	

Veterinary medicines

Florfenicol was quantified in three soil samples from Estonia (EST1 and EST2) and Latvia in concentrations up to 0.19 µg/kg d.w. The highest concentration was detected in a soil sample from Latvia. Concentrations above LOQ of the two veterinary medicines were found in only one soil sample each – ivermectin (11 µg/kg d.w.) in sample SWE 2 from Sweden and tiamulin (4.9 µg/kg d.w.) in a sample from Latvia. Ivermectin concentration in soil exceeded the PNEC value up to 2700

times. Measurements of three other veterinary medicines – emamectin, toltrazuril, tylosin were below LOQ in all samples. Findings of fenbendazole in all the soil samples can be expected due to the wide use of this veterinary medication as an anthelmintic agent for cattle and domestic animals – cats and dogs. It is unlikely that there will be a decrease of fenbendazole in the environment because of a regular use of this medication in farms and households to treat animals from numerous helminth intestinal parasites.

Caffeine

Caffeine was quantified in four soil samples from Estonia (EST1), Germany, Latvia and Sweden (SWE1) in concentrations up to 1.3 µg/kg d.w. The highest concentration was observed in a soil sample from Sweden (SWE1).

7.3.3 Conclusions

Both human and veterinary APIs were detected in all the soil samples collected in the CWPharma project. We did not find a clear difference between the soils fertilized by manure or sludge. One potential explanation is that the residues of human and/or veterinary APIs can result from previous soil fertilization events. Pharmaceuticals can affect the organisms at relatively low concentrations. Due to their persistence and low degradation, fluorinated antibiotics, hydrochlorothiazide, metformin, trimethoprim and ketoprofen can be considered as a concern for the aquatic and terrestrial environment.

Exceedance of PNECs were often observed for paracetamol and metformin. Single exceedances of PNECs were observed for ciprofloxacin, ofloxacin, diclofenac, estrone and the veterinary medicine ivermectin in soil. For some APIs the environmental risk cannot be excluded because their limits of quantification were higher than the PNECs. Our results show that more research is needed on the fate of APIs in soil after fertilization.

Soils fertilised by manure or sewage sludge were analysed for APIs. Photo: Helene Ek Henning, CAB.

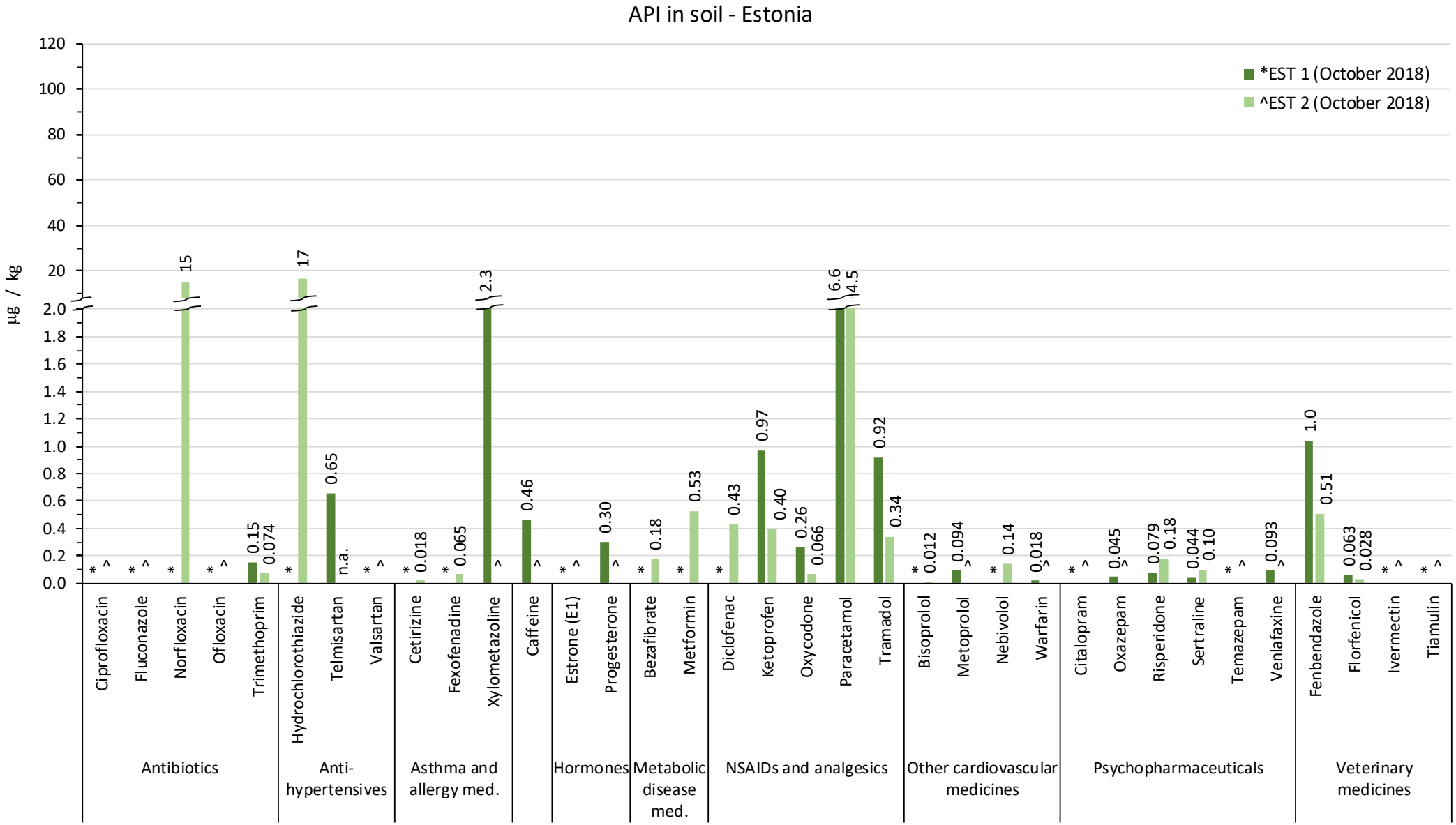

Figure 7.14. API in soil in two study areas of Estonia; EST 1 and EST 2. API below detection limit are marked with "*" for EST 1 and "^" for EST 2.

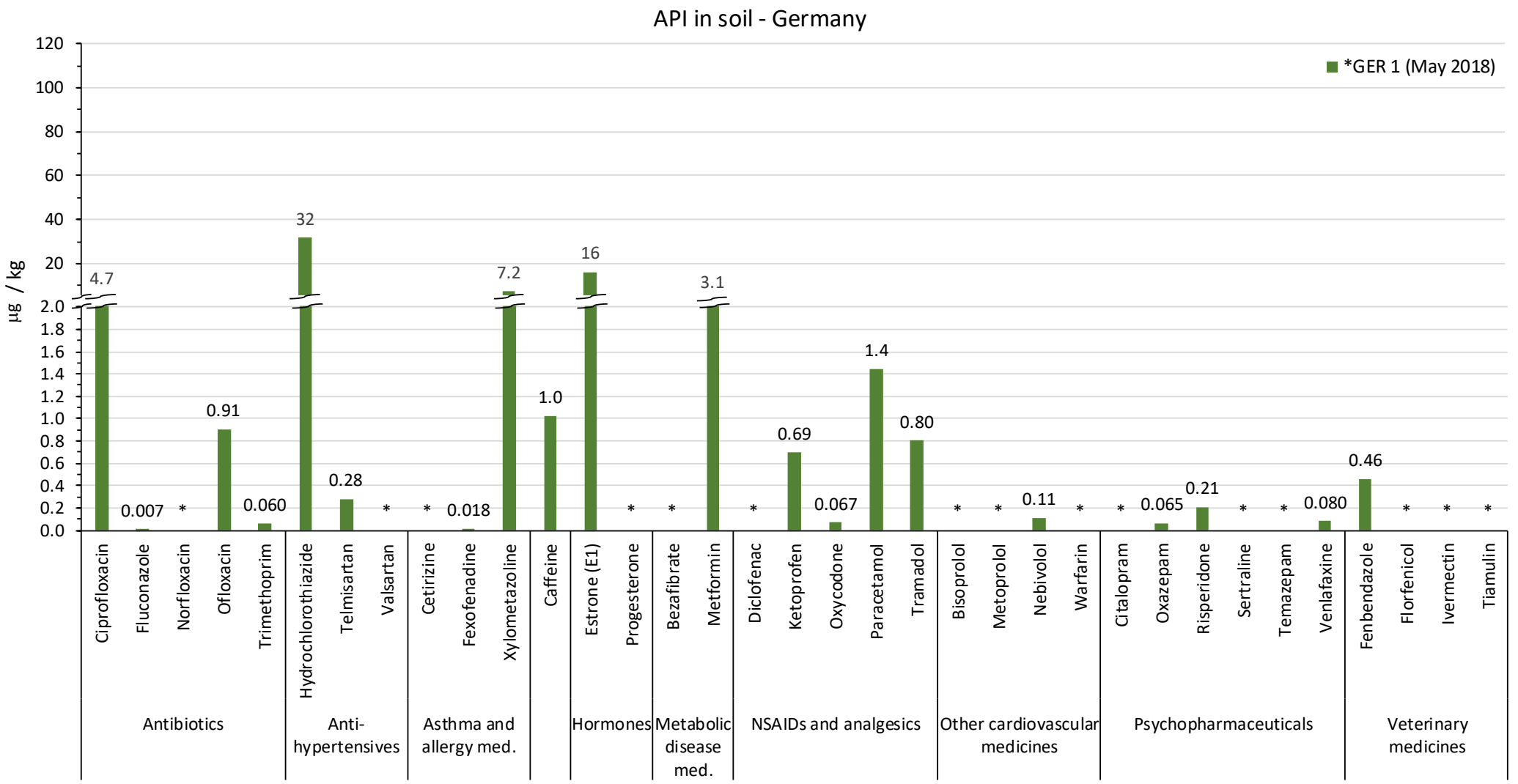

Figure 7.15. API in soil in study area of Germany; GER 1. API below detection limit are marked with "*".

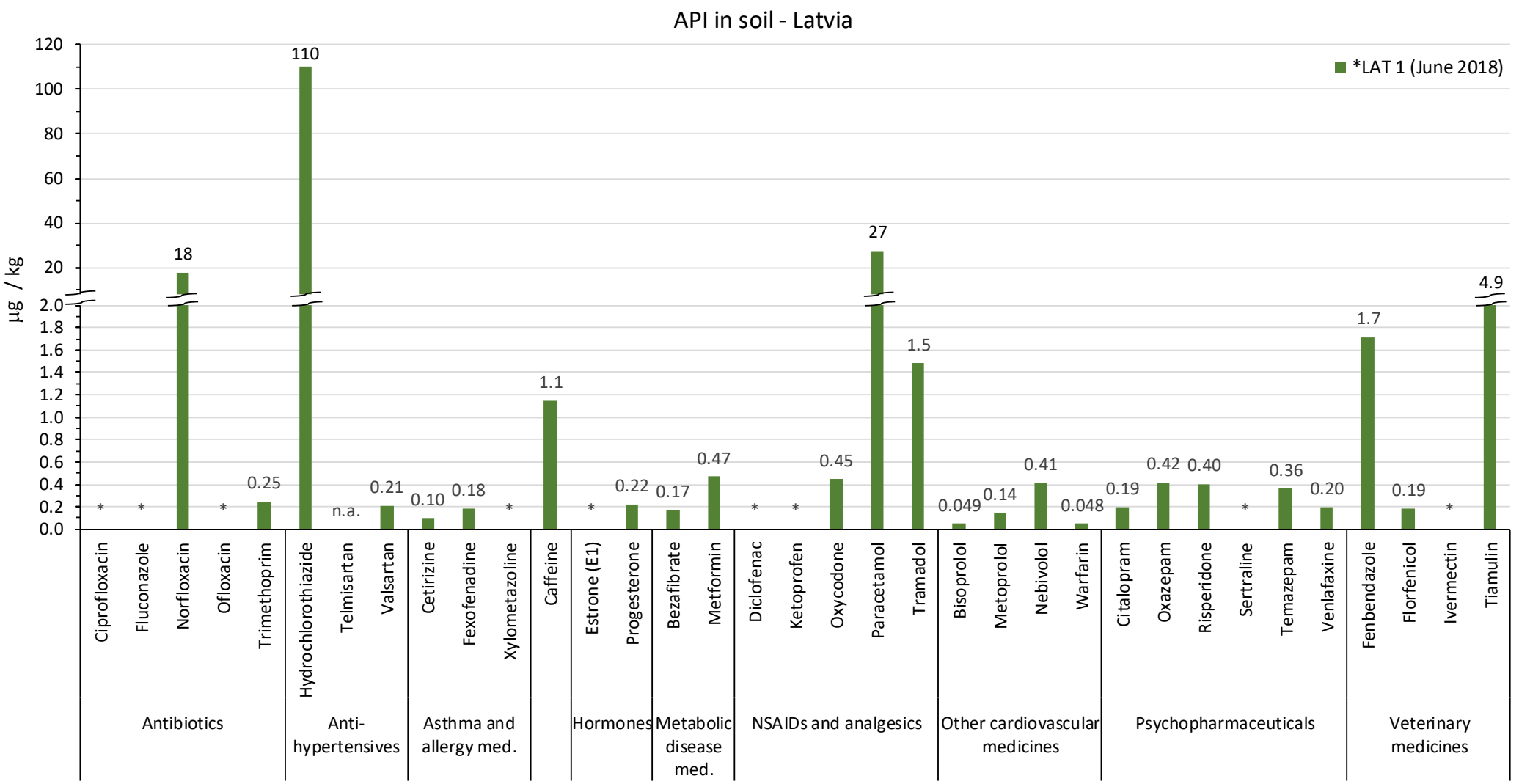

Figure 7.16. API in soil in study area of Latvia; LAT 1. API below detection limit are marked with "*".

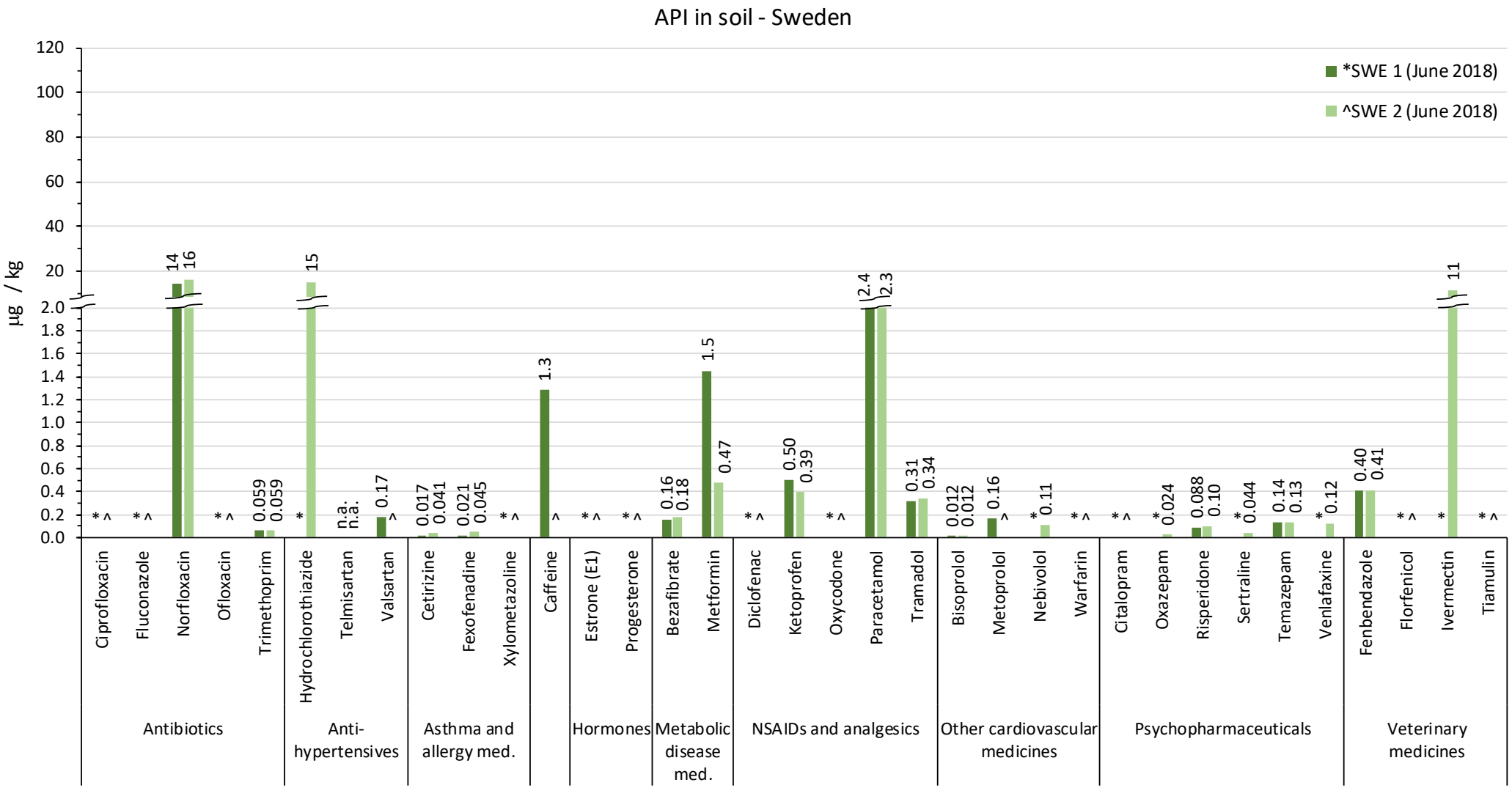

Figure 7.17. API in soil in two study areas of Sweden; SWE 1 and SWE 2. API below detection limit are marked with "*" for SWE 1 and "^" for SWE 2.

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8 Linkage between API consumption and levels in WWTP influents

8.1 Materials and methods

Country specific consumption data were used to predict the API load at the WWTP, which then was compared with the measured API load based on sampling campaigns at 15 WWTPs in Estonia, Finland, Germany, Latvia, Poland and Sweden. Within this chapter, we evaluated how well the predicted load to the WWTP (based on the consumption data described in chapter 4) is in agreement with the actual measured load (mload) at the WWTP influent based on the conducted sampling campaigns (described in chapter 6). The predicted API load (pload, average API consumption per capita) was calculated based on the following equation 1, using the averaged country specific consumption data of the years 2015–2017, as described in chapter 4.

$$p_{load} = \frac{m_{API} * 10^6}{pop * 365} \quad [1]$$

with

p_{load} = predicted specific API − load $\left[\frac{mg}{inh * d}\right]$

m_{API} = total quantity of consumed API $\left[\frac{kg}{a}\right]$

pop = population of specific Baltic Sea country [inh]

For validation of the predicted specific API load, the measured specific API load based on the measured API concentration was calculated according to equation 2. According to chapter 6 the dataset of the measured API concentration in the influent of the selected WWTPs was cleaned by means of:

- data of samples, that were melted during delivery;
- interference for the specific API due to matrix effects.

$$m_{load} = \frac{C_{API} * Q * 10^{-6}}{pop_{WWTP}} \quad [2]$$

with

m_{load} = measured specific API − load $\left[\frac{mg}{inh * d}\right]$

C_{API} = API concentration measured at WWTP influent $\left[\frac{ng}{L}\right]$

Q = flow at WWTP at sampling day $\left[\frac{L}{d}\right]$

pop_{WWTP} = real inhabitants connected to WWTP $[inh]$

To get a country specific measured API-load, the average for each API load and country was calculated, based on the sampling campaign for each WWTP (three WWTPs per country, one winter-sampling, one summer-sampling).

To evaluate if the measured and the predicted loads are in good argeement, the following criteria were used:

- prediction too high: $m_{load} < 0.5 * p_{load}$
- prediction similar to measurement: $0.5 * p_{load} \leq m_{load} \leq 2 * p_{load}$
- prediction too low: $m_{load} > 2 * p_{load}$

8.2 Results and discussion

The calculations of the predicted and measured API loads were performed for 22 of the 75 measured APIs. The other 53 APIs were excluded in this evaluation as their consumption data were not available in all countries or they were below LOQ at the monitored WWTPs. The selected 22 APIs cover all API groups, except asthma medication. The determined API loads are summarized in the following table 8.1.

Table 8.1. Compaison of predicted and measured API load for the 22 evaluated APIs

API	Finland		Sweden		Germany		Latvia		Estonia	
	p-load	m-load	p-load	m-load	p-load	m-load	p-load	m-load	p-load	m-load
	[mg/inh*d]		[mg/inh*d]		[mg/inh*d]		[mg/inh*d]		[mg/inh*d]	
Carbamazepine	1.53	0.06	1.55	0.12	1.22	0.27	1.98	0.14	2.16	0.49
Citalopram	0.36	0.13	0.45	0.07	0.23	0.08	0.01	0.01	0.03	0.02
Codeine	0.82	0.91	0.45	0.21	0.02	0.08	0.08	0.02	0.31	0.45
Diclofenac	1.23	1.27	0.78	0.62	0.90	1.31	2.72	0.78	3.14	1.81
Erythromycin	0.02	0.06	0.15	0.20	0.49	1.07	0.06	0.06	0.00	2.67
Fluconazole	0.06	0.06	0.05	0.03	0.01	0.02	0.03	0.02	0.03	0.01
Gabapentin	4.10	5.61	4.12	10.88	2.77	2.81	2.99	1.63	1.66	1.77
Hydrochlorothiazide	1.03	1.19	0.15	1.36	1.80	1.21	0.37	0.69	0.55	1.99
Ketoprofen	0.19	0.08	0.50	0.13	0.01	0.02	0.12	0.08	0.47	0.27
Levetiracetam	3.38	2.77	2.33	1.85	4.20	3.17	0.37	0.28	0.58	0.55
Mesalacine	9.54	2.20	8.56	1.03	3.62	1.69	0.64	0.96	1.59	2.08
Metformin	74.57	39.23	31.81	22.54	54.02	30.83	40.70	9.42	47.47	15.30
Naproxen	3.86	1.15	6.05	1.69	0.57	0.19	1.06	0.21	3.95	1.21
Norethisterone	0.01	0.23	0.00	0.26	0.00	0.13	0.00	0.10	0.00	0.03
Oxazepam	0.27	0.44	0.00	0.08	0.01	0.02	0.03	0.01	0.00	0.02
Paracetamol	102.40	145.88	151.89	127.67	1.08	27.37	20.73	43.42	38.84	27.54
Sotalol	0.08	0.03	0.09	0.02	0.07	0.01	0.08	0.02	0.23	0.04
Sulfamethoxazole	0.19	0.04	0	0.04	0.56	0.05	1.43	0.07	0.85	0.07
Telmisartan	0.57	1.14	0.01	0.03	0.23	0.58	0.71	0.35	2.14	1.49
Tramadol	0.86	0.14	0.97	0.22	0.72	0.10	0.50	0.05	0.67	0.11
Trimethoprim	0.45	0.21	0.05	0.04	0.16	0.05	0.30	0.07	0.17	0.05
Venlafaxine	0.98	0.26	0.99	0.16	0.64	0.15	0.08	0.01	0.24	0.06

p-load: predicted API load based on consumption data, m-load: measured API load at WWTP influent

As an example, a detailed comparison of the measured and predicted load is presented for the four selected APIs: carbamazepine, diclofenac, metformin, and paracetamol. APIs were selected due to their consumption, removal in WWTPs, and occurrence in surface waters.

Carbamazepine is one of the most commonly used anti-epileptics and is also used off-label for treatment of bipolar disorder. Carbamazepine is highly persistent and is usually not degraded in WWTPs (Verlicchi et al. 2012). There is a lot of discussion about including carbamazepine in the European Watch List (EU COM 2015/495). Sampling campaign within CWPharma detected carbamazepine in inland and coastal waters in a range from < 0.005 ng/L to 920 ng/L with a median

concentration of 3.7 ng/L (inland waters) and 2.0 ng/L (coastal waters), respectively.

Diclofenac is a commonly used nonsteroidal anti-inflammatory drug (NSAID) and is hardly biodegradable in WWTPs. Diclofenac was a monitoring parameter of the "Surface Water Watch List" or the first "Watch List" of the European Union (EU COM 2015/495) and it is considered as a candidate to the list of priority substances under European union water policy. Diclofenac was detected in inland and coastal waters within the CWPharma screening campaigns in a range from < 1.2 ng/L to 2200 ng/L, with a median concentration of 33 ng/L (inland waters) and 2.7 ng/L (coastal waters), respectively.

Metformin is a pharmaceutical for the treatment of type 2 diabetes and was selected due to its high consumption as it is among the top three consumed APIs in all Baltic Sea countries. Metformin is partially biodegraded to guanyl urea in WWTPs. Due to its high loads, metformin and guanyl urea are ubiquitously detected in surface waters. In CWPharma, metformin was detected within a range from < 0.24 ng/L to 2 300 ng/L. Median concentrations were 78 ng/L for inland waters and 12 ng/L for coastal waters, respectively. Guanyl urea was not analysed within CWPharma.

Paracetamol is a moderate pain killer and used to relieve fever. Similar to metformin, paracetamol is in the top three of the most consumed pharmaceuticals in almost all Baltic Sea countries. Despite its high consumption, paracetamol can only be detected in low concentrations in surface waters as it is biodegradable at WWTPs. Within CWPharma paracetamol was not included in surface water monitoring campaign.

Figure 8.1 shows the correlations between the predicted and the measured API load of the four selected APIs (carbamazepine, diclofenac, metformin and paracetamol). The rest of the evaluated APIs are presented in Annex 18.

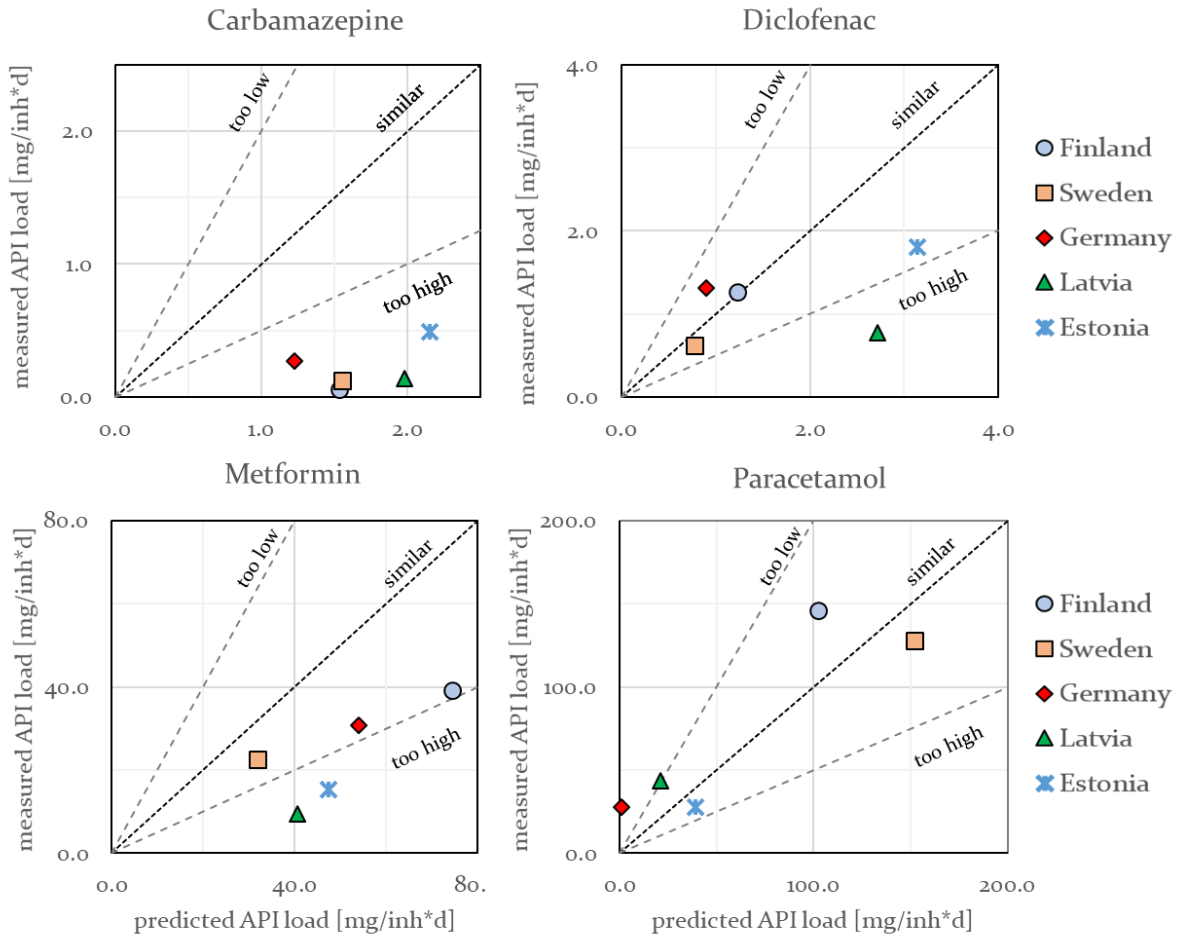
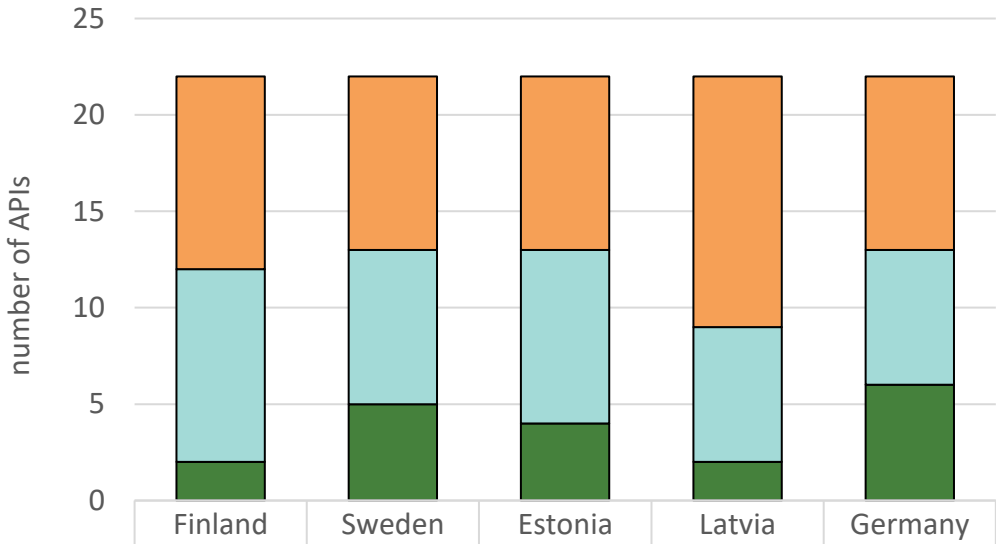


Figure 8.1. Correlation between predicted API load and measured API load for carbamazepine, diclofenac, metformin and paracetamol.

For carbamazepine, the predicted API load was always overestimated (prediction too high). A possible explanation could be not considering pharmacokinetic mechanisms of action for carbamazepine. Only 2–3% of the consumed carbamazepine is excreted by the human body in its original form, whereas the rest is transformed into metabolites (e.g. carbamazepine-10,11 epoxide) and thus, is not considered in this evaluation (gelbe-liste.de 2020). In the case of diclofenac, predicted API load for Finland and Sweden is in a very good agreement with the measured API load. Diclofenac load for Estonia and Germany is also in a good agreement, whereas for Latvia the predicted load is too high. Even though less than 1% of the oral diclofenac intake is excreted as unchanged (gelbe-liste.de 2020), pharmacokinetic mechanism of action is not expected to have a similar impact on API load as it might have for carbamazepine, because a large fraction of diclofenac is used within topical formulations (≥ 65% in Finland, see chapter 4) and can therefore be washed off from the body as is. Prediction for metformin load was found to be in good agreement with the measurements for Finland, Sweden and Germany, whereas prediction was too high for Latvia and Estonia. Predicted API loads for paracetamol are in good agreement with the measured API loads, except for Germany (prediction too low). 70% and 90% of the consumed metformin and paracetamol, respectively, is excreted as is.

To evaluate whether pharmacokinetic mechanisms of action have an impact on the overall picture, a simplified evaluation was performed for these four APIs by multiplying the predicted API-loads with the factor of APIs leaving the human body as is: carbamazepine (2.5 %), diclofenac (65%, assuming most of the topical applied diclofenac is washed off), metformin (70%), and paracetamol (90%). All in all, agreement of predicted and measured API-load hardly changed based on the used criteria and therefore a more detailed analysis was not conducted. However, it should be noted that the correction of the API load prediction for carbamazepine resulted in a change from over- to an underestimation for all countries and the absolute difference to the measured load was much lower. Agreement of the measured and predicted API load of the 22 selected APIs is summarized in figure 8.2. 100% pharmacokinetic elimination was assumed for all evaluated APIs.



	Finland	Sweden	Estonia	Latvia	Germany
prediction too high	10	9	9	13	9
prediction similar to measurement	10	8	9	7	7
prediction too low	2	5	4	2	6

Figure 8.2: Agreement of predicted API load and measured API load based on all 22 evaluated APIs (table 8.3.1)

The best agreement of the predicted and measured API load was found for Finland (45 % of all APIs), followed by Estonia (41% of all APIs) and Sweden (36 % of all APIs), whereas worst agreement was found for Germany and Latvia (32% of all APIs). In most cases API loads showed an overestimation tendency for all countries. A possible explanation for this overestimation tendency could be the quality of the used API consumption datasets. For Finland, Sweden, Latvia, and Estonia, all prescriptions and privately sold APIs are recorded and included in the public available datasets. In contrast, publicly available consumption data from Germany only include prescribed pharmaceuticals from statutory health insurance (73.24 million customers) (GKV 2020). Thus, pharmaceuticals that are sold over the counter or billed by private health insurance companies (8.74 million customers) (PKV 2020), are not included within this dataset. In general, total amounts of sold pharmaceuticals are provided in "defined daily dose" (DDD) per year for all countries within CWPharma project, which results in additional uncertainties when converting it into kg API/year. DDDs for the same API can differ for the drug's route of administration, combination products and formulations (e.g. for Diclofenac). This overestimation of the predicted API load might be attributed to the following reasons:

- Not all sold or prescribed APIs have been consumed by the customer
- Regional differences in API consumption are not considered (e.g. demographics)
- Pharmacokinetic mechanisms of action are not considered in calculation.

8.3 Conclusions

This study showed that the measured and predicted load are in good agreement for some APIs (e.g. diclofenac and paracetamol) in most of the countries, whereas load prediction for other APIs (e.g. carbamazepine) will result either in an over- or underestimation.

The best agreement of the predicted and measured API load for 22 APIs was found for Finland (50% of all APIs), followed by Estonia (41% of all APIs) and Sweden (36 % of all APIs), whereas worst agreement was found for Germany and Latvia (32% of all APIs). In most cases API loads showed an overestimation tendency for all countries.

Country wise comparison of the predicted and measured API load provides a clear indication that usage of high-quality consumption data (e.g. inclusion all sold APIs) result in a general better agreement of the API loads. Taking into account other factors such as regional differences (e.g. demographic) or pharmacokinetic mechanisms of action (e.g. metabolism) might also improve the prediction of the API load. In addition, as measured API-loads are only based on two sample campaigns in two different seasons, with only one to four WWTPs per country, the overall picture might change with an increased database.

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9 Environmental risk assessments of pharmaceuticals

9.1 Materials and methods

9.1.1 General

Environmental risk assessments of pharmaceuticals in the Baltic Sea Region were performed by comparing measured environmental concentrations of 82 active pharmaceutical ingredients (APIs) with calculated predicted no effect concentrations. For this purpose, we collected an extended database on the ecotoxicity of the APIs. Sources of ecotoxicological endpoints were screened from literature and databases. Additionally, we performed ecotoxicological tests on two APIs (nebivolol and cetirizine) for which data were not available. Predicted no effect concentrations (PNECs) were calculated based on collected data points, i.e. EC(LC)50-t[9], NOEC-t[10] and LOEC-t[11]. These values were compared to the measured pharmaceuticals concentrations of the samples collected in the CWPharma project case studies (Chapters 5-7).

9.1.2 Substance characteristics

Physico-chemical and biological information about the studied APIs is presented in Annex 19.

9.1.3 Information sources

Numerous information sources were used to generate a database on the ecotoxicity of the selected APIs. These included in particular the databases and journals described in tables 9.1 and 9.2.

For the estimation of unknown properties of APIs (especially octanol-water partition coefficient) EPI SUITE Software[12] was used.

Table 9.1. Alphabetical list of databases used as a source of ecotoxicity endpoints.

Database	Link
Agency for Toxic Substances and Disease Registry database	http://www.atsdr.cdc.gov/toxprofiles/index.asp
Cal/Ecotox	http://oehha.ca.gov/cal_ecotox/
Columbia Environmental Research Center Acute Toxicity Database	http://www.cerc.usgs.gov/data/acute/acute.html
ECHA	http://echa.europa.eu/search-for-chemicals
ECOTOX	https://cfpub.epa.gov/ecotox/
EPA	http://www.ipmcenters.org/ecotox/
FASS	https://www.fass.se/LIF/startpage
PAN Pesticide Database	http://www.pesticideinfo.org/Search_Ecotoxicity.jsp
TOXicology Data NETwork	http://toxnet.nlm.nih.gov/
WikiPharma	http://www.wikipharma.org/welcome.asp

[9] Median effect (lethal) concentrations
[10] No observable effect concentration
[11] Lowest observable effect concentration

[12] https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

Table 9.2. Alphabetical list of science paper repositories used as a source of ecotoxicity endpoints.

Journal repository	Link
ACS Publications	http://pubs.acs.org/
Directory of Open Access Journals	https://doaj.org/
EBSCO Information Services	https://www.ebscohost.com/title-lists
Google Scholar	https://scholar.google.com/
Ingenta Connect	http://www.ingentaconnect.com/
Knovel Engineering Data and Technical References	https://app.knovel.com/web/index.v
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/
ScienceDirect	http://www.sciencedirect.com/
Scopus Preview	https://www.scopus.com/
SpringerLink	http://link.springer.com
Taylor & Francis Online	http://www.tandfonline.com/
The Royal Society of Chemistry's Journals, Books and Databases	http://pubs.rsc.org/
Web of Science	http://webofscience.com/
Wiley Online Library	http://onlinelibrary.wiley.com

9.1.4 Ecotoxicological testing

Ecotoxicological data were not found for nebivolol and cetirizine in the literature. Therefore, ecotoxicological tests were carried out using three different trophic level bioindicators: bacteria, algae, and crustaceans.

9.1.4.1 Bacterial bioluminescence test

The purpose of this study was to determine the effects of cetirizine and nebivolol on the bioluminescence of bacteria *Aliivibrio fischeri* (lyophilized luminescent marine bacteria, strain NRRL-B 11177) using Microtox®500 system analysis (Strategic Diagnostic Ink, Newark, USA). As the test system requires aqueous dilutions, solutions were prepared considering the internal dilution of samples within the test.

Test conditions

The study was conducted in a test room with temperature control and continuous lighting. Incubation conditions were:

- Temperature in the test vessels: 15 ± 0.5°C,
- Temperature in Reagent Well vessel: 5.5 ± 1°C,
- Readings at times: 5, 15 and 30 minutes after sample introduction to the vessel with bacteria
- Number of replications: 2
- Number of dilutions: 5
- Dilution factor: q = 2
- Test procedure: 81.9% Basic test procedure

The bacteria preparation

The bacteria used in the test were preincubated in Reconstitution Solution for about 15 minutes to revive. Then dilutions of bacteria were made and incubated about 15–25 minutes before sample introduction.

Test item preparation

In the test procedure, the introduced sample was diluted to 81.9% of the original concentration. Therefore, it was necessary to prepare the input concentration 18.1% higher than the wanted test concentration (to finally have the maximum concentration of 5 mg/L for nebivolol hydrochloride

and 100 mg/L for cetirizine hydrochloride in the test). The highest concentration was prepared using redistilled water. Then the sample was brought to the appropriate osmotic pressure with Osmotic Adjusting Solution and next the geometric series of dilution were prepared using the Diluent Solution according to the manufacturer's test procedure. The tests were performed in five concentrations:
Nebivolol hydrochloride: 5.000, 2.500, 1.250, 0.625 and 0.313 mg/L
Cetirizine hydrochloride: 100.00, 50.00, 25.00, 12.50 and 6.25 mg/L

Measurements

The reaction of the bacteria on the test items was measured after 5, 15 and 30 minutes incubation in temperature +15°C. The Diluent was used as a negative control. The results were expressed as the percentage of bioluminescence inhibition 5, 15 and 30 minutes after sample introduction. Additionally, the EC- 10, EC- 20, EC- 50 effects and Toxicity Unit values were calculated. The analysis of the results was done using Microtox® Omni software.

9.1.4.2 Algal growth inhibition test

The purpose of this test was to determine the effects of cetirizine and nebivolol on the growth of algae *Pseudokirchneriella subcapitata* according to OECD 201. OECD medium was used as a test medium. Toxic effects were assessed based on changes in the algae yield and growth rate under the test conditions.

Test conditions

The test was carried out in a room with controlled temperature and lighting. The test conditions were in agreement with the OECD 201 requirements:

- Temperature in test vessels: within 23.4–23.8 ºC and did not change more than ± 2ºC during the test.
- Medium pH: for cetirizine pH at the test initiation day was 8.12 and ranged from 7.73 to 7.83 in tested concentrations. At the end of the test pH in controls ranged from 8.13 to 8.81 and 7.83 to 8.52 in the test item solutions. The pH of medium and tested concentration did not vary by more than 1.5 units during the test. For nebivolol pH at the test initiation day was 8.12 and ranged from 7.81 to 7.88 in tested concentrations. At the end of the test pH in controls ranged from 8.13 to 8.81 and 7.87 to 8.24 in the test item solutions. The pH of medium and tested concentration did not vary by more than 1.5 units during the test.
- Lighting: continuous, cool fluorescent light, with the intensity of 7650-8480 lux for cetirizine and 7820-8640 lux for nebivolol was used. Maximal difference in lighting measured daily did not exceed recommended value of 15%
- Continuous shaking on orbital shaker at 100–150 rpm
- Test duration: 72 hours.

The test vessels were closed with sterile cellulose plugs, to limit evaporation and avoid cross contamination but allowing gas exchange and incubated under the conditions described above. The test was carried out in sterile 250-mL Erlenmayer flasks, made from class 3.3 borosilicate glass. The pre-culture of algae inoculum in the test medium was prepared 2–4 days before the start of the test, in order to ensure the algae were in an exponential growth phase.

Algal cell density in pre-culture inoculum was counted at the beginning of the test. The initial volume of inoculum introduced into test vessels was calculated based on the cell density, to reach the recommended initial number of algal cells in every flask (5 000–10 000 cells/mL). Algal culture suspension was introduced into the test item solutions in all test vessels. In the same way control vessels (without any test item addition) were prepared containing only OECD test medium. Additional test vessel containing only the OECD medium to measure the temperature during the test was prepared and incubated in parallel with other vessels.

The test was carried out under static conditions due to the expected stability of the test substances in aqueous solutions.

Test item preparation

The test was carried out with five nominal concentrations of the test material:

Cetirizine: 100.0, 40.0, 16.0, 6.4, 2.6 and 1.0 mg/L

Nebivolol: 6.0, 2.4, 0.96, 0.38, 0.15 and 0.06 mg/L

Measurements

The test was conducted in three replicates per each test item concentration and six replicates for negative control. Each test vessel contained the same volume of solution (100 mL). *Pseudokirchneriella subcapitata* inoculum was introduced into each vessel. Test vessels were randomly put on orbital shakers and the position of each vessel was randomly changed daily to reduce possible unequal lighting conditions.
A calibration curve was prepared to determine the relationship between the fluorescence of the algae suspension and the number of algae cells. The fluorescence measurement was carried out using the microplate reader BMG Clariostar with the following working parameters:

- time of shaking of microplates: 15 s,
- length of the excitation beam: 410 nm with a band width of about 40 nm,
- length of the emitted light 670 nm, band width 25 nm,
- orbital averaging.

Algal number was measured in each test vessel indirectly by measuring the fluorescence of the test solutions after 24, 48 and 72 hours. On the experimental termination day additional microscopic observation was carried out to verify any abnormal appearance of algae cells at each tested concentration. In addition, the pH of the test and control solutions was determined at the beginning and the end of the test. The intensity of light was also measured daily at five points on the surface where the test vessels were placed and the temperature in the additional control vessel was recorded.

ToxRat Profesional software (version 3.2.1) was used for calculating the endpoints and analysing biological data.

9.1.4.3 Daphnia magna immobilization test

The aim of the study was an assessment of acute toxicity of cetirizine and nebivolol to *Daphnia magna*, according to OECD test guideline 202. A standard Elendt M4 medium was used as a test medium. Toxic effects were evaluated based on the immobilisation of the test organisms. The study was conducted in a test room with controlled temperature and lighting.

Test conditions

Incubation conditions were the following for cetirizine and nebivolol:

- Temperature in the test vessels was 21.7-22.0 °C during the 48 h test,
- Medium pH 7.36 used for preparation of the test solutions, the pH values at the end of the test were 7.47 – 7.55 (controls) and 7.41 – 7.62 (the highest concentration).
- Medium hardness: 242.35 mg/L (as $CaCO_3$),
- Lighting: no light,
- Oxygen: the dissolved oxygen concentration at the beginning of test was 5.58 mg O_2/L in control and test vessels, after 48 hours, the oxygen concentration in the test vessels was on average 4.81 mg O2/L (control), and 4.55 mg O2/L (the highest concentration).
- Test duration: 48 hours.

The test vessels were loosely covered with a pane of glass to limit evaporation and external contamination and were incubated in accordance with the conditions described above.
The test vessels were not aerated and the daphnids were not fed during the test. Test was performed in clean 50-mL beakers (borosilicate 3.3.).

One day before the beginning of the exposure, the adult female daphnids (after first brood) were isolated and transferred to fresh Elendt M4 medium. Young daphnids, aged less than 24 hours at the start of the test, were used. The neonates used in the test came from healthy parent organisms.

Test item preparation
The test was performed using the following concentrations:
Cetirizine: 100, 40, 16, 6.4 and 2.6 mg/L
Nebivolol: 3, 1.5, 0.75, 0.36 and 0.19 mg/L
The test solutions were prepared in Elendt M4 medium.

Measurements
Four replicates were used for the test item concentration and for the control. Control vessels contained the same nutrient medium and number of daphnids as the test vessels but without the test substance. Each test vessel contained the same volume of solution, approximately 40 mL, and the same number of daphnids (five for one vessel). In total 20 daphnids were used for single test item concentration as well as for the controls (4 vessels x 5 daphnids). Neonates of *Daphnia magna* were randomly placed into the test vessels. Additional test vessel containing only the Elendt M4 medium was prepared for temperature measurements and incubated in parallel with other vessels.

The number of the immobilised daphnids was counted, and the medium temperature was measured, in the beginning of the test and after 24 and 48 hours of exposure.

Before starting the test, the hardness of the test medium was measured.
The pH and the dissolved oxygen content of the test solutions and control samples were measured in the beginning and at the end of the experiment. The illumination intensity was measured on the experiment starting day at the five points of the surface on which the test vessels were placed.
ToxRat Professional (version 3.2.1) software was used to analyse the data from the study.

9.1.5 Risk assessment methodology
To assess environmental risk caused by APIs in the Baltic Sea region, the risk quotient (RQ) approach was used. Measured environmental concentrations (MEC) were compared with the PNECs derived from the ecotoxicological studies.

1. $RQ = \frac{MEC}{PNEC}$

When RQ is equal or above 1 (that means the concentration in the environment exceeds the safe concentration for biota) unacceptable risk is identified.

9.1.5.1 Determination of $PNEC_{water}$
PNECs for water were derived from the ecotoxicity data in the literature and produced within the project. Depending on quality and quantity of ecotoxicological endpoints, an assessment factor (AF) method or species sensitivity distributions (SSD) approach were used.

9.1.5.2 Assessment factors
When limited amount of ecotoxicity data points (less than 8) was available, the $PNEC_{water}$ was defined as:

2. $PNEC_{water} = \frac{lowest\ EC(LC)50}{AF}$

Assessment factors (AFs) vary depending on the type (acute/chronic) and number of the available test results. The assessment factors and their criteria are presented in Table 9.3.

Table 9.3. Assessment factors used to derive PNEC.

Available data	Assessment factor
Up to 8 acute test results	AF=1000
Up to 2 chronic test results	AF=100
At least 3 chronic test results, from 3 trophic levels	AF=10

9.1.5.3 Species sensitivity distributions

When eight or more data points were available for an API, species sensitivity distribution (SSD) approach was used. The idea of the SSD was proposed nearly four decades ago as an ecotoxicological tool that is useful for the derivation of environmental quality criteria and ecological risk assessment (Posthuma at al. 2001). SSD method assumes that results of ecotoxicity tests (usually chronic endpoints line NOEC) are subjected to statistical distribution. Different types of distribution are assigned a priori including e.g. log-normal, Weibull and log-logistic. SSD is therefore a statistical distribution describing the variation in the toxicity of a certain compound or mixture among a set of species. For such constructed distribution value of 5th percentile is calculated. This value corresponds to hazardous concentration for 5% (HC5) of species in the ecosystem. Two approaches might then be applied to convert HC5 into PNEC value. First one is the use of arbitrary set assessment factor ranging from 1 to 10. Second one, slightly more conservative (that additionally take into account variability of input SSD data) is to use lower 95% confidence interval (LCL) of HC5 as an estimate of real PNEC value. When estimating the PNECs with the SSD method, using the LCL approach, a highly variable data set will result in a relatively conservative PNEC. Hence, the PNECs derived from the LCL approach may lead to overestimation of the environmental risk, especially in case of large and diverse (i.e. with high range) data set.

Chronic data were used to derive SSD for all APIs of interests under CWPharma project. If only acute data were available, they were transformed into chronic data based on an acute-to-chronic ratios (ACR) approach. Analysis of ACR is an important tool to derive acceptable no-effect levels and to re-evaluate and support current risk assessment approaches. The acute endpoints were converted into chronic ones with the following equation:

3. $NOEC = \frac{\mathrm{LC(EC)50}}{\mathrm{ACR}}$

Numerous values are assigned as ACR depending on the class of chemicals and their mode of action, but factor of 10 is the most often used and was used for transforming acute endpoint into chronic one.

$PNEC_{water}$ was defined as:

4. $PNEC_{water} = LCL(HC_5)$,

where LCL(HC5) is the lower confidence interval (LCL) of hazardous concentration for 5% of species (HC5).

Hazardous concentrations (HC5) were calculated based on chronic endpoints using *ssdtool*[13] package for language and environment for the statistical computing and graphics software *R*[14]. Seven different distributions were fitted to data points (i.e. log-normal, log-logistic, log-Gumbel, Gompertz, gamma, Weibull and Pareto). Based on Akaike's Information Criterion corrected for sample size, the best fit distribution was selected. Confidence intervals were calculated using bootstrap methods with n=500 subsamples.

9.1.5.4 Determination of $PNEC_{sediment}$ and $PNEC_{soil}$

Calculated $PNEC_{water}$ were used to estimate analogous values for soil and sediment compartments. Recalculation was done based on a method for risk assessment for organic chemicals (European Centre for Ecotoxicology and Toxicology of Chemicals, 2004) using the following equations:

1. $PNEC_{sediment} = PNEC_{water} * (0.783 + 0.0217 * K_{oc})$,
2. where K_{oc} is the organic-carbon partition coefficient, and $PNEC_{soil} = \frac{K_{oc} * PNEC_{water}}{85}$,

where 85 is the conversion factor taking into account normalized fraction of organic carbon in soil (0.02) and the bulk density of wet soil (1700 kg/m^3).

When available, the experimental K_{oc} values of the APIs were applied directly (or a geometric mean if more than one K_{oc} value was reported). If an experimental K_{oc} was not available, EU TGD QSAR with the following equations was used to predict the K_{oc} value:

- For hydrophilic substances (i.e. log K_{ow}<3)

3. $logK_{OC} = 0.52logK_{OW} + 1.02$

- For hydrophobic substances (i.e. log K_{ow}≥3)

4. $logK_{OC} = 0.81logK_{OW} + 0.1$

The octanol-water and octanol-carbon partition coefficients that were applied in the PNEC calculations are presented in Table 9.4

[13] https://cran.r-project.org/web/packages/ssdtools/index.html
[14] RStudio Team (2019). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.

Table 9.4. Octanol-water and octanol-carbon partition coefficients used for $PNEC_{soil}$ and $PNEC_{sediment}$ calculations.

Substance	API group	$logK_{ow}$	$logK_{oc}$
Ciprofloxacin	Antibiotics	0.28	4.78*)
Clarithromycin		3.16	2.66
Doxycycline		-0.02	1.01
Erythromycin		3.06	2.79*)
Fluconazole		0.58	4.72*)
Lincomycin		0.56	1.31
Norfloxacin		0.46	4.79*)
Ofloxacin		-0.39	3.31*)
Sulfadiazine		-0.09	0.97
Sulfamethoxazole		0.84	1.88*)
Tetracycline		-1.37	0.31
Trimethoprim		1.08	1.88*)
Carbamazepine	Antiepileptics	2.45	2.51*)
Gabapentin		-1.10	0.45
Levetiracetam		-0.60	0.71
Primidone		0.86	1.47
Amlodipine	Antihypertensives	3.00	2.53
Candesartan		6.10	5.04
Enalapril		0.07	1.06
Eprosartan		3.90	3.26
Hydrochlorothiazide		-0.07	1.08*)
Irbesartan		6.00	4.96
Losartan		6.10	5.04
Ramipril		2.90	2.53
Telmisartan		6.77	2.20*)
Valsartan		3.07	2.40*)
Cetirizine	Asthma and allergy medications	2.80	2.30*)
Fexofenadine		2.60	3.64*)
Fluticasone		2.69	2.42
Mometasone		2.10	2.11
Xylometazoline		3.84	4.83*)
Esomeprazole	Gastrointestinal disease medications	0.60	1.33
Mesalazine		1.20	1.64
Omeprazole		2.08	2.10
Pantoprazole		2.11	2.12
17-α-ethinyl estradiol (EE2)	Hormones	4.15	3.68*)
17-β-estradiol (E2)		3.40	3.52*)
Estriol (E3)		2.45	2.29
Estrone (E1)		3.13	3.04*)
Norethisterone		2.97	2.56
Progesterone		3.87	3.45*)
Testosterone		3.32	2.79
α-Estradiol		3.99	3.33
Allopurinol	Metabolic disease medications	-0.55	0.73
Atorvastatin		5.70	4.72

Substance	API group	$logK_{ow}$	$logK_{oc}$
Bezafibrate		4.25	2.06*)
Gemfibrozil		3.40	2.85
Metformin		-1.37	1.28*)
Simvastatin		4.68	3.89
Acetylsalicylic acid	NSAIDs and analgesics	1.28	1.69
Codeine		1.19	1.64
Diclofenac		4.51	2.34*)
Ibuprofen		3.97	3.32
Ketoprofen		3.12	2.45*)
Naproxen		3.18	2.45*)
Oxycodone		0.70	1.38
Paracetamol		0.46	1.32*)
Tramadol		2.07	2.79*)
Caffeine	Other	-0.07	2.87*)
Atenolol	Other cardiovascular medicines	0.02	1.70*)
Bisoprolol		1.87	2.15*)
Dipyridamole		1.50	1.80
Furosemide		2.03	2.08
Metoprolol		1.88	1.78*)
Nebivolol		2.80	2.65*)
Sotalol		0.24	1.14
Warfarin		2.61	1.48*)
Citalopram	Psychopharmaceuticals	3.50	2.96*)
Quetiapine		0.50	1.28
Olanzapine		2.90	2.53
Oxazepam		2.24	2.18
Risperidone		3.49	3.22*)
Sertraline		5.10	4.17*)
Temazepam		2.19	2.85
Venlafaxine		2.71	2.28*)
Carprofen	Veterinary medicines	3.80	3.18
Emamectin benzoate		5.00	4.15
Fenbendazole		2.30	4.73*)
Florfenicol		0.36	1.26*)
Ivermectin		5.83	4.15*)
Tiamulin hydrogen fumarate		4.73	4.56*)
Toltrazuril		4.40	3.66
Tylosin		1.84	1.98

*) indicates experimental K_{oc} used for $PNEC_{sediment}$ and $PNEC_{soil}$ calculations

9.2 Results and discussion

9.2.1 Measured environmental concentrations

Measured environmental concentrations are presented in Annexes 3, 4, 14 – 17 and are discussed in the previous chapters of this report. The measured environmental concentrations were compared to PNEC values to assess the risks the APIs may pose to surface water, sediment and soil organisms.

9.2.2 Predicted no-effect concentrations for water, soil and sediment

The calculated PNEC-values of the studied APIs in water, soil and sediment are presented in Table 9.5. The PNEC values are highly dependent on the data available and the calculation methods applied. For instance, when using the assessment factor approach, the quality and quantity of data implies certain factor to be used. This may have a tendency to increase the PNEC values. On the other hand, when estimating the PNECs with the SSD method, using the LCL approach, a highly variable data set (ie. data set with high range) will result in a relatively conservative PNEC. Nevertheless, some APIs may simply be more toxic to aquatic organisms than others. For example, the surface water PNEC values range from 0.03 ng/L of 17-β-estradiol and ivermectin to 3.3 million ng/L of oxycodone. A summary of ecotoxicological data and the calculated PNEC values are presented in Annex 20. The data sources and the NOEC values that were used for deriving PNEC values are available at external repository: https://helda.helsinki.fi/handle/10138/317151.

While many surface water PNEC values have high uncertainties, the soil and sediment PNECs, which were derived directly from the surface water PNECs (due to lack of ecotoxicity test results for these compartments), are at least as uncertain. Therefore, when applying these PNECs, we advice to check and assess also the recently published ecotoxicity data for certain APIs.

The sensitivity of different species to APIs varies. Photo: Riku Lumiaro, SYKE.

Table 9.5. Predicted No Effect Concentrations for active pharmaceutical ingredients.

Substance	API group	Method for deriving PNEC	PNEC $_{water}$ ng/L	PNEC $_{sediment}$ µg/kg dw	PNEC $_{soil}$ µg/kg dw
Ciprofloxacin	Antibiotics	SSD	5.1	6.66	3.61
Clarithromycin		SSD	3.9	0.41	0.021
Doxycycline		AF=1000	36.9	0.037	0.0044
Erythromycin		SSD	83.5	1.18	0.61
Fluconazole		SSD	15 000	17 300	9 350
Lincomycin		SSD	1 290	1.58	0.31
Norfloxacin		SSD	481	637	345
Ofloxacin		SSD	20.4	0.93	0.49
Sulfadiazine		AF=1000	135	0.13	0.015
Sulfamethoxazole		SSD	43.8	0.11	0.039
Tetracycline		SSD	1 730	1.43	0.042
Trimethoprim		SSD	508 000	1 220	448
Carbamazepine	Antiepileptics	SSD	1 280	10	4.9
Gabapentin		AF=1000	100 000	84.4	3.3
Levetiracetam		AF=1000	100 000	89.4	6
Primidone		AF=1000	100 000	142	34.4
Amlodipine	Antihyper-tensives	SSD	99.5	0.81	0.397
Candesartan		AF=1000	421	1000	544
Enalapril		AF=1000	44 700	46.1	5.99
Eprosartan		AF=1000	100 000	4020	2 140
Hydrochloro-thiazide		AF=10	1 000 000	1040	141
Irbesartan		AF=1000	100 000	198 000	107 000
Losartan		AF=100	7 800	18 600	10 100
Ramipril		AF=1000	100 000	810	397
Telmisartan		AF=1000	9 880	41.4	18.2
Valsartan		AF=100	125 000	776	368
Cetirizine	Asthma and allergy medications	AF=1000	78 600	403	185
Fexofenadine		AF=1000	200 000	19 000	10 200
Fluticasone		AF=1000	550	3.56	1.7
Mometasone		AF=100	14	0.05	0.021
Xylometazoline		AF=1000	2 030	2 970	1 610
Esomeprazole	Gastrointestinal disease medications	AF=10	100 000	125	25.3
Mesalazine		AF=100	911 000	1584	472
Omeprazole		AF=1000	1 760	6.2	2.62
Pantoprazole		AF=1000	48 000	174	74.2
17-α-ethinyl estradiol (EE2)	Hormones	SSD	0.41	0.043	0.023
17-β-estradiol (E2)		SSD	0.03	0.0023	0.0013
Estriol (E3)		AF=100	0.75	0.0038	0.0017
Estrone (E1)		AF=100	0.008	0.0002	0.0001
Norethisterone		AF=10	0.50	0.0044	0.0022
Progesterone		AF=50	2 000	123	65.9
Testosterone		AF=100	1 500	21.2	10.9

Substance	API group	Method for deriving PNEC	PNEC $_{water}$ ng/L	PNEC $_{sediment}$ µg/kg dw	PNEC $_{soil}$ µg/kg dw
α-Estradiol		SSD	0.85	0.04	0.021
Allopurinol	Metabolic disease medications	AF=1000	100 000	90	6.38
Atorvastatin		SSD	2 100	2 380	1 290
Bezafibrate		SSD	1 260	4.13	1.7
Gemfibrozil		SSD	825	13.4	6.94
Metformin		AF=1000	1 350	1.61	0.30
Simvastatin		AF=1000	22 800	3 870	20 90
Acetylsalicylic-acid	NSAIDs and analgesics	SSD	142 000	261	81.2
Codeine		AF=1000	16 000	27.6	8.19
Diclofenac		SSD	85.2	0.47	0.22
Ibuprofen		SSD	0.12	0.0054	0.0029
Ketoprofen		AF=1000	2 000	13.9	6.68
Naproxen		SSD	4 980	34.3	16.5
Oxycodone		AF=1 000	3 300 000	4 320	941
Paracetamol		SSD	1 020	1.26	0.25
Tramadol		AF=1000	170 000	2 410	1 230
Caffeine	Other	AF=1000	87 000	1 470	758
Atenolol	Other cardiovascular medicines	SSD	194 000	363	115
Bisoprolol		AF=1000	8 000	30.6	13.2
Dipyridamole		AF=1000	2 360	5.08	1.75
Furosemide		SSD	15 900	53.5	22.3
Metoprolol		SSD	4 380	9.16	3.11
Nebivolol		AF=1000	377	3.96	1.99
Sotalol		AF=1000	300 000	326	49.3
Warfarin		SSD	67 600	97.7	24.3
Citalopram	Psychopharmaceuticals	SSD	15 400	317	165
Quetiapine		AF=1000	10 000	12	2.24
Olanzapine		SSD	1 200	9.76	4.78
Oxazepam		AF=100	810	3.32	1.46
Risperidone		AF=1000	5 800	216	114
Sertraline		SSD	1 070	344	186
Temazepam		AF=100	930	15	7.74
Venlafaxine		AF=1000	3 220	15.8	7.2
Carprofen	Veterinary medicines	AF=1000	37 300	1 250	660
Emamectin benzoate		AF=1000	1	0.31	0.17
Fenbendazole		AF=100	15	17.5	9.48
Florfenicol		SSD	40 900	48.3	8.84
Ivermectin		AF=1000	0.03	0.0077	0.0041
Tiamulin hydrogen fumarate		AF=1000	165	129	69.9
Toltrazuril		AF=1000	440	44.4	23.9
Tylosin		AF=1000	34	0.097	0.038

9.2.3 Risk quotients

Risk quotients were calculated for each sampling point, each API and each environmental compartment (water, sediment and soil). Risk quotients (RQs) for the substances for which unacceptable risk was identified in at least one sample are presented in Annex 21.

The APIs for which the concentration in inland surface water, coastal water, sediment or soil samples exceeded the PNEC in at least one sample are listed in Tables 9.6–9.11. To summarize, exceedances of the PNECs were identified for:

Antibiotics
- Clarithromycin in inland surface waters, coastal waters and sediments.
- Ofloxacin in inland surface waters, sediments and soils.
- Tetracycline and doxycycline (sum) in one inland surface water sample and in sediments.
- Ciprofloxacin in sediments and soils.

Hormones
- Estrone in inland surface waters, coastal waters, sediments and soils.
- Norethisterone in inland surface waters, coastal waters and sediments.

NSAID and analgesics
- Diclofenac in inland surface waters, sediments and soils.
- Paracetamol in sediments and soils.

Veterinary medicines
- Emamectin in inland surface waters, coastal waters and sediments.
- Ivermectin in soils.

Metabolic disease medication
- Metformin in an inland surface water sample and in sediments and soils.

Asthma and allergy medications
- Mometasone in an inland surface water sample.

For some APIs, the limit of quantification (LOQ) was higher than the PNEC, and therefore also some non-detects may have been above PNEC (e.g. estrone in waters, sediment and soil). In addition to the listed APIs, the PNEC may have been exceeded for the following APIs, which were not detected in the samples but for which the LOQ was higher than the PNEC:
- Antibiotic ciprofloxacin in coastal waters and in surface waters near fish farms.
- Antibiotics erythromycin and sulfamethoxazole, hormone estriol, veterinary medicines ivermectin and tylosin, and asthma and allergy medicine mometasone in sediments.
- Antibiotics clarithromycin, erythromycin, doxycycline and sulfamethoxazole, veterinary medicines emamectin and tylosin, hormones estriol and norethisterone and allergy medicine mometasone in soils.

Another API that may pose an environmental risk is ibuprofen. Ibuprofen was not analysed in surface waters, but it was identified to have a very low PNEC (0.12 ng/L). Ibuprofen was detected in 40% of wastewater effluent samples with concentrations ranging from 3.7 to 44 µg/L. These effluents would require very high dilution not to exceed the PNEC in the receiving waterbody. Therefore, it is very probable that ibuprofen exceeds its PNEC value in inland surface waters.

Table 9.6. APIs exceeding the PNEC in inland surface waters.

Compound	API group	PNEC (ng/L)	Number of samples above LOQ exceeding PNEC
Estrone	Hormone	0.008	14/55[a)]
Clarithromycin	Antibiotic	3.9	25/55
Norethisterone	Hormone	0.50	23/55
Diclofenac	NSAID	85.2	19/55
Ofloxacin	Antibiotic	20.4	8/55
Emamectin	Veterinary	1.0	2/55[b)]
Sum of tetracycline and doxycycline	Antibiotic	36.9 (doxycycline)	1/55
Metformin	Metabolic disease	1350	1/55
Mometasone	Asthma and allergy	14	1/55

a) 31/55 samples were non-detects, but LOQ > PNEC
b) LOQ > PNEC in two samples

Table 9.7. APIs exceeding the PNEC in Baltic Sea coastal water.

Compound	API group	PNEC (ng/L)	Number of samples above LOQ exceeding PNEC
Estrone	Hormone	0.008	14/26[a)]
Emamectin	Veterinary	1.0	5/26[b)]
Clarithromycin	Antibiotic	3.9	1/26
Norethisterone	Hormone	0.50	4/26

a) 12/26 samples were non-detects, but LOQ > PNEC
b) LOQ > PNEC in three samples

Table 9.8. APIs exceeding the PNEC in inland and Baltic Sea coastal sediments.

Compound	API group	PNEC (µg/kg dw)	Number of samples above LOQ exceeding PNEC
Metformin	Metabolic disease	1.6	10/10
Paracetamol	NSAID	1.3	7/10
Ciprofloxacin	Antibiotic	6.7	6/10
Sum of tetracycline and doxycycline	Antibiotic	0.037 (doxycycline)	5/10[a)]
Estrone	Hormone	0.0002	4/10[b)]
Norethisterone	Hormone	0.0044	2/7[c)]
Clarithromycin	Antibiotic	0.41	3/10
Emamectin	Veterinary	0.31	3/10
Ofloxacin	Antibiotic	0.93	2/10
Diclofenac	NSAID	0.47	1/10

a) 5/10 samples non-detects, but LOQ > PNEC
b) 6/10 samples non-detects, but LOQ > PNEC
c) 5/7 samples non-detects, but LOQ > PNEC

Table 9.9. APIs exceeding the PNEC in soils fertilized with manure or WWTP sludge.

Compound	API group	PNEC (µg/kg dw)	Number of samples above LOQ exceeding PNEC
Paracetamol	NSAID	0.25	6/6
Metformin	Metabolic disease	0.30	5/6
Ivermectin	Veterinary	0.004	1/6[a)]
Estrone	Hormone	0.0001	1/6[a)]
Ofloxacin	Antibiotic	0.49	1/6[a)]
Diclofenac	NSAID	0.22	1/6
Ciprofloxacin	Antibiotic	3.6	1/6

a) 5/6 samples non-detects, but LOQ > PNEC

Table 9.10. APIs exceeding the PNEC in surface waters near fish farms.

Compound	API group	PNEC (ng/L)	Number of samples above LOQ exceeding PNEC
Estrone	Hormone	0.008	5/14[a)]
Norethisterone	Hormone	0.50	1/14

a) 9/14 samples were non-detects, but LOQ > PNEC

Table 9.11. APIs exceeding the PNEC in surface waters near pig and poultry farms.

Compound	API group	PNEC (ng/L)	Number of samples above LOQ exceeding PNEC
Estrone	Hormone	0.008	1/4[a)]

a) 3/4 samples were non-detects, but LOQ > PNEC

9.3 Conclusions

Environmental risk assessments were carried out for 82 active pharmaceutical ingredients belonging to different classes of medicines including antibiotics, antiepileptics, antihypertensives, asthma and allergy medications, gastrointestinal disease medications, hormones, metabolic disease medications, NSAIDS and analgesics, other cardiovascular medicines, psychopharmaceuticals, as well as veterinary medications. Predicted no effect concentrations were calculated based on literature and our own ecotoxicological studies. Risk quotients and PNECs were calculated for surface waters, soils, and sediments. Some of the analysed APIs, especially some antibiotics and hormones, are present at levels that may negatively affect organisms in surface water, sediment and soil. For some of the APIs the environmental risk could not be excluded because the quantitation limits (LOQ) were higher than the PNECs. In this study, several APIs contributed to the combined environmental risk, although their concentrations did not exceed the PNEC. More ecotoxicological data are needed on single APIs and their metabolities as well on mixture toxicity to assess the combined ecological risks.

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APIs are not visible but are found everywhere in the environment. Photo: Helene Ek Henning, CAB.

10 Overall conclusions and recommendations

Increased knowledge about usage, sources, environmental levels and risks

This report increases the knowledge about the active pharmaceutical ingredients (APIs) in the Baltic Sea Region. Sources and environmental levels of APIs were studied in selected river basin districts in Estonia, Latvia, Finland, Germany, Poland and Sweden, and a coastal fish farm outside the case study area in Finland. The measured environmental levels of up to 80 APIs were compared to the predicted no-effect concentrations to assess environmental risks. This report also presents data on human and veterinary consumption of these APIs. Major findings and remaining knowledge gaps are highlighted below.

APIs present in all environmental samples

This study showed a widespread prevalence of APIs in the environment. APIs were detected in all the studied rivers, lakes, coastal waters, sediments and manure or sewage sludge fertilized soils. The sum concentrations of detected APIs were 0.0018–12 µg/L in surface water, 37–188 µg/kg d.w. in sediment and 15–166 µg/kg d.w.in soil. 8–49 out of 63 analysed APIs were detected in each surface water sample, 13–41 out of 64 in sediment, and 18–25 out of 64 in soil.

API concentrations varied widely between the sampling occasions and locations, e.g. upstream and downstream WWTPs. Sampling was generally performed twice, during warm and cold season, and more data are needed to draw conclusions about the seasonal variation of the API concentrations in the environment. Previous studies have mainly focused on APIs in surface water. This study, however, indicated that the prevalence of APIs in sediment and soil also needs further attention. More knowledge is needed on the plant uptake of APIs in soil and the dispersal of APIs from soil to nearby water courses.

Some APIs frequently detected in the environment

The most frequently detected APIs in surface waters were carbamazepine (antiepileptic), tramadol and diclofenac (NSAIDs and analgesics), cetirizine (asthma and allergy medication), and venlafaxine and citalopram (psychopharmaceuticals). Tramadol and risperidone (psychopharmaceutical) were found in all sediment and soil samples. Other APIs that were found in all sediment samples were metformin (metabolic disease medication), oxazepam (psychopharmaceutical) and caffeine, whereas trimethoprim (antibiotic), paracetamol (NSAID and analgesic) and fenbendazole (veterinary medicine) were found in all soil samples. APIs were frequently detected in the environment due to their high usage, persistence and/or poor removal efficiencies at WWTPs.

This study covered analyses of up to 80 APIs, representing antibiotics, antiepileptics, antihypertensives, asthma and allergy medications, gastrointestinal disease medications, hormones, metabolic disease medications, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, other cardiovascular medicines, psychopharmaceuticals and veterinary medicines. Still, there are more than 2000 APIs used for human and veterinary consumption. Analytical methods should be further developed to be able to make more comprehensive estimates of total API levels in the environment, including metabolites. Measurements of APIs should be included in regular environmental monitoring programmes, focusing on the most environmentally risky substances.

APIs present at risky levels

Some of the analysed APIs, especially some antibiotics and hormones, are present at levels that may negatively affect organisms in surface water, sediment and soil. At least one API was present at

concentrations which may pose environmental risk in 75% of the surface water samples. The highest risks in surface waters were related to the hormones estrone and norethisterone, antibiotics clarithromycin and ofloxacin, and the NSAID diclofenac. In addition, emamectin (veterinary medicine), mometasone furoate (asthma and allergy medication) and metformin (metabolic disease medication) were found at risky levels in some surface water samples. Ibuprofen (NSAID and analgesic) was not analysed in surface waters, but its low PNEC-value and the observed high levels in WWTP effluents suggest that also ibuprofen may pose an environmental risk in some surface waters.

The APIs that most frequently exceeded their PNECs in sediments were ciprofloxacin (antibiotic), metformin and paracetamol. In some sediment samples, risks were also observed related to diclofenac, emamectin, estrone and norethisterone, and clarithromycin, ofloxacin and the sum concentration of doxycycline and tetracycline. In soils, exceedance of PNECs were often observed for paracetamol and metformin. Single exceedances of PNECs were observed for ciprofloxacin, ofloxacin, diclofenac, estrone and the veterinary medicine ivermectin in soil. For some APIs the environmental risk cannot be excluded because their limits of quantification were higher than the PNECs.

This study showed that the use and dispersal of veterinary medicines is problematic and poses a risk to the environment. APIs used for animals are dispersed to nearby watercourses via the manure-fertilized fields. The APIs used for animals are more difficult to collect and treat compared to human APIs that are mostly collected and treated at municipal WWTPs. It is therefore recommended to optimize and reduce the usage of veterinary medicines. Additionally, it is recommended to implement best practices for manure storage, treatment and application as fertilizer in regards of decreasing the amount of APIs from veterinary use ending up on fields and in surface waters. The use of herd treatments and broad-spectrum antibiotics should be avoided, and a strict policy for the use of antibiotics should be implemented in the Baltic Sea member states.

Pharmaceuticals are designed to have biological effects and to be bioavailable at low doses. Low environmental levels of APIs, such as hormones and antibiotics may therefore be problematic. The hormone estrone is excreted naturally from humans and animals and the proportion caused by medicinal use is not clear. Estrone is not available as human medicine in any of the countries from which consumption data were available in this project. The widespread prevalence of antibiotics in the environment is risky because of the development of antibiotic resistance, threatening the effective prevention and treatment of infections caused by bacteria. Hence, measures are urgently needed to reduce any unnecessary use and dispersal of antibiotics into the environment. Further studies are recommended on antibiotics and the spread of antibiotic resistance genes.

The current predicted no-effect concentrations (PNECs) are based on the best available knowledge that often is limited. More ecotoxicological data are needed to improve the environmental risk assessment of APIs and their metabolites. In this study, several APIs contributed to the combined environmental risk, although their concentrations did not exceed the PNEC. The sums of risk quotients were high indicating an urgent need to decrease the loading. More knowledge on mixture toxicity and long-term effects of exposure to APIs are needed to fully assess the combined ecological risks. Especially, there is a lack of data on the ecotoxicological effects of APIs on the biota in soil, sediment, and marine and brackish water like the Baltic Sea.

Improved consumption data

Data on API consumption showed that the most consumed APIs (in kg) were used for pain and fever, epilepsy, and for major public health problems such as type II diabetes, hypertension and heart failure. Some medicines are metabolized, while others remain intact until they are excreted. This means that large quantities of APIs are spread via the wastewater treatment plants to receiving aquatic environments.

The load of APIs in wastewater influents were predicted based on the collected consumption data. The predicted loads were then compared to the measured loads in the sixteen studied WWTPs in Estonia, Latvia, Finland, Germany, Poland and Sweden. The measured and predicted load of APIs in wastewater influents were in good agreement for some APIs (e.g. diclofenac and paracetamol) in most of the countries, whereas load prediction for other APIs (e.g. carbamazepine) resulted in either an over- or underestimation. The agreement may be improved for instance by including more comprehensive consumption data and measurements.

It is still difficult or impossible to obtain complete consumption data of APIs in mass units. It is recommended that public authorities in the Baltic states make drug statistics publicly available, not only in DDD format but also in kg of API, including combination products and topical formulations. All medicines should be included, despite of reimbursement status. Also veterinary medicines consumption data for all APIs and especially for antibiotics, in kg of API, should be made publicly available.

Several sources and pathways of APIs

Conventional WWTPs are not designed to remove APIs from wastewater. Still, this study showed that the concentrations of about half of the analysed APIs were lower in the effluent compared to the influent, indicating that they are at least partly removed in the sixteen studied WWTPs. The sum concentration of detected APIs was 53–1550 µg/L (median 300 µg/L) in influents, 14–1280 µg/L (median 40 µg/L) in effluents and 550–11600 µg/kg d.w. (median 2440 µg/kg d.w.) in sludge. 17–45 out of 75 analysed APIs were detected in the influent samples, 19–37 out of 75 in effluents, and 15–26 out of 31 in sludge samples.

Seventeen APIs were detected in at least 90% of influents: caffeine, codeine, diclofenac, fluconazole, gabapentin, hydrochlorothiazide, ketoprofen, levetiracetam, mesalazine, metformin, naproxen, oxazepam, paracetamol, sulfamethoxazole, trimethoprim, valsartan and venlafaxine. Six of them were found in all influent samples: diclofenac, gabapentin, ketoprofen, metformin, naproxen and trimethoprim. Paracetamol was the most abundant API in influents with the maximum concentration of 1000 µg/L.

Fifteen APIs were detected in at least 90% of the effluents: carbamazepine, citalopram, clarithromycin, diclofenac, erythromycin, fluconazole, hydrochlorothiazide, ketoprofen, metoprolol, naproxen, oxazepam, sotalol, tramadol, trimethoprim and venlafaxine. Three of them were found in all effluent samples: diclofenac, metoprolol and oxazepam. In the effluents, ibuprofen had the highest concentration (up to 44 µg/L), followed by diclofenac (up to 38 µg/L) and caffeine (up to 32 µg/L). Eight APIs were found in all WWTP sludge samples: diclofenac, carbamazepine, venlafaxine, metformin, caffeine, metoprolol, citalopram and sertraline. In sludge, the most abundant APIs were telmisartan (up to 8700 µg/kg d.w.) and ofloxacin (up to 8600 µg/kg d.w.). Hence, this study confirmed that many APIs are incompletely removed at conventional WWTPs. The studied APIs were mostly partitioning in effluents and less in sludge. Installment of advanced purification techniques would therefore be reasonable, especially if the receiving waters are sensitive.

In surface waters, the highest API concentrations were detected downstream WWTPs and during low flow conditions. This study showed that some APIs also accumulate in coastal sediments and pose a risk to benthic organisms. It is recommended that APIs should be monitored in WWTP effluents, especially those API that pose environmental risks.

This study showed that the total load (in g/day) of analysed APIs from hospitals was at maximum 3% of the overall load to the WWTPs. It is therefore more cost-efficient to install advanced treatment technologies at the WWTPs than at the hospitals. However, the hospitals may be

significant sources of some APIs that are predominantly used at hospitals. Also, the effluents of manufacturing facilities of APIs contained high levels of certain APIs.
This study also showed that APIs are leaking from landfills and sludge composting sites. The sum concentrations of detected APIs varied over the year from 3.5 to 172 µg/L in untreated leachate and from 1.1 to 41 µg/L in treated effluents of the landfill WWTP, indicating an overall decrease of about 35–76% during the treatment. The APIs found at highest concentrations in untreated leachates were hydrochlorothiazide (up to 79 µg/L), paracetamol (74 µg/L) and gabapentin (7.0 µg/L), whereas caffeine (8.8 µg/L), hydrochlorothiazide (4.4 µg/L) and erythromycin (1.8 µg/L) were found at highest concentrations in the treated effluents. There are many landfills in the Baltic Sea region as well as globally that have no treatment at all or limited treatment of landfill leachate. Although the studied landfill was not a major API source compared to the municipal WWTPs in the case study area, some landfills may be a significant source of APIs locally. Further studies of landfill leachates are recommended, especially where household waste is or has been disposed of at landfills.

This study also covered the analyses of APIs in surface waters and sediments at Finnish and Estonian fish farms. Temporarily elevated surface water concentrations of the antibiotic trimethoprim were obtained near one of the fish farms after an onsite medication event. Otherwise, the number of detected APIs and their sum concentration (0.005–0.09 µg/L) was about the same or lower in the fish farm waters compared to other studied surface waters.

The watercourses downstream a pig farm and a poultry farm in Latvia contained 7–21 out of 59 analysed APIs. The sum concentration of the detected APIs was 0.18–0.62 µg/L, which is within the range found in other surface water samples of the case study areas. However, the concentrations of the veterinary medicines tiamulin and toltrazuril were higher downstream the pig farm than in other surface water samples. Hence, this study suggests that at least some livestock farms may be significant sources of APIs used for veterinary purposes, an issue that needs further attention.

Reducing the API emissions

To summarize, this study showed a widespread prevalence of APIs in the environment. The analysed APIs were mainly spread into the Baltic Sea environment via municipal wastewater treatment plants (WWTPs). Other sources, such as hospitals, manufacturing facilities, landfills, fish farms, pig farms and poultry farms, contributed to a lesser degree to the total load of APIs in the receiving waters. Some APIs were present in environmentally risky levels, indicating an urgent need to decrease the emissions. The combined environmental risk of the APIs, as well as the combined effects they may have with other pollutants, is still unknown.

This report increases knowledge about the sources, environmental levels and risks of APIs in the Baltic Sea region. The data will be further used as a basis for modelling of APIs within the Baltic Sea region and to identify measures to reduce the emissions and environmental risks of APIs. These results will be published in upcoming reports within the three-year project Clear Waters from Pharmaceuticals (CWPharma) funded by the EU's Interreg Baltic Sea Region Programme.

Recommendations

- APIs should be included in regular environmental monitoring programmes, focusing on APIs that pose environmental risks. The API list should be continuously updated as we receive new information on environmental levels and risks.

- The analytical methods should be further refined and developed to make comprehensive estimates of API concentrations in the environment, including metabolites.

- The statistics on the usage of human and veterinary medicines should be improved, by making data publicly available in DDD format (defined daily dose) and in mass units (kg of API) for all types of medicines.

- Further studies should be performed on the use of veterinary medicines and their dispersal in the environment. Any unnecessary use should be restricted and best practices for manure storage and application on agricultural fields should be implemented.

- More ecotoxicological data are needed on single APIs and their metabolities as well on mixture toxicity to assess the combined ecological risks. Ecotoxicological studies should be performed on different trophic levels and on different matrixes e.g. freshwater, coastal and marine waters, sediment and soil. Also, knowledge on chronic effects from long-term exposure to APIs should be improved.

- Further studies should be performed on the environmental levels and risks of antibiotics, including the spread of antibiotic resistance genes.

- Emissions of APIs from landfill leachates should be further analysed, especially where household waste is or has been disposed of at landfills.

- The emissions of environmentally risky APIs should be reduced by improved wastewater treatment and upstream measures.

- The discharges of APIs via WWTP effluents should be followed up, focusing on APIs that pose environmental risks. The list of environmentally risky APIs should be updated regularly when new ecotoxicological data and risk assessments are available.

11 Annexes

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Annex 1. Method performance of chemical analyses

Recovery correction method and the limit of quantification (LOQ) of the active pharmaceutical ingredients (APIs) in water samples. The APIs that were not analysed in the given matrix are marked with -.

	Surface water		Estuary water		WTTP influent		WTTP effluent	
	Recovery correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)	Recovery Correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)
Allopurinol	-	-	-	-	STA	14 000	STA	120
Amlodipine	STA	7.7	STA	0.003	STA	400	STA	110
Atenolol	STA	12	STA	8.0	STA	210	STA	110
Atorvastatin	^{13}C	15	-	-	^{13}C	10 000	^{13}C	10 000
Bezafibrate	STA	0.83	STA	0.40	STA	27	STA	13
Bisoprolol	STA	0.52	STA	0.21	STA	30	STA	15
Caffeine	^{13}C	0.75	^{13}C	0.24	^{13}C	17	STA	870
Candesartan	STA	0.68	STA	0.22	STA	770	STA	11
Carbamazepine	^{13}C	0.005	^{13}C	0.034	^{13}C	17	^{13}C	7.7
Carprofen	^{13}C	0.77	^{13}C	0.58	^{13}C	14	^{13}C	7.1
Cetirizine	STA	0.11	STA	0.028	STA	3200	STA	1200
Ciprofloxacin	-	-	^{13}C	35	STA	3100	STA	1600
Citalopram+escitalopram	^{13}C	0.058	^{13}C	0.037	^{13}C	2.2	^{13}C	1.1
Clarithromycin	STA	1.0	STA	0.33	STA	31	STA	16
Codeine	^{13}C	0.070	^{13}C	0.015	^{13}C	42	^{13}C	11
Diclofenac	^{13}C	1.2	^{13}C	0.34	^{13}C	44	^{13}C	22
Dipyridamole	STA	1.1	STA	0.67	STA	190	STA	87
Doxycycline/	STA	5.7	STA	3.2	STA	240	STA	120

	Surface water		Estuary water		WTTP influent		WTTP effluent	
	Recovery correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)	Recovery Correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)
Tetracycline								
Emamectin	STA	0.090	STA	0.021	STA	29	STA	11
Enalapril	STA	2.8	STA	-	STA	170	STA	83
Eprosartan	STA	0.22	STA	-	STA	10	STA	5.2
Erythromycin	-	-	STA	-	STA	39	^{13}C	8.5
Esomeprazole+omeprazole	-	-	-	-	STA	8400	STA	8400
Estriol (E3)	-	-	STA	-	STA	12	STA	8400
Estrone (E1)	STA	0.74	STA	0.17	STA	26	STA	13
Fenbendazole	STA	0.068	STA	0.025	STA	36	STA	11
Fexofenadine	STA	0.086	STA	-	STA	4300	STA	1600
Florfenicol	STA	-	STA	-	STA	64	STA	32
Fluconazole	^{13}C	0.046	^{13}C	0.017	^{13}C	20	^{13}C	9.6
Fluticasone	STA	0.059	STA	0.002	STA	410	STA	150
Gabapentin	^{13}C	0.88	^{13}C	0.28	^{13}C	910	^{13}C	910
Gemfibrozil	STA	1.5	^{13}C	0.022	STA	170	^{13}C	100
Hydrochlorothiazide	-	-	-	-	STA	7.5	STA	110
Ibuprofen	-	-	-	-	STA	2300	STA	1100
Irbesartan	STA	0.063	STA	0.018	STA	53	STA	70
Ivermectin	-	-	-	-	-	-	-	-
Ketoprofen	^{13}C	0.72	^{13}C	0.38	^{13}C	18	STA	11
Levetiracetam	^{13}C	3.5	^{13}C	5.4	^{13}C	220	^{13}C	110
Lincomycin	STA	0.10	STA	0.036	STA	18	STA	9.8

	Surface water		Estuary water		WTTP influent		WTTP effluent	
	Recovery correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)	Recovery Correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)
Losartan	STA	0.14	STA	0.023	STA	510	STA	250
Mesalazine	-	-	STA	0.82	STA	280	STA	63
Metformin	^{13}C	0.24	^{13}C	0.12	^{13}C	250	^{13}C	7.5
Metoprolol	^{13}C	0.54	^{13}C	0.35	^{13}C	14	STA	29
Mometasone	STA	1.3	STA	0.29	STA	830	STA	27
Naproxen	^{13}C	0.57	^{13}C	0.47	^{13}C	11	STA	5.4
Nebivolol	STA	0.052	STA	0.013	STA	970	STA	16
Norethisterone	STA	0.079	STA	0.037	STA	24	STA	9.5
Norfloxacin	-	-	-	-	STA	12 000	STA	12 000
Ofloxacin	^{13}C	10	^{13}C	4.6	^{13}C	420	^{13}C	210
Olanzapine	-	-	-	-	STA	5.9	STA	0.96
Oxazepam	^{13}C	0.033	^{13}C	0.032	^{13}C	23	^{13}C	11
Oxycodone	^{13}C	0.042	^{13}C	0.027	^{13}C	260	^{13}C	120
Pantoprazole	-	-	-	-	STA	760	STA	760
Paracetamol	-	-	-	-	^{13}C	77	^{13}C	77
Primidone	STA	1.4	STA	0.71	STA	35	STA	18
Progesterone	STA	0.086	STA	0.028	STA	31	STA	12
Quetiapine	^{13}C	0.15	STA	0.014	STA	470	STA	120
Ramipril	STA	0.72	-	-	STA	32	STA	16
Risperidone	-	-	-	-	STA	800	STA	10
Sertraline	^{13}C	0.041	^{13}C	0.031	^{13}C	20	^{13}C	10
Simvastatin	-	-	STA	0.020	STA	1.4	STA	1.5

	Surface water		Estuary water		WTTP influent		WTTP effluent	
	Recovery correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)	Recovery Correction	LOQ (ng/L)	Recovery correction	LOQ (ng/L)
Sotalol	STA	0.89	STA	0.68	STA	15	STA	7.7
Sulfadiazine	STA	17	-	-	STA	590	STA	300
Sulfamethoxazole	-	-	-	-	^{13}C	42	^{13}C	8.9
Telmisartan	STA	1.4	-	-	STA	49	STA	11
Temazepam	^{13}C	0.36	^{13}C	0.34	^{13}C	17	^{13}C	8.3
Testosterone	^{13}C	0.080	^{13}C	0.047	STA	81	^{13}C	18
Tiamulin	STA	0.62	STA	0.014	STA	38	STA	19
Toltrazuril	^{13}C	4.8	^{13}C	3.6	^{13}C	9000	^{13}C	9000
Tramadol	^{13}C	0.038	^{13}C	0.022	^{13}C	77	STA	38
Trimethoprim	^{13}C	0.37	^{13}C	0.022	^{13}C	22	STA	11
Tylosin	STA	3.7	STA	1.9	STA	320	STA	100
Valsartan	STA	6.4	-	-	STA	300	STA	150
Warfarin	^{13}C	0.87	^{13}C	0.58	^{13}C	13	STA	6.3
Venlafaxine	^{13}C	0.034	^{13}C	0.026	^{13}C	20	^{13}C	10
Xylometazoline	STA	0.054	STA	0.019	STA	51	STA	26

^{13}C = Stable isotope method. STA = Standard-addition method

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Recovery correction method and the limit of quantification (LOQ) of the anlysed active pharmaceutical ingredients (APIs) in solid matrices. The APIs that were not analysed in the given matrix are marked with -.

	Soil & sediment		WTTP sludge	
	Recovery correction	LOQ (µg/kg d.w.)	Recovery correction	LOQ (µg/kg d.w.)
Allopurinol	-	-	-	-
Amlodipine	STA	0.062	-	-
Atenolol	STA	0.050	-	-
Atorvastatin	-	-	-	-
Bezafibrate	STA	0.076	-	-
Bisoprolol	STA	0.011	STA	0.050
Caffeine	STA	0.11	^{13}C	0.16
Candesartan	-	-	-	-
Carbamazepine	^{13}C	0.090	^{13}C	0.20
Carprofen	-	-	-	-
Cetirizine	STA	0.014	-	-
Ciprofloxacin	STA	0.62	-	-
Citalopram	^{13}C	0.093	^{13}C	0.19
Clarithromycin	STA	0.085	-	-
Codeine	^{13}C	0.77	^{13}C	1.8
Diclofenac	^{13}C	0.10	^{13}C	0.20
Dipyridamole	STA	0.22	-	-
Doxycycline/ Tetracycline	STA	1.6	-	-
Emamectin	STA	0.24	-	-
Enalapril	STA	0.047	STA	0.39
Eprosartan	STA	0.047	-	-
Erythromycin	STA	16	-	-
Esomeprazole	-	-	-	-
Estriol (E3)	STA	1.1	-	-
Estrone (E1)	STA	0.51	-	-
Fenbendazole	STA	0.012	-	-
Fexofenadine	STA	0.017	-	-
Florfenicol	STA	0.010	-	-
Fluconazole	^{13}C	0.008	^{13}C	0.18
Fluticasone	STA	0.15	-	-
Gabapentin	-	-	STA	0.32
Gemfibrozil	STA	0.18	-	-
Hydrochlorothiazide	STA	10	-	-

	Soil & sediment		WTTP sludge	
	Recovery correction	LOQ (µg/kg d.w.)	Recovery correction	LOQ (µg/kg d.w.)
Ibuprofen	-	-	-	-
Irbesartan	STA	0.013	STA	0.040
Ivermectin	STA	6.2	-	-
Ketoprofen	STA	0.059	^{13}C	0.17
Levetiracetam	^{13}C	0.043	^{13}C	0.16
Lincomycin	STA	0.01	STA	0.042
Losartan	-	-	-	-
Mesalazine	-	-	-	-
Metformin	^{13}C	0.008	^{13}C	0.014
Metoprolol	STA	0.050	^{13}C	0.20
Mometasone	STA	0.75	-	-
Naproxen	STA	0.52	^{13}C	1.5
Nebivolol	STA	0.099	-	-
Norethisterone	STA	0.12	-	-
Norfloxacin	STA	1.5	-	-
Ofloxacin	^{13}C	0.60	^{13}C	1.8
Olanzapine	STA	1.1	STA	4.4
Oxazepam	^{13}C	0.010	STA	0.027
Oxycodone	^{13}C	0.065	STA	0.26
Pantoprazole	-	-	-	-
Paracetamol	STA	0.25	-	-
Primidone	STA	0.057	STA	0.39
Progesterone	STA	0.092	-	-
Quetiapine	STA	0.010	-	-
Ramipril	STA	0.052	STA	0.46
Risperidone	STA	0.018	STA	0.039
Sertraline	^{13}C	0.038	^{13}C	0.16
Simvastatin	STA	0.11	-	-
Sotalol	STA	0.11	-	-
Sulfadiazine	-	-	-	-
Sulfamethoxazole	STA	0.12	-	-
Telmisartan	STA	0.14	STA	1.4
Temazepam	^{13}C	0.087	STA	0.77
Testosterone	STA	0.20	-	-
Tiamulin	STA	0.044	-	-
Toltrazuril	^{13}C	4.4	^{13}C	17

	Soil & sediment		WTTP sludge	
	Recovery correction	**LOQ (µg/kg d.w.)**	**Recovery correction**	**LOQ (µg/kg d.w.)**
Tramadol	STA	0.01	STA	0.047
Trimethoprim	STA	0.050	^{13}C	0.16
Tylosin	STA	3.2	STA	53
Valsartan	STA	0.092	-	-
Warfarin	STA	0.010	-	-
Venlafaxine	^{13}C	0.044	^{13}C	0.16
Xylometazoline	STA	0.046	-	-

^{13}C = Stable isotope method. STA = Standard-addition method.

Annex 2. ATC codes and human consumption of the selected APIs

List of available ATC codes for human and veterinary medicines for APIs in CWPharma.

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
17-α-ethinyl estradiol (EE2)	G03AA15 chlormadinone and ethinylestradiol G03AB07 chlormadinone and ethinylestradiol G03AA09 desogestrel and ethinylestradiol G03AB05 desogestrel and ethinylestradiol G03AA16 dienogest and ethinylestradiol G03AA12 drospirenone and ethinylestradiol G03CA01 ethinylestradiol L02AA03 ethinylestradiol G03AA01 etynodiol and ethinylestradiol G03AA10 gestodene and ethinylestradiol G03AB06 gestodene and ethinylestradiol G03AA07 levonorgestrel and ethinylestradiol G03AB03 levonorgestrel and ethinylestradiol G03AA03 lynestrenol and ethinylestradiol G03AB02 lynestrenol and ethinylestradiol G03AA08 medroxyprogesterone and ethinylestradiol G03AA04 megestrol and ethinylestradiol G03AB01 megestrol and ethinylestradiol G03AA13 norelgestromin and ethinylestradiol G03AA05 norethisterone and ethinylestradiol G03AB04 norethisterone and ethinylestradiol G03AA11 norgestimate and ethinylestradiol G03AA06 norgestrel and ethinylestradiol G03AA02 quingestanol and ethinylestradiol	QG03AA01 etynodiol and ethinylestradiol QG03AA02 quingestanol and ethinylestradiol QG03AA03 lynestrenol and ethinylestradiol QG03AA04 megestrol and ethinylestradiol QG03AA05 norethisterone and ethinylestradiol QG03AA06 norgestrel and ethinylestradiol QG03AA07 levonorgestrel and ethinylestradiol QG03AA08 medroxyprogesterone and ethinylestradiol QG03AA09 desogestrel and ethinylestradiol QG03AA10 gestodene and ethinylestradiol QG03AA11 norgestimate and ethinylestradiol QG03AA12 drospirenone and ethinylestradiol QG03AA13 norelgestromin and ethinylestradiol QG03AA15 chlormadinone and and ethinylestradiol QG03AA16 dienogest and ethinylestradiol QG03AB01 megestrol and ethinylestradiol QG03AB02 lynestrenol and ethinylestradiol QG03AB03 levonorgestrel and ethinylestradiol QG03AB04 norethisterone and ethinylestradiol QG03AB05 desogestrel and ethinylestradiol QG03AB06 gestodene and ethinylestradiol QG03AB07 chlormadinone and ethinylestradiol QG03CA01 ethinylestradiol QL02AA03 ethinylestradiol
17-β-estradiol (E2)	G03AB08 dienogest and estradiol G03CA03 estradiol G03CA53 estradiol, combinations G03AA14 nomegestrol and estradiol G03FA01 norethisterone and estrogen G03FA02 hydroxyprogesterone and estrogen G03FA03 ethisterone and estrogen G03FA04 progesterone and estrogen G03FA05 methylnortestosterone and estrogen G03FA06 etynodiol and estrogen G03FA07 lynestrenol and estrogen G03FA08 megestrol and estrogen G03FA09 noretynodrel and estrogen G03FA10 norgestrel and estrogen G03FA11 levonorgestrel and estrogen G03FA12 medroxyprogesterone and estrogen G03FA13 norgestimate and estrogen G03FA14 dydrogesterone and estrogen G03FA15 dienogest and estrogen G03FA16 trimegestone and estrogen G03FA17 drospirenone and estrogen G03FB01 norgestrel and estrogen G03FB02 lynestrenol and estrogen G03FB03 chlormadinone and estrogen G03FB04 megestrol and estrogen G03FB05 norethisterone and estrogen G03FB06 medroxyprogesterone and estrogen G03FB07 medrogestone and estrogen G03FB08 dydrogesterone and estrogen G03FB09 levonorgestrel and estrogen G03FB10 desogestrel and estrogen G03FB11 trimegestone and estrogen G03FB12 nomegestrol and estrogen	QG03CA03 estradiol QG03CA53 estradiol, combinations QG03AB08 dienogest and estradiol QG03AA14 nomegestrol and estradiol
α-Estradiol	No ATC code	No ATC code
Amlodipine	C09XA53 aliskiren and amlodipine	QC07FB07 bisoprolol and amlodipine

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
	C09XA54 aliskiren, amlodipine and hydrochlorothiazide C08CA01 amlodipine C08GA02 amlodipine and diuretics C10BX03 atorvastatin and amlodipine C10BX11 atorvastatin, amlodipine and perindopril C07FB07 bisoprolol and amlodipine C09DB07 candesartan and amlodipine C09DB05 irbesartan and amlodipine C09BB03 lisinopril and amlodipine C09DB06 losartan and amlodipine C07FB13 metoprolol and amlodipine C07FB12 nebivolol and amlodipine C09DB02 olmesartan medoxomil and amlodipine C09DX03 olmesartan medoxomil, amlodipine and hydrochlorothiazide C09BB04 perindopril and amlodipine C09BX01 perindopril, amlodipine and indapamide C09BB07 ramipril and amlodipine C09BX03 ramipril, amlodipine and hydrochlorothiazide C10BX09 rosuvastatin and amlodipine C10BX07 rosuvastatin, amlodipine and lisinopril C10BX14 rosuvastatin, amlodipine and perindopril C09DB04 telmisartan and amlodipine C09DB01 valsartan and amlodipine C09DX01 valsartan, amlodipine and hydrochlorothiazide	QC07FB12 nebivolol and amlodipine QC07FB13 metoprolol and amlodipine QC08CA01 amlodipine QC08GA02 amlodipine and diuretics QC09BB03 lisinopril and amlodipine QC09BB04 perindopril and amlodipine QC09BB07 ramipril and amlodipine QC09BX01 perindopril, amlodipine and indapamide QC09BX03 ramipril, amlodipine and hydrochlorothiazide QC09DB01 valsartan and amlodipine QC09DB02 olmesartan medoxomil and amlodipine QC09DB04 telmisartan and amlodipine QC09DB05 irbesartan and amlodipine QC09DB06 losartan and amlodipine QC09DB07 candesartan and amlodipine QC09DX01 valsartan, amlodipine and hydrochlorothiazide QC09DX03 olmesartan medoxomil, amlodipine and hydrochlorothiazide QC09XA53 aliskiren and amlodipine QC09XA54 aliskiren, amlodipine and hydrochlorothiazide QC10BX03 atorvastatin and amlodipine QC10BX07 rosuvastatin, amlodipine and lisinopril QC10BX09 rosuvastatin and amlodipine QC10BX11 atorvastatin, amlodipine and perindopril QC10BX14 rosuvastatin, amlodipine and perindopril
Atenolol	C07AB03 atenolol C07FB03 atenolol and nifedipine C07CB03 atenolol and other diuretics C07CB53 atenolol and other diuretics, combinations C07BB03 atenolol and thiazides C07DB01 atenolol, thiazides and other diuretics C07AB11 s-atenolol	QC07AB03 atenolol QC07AB11 s-atenolol QC07BB03 atenolol and thiazides QC07CB03 atenolol and other diuretics QC07CB53 atenolol and other diuretics, combinations QC07DB01 atenolol, thiazides and other diuretics QC07FB03 atenolol and nifedipine
Atorvastatin	C10AA05 atorvastatin C10BX08 atorvastatin and acetylsalicylic acid C10BX03 atorvastatin and amlodipine C10BA05 atorvastatin and ezetimibe C10BX15 atorvastatin and perindopril C10BX12 atorvastatin, acetylsalicylic acid and perindopril C10BX06 atorvastatin, acetylsalicylic acid and ramipril C10BX11 atorvastatin, amlodipine and perindopril	QC10AA05 atorvastatin QC10BA05 atorvastatin and ezetimibe QC10BX03 atorvastatin and amlodipine QC10BX06 atorvastatin, acetylsalicylic acid and ramipril QC10BX08 atorvastatin and acetylsalicylic acid QC10BX11 atorvastatin, amlodipine and perindopril QC10BX12 atorvastatin, acetylsalicylic acid and perindopril QC10BX15 atorvastatin and perindopril
Bezafibrate	C10AB02 bezafibrate	QC10AB02 bezafibrate
Bisoprolol	C07AB07 bisoprolol C07FX04 bisoprolol and acetylsalicylic acid C07FB07 bisoprolol and amlodipine C07BB07 bisoprolol and thiazides C09BX02 perindopril and bisoprolol	QC07AB07 bisoprolol QC07BB07 bisoprolol and thiazides QC07FB07 bisoprolol and amlodipine QC07FX04 bisoprolol and acetylsalicylic acid QC09BX02 perindopril and bisoprolol
Caffeine	N06BC01 caffeine V04CG30 caffeine and sodium benzoate	QN06BC01 caffeine QV04CG30 caffeine and sodium benzoate
Candesartan	C09CA06 candesartan C09DB07 candesartan and amlodipine C09DA06 candesartan and diuretics	QC09CA06 candesartan QC09DA06 candesartan and diuretics QC09DB07 candesartan and amlodipine
Carbamazepine	N03AF01 carbamazepine	QN03AF01 carbamazepine
Ciprofloxacin	J01MA02 ciprofloxacin S01AE03 ciprofloxacin S02AA15 ciprofloxacin S03AA07 ciprofloxacin	QJ01MA02 ciprofloxacin QJ01RA10 ciprofloxacin and metronidazole QJ01RA11 ciprofloxacin and tinidazole QJ01RA12 ciprofloxacin and ornidazole

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
	J01RA10 ciprofloxacin and metronidazole J01RA12 ciprofloxacin and ornidazole J01RA11 ciprofloxacin and tinidazole	QS01AE03 ciprofloxacin QS02AA15 ciprofloxacin QS03AA07 ciprofloxacin
Diclofenac	D11AX18 diclofenac M01AB05 diclofenac M02AA15 diclofenac S01BC03 diclofenac S01CC01 diclofenac and antiinfectives M01AB55 diclofenac, combinations QM02AA15 diclofenac	QD11AX18 diclofenac QM01AB05 diclofenac QM01AB55 diclofenac, combinations QS01BC03 diclofenac QS01CC01 diclofenac and antiinfectives
Dipyridamole	B01AC07 dipyridamole B01AC30 combinations	QB01AC07 dipyridamole QB01AC30 combinations
Doxycycline	A01AB22 doxycycline J01AA02 doxycycline	QA01AB22 doxycycline QJ01AA02 doxycycline
Enalapril	C09AA02 enalapril C09BA02 enalapril and diuretics C09BB02 enalapril and lercanidipine C09BB06 enalapril and nitrendipine	QC09AA02 enalapril QC09BA02 enalapril and diuretics QC09BB02 enalapril and lercanidipine QC09BB06 enalapril and nitrendipine
Erythromycin	D10AF02 erythromycin J01FA01 erythromycin S01AA17 erythromycin D10AF52 erythromycin, combinations	QD10AF02 erythromycin QD10AF52 erythromycine, combinations QJ01FA01 erythromycin QJ51FA01 erythromycin QJ51RF02 erythromycin, combinations with other antibacterials QS01AA17 erythromycin
Estriol (E3)	G03CA04 estriol G03CC06 estriol	QG03CA04 estriol QG03CC06 estriol
Estrone (E1)	G03CA07 estrone G03CC04 estrone	
Fexofenadine	R06AX26 fexofenadine	QR06AX26 fexofenadine
Fluconazole	J01RA07 azithromycin, fluconazole and secnidazole D01AC15 fluconazole J02AC01 fluconazole	QD01AC15 fluconazole QJ01RA07 azithromycin, fluconazole and secnidazole QJ02AC01 fluconazole
Furosemide	C03CA01 furosemide C03CB01 furosemide and potassium C03EB01 furosemide and potassium-sparing agents	QC03CA01 furosemide QC03CB01 furosemide and potassium QC03EB01 furosemide and potassium-sparing agents
Gemfibrozil	C10AB04 gemfibrozil	QC10AB04 gemfibrozil
Ibuprofen Dexibuprofen is a dextrorotatory enenthiomer of ibuprofen.	N02AJ08 codeine and ibuprofen M01AE14 dexibuprofen C01EB16 ibuprofen G02CC01 ibuprofen M01AE01 ibuprofen M02AA13 ibuprofen R02AX02 ibuprofen M01AE51 ibuprofen, combinations N02AJ19 oxycodone and ibuprofen	QC01EB16 ibuprofen QG02CC01 ibuprofen QM01AE01 ibuprofen QM01AE14 dexibuprofen QM01AE51 ibuprofen, combinations QM02AA13 ibuprofen QN02AJ08 codeine and ibuprofen QN02AJ19 oxycodone and ibuprofen QR02AX02 ibuprofen
Ketoprofen Dexketoprofen is the S(+)-enanthiomer of ketoprofen	M01AE17 dexketoprofen M02AA27 dexketoprofen M01AE03 ketoprofen M02AA10 ketoprofen M01AE53 ketoprofen, combinations N02AJ14 tramadol and dexketoprofen	QM01AE03 ketoprofen QM01AE17 dexketoprofen QM01AE53 ketoprofen, combinations QM02AA10 ketoprofen QM02AA27 dexketoprofen QN02AJ14 tramadol and dexketoprofen QN06AJ14 tramadol and dexketoprofen
Losartan	C09CA01 losartan C09DB06 losartan and amlodipine C09DA01 losartan and diuretics	QC09CA01 losartan QC09DA01 losartan and diuretics QC09DB06 losartan and amlodipine
Metoprolol	C07AB02 metoprolol C07FX03 metoprolol and acetylsalicylic acid C07FB13 metoprolol and amlodipine C07FB02 metoprolol and felodipine C07FX05 metoprolol and ivabradine C07CB02 metoprolol and other diuretics C07BB02 metoprolol and thiazides C07BB52 metoprolol and thiazides, combinations	QC07AB02 metoprolol QC07BB02 metoprolol and thiazides QC07BB52 metoprolol and thiazides, combinations QC07CB02 metoprolol and other diuretics QC07FB02 metoprolol and felodipine QC07FB13 metoprolol and amlodipine QC07FX03 metoprolol and acetylsalicylic acid QC07FX05 metoprolol and ivabradine

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
Naproxen	G02CC02 naproxen M01AE02 naproxen M02AA12 naproxen M01AE52 naproxen and esomeprazole	QG02CC02 naproxen QM01AE02 naproxen QM01AE52 naproxen and esomeprazole QM01AE56 naproxen and misoprostol QM02AA12 naproxen
Norethisterone	G03AC01 norethisterone G03DC02 norethisterone G03FA01 norethisterone and estrogen G03FB05 norethisterone and estrogen G03AA05 norethisterone and ethinylestradiol G03AB04 norethisterone and ethinylestradiol QG03AA05 norethisterone and ethinylestradiol	QG03AB04 norethisterone and ethinylestradiol QG03AC01 norethisterone QG03DC02 norethisterone QG03FA01 norethisterone and estrogen QG03FB05 norethisterone and estrogen
Norfloxacin	J01MA06 norfloxacin S01AE02 norfloxacin J01RA13 norfloxacin and tinidazole	QJ01MA06 norfloxacin QJ01RA13 norfloxacin and tinidazole QS01AE02 norfloxacin
Ofloxacin	J01MA01 ofloxacin S01AE01 ofloxacin S02AA16 ofloxacin J01RA09 ofloxacin and ornidazole	QJ01MA01 ofloxacin QJ01RA09 ofloxacin and ornidazole QS01AE01 ofloxacin QS02AA16 ofloxacin
Paracetamol	N02AJ06 codeine and paracetamol N02AJ01 dihydrocodeine and paracetamol N02AJ17 oxycodone and paracetamol N02BE01 paracetamol N02BE51 paracetamol, combinations excl. psycholeptics N02BE71 paracetamol, combinations with psycholeptics N02AJ13 tramadol and paracetamol	QN02AJ01 dihydrocodeine and paracetamol QN02AJ06 codeine and paracetamol QN02AJ13 tramadol and paracetamol QN02AJ17 oxycodone and paracetamol QN02BE01 paracetamol QN02BE51 paracetamol, combinations excl. psycholeptics QN02BE71 paracetamol, combinations with psycholeptics QN06AJ06 codeine and paracetamol QN06AJ13 tramadol and paracetamol
Progesterone	G03DA04 progesterone G03FA04 progesterone and estrogen	QG03DA04 progesterone QG03FA04 progesterone and estrogen
Quetiapine	N05AH04 quetiapine	QN05AH04 quetiapine
Ramipril	C10BX06 atorvastatin, acetylsalicylic acid and ramipril C09AA05 ramipril C09BB07 ramipril and amlodipine C09BA05 ramipril and diuretics C09BB05 ramipril and felodipine C09BX03 ramipril, amlodipine and hydrochlorothiazide C10BX04 simvastatin, acetylsalicylic acid and Ramipril	QC10BX06 atorvastatin, acetylsalicylic acid and ramipril QC09AA05 ramipril QC09BB07 ramipril and amlodipine QC09BA05 ramipril and diuretics QC09BB05 ramipril and felodipine QC09BX03 ramipril, amlodipine and hydrochlorothiazide QC10BX04 simvastatin, acetylsalicylic acid and Ramipril
Risperidone	N05AX08 risperidone	QN05AX08 risperidone
Simvastatin	C10AA01 simvastatin C10BX01 simvastatin and acetylsalicylic acid C10BA02 simvastatin and ezetimibe C10BA04 simvastatin and fenofibrate C10BX04 simvastatin, acetylsalicylic acid and ramipril A10BH51 sitagliptin and simvastatin	QA10BH51 sitagliptin and simvastatin QC10AA01 simvastatin QC10BA02 simvastatin and ezetimibe QC10BA04 simvastatin and fenofibrate QC10BX01 simvastatin and acetylsalicylic acid QC10BX04 simvastatin, acetylsalicylic acid and ramipril
Sotalol	C07AA07 sotalol C07FX02 sotalol and acetylsalicylic acid C07BA07 sotalol and thiazides	QC07AA07 sotalol QC07BA07 sotalol and thiazides QC07FX02 sotalol and acetylsalicylic acid
Sulfadiazine	D06BA01 silver sulfadiazine D06BA51 silver sulfadiazine, combinations J01EC02 sulfadiazine J01EE06 sulfadiazine and tetroxoprim J01EE02 sulfadiazine and trimethoprim	QD06BA01 silver sulfadiazine QD06BA51 silver sulfadiazine, combinations QJ01EQ10 sulfadiazine QJ01EW10 sulfadiazine and trimethoprim QJ51RE01 sulfadiazine and trimethoprim
Sulfamethoxazole	J01EC01 sulfamethoxazole J01EE01 sulfamethoxazole and trimethoprim	QJ01EQ11 sulfamethoxazole QJ01EW11 sulfamethoxazole and trimethoprime
Telmisartan	C09CA07 telmisartan C09DB04 telmisartan and amlodipine C09DA07 telmisartan and diuretics	QC09CA07 telmisartan QC09DA07 telmisartan and diuretics QC09DB04 telmisartan and amlodipine
Testosterone	G03BA03 testosterone G03EA02 testosterone and estrogen	QG03BA03 testosterone QG03EA02 testosterone and estrogen

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
Tetracycline	A02BD08 bismuth subcitrate, tetracycline and metronidazole J01AA20 combinations of tetracyclines A02BD02 lansoprazole, tetracycline and metronidazole A01AB13 tetracycline D06AA04 tetracycline J01AA07 tetracycline S01AA09 tetracycline S02AA08 tetracycline S03AA02 tetracycline J01RA08 tetracycline and oleandomycin	QA01AB13 tetracycline QA02BD02 lansoprazole, tetracycline and metronidazol QA02BD08 bismuth subcitrate, tetracycline and metronidazol QD06AA04 tetracycline QD06AA54 tetracycline, combinations QG01AA90 tetracycline QG51AA02 tetracycline QG51AG03 tetracycline, neomycin and sulfadimidine QJ01AA07 tetracycline QJ01AA20 combinations of tetracyclines QJ01RA08 tetracycline and oleandomycin QJ01RA90 tetracyclines, combinations with other antibacterials QJ51AA07 tetracycline QS01AA09 tetracycline QS02AA08 tetracycline QS03AA02 tetracycline
Tramadol	N02AX02 tramadol N02AJ14 tramadol and dexketoprofen N02AJ15 tramadol and other non-opioid analgesics N02AJ13 tramadol and paracetamol	QN02AJ13 tramadol and paracetamol QN02AJ14 tramadol and dexketoprofen QN02AJ15 tramadol and other non-opioid analgesics QN02AX02 tramadol QN06AJ13 tramadol and paracetamol QN06AJ14 tramadol and dexketoprofen QN06AJ15 tramadol and other non-opioid analgesics
Trimethoprim	J01EE02 sulfadiazine and trimethoprim J01EE05 sulfadimidine and trimethoprim J01EE07 sulfamerazine and trimethoprim J01EE01 sulfamethoxazole and trimethoprim J01EE03 sulfametrole and trimethoprim J01EE04 sulfamoxole and trimethoprim J01EA01 trimethoprim	QJ01EA01 trimethoprim QJ01EW03 sulfadimidine and trimethoprim QJ01EW09 sulfadimethoxine and trimethoprim QJ01EW10 sulfadiazine and trimethoprim QJ01EW11 sulfamethoxazole and trimethoprime QJ01EW12 sulfachlorpyridazine and trimethoprim QJ01EW13 sulfadoxine and trimethoprim QJ01EW14 sulfatroxazol and trimethoprim QJ01EW15 sulfamethoxypyridazine and trimethoprim QJ01EW16 sulfaquinoxaline and trimethoprim QJ01EW17 sulfamonomethoxine and trimethoprim QJ01EW18 sulfamerazine and trimethoprim QJ01EW30 combinations of sulfonamides and trimethoprim QJ01RA02 sulfonamides, combinations with other antibacterials excl. trimethoprim QJ51EA01 trimethoprim QJ51RE01 sulfadiazine and trimethoprim
Warfarin	B01AA03 warfarin	QB01AA03 warfarin
Venlafaxine	N06AX16 venlafaxine	QN06AX16 venlafaxine
Hydrochlorothiazide	C03AA03 hydrochlorothiazide C03AB03 hydrochlorothiazide and potassium C03AX01 hydrochlorothiazide, combinations C09BA01 captopril and diuretics C09BA02 analapril and diuretics C09BA03 lisinopril and diuretics C09BA04 perindopril and diuretics C09BA05 ramipril and diuretics C09BA06 quinapril and diuretics C09BA07 benazepril and diuretics C09BA08 cilazapril and diuretics C09BA09 fosinopril and diuretics C09BA12 delapril and diuretics C09BA13 moexipril and diuretics C09BA15 zofenopril and diuretics C07BB02 metoprolol and thiazides C07BB03 atenolol and thiazides	QC03AA03 hydrochlorothiazide QC03AB03 hydrochlorothiazide and potassium QC03AX01 hydrochlorothiazide, combinations QC03EA01 hydrochlorothiazide and potassium-sparing agents QC09BX03 ramipril, amlodipine and hydrochlorothiazide QC09DX01 valsartan, amlodipine and hydrochlorothiazide QC09DX03 olmesartan medoxomil, amlodipine and hydrochlorothiazide QC09XA52 aliskiren and hydrochlorothiazide QC09XA54 aliskiren, amlodipine and hydrochlorothiazide

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
	C07BB04 acebutolol and thiazides C07BB06 bevantolol and thiazides C07BB07 bisoprolol and thiazides C07BB12 nebivolol and thiazides C07BB52 metoprolol and thiazides, combinations C09BX03 ramipril, amlodipine and hydrochlorothiazide C09DA01 losartan and diuretics C09DA02 eprosartan and diuretics C09DA03 valsartan and diuretics C09DA04 irbesartan and diuretics C09DA06 candesartan and diuretics C09DA07 telmisartan and diuretics C09DA08 olmesartan medoxomil and diuretics C09DA09 azilsartan medoxomil and diuretics C09DA10 fimasartan and diuretics C09DX01 valsartan, amlodipine and hydrochlorothiazide C09DX03 olmesartan medoxomil, amlodipine and hydrochlorothiazide C03EA01 hydrochlorothiazide and potassium-sparing agents C09XA52 aliskiren and hydrochlorothiazide C09XA54 aliskiren, amlodipine and hydrochlorothiazide	
Nebivolol	C07AB12 nebivolol C07FB12 nebivolol and amlodipine C07BB12 nebivolol and thiazides	QC07AB12 nebivolol QC07BB12 nebivolol and thiazides QC07FB12 nebivolol and amlodipine
Olanzapine	N05AH03 olanzapine	QN05AH03 olanzapine
Citalopram escitalopram is s-enanthiomer of citalopram	N06AB04 citalopram N06AB10 escitalopram	QN06AB04 citalopram QN06AB10 escitalopram
Sertraline	N06AB06 sertraline	QN06AB06 sertraline
Acetylsalisylic acid	A01AD05 acetylsalicylic acid B01AC06 acetylsalicylic acid B01AC30 combinations N02BA01 acetylsalicylic acid M01BA03 acetylsalicylic acid and corticosteroids N02BA51 acetylsalicylic acid, combinations excl. psycholeptics B01AC56 acetylsalicylic acid, combinations with proton pump inhibitors N02BA71 acetylsalicylic acid, combinations with psycholeptics C10BX08 atorvastatin and acetylsalicylic acid C10BX12 atorvastatin, acetylsalicylic acid and perindopril C10BX06 atorvastatin, acetylsalicylic acid and ramipril C07FX04 bisoprolol and acetylsalicylic acid N02AJ07 codeine and acetylsalicylic acid N02AJ02 dihydrocodeine and acetylsalicylic acid C07FX03 metoprolol and acetylsalicylic acid N02AJ18 oxycodone and acetylsalicylic acid C10BX02 pravastatin and acetylsalicylic acid C10BX05 rosuvastatin and acetylsalicylic acid C10BX01 simvastatin and acetylsalicylic acid C10BX04 simvastatin, acetylsalicylic acid and ramipril C07FX02 sotalol and acetylsalicylic acid	QA01AD05 acetylsalicylic acid QB01AC06 acetylsalicylic acid QB01AC56 acetylsalicylic acid, combinations with proton pump inhibitors QC07FX02 sotalol and acetylsalicylic acid QC07FX03 metoprolol and acetylsalicylic acid QC07FX04 bisoprolol and acetylsalicylic acid QC10BX01 simvastatin and acetylsalicylic acid QC10BX02 pravastatin and acetylsalicylic acid QC10BX04 simvastatin, acetylsalicylic acid and ramipril QC10BX06 atorvastatin, acetylsalicylic acid and ramipril QC10BX08 atorvastatin and acetylsalicylic acid QC10BX12 atorvastatin, acetylsalicylic acid and perindopril QM01BA03 acetylsalicylic acid and corticosteroids QN02AJ02 dihydrocodeine and acetylsalicylic acid QN02AJ07 codeine and acetylsalicylic acid QN02AJ18 oxycodone and acetylsalicylic acid QN02BA01 acetylsalicylic acid QN02BA51 acetylsalicylic acid, combinations excl. psycholeptics QN02BA71 acetylsalicylic acid, combinations with psycholeptics QN06AJ07 codeine and acetylsalicylic acid QN06AJ18 oxycodone and acetylsalicylic acid
Omeprazole esomeprazole is s-enanthiomer of omeprazole	A02BC05 esomeprazole A02BD06 esomeprazole, amoxicillin and clarithromycin M01AE52 naproxen and esomeprazole A02BC01 omeprazole	QA02BC01 omeprazole QA02BC05 esomeprazole QA02BD01 omeprazole, amoxicillin and metronidazole

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
	A02BD05 omeprazole, amoxicillin and clarithromycin A02BD01 omeprazole, amoxicillin and metronidazole	QA02BD05 omeprazole, amoxicillin and clarithromycin QA02BD06 esomeprazole, amoxicillin and clarithromycin QM01AE52 naproxen and esomeprazole
Pantoprazole	A02BC02 pantoprazole A02BD04 pantoprazole, amoxicillin and clarithromycin A02BD11 pantoprazole, amoxicillin, clarithromycin and metronidazole	QA02BC02 pantoprazole QA02BD04 pantoprazole, amoxicillin and clarithromycin QA02BD11 pantoprazole, amoxicillin, clarithromycin and metronidazole
Esomeprazole	See omeprazole	
Xylometazoline	R01AA07 xylometazoline R01AB06 xylometazoline S01GA03 xylometazoline S01GA53 xylometazoline, combinations	QR01AA07 xylometazoline QR01AB06 xylometazoline QS01GA03 xylometazoline QS01GA53 xylometazoline, combinations
Mometasone	R03AK09 formoterol and mometasone D07AC13 mometasone D07XC03 mometasone R01AD09 mometasone R03BA07 mometasone	QD07AC13 mometasone QD07XC03 mometasone QR01AD09 mometasone QR03AK09 formoterol and mometasone QR03BA07 mometasone QS02CA91 mometasone and antiinfectives
Fluticasone	D07AC17 fluticasone R01AD08 fluticasone R03BA05 fluticasone R01AD12 fluticasone furoate R03BA09 fluticasone furoate R01AD58 fluticasone, combinations R03AK11 formoterol and fluticasone R03AK06 salmeterol and fluticasone R03AK10 vilanterol and fluticasone furoate R03AL08 vilanterol, umeclidinium bromide and fluticasone furoate	QD07AC17 fluticasone QR01AD08 fluticasone QR01AD12 fluticasone furoate QR01AD58 fluticasone, combinations QR03AK06 salmeterol and fluticasone QR03AK10 vilanterol and fluticasone furoate QR03AK11 formoterol and fluticasone QR03AL08 vilanterol, umeclidinium bromide and fluticasone furoate QR03BA05 fluticasone QR03BA09 fluticasone furoate
Cetirizine levocetirizine is the r-enanthiomer of cetirizine	R06AE07 cetirizine R06AE09 levocetirizine	QR06AE07 cetirizine QR06AE09 levocetirizine
Primidone	N03AA03 primidone	QN03AA03 primidone
Allopurinol	M04AA01 allopurinol M04AA51 allopurinol, combinations	QM04AA01 allopurinol QM04AA51 allopurinol, combinations
Gabapentin	N03AX12 gabapentin	QN03AX12 gabapentin
Levetiracetam	N03AX14 levetiracetam	QN03AX14 levetiracetam
Mesalazin	A07EC02 mesalazine	QA07EC02 mesalazine
Valsartan	C10BX10 rosuvastatin and valsartan C09CA03 valsartan C09DX02 valsartan and aliskiren C09DB01 valsartan and amlodipine C09DA03 valsartan and diuretics C09DB08 valsartan and lercanidipine C09DX04 valsartan and sacubitril C09DX01 valsartan, amlodipine and hydrochlorothiazide	QC09CA03 valsartan QC09DA03 valsartan and diuretics QC09DB01 valsartan and amlodipine QC09DB08 valsartan and lercanidipine QC09DX01 valsartan, amlodipine and hydrochlorothiazide QC09DX02 valsartan and aliskiren QC09DX04 valsartan and sacubitril QC10BX10 rosuvastatin and valsartan

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
Codeine	R05DA04 codeine N02AJ07 codeine and acetylsalicylic acid N02AJ08 codeine and ibuprofen N02AJ09 codeine and other non-opioid analgesics N02AJ06 codeine and paracetamol N02AA59 codeine, combinations excl. psycholeptics N02AA79 codeine, combinations with psycholeptics R05FA01 opium derivatives and mucolytics R05FA02 opium derivatives and expectorants	QN02AA59 codeine, combinations QN02AA79 codeine, combinations with psycholeptics QN02AJ06 codeine and paracetamol QN02AJ07 codeine and acetylsalicylic acid QN02AJ08 codeine and ibuprofen QN02AJ09 codeine and other non-opioid analgesics QN06AJ06 codeine and paracetamol QN06AJ07 codeine and acetylsalicylic acid QN06AJ09 codeine and other non-opioid analgesics QR05DA04 codeine
Irbesartan	C09CA04 irbesartan C09DB05 irbesartan and amlodipine C09DA04 irbesartan and diuretics	QC09CA04 irbesartan QC09DA04 irbesartan and diuretics QC09DB05 irbesartan and amlodipine
Clarithromycin	J01FA09 clarithromycin A02BD06 esomeprazole, amoxicillin and clarithromycin A02BD07 lansoprazole, amoxicillin and clarithromycin A02BD09 lansoprazole, clarithromycin and tinidazole A02BD05 omeprazole, amoxicillin and clarithromycin A02BD04 pantoprazole, amoxicillin and clarithromycin A02BD11 pantoprazole, amoxicillin, clarithromycin and metronidazole	QA02BD04 pantoprazole, amoxicillin and clarithromycin QA02BD05 omeprazole, amoxicillin and clarithromycin QA02BD06 esomeprazole, amoxicillin and clarithromycin QA02BD07 lansoprazole, amoxicillin and clarithromycin QA02BD09 lansoprazole, clarithromycin and tinidazole QA02BD11 pantoprazole, amoxicillin, clarithromycin and metronidazole QJ01FA09 clarithromycin
Eprosartan	C09CA02 eprosartan C09DA02 eprosartan and diuretics	QC09CA02 eprosartan QC09DA02 eprosartan and diuretics
Metformin	A10BA02 metformin A10BD17 metformin and acarbose A10BD13 metformin and alogliptin A10BD16 metformin and canagliflozin A10BD15 metformin and dapagliflozin A10BD20 metformin and empagliflozin A10BD22 metformin and evogliptin A10BD18 metformin and gemigliptin A10BD11 metformin and linagliptin A10BD05 metformin and pioglitazone A10BD14 metformin and repaglinide A10BD03 metformin and rosiglitazone A10BD10 metformin and saxagliptin A10BD07 metformin and sitagliptin A10BD02 metformin and sulfonylureas A10BD08 metformin and vildagliptin	QA10BA02 metformin QA10BD02 metformin and sulfonylureas QA10BD03 metformin and rosiglitazone QA10BD05 metformin and pioglitazone QA10BD07 metformin and sitagliptin QA10BD08 metformin and vildagliptin QA10BD10 metformin and saxagliptin QA10BD11 metformin and linagliptin QA10BD13 metformin and alogliptin QA10BD14 metformin and repaglinide QA10BD15 metformin and dapagliflozin QA10BD16 metformin and canagliflozin QA10BD17 metformin and acarbose QA10BD18 metformin and gemigliptin QA10BD20 metformin and empagliflozin QA10BD22 metformin and evogliptin
Florfenicol	No ATC code	QJ01BA90 florfenicol QJ51BA90 florfenicol
Tiamulin hydrogen fumarate	No ATC code	QJ01XQ01 tiamulin

API	List of available ATC codes for human use	List of available ATC codes for veterinary use
Tylosin	No ATC code	QJ01FA90 tylosin QJ51FA90 tylosin
Lincomycin	J01FF02 lincomycin	QJ01FF02 lincomycin QJ01FF52 lincomycin, combinations QJ51RF03 lincomycin, combinations with other antibacterials
Fenbendazole	P02CA06 fenbendazole	QP02CA06 fenbendazole QP52AC13 fenbendazole
Toltrazuril	No ATC code	QP51AJ01 toltrazuril QP51AJ51 toltrazuril, combinations QP52AX60 emodepside and toltrazuril
Carprofen	No ATC code	QM01AE91 carprofen
Emamectinbenzoate	No ATC code	QP54AA06 emamectin
Ivermectin	D11AX22 ivermectin P02CF01 ivermectin	QD11AX22 ivermectin QP54AA01 ivermectin QP54AA51 ivermectin, combinations QS02QA03 ivermectin
Oxazepam	N05BA04 oxazepam	QN05BA04 oxazepam
Temazepam	N05CD07 temazepam	QN05CD07 temazepam
Oxycodone	N02AA05 oxycodone N02AA05 oxycodone N02AJ18 oxycodone and acetylsalicylic acid N02AJ19 oxycodone and ibuprofen N02AA55 oxycodone and naloxone N02AA56 oxycodone and naltrexone N02AJ17 oxycodone and paracetamol	QN02AA05 oxycodone QN02AA55 oxycodone and naloxone QN02AA56 oxycodone and naltrexone QN02AJ17 oxycodone and paracetamol QN02AJ18 oxycodone and acetylsalicylic acid QN02AJ19 oxycodone and ibuprofen

Human consumption data in kg/year for Estonia, Finland, Germany, Latvia and Sweden.

	Estonia			Finland			Germany*			Latvia			Sweden		
Compound/year	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**
17-α-ethinyl estradiol (EE2)	0.027	0.027	0.023	1.8	1.6	1.6	414.0	381.9	356.2	0.3	0.3	0.3	1.5	1.5	1.4
17-β-estradiol (E2)	-	-	-	53.3	52.1	52.1	469.8	431.2	430.2	-	-	-	1.5	1.5	1.4
α-Estradiol	-	-	-							27.4	27.1	28.0	-	-	-
Amlodipine	148.5	160.6	173.2	582.3	606.5	621.9	9180.0	9532.0	9705.0	203.0	220.8	246.6	876.0	943.6	1015.0
Atenolol	31.3	28.6	25.4	376.8	350.3	316.8	4050.0	3375.0	3075.0	25.8	24.9	22.1	2568.7	2560.4	2231.7
Atorvastatin	154.0	171.7	195.4	1468.7	1589.4	1787.0	8900.0	12420.0	15378.0	595.5	639.4	729.2	3243.9	4002.8	4823.9
Bezafibrate	-	-	-	81.0	78.6	78.2	9000.0	8400.0	7020.0	-	-	-	336.2	314.3	296.6
Bisoprolol	6.6	8.6	10.7	795.9	785.7	783.6	9010.0	9040.0	8970.0	146.1	150.0	158.2	286.5	306.9	323.0
Caffeine	117.4	125.1	132.1	170.8	7.1	0.3	492.0	492.0	492.0	736.5	715.4	754.6	255.0	121.9	67.7
Candesartan	44.8	46.6	55.6	597.3	644.5	702.6	9376.0	10512.0	11492.9	14.7	16.8	21.7	1210.3	1342.0	1470.2
Carbamazepine	1053.2	1034.2	1019.1	3240.9	3071.1	2909.7	39000.0	37000.0	33900.0	1351.4	1386.5	1538.5	5818.0	5600.5	5349.1
Ciprofloxacin	379.5	347.1	325.0	461.8	175.1	234.1	27000.0	26000.0	17300.0	656.4	655.9	663.4	2751.8	2713.0	2555.4
Diclofenac	1496.3	1519.7	1511.73	2317.2	2511.6	2561.0	29100.0	26600.0	24860.0	1973.8	1942.0	1943.6	2923.0	2805.0	2685.0
Dipyridamole	0.05	0	0.05	4202.5	3564.4	4015.6	1480.0	560.0	0	0.15	0.2	0.3	1921.6	1705.6	1476.0
Doxycycline	1647.2	1601.6	1420.1	514.2	507.8	436.8	4600.0	4500.0	4330.0	168.2	168.8	165.7	490.8	453.6	456.4
Enalapril	159.1	141.9	127.0	822.8	790.6	750.7	6190.0	5730.0	4721.0	186.9	164.8	148.4	1977.2	1965.9	1945.6

	Estonia			Finland			Germany*			Latvia			Sweden		
Compound/year	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**
Erythromycin	1.5	1.6	1.4	111.6	28.8	2.7	15855.0	14865.0	12945.0	47.5	39.0	36.2	582.7	548.1	504.5
Estriol (E3)	35.5	29.6	26.2	2.6	2.7	2.6	466.0	476.0	492.6	0.02	0.03	0.03	8.14	8.11	7.9
Estrone (E1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fexofenadine	-	-	-	616.3	626.8	673.7	2400.0	2520.0	2340.0	0.2	0.10	0.0	500.6	531.7	573.5
Fluconazole	15.5	15.3	15.2	130.9	122.4	114.3	420.0	440.0	440	24.7	22.9	23.1	185.5	190.2	183.4
Furosemide	100.5	97.8	90.2	2999.1	2956.9	2894.0	15560.0	14360.0	0	85.8	78.0	74.5	5054.8	4969.7	4847.4
Gemfibrozil	-	-	-	86.5	74.4	67.6	-	-	-	-	-	-	888.5	838.5	762.1
Ibuprofen	15229.6	15282.5	14976.9	120077.8	124173.6	120408.8	337020.0	346860.0	335913.0	20263.7	20599.4	20239.0	105806.5	119260.9	12372.6
Ketoprofen	210.6	230.3	239.2	428.3	388.2	325.3	235.6	199.4	181.3	92.2	82.5	78.71	1781.5	1803.8	1817.4
Losartan	196.8	170.9	162.1	5213.1	5336.3	5793.8	11100.0	10700.0	9830.0	188.9	194.8	198.4	6011.1	6660.0	7425.0
Metoprolol	1666.9	1708.8	1789.2	4193.9	3843.5	3671.2	146550.0	143400.0	138615.0	1432.9	1395.4	1350.3	11146.6	11203.1	11197.3
Naproxen	1720.3	1876.8	2094.7	7696.1	7831.1	7658.5	15500.0	16500.0	19500.0	744.6	766.6	775.3	21233.6	22138.6	21932.0
Norethisterone	0.5	0.5	0.5	18.6	18.6	19.3	109.1	97.1	87.0	1.2	1.2	1.1	16.0	14.9	13.6
Norfloxacin	89.9	78.0	71.2	5.4	0	0	240.0	480.0	344.0	107.9	99.1	94.5	27.6	21.7	18.0
Ofloxacin	3.8	3.6	3.6	17.1	14.5	0.7	22400.0	22000.0	22480.0	31.0	27.6	21.1	0.0	0.0	0.0
Paracetamol	16803.6	18756.7	20390.9	193125.7	205275.7	216904.1	33000.0	33000.0	31200.0	14649.5	14762.2	15272.3	543929.4	556213.8	540486.0
Progesterone	15.2	24.87	36.9	124.8	119.9	111.7	1785.0	2082.5	2870.9	104.4	117.3	126.0	122.8	126.0	133.3
Quetiapine	417.9	430.9	465.6	4324.2	4187.8	4247.9	22800.0	23600.0	23880.0	424.8	447.0	514.3	4301.0	4029.6	4131.4

	Estonia			Finland			Germany*			Latvia			Sweden		
Compound/year	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**
Ramipril	84.7	82.4	81.3	363.2	368.5	369.0	11550.0	11780.0	11868.8	55.9	56.0	57.1	255.3	253.0	249.6
Risperidone	1.5	1.5	1.5	19.5	18.2	17.1	185.0	185.0	185.5	3.3	3.3	3.3	15.2	15.1	14.8
Simvastatin	94.4	88.6	82.6	2673	2435.7	2327.3	41760.0	40980.0	38934.0	9.7	8.8	7.7	4505.3	4082.1	3694.8
Sotalol	121.2	109.8	97.6	186.3	176.1	143.5	2560.0	2240.0	1920.0	46.1	55.5	71.4	404.1	331.0	271.8
Sulfadiazine	63.7	90.9	90.1	384.9	397.6	363.8	3000.0	3000.0	3200.0	2.7	2.5	2.4	0.7	0.1	0.6
Sulfamethoxazole	347.4	329.6	543.7	338.6	405.3	422.3	16960.0	16480.0	16800.0	1048.0	1010.1	1016.1	0.0	0.0	0.0
Telmisartan	1055.2	1014.7	1010.0	1131.2	1132.8	1167.0	6840.0	7036.0	6832.0	498.9	486.9	543.4	51.4	52.2	52.1
Testosterone	1.68	1.84	1.91	126.8	110.3	115.2	2148.0	2376.0	2556.0	4.0	3.9	4.5	264.0	280.0	288.4
Tetracycline (lymecycline)	0.51	0.1	0.2	1268.9	1065.7	923.2	50000.0	49000.0	46000.0	1.8	2.6	2.4	304.9 (2716)	273.1 (2680)	232.5 (2659)
Tramadol	314.7	318.0	332.3	1761.4	1712.5	1700.8	22530.0	21420.0	20370.0	363.6	349.3	367.3	3933.1	3502.6	3022.1
Trimethoprim	82.3	86.2	82.1	959.7	918.6	854.1	4760.0	4640.0	4720.0	224.5	205.7	205.6	220	185	170
Warfarin	27.1	25.4	23.0	264.0	242.5	223.7	27.0	24.75	23.25	29.2	30.1	31.1	262.9	233.6	204.4
Venlafaxine	103.1	115.6	127.8	1941.8	1917.5	2028.2	18530.0	18990.0	19600.0	48.2	57.3	64.1	3415.5	3547.9	3692.1
Hydrochlorothiazide	282.8	257.2	250.7	2119.5	2049.1	2004.8	56177.5	51602.5	53757.5	269.1	259.7	265.1	551.8	552.6	549.9
Nebivolol	46.2	48.5	51.1	15.4	16.4	17.1	895.0	925.0	938.5	48.5	52.9	58.6	0.0	0.0	0.0
Olanzapine	8.7	8.9	9.4	117.9	121.7	118.3	400.0	420.0	437.0	8.4	9.8	11.1	678.2	780.9	844.5
Citalopram (Escitalopram)	14.52	14.2	13.7	482.1 (276.6)	435.5 (286.6)	399.6 (308.0)	6136.0 (863.0)	5800.0 (1035)	5500.0 (1187.0)	9.00	10.1	11.0	1396.0 (293.6)	1292.2 (333.2)	1173.1 (375.6)
Sertraline	72.4	86.7	94.8	719.1	720.1	792.5	5920.0	6670.0	7550.0	32.2	34.4	40.0	4640.2	5009.4	5330.0

	Estonia			Finland			Germany*			Latvia			Sweden		
Compound/year	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**
Acetylsalisylic acid	11004.3	10437.8	10175.4	28 250.4	26 696.9	24 916.4	1600666.7	1631000.0	1605566.7	10146.5	9940.5	10093.5	55604.6	52248.1	50658
Omeprazole/ esomeprazole	252.2	264.3	262.8	1357.3	1352.4	1296.8	17280.0	16380.0	14602.0		384.4	390.4	5776.5	6120.2	6400.0
Pantoprazole	140.8	172.7	196.7	2312.4	2449.8	2588.9	52240.0	55880.0	54174.0	201.8	218.0	236.2	288.0	326.2	363.1
Esomeprazole	139.2	159.9	181.7				3360.0	3620.0	3610.0	59.5	73.1	88.3	-	-	-
Xylometazoline	11.7	12.5	15.8	13.5	15.3	16.0	111.2	112.0	101.6	10.5	9.4	9.7	67.6	74.0	89.8
Mometasone	-	-	-	10.6	11.0	10.8	88.9	97.3	38.7	1.5	1.7	1.9	34.2	34.7	35.1
Fluticasone	0.3	0.3	0.3	14.2	14.6	14.5				1.4	1.3	1.2	3.0	3.4	3.5
Cetirizine (Levocetirizine) ((hydroxyzine))	32.2	33.9	35.8	488.3 (49.2	478.5 (48.9)	536.1 (45.6)	132.0 (68.5)	141.0 (61.0)	155.0 (58.5)	19.1	20.8	20.7	357.0	358.6	363.6
Primidone	34.0	34.8	30.4	-	-	-	5462.5	5362.5	5125.0	2.5	2.6	2.5	1.9	1.9	2.1
Allopurinol	760.2	863.9	993.0	2798.2	2812.5	2821.0	133600.0	132400.0	130080.0	617.4	686.7	812.5	4453.5	4707.2	4991.4
Gabapentin	657.1	776.7	958.2	6826.0	8090.4	9709.9	82800.0	82800.0	82800.0	1806.6	2081.0	2565.0	12984.3	14851.2	16676.6
Levetiracetam	227.8	282.1	323.1	6262.5	6738.3	7292.3	117000.0	126000.0	133950.0	194.4	262.4	332.3	7518.9	8388.0	9306.8
Mesalazin	663.8	778.3	844.9	18427.2	19037.4	19857.8	106500.0	108000.0	110100.0	371.6	450.2	553.9	29443.7	30911.8	32131.4
Valsartan	346	331	317	4441.1	4527.9	4702.2	80376.0	88008.0	94112.0	314.0	335.7	357.3	1345.3	1367.5	1417.2
Codeine	121.5	144.8	176.6	1725.5	1622.8	1568.3	720.0	610.0	630.0	51.3	57.9	72.7	1750.7	1641.8	1504.3
Irbesartan	0	0	0	-	-	-	19950.0	19005.0	18015.0	34.3	29.6	26.3	1188	1151	1087
Clarithromycin	435.3	393.9	406.0.04	245.6	215.1	185.9	12000.0	10500.0	10500.0	444.1	435.7	469.3	630.1	638.5	615.2

	Estonia			Finland			Germany*			Latvia			Sweden		
Compound/year	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**	**2015**	**2016**	**2017**
Eprosartan	3.04	2.57	1.56	1124.0	1037.2	968.9	10800.0	7800.0	4800.0	2.6	2.7	2.2	93.8	80.8	71.8
Metformin	21710.8	22813.7	23857.5	149 405.8	151 083.9	147 566.6	1584000.0	1624000.0	1640000.0	27974.0	29127.2	30617.9	110573.0	114807.2	118190.0
Lincomycin										19.1	16.3	9.9			
Ivermectin	-	-	-	0.4	1.9	2.7	20.40	75.60	82.80	-	0.01	0.3			
Oxazepam	1.0	1.1	1.2	565.6	535.0	512.0				23.1	20.2	19.0	0.6	0.6	0.5
Temazepam	-	-	-	346.2	306.1	270.3				-	-	-			
Oxycodone	9.6	11.7	13.1	247.6	254.3	263.5				0.0	0.0	0.0	586	635	654

*only reimbursed medicines included

Annex 3. Environmental levels of APIs in inland and coastal waters

Surface water sampling sites and the number of samples (sampling times) in each of them are listed below.

Estonia	Code	Short name	Site description	Samples
	EE1	Pärnu1	Pärnu river after river Esna, before city of Paide	2
	EE2	Pärnu2	Pärnu river, Jändja, SJA6245000	2
	E-BSE0	Pärnu3	Pärnu river in Pärnu by Tallinn road bridge, SJB1092000 (river mouth)	1
	E-BSE1	Pärnu bay	Pärnu bay, middle depth	1
Poland	**Code**	**Short name**	**Site description**	
	PL2	Rokitnica1	Rokitnica river, upstream Błonie WWTP	2
	PL1	Rokitnica2	Rokitnica river, downstream Błonie WWTP	2
	PL-BSE	Vistula mouth	Vistula River, Kiezmark	2
Germany	**Code**	**Short name**	**Site description**	
	DE1	Tollense1	Tollense river, upstream WWTP Neubrandenburg	2
	DE2	Tollense2	Tollense river, downstream WWTP Neubrandenburg	2
	D-BSE1	Peene	Estuary of Tollense river (BSE)	2
	DE3	Warnow1	Warnow river, upstream Rostock	2
	D-BSE2	Warnow2	Estuary of Warnow river, BSE	2
Latvia	**Code**	**Short name**	**Site description**	
	LV1	Mēmele	Mēmele, 0.5 km below Skaistkalne	2
	LV2	Mūsa	Mūsa river, Latvia - Lithuania border	2
	LV3	Driksa1	Driksa river, upstream Jelgava	2
	LV4	Driksa2	Driksa river, downstream Jelgava	2
	LV5	Pupla1	Pupla river, upstream Olaine	2
	LV6	Pupla2	Pupla river, downstream Olaine	2
	LV7	Lielupe	Lielupe, 0.5 km below Kalnciems	2
	LV-BSE	Riga	Riga coast, site at/close to outlet pipe of WWTP, sampling depths 1-m (Riga-s) and 12-m (close to bottom; Riga_b)	2 x 2
Sweden	**Code**	**Short name**	**Site description**	
	SE1	Vättern	Upstream from the other sites. No WWTP close to sampling point, but there are WWTPs in the drainage area.	2
	SE2	Boren	Downstream from WWTP in Motala. Upstream sample for Glan, Dovern and Bråviken.	2
	SE3	Svartån	Downstream from a large drainage area with several WWTPs. Upstream sample for lake Roxen	2
	SE4	Stångån upstr.	Upstream WWTP in Linköping but influenced by other WWTPs further upstream the drainage area.	2
	SE5	Stångån-Roxen	Downstream WWTP in Linköping at the outlet to lake Roxen.	2
	SE6	Dovern	Downstream WWTP in Finspång, upstream from Glan.	2
	SE7	Glan	Downstream sample from Vättern and Boren. Upstream sample from Bråviken. No WWTP effluent directly to this large lake.	2
	SE-BSE	Bråviken	BSE, downstream WWTP in Norrköping; Pampusfjärden, sampling depth 1-m	2
Finland	**Code**	**Short name**	**Site description**	
	FI1	Vantaa1	Vantaa 68,2, located 68 km up from river mouth; upstream WWTP Kalteva, but site may be nfluenced by a WWTP 20 km upstream	3
	FI2	Vantaa2	Vantaa 64,8 (65 km up from river mouth); downstream WWTP Kalteva	3
	FI3	Vantaa3	Vantaa 44,1 (44 km up from river mouth); downstream from WWTPs Kalteva and Nurmijärvi	3
	FI4	Luhtaj.	Luhtajoki, a tributary, which runs to river Vantaa between Vantaa3 & Vantaa4; downstream WWTP Klaukkala and the landfill site Metsä-Tuomela	1
	FI5	Vantaa4	Vantaa 4,2 (ca 4 km up from river mouth)	3
	FI6	Matins	Matinsilta, estuary site close to river mouth, sampling at 1-m from surface; sampes taken from a bridge over the estuary bay / from icehole in winter	3
	FI7	Vanhank.	Vanhankaupunginselkä; estuary area for river Vantaa, sampling site about 2 km from river mouth, sampling at 1-m depth	2
	FI-BSE1	WWTP pipe	Helsinki coast at the outlet of WWTP Viikinmäki pipe (16 km long pipe) in the bottom; sampling at mid-depth	1
	F-BSE2	Katajaluoto	"Katajaluoto 125", a coastal site about a nautical mile from the WWTP outlet; sampling depths 1-m (surface), midle-depth and 1-m from bottom	2 x 3

Measured API concentrations in the 81 surface water samples are presented in the following tables.

Estonia 1/2	Site code		EE1	EE1	EE2	EE2	E-BSE0	E-BSE1
	Surface water type		river	River	River	river	river mouth	sea
	Date	dd.mm.yy	6.12.17	4.6.18	6.12.17	4.6.18	13.12.17	6.6.18
	N cordinates	L-Est 97	58.883306		58.753609		58.389707	58.355054
	E cordinates	L-Est 97	25.57894		25.321941		24.496484	24.42677
API	**API group**	**Unit**	**Pärnu1**		**Pärnu2**		**Pärnu3**	**Pärnu bay**
Amlodipine	Antihypertensives	ng/L	<7.7	<7.7	<7.7	<7.7	<0.003	1.7
Atenolol	Other cardiovascular med.	ng/L	<12	<12	<12	<12	<8.0	<8.0
Atorvastatin	Metabolic disease med.	ng/L	<15	<15	<15	<15	N/A	N/A
Bezafibrate	Metabolic disease med.	ng/L	<0.83	<0.83	<0.83	<0.83	<0.40	<0.40
Bisoprolol	Other cardiovascular med.	ng/L	<0.52	<0.52	<0.52	<0.52	<0.21	<0.21
Caffeine	Other	ng/L	46	18	160	6.6	2.5	<0.24
Candesartan	Antihypertensives	ng/L	<0.68	2.1	<0.68	<0.68	<0.22	<0.22
Carbamazepine	Antiepileptics	ng/L	1.0	3.4	2.3	26	0.56	1.2
Carprofen	Veterinary medicines	ng/L	<0.77	<0.77	9.8	<0.77	<0.58	<0.58
Cetirizine	Asthma and allergy med.	ng/L	0.25	0.53	0.28	<0.11	0.04	0.2
Ciprofloxacin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	<35	<35
Citalopram	Psycopharmaceuticals	ng/L	0.32	<0.06	0.56	3.7	<0.04	<0.04
Clarithromycin	Antibiotics	ng/L	5.0	<1.0	3.5	<1.0	<0.33	<0.33
Codeine	NSAIDs and analgesics	ng/L	N/A	<0.07	N/A	<0.07	0.08	<0.01
Diclofenac	NSAIDs and analgesics	ng/L	11	11	53	28	3.3	<0.34
Dipyridamole	Other cardiovascular med.	ng/L	<1,1	<1.1	<1.1	<1.1	<0.67	<0.67
Emamectin	Veterinary medicines	ng/L	1.0	<0.09	0.42	<0.09	<0.02	1.2
Enalapril	Antihypertensives	ng/L	<2,8	<2.8	<2.8	<2.8	N/A	N/A
Eprosartan	Antihypertensives	ng/L	<0.22	<0.22	<0.22	<0.22	N/A	N/A
Erythromycin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	<0.92	<0.92
Estrone (E1)	Hormones	ng/L	<0.70	<0.70	<0.70	<0.70	0.80	1.7
Fenbendazole	veterinary medicines	ng/L	0.13	<0.07	0.10	<0.07	<0.03	<0.03
Fexofenadine	asthma and allergy med.	ng/L	<0.09	0.85	<0.09	0.21	N/A	N/A
Fluconazole	Antibiotics	ng/L	0.90	<0.05	<0.05	6.2	<0.25	<0.25
Fluticasone	Asthma and allergy med.	ng/L	0.08	<0.06	<0.06	<0.06	<0.002	<0.002
Gabapentin	Antiepileptics	ng/L	280	<0.88	50	<0.88	N/A	N/A
Gemfibrozil	Metabolic disease med.	ng/L	3.1	<1.5	<1.5	<1.5	0.84	<0.02
Irbesartan	Antihypertensives	ng/L	<0.06	<0.06	<0.06	<0.06	<0.02	<0.02
Ketoprofen	NSAIDs and analgesics	ng/L	1.4	<0.72	2.1	<0.72	<0.38	<0.38
Levetiracetam	Antiepileptics	ng/L	3.9	9.5	5.3	120	<5.4	<5.4
Lincomycin	Antibiotics	ng/L	<0.10	<0.10	<0.10	<0.10	<0.04	<0.04
Losartan	Antihypertensives	ng/L	0.20	<0.14	0.17	<0.14	<0.02	0.17
Mesalazine	Gastrointestinal disease m.	ng/L	N/A	N/A	N/A	N/A	157	33
Metformin	Metabolic disease med.	ng/L	23	<0.24	83	78	87	9.1
Metoprolol	Other cardiovascular med.	ng/L	1.1	<0.54	6.0	6.1	<0.35	<0.35
Mometasone furoate	Asthma and allergy med.	ng/L	10	28	<1.3	<1.3	<0.29	<0.29
Naproxen	NSAIDs and analgesics	ng/L	5.3	1.0	9.7	1.6	12	1.3
Nebivolol	Other cardiovascular med.	ng/L	1.3	<0.052	0.84	<0.052	0.17	1.9
Norethisterone	Hormones	ng/L	<0.08	<0.080	1.3	0.39	<0.04	<0.04
Ofloxacin	Antibiotics	ng/L	<10	<10	<10	<10	<4.2	<4.2
Oxazepam	Psycopharmaceuticals	ng/L	N/A	<0.033	N/A	1.2	0.11	<0.03
Oxycodone	NSAIDs and analgesics	ng/L	N/A	<0.042	N/A	2.0	<0.03	<0.03
Primidone	Antiepileptics	ng/L	<1,4	<1.37	<1.37	<1.37	<0.71	<0.71
Progesterone	Hormones	ng/L	1.4	<0.086	0.11	<0.086	<0.03	<0.03
Quetiapine	Psycopharmaceuticals	ng/L	<0.15	<0.15	<0.15	<0.15	<0.01	<0.01
Ramipril	Antihypertensives	ng/L	<0.72	<0.72	<0.72	<0.72	N/A	N/A
Sertraline	Psycopharmaceuticals	ng/L	0.39	<0.04	0.40	5.0	<0.03	<0.03
Simvastatin	Metabolic disease med.	ng/L	N/A	N/A	N/A	N/A	<0.02	<0.02
Sotalol	Other cardiovascular med.	ng/L	<0.89	<0.89	<0.89	<0.89	<0.68	<0.68
Sulfadiazine	Antibiotics	ng/L	<17	<17	<17	<17	N/A	N/A
Telmisartan	Antihypertensives	ng/L	4.3	18	4.9	9.4	N/A	N/A
Temazepam	Psycopharmaceuticals	ng/L	N/A	<0.36	N/A	<0.36	<0.34	<0.34
Testosterone	Hormones	ng/L	<0.08	<0.080	0.10	<0.080	<0.05	<0.05
Tetracycline / Doxycycline	Antibiotics	ng/L	<5.7	<5.7	<5.7	<5.7	4.9	<3.2

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Estonia 2/2	Site code		EE1	EE1	EE2	EE2	E-BSE0	E-BSE1
	Surface water type		river	River	River	river	river mouth	sea
	Date	dd.mm.yy	6.12.17	4.6.18	6.12.17	4.6.18	13.12.17	6.6.18
	N cordinates	L-Est 97	58.883306		58.753609		58.389707	58.355054
	E cordinates	L-Est 97	25.57894		25.321941		24.496484	24.42677
API	**API group**	**Unit**	**Pärnu1**		**Pärnu2**		**Pärnu3**	**Pärnu bay**
Tiamulin	Veterinary medicines	ng/L	0.56	<0.079	0.45	<0.079	<0.01	0.22
Toltrazuril	Veterinary medicines	ng/L	<4.8	<4.8	<4.8	<4.8	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/L	0.39	0.93	0.60	18	0.08	<0.02
Trimethoprim	Antibiotics	ng/L	<0.37	<0.37	0.69	1.2	<0.17	0.39
Tylosin	Veterinary medicines	ng/L	20	<3.7	20	<3.7	<1.9	<1.9
Valsartan	Antihypertensives	ng/L	<6.4	<6.4	<6.4	<6.4	N/A	N/A
Warfarin	Other cardiovascular med.	ng/L	<0.87	<0.87	<0.87	<0.87	<0.58	<0.58
Venlafaxine	Psycopharmaceuticals	ng/L	0.16	0.21	0.25	13	<0.03	<0.03
Xylometazoline	Asthma and allergy medi.	ng/L	1.8	<0.05	1.8	<0.05	<0.19	<0.19
Sum concentration		ng/L	424	93	418	325	268	50
Number of detected / analysed APIs			28/54	12/58	28/54	18/58	14/53	11/53

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Poland	Site code		PL2	PL2	PL1	PL1	PL-BSE	PL-BSE
	Surface water type		River	river	river	river	estuary	estuary
	Date	dd.mm.yy	29.11.17	18.7.18	29.11.17	18.7.18	21.11.17	23.7.18
	N coordinates	WGS84	52.195026		52.198344		54.256980	
	E coordinates	WGS84	20.609962		20.604209		18.946839	
API	**API group**	**Unit**	**Rokitnica1**		**Rokitnica2**		**Vistula mouth**	
Amlodipine	Antihypertensives	ng/L	<7.7	<7.7	<7.7	<7.7	<0.003	1.8
Atenolol	Other cardiovascular med.	ng/L	<12	<12	52	<12	<8.0	<8.0
Atorvastatin	Metabolic disease med.	ng/L	210	17	<15	<15	N/A	N/A
Bezafibrate	Metabolic disease med.	ng/L	<0.83	<0.83	<0.83	<0.83	<0.40	<0.40
Bisoprolol	Other cardiovascular med.	ng/L	2.7	15	52	16	0.49	<0.21
Caffeine	Other	ng/L	400	41	<0.75	32	5.8	7.9
Candesartan	Antihypertensives	ng/L	12	<0.68	19	<0.68	1.1	<0.22
Carbamazepine	Antiepileptics	ng/L	35	320	920	920	9.2	60
Carprofen	Veterinary medicines	ng/L	2.8	1.8	8.2	2.5	<0.58	<0.58
Cetirizine	Asthma and allergy med.	ng/L	11	110	310	240	3.1	17
Ciprofloxacin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	<35	<35
Citalopram	Psycopharmaceuticals	ng/L	4.1	2.9	24	26	0.20	0.46
Clarithromycin	Antibiotics	ng/L	19	8.3	590	65	0.38	0.59
Codeine	NSAIDs and analgesics	ng/L	0.65	2.3	9.4	2.6	0.26	0.11
Diclofenac	NSAIDs and analgesics	ng/L	62	730	2200	2100	12	1.3
Dipyridamole	Other cardiovascular med.	ng/L	<1.1	<1.1	<1.1	<1.1	<0.67	<0.67
Emamectin	Veterinary medicines	ng/L	0.54	<0.09	0.17	<0.09	<0.02	1.6
Enalapril	Antihypertensives	ng/L	<2.8	<2.8	<2.8	<2.8	N/A	N/A
Eprosartan	Antihypertensives	ng/L	<0.22	<0.22	0.23	<0.22	N/A	N/A
Erythromycin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	8.4	<0.92
Estrone (E1)	Hormones	ng/L	<0.70	2.8	<0.70	1.8	0.25	<0.17
Fenbendazole	Veterinary medicines	ng/L	0.23	<0.07	0.25	<0.07	<0.03	<0.03
Fexofenadine	Asthma and allergy med.	ng/L	21	350	340	520	N/A	N/A
Fluconazole	Antibiotics	ng/L	6.9	130	280	270	3.5	7.4
Fluticasone	Asthma and allergy med.	ng/L	<0.06	<0.06	0.27	<0.06	0.02	<0.002
Gabapentin	Antiepileptics	ng/L	35	600	1900	1200	N/A	N/A
Gemfibrozil	Metabolic disease med.	ng/L	<1.5	4.3	73	2.5	1.4	2.3
Irbesartan	Antihypertensives	ng/L	0.20	7.0	0.80	3.1	1.5	0.12
Ketoprofen	NSAIDs and analgesics	ng/L	12	2.4	280	3.0	0.45	3.9
Levetiracetam	Antiepileptics	ng/L	<3.5	<3.5	60	<3.5	<5.4	<5.4
Lincomycin	Antibiotics	ng/L	0.24	2.6	7.0	9.4	0.55	0.57
Losartan	Antihypertensives	ng/L	3.5	97	110	44	0.6	0.78
Mesalazine	Gastrointestinal disease m.	ng/L	N/A	N/A	N/A	N/A	<0.82	71
Metformin	Metabolic disease medi.	ng/L	220	220	290	330	11	80
Metoprolol	Other cardiovascular m.	ng/L	4.6	50	290	170	1.9	<0.35
Mometasone furoate	Asthma and allergy med.	ng/L	<1.3	<1.3	<1.3	<1.3	0.36	<0.29
Naproxen	NSAIDs and analgesics	ng/L	27	8.2	56	5.7	1.4	1.8
Nebivolol	Other cardiovascular medi.	ng/L	1.2	<0.052	2.2	0.34	0.02	1.7
Norethisterone	Hormones	ng/L	0.70	<0.080	<0.080	<0.080	<0.04	1.2
Ofloxacin	Antibiotics	ng/L	61	<10	36	<10	<4.2	<4.2
Oxazepam	Psycopharmaceuticals	ng/L	<0.033	3.9	14	12	0.2	0.92
Oxycodone	NSAIDs and analgesics	ng/L	0.17	<0.042	1.2	<0.042	<0.03	<0.03
Primidone	Antiepileptics	ng/L	2.0	31	11	12	<0.71	1.5
Progesterone	Hormones	ng/L	0.89	<0.086	0.75	<0.086	<0.03	<0.03
Quetiapine	Psycopharmaceuticals	ng/L	1.2	<0.15	0.64	<0.15	0.2	<0.01
Ramipril	Antihypertensives	ng/L	<0.72	18	11	3.64	N/A	N/A
Sertraline	Psycopharmaceuticals	ng/L	0.78	<0.04	5.6	5.40	0.03	<0.03
Simvastatin	Metabolic disease med.	ng/L	N/A	N/A	N/A	N/A	0.11	<0.02
Sotalol	Other cardiovascular med.	ng/L	7.3	94	190	91	2.3	1.3
Sulfadiazine	Antibiotics	ng/L	<17	<17	<17	<17	N/A	N/A
Telmisartan	Antihypertensives	ng/L	99	1200	2800	2500	N/A	N/A
Temazepam	Psycopharmaceuticals	ng/L	1.1	7.1	12	12	<0.34	2.4
Testosterone	Hormones	ng/L	0.48	<0.080	0.40	<0.080	<0.05	<0.05
Tetracycline/ Doxycycline	Antibiotics	ng/L	<5.7	<5.7	<5.7	<5.7	<3.17	3.4
Tiamulin	Veterinary medicines	ng/L	0.21	<0.079	0.11	<0.079	0.01	0.52
Toltrazuril	Veterinary medicines	ng/L	<4.8	<4.8	<4.8	<4.8	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/L	10	320	550	690	3.7	8.5
Trimethoprim	Antibiotics	ng/L	<0.37	<0.37	54	25	<0.17	0.26
Tylosin	Veterinary medicines	ng/L	<3.7	<3.7	<3.7	<3.7	<1.9	<1.9
Valsartan	Antihypertensives	ng/L	40	45	30	24	N/A	N/A
Warfarin	Other cardiovascular med.	ng/L	<0.87	<0.87	<0.87	1.1	<0.58	<0.58
Venlafaxine	Psycopharmaceuticals	ng/L	2.9	34	120	100	0.72	<0.03
Xylometazoline	Asthma and allergy medi.	ng/L	0.43	1.1	3.8	2.0	<0.19	<0.19
Sum concentration		ng/L	1319	4477	11715	9442	71	278
Number of detected / analysed APIs			40/58	32/58	45/58	35/58	31/53	27/53

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Germany (1/2)		DE1	DE1	DE2	DE1	D-BSE1	D-BSE1
Surface water type		River	river	River	river	estuary	estuary
Date	dd.m.yy	21.2.18	23.5.18	21.2.18	23.5.18	21.2.18	23.5.18
N coordinates	WGS84	53.56597		53.5722		53.865681	
E coordinates	WGS84	13.23787		13.23409		13.828045	
API	**Unit**	**Tollense1**		**Tollense2**		**Peene**	
Amlodipine	ng/L	<7.7	<7.7	<7.74	<7.7	0.02	5.0
Atenolol	ng/L	<12	<12	<12	<12	<8.0	<8.0
Atorvastatin	ng/L	<15	<15	<15	16	N/A	N/A
Bezafibrate	ng/L	<0.83	<0.83	8.3	10	<0.40	<0.40
Bisoprolol	ng/L	<0.52	<0.52	20	40	0.58	<0.21
Caffeine	ng/L	300	74	280	79	13	20
Candesartan	ng/L	13	<0.68	15	12	1.6	<0.22
Carbamazepine	ng/L	3.2	2.9	52	190	7.3	26
Carprofen	ng/L	<0.77	<0.77	<0.77	<0.77	<0.58	<0.58
Cetirizine	ng/L	0.13	<0.11	6.3	50	1.8	6.3
Ciprofloxacin	ng/L	N/A	N/A	N/A	N/A	<35	<35
Citalopram	ng/L	0.67	<0.06	11	15	0.25	0.36
Clarithromycin	ng/L	<1.0	<1.0	46	27	0.61	<0.33
Codeine	ng/L	0.16	<0.07	1.1	0.8	0.08	0.18
Diclofenac	ng/L	4.0	<1.2	330	350	6.7	0.41
Dipyridamole	ng/L	<1.1	<1.1	<1.1	<1.1	<0.67	0.92
Emamectin	ng/L	0.21	<0.09	0.19	<0.09	<0.02	7.2
Enalapril	ng/L	<2.8	<2.8	<2.8	<2.8	N/A	N/A
Eprosartan	ng/L	<0.22	<0.22	2.6	0.88	N/A	N/A
Erythromycin	ng/L	N/A	N/A	N/A	N/A	9.8	<0.92
Estrone (E1)	ng/L	<0.70	<0.70	<0.70	2.7	0.69	2.6
Fenbendazole	ng/L	0.10	<0.07	0.13	<0.07	<0.03	0.51
Fexofenadine	ng/L	0.21	<0.09	7.4	51	N/A	N/A
Fluconazole	ng/L	<0.05	<0.05	11	12	1.9	3.3
Fluticasone	ng/L	0.11	<0.06	0.08	<0.06	<0.002	<0.002
Gabapentin	ng/L	27	31	310	670	N/A	N/A
Gemfibrozil	ng/L	11	1.8	11	1.8	<0.02	<0.02
Irbesartan	ng/L	0.08	<0.06	30	110	0.55	0.86
Ketoprofen	ng/L	<0.72	<0.72	2.13	<0.72	<0.38	<0.38
Levetiracetam	ng/L	7.0	<3.52	12	45	<5.43	<5.43
Lincomycin	ng/L	<0.10	<0.10	0.22	<0.10	0.13	0.52
Losartan	ng/L	0.50	<0.14	10	12	0.2	0.28
Mesalazine	ng/L	N/A	N/A	N/A	N/A	5.8	150
Metformin	ng/L	11	26	160	570	9.1	58
Metoprolol	ng/L	1.2	<0.54	67	120	1.6	<0.35
Mometasone furoate	ng/L	1.8	<1.3	<1.3	<1.3	<0.29	<0.29
Naproxen	ng/L	<0.57	2.7	27	35	0.93	<0.47
Nebivolol	ng/L	0.49	<0.052	0.40	<0.052	0.02	8.9
Norethisterone	ng/L	6.9	<0.080	0.23	<0.080	0.87	0.67
Ofloxacin	ng/L	<10	<10	12	<10	<4.2	<4.2
Oxazepam	ng/L	0.05	<0.033	1.3	3.1	0.23	0.57
Oxycodone	ng/L	0.12	<0.042	1.1	1.6	0.04	0.97
Primidone	ng/L	<1.37	<1.37	16	62	0.97	0.99
Progesterone	ng/L	0.48	<0.086	0.41	<0.086	0.07	<0.03
Quetiapine	ng/L	<0.15	<0.15	0.35	0.57	0.01	1.5
Ramipril	ng/L	<0.72	<0.72	3.5	19	N/A	N/A
Sertraline	ng/L	0.20	<0.04	0.51	0.19	<0.03	3.19
Simvastatin	ng/L	N/A	N/A	N/A	N/A	<0.02	<0.02
Sotalol	ng/L	<0.89	<0.89	<0.89	<0.89	<0.68	<0.68
Sulfadiazine	ng/L	<17	<17	<17	<17	N/A	N/A
Telmisartan	ng/L	1.7	<1.4	160	480	N/A	N/A
Temazepam	ng/L	<0.36	<0.36	1.5	4.6	<0.34	0.85
Testosterone	ng/L	<0.080	<0.080	0.42	<0.080	0.06	<0.05
Tetracycline / Doxycycline	ng/L	<5.7	<5.7	<5.7	<5.7	<3.17	3.7
Tiamulin	ng/L	0.09	<0.079	0.13	<0.079	0.02	3.1
Toltrazuril	ng/L	<4.8	<4.8	<4.8	<4.8	<3.60	<3.60
Tramadol	ng/L	2.2	0.59	21	40	3.3	6.5
Trimethoprim	ng/L	0.39	<0.37	2.8	5.7	<0.17	<0.17
Tylosin	ng/L	16	<3.7	<3.7	<3.7	<1.9	<1.9
Valsartan	ng/L	<6.4	<6.4	450	480	N/A	N/A
Warfarin	ng/L	1.02	<0.87	<0.87	<0.87	<0.58	<0.58
Venlafaxine	ng/L	0.81	<0.03	27	43	0.78	1.6
Xylometazoline	ng/L	0.25	<0.05	1.6	2.5	<0.19	0.27
Sum concentration	ng/L	412	139	2120	3563	69	310
Number of detected APIs		33/58	7/58	45/58	36/58	30/53	29/53

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Germany (2/2)

			DE3	DE3	D-BSE2	D-BSE2
	Surface water type		river	river	estuary	estuary
	Date	dd.mm.yy	22.2.18	23.5.18	22.2.18	24.5.18
	N coordinates	WGS84	54.09117		54.18652	
	E coordinates	WGS84	12.15395		12.08725	
API	**API group**	**Unit**	**Warnow1**		**Warnow2**	
Amlodipine	Antihypertensives	ng/L	<7.7	<7.7	<0.003	2.7
Atenolol	Other cardiovascular med.	ng/L	<12	<12	<8.0	<8.0
Atorvastatin	Metabolic disease med.	ng/L	<15	<15	N/A	N/A
Bezafibrate	Metabolic disease med.	ng/L	13	<0.83	0.59	0.43
Bisoprolol	Other cardiovascular m.	ng/L	26	0.87	0.77	0.67
Caffeine	Other	ng/L	130	50	4.1	42
Candesartan	Antihypertensives	ng/L	15	8	1.6	<0.22
Carbamazepine	Antiepileptics	ng/L	52	20	1.5	5.5
Carprofen	Veterinary medicines	ng/L	3.7	1.5	<0.58	<0.58
Cetirizine	Asthma and allergy med.	ng/L	6.3	3.8	0.24	2.1
Ciprofloxacin	Antibiotics	ng/L	N/A	N/A	<35	<35
Citalopram	Psycopharmaceuticals	ng/L	11	1.0	0.28	0.15
Clarithromycin	Antibiotics	ng/L	46	1.6	0.52	<0.33
Codeine	NSAIDs and analgesics	ng/L	1.13	<0.07	0.08	<0.01
Diclofenac	NSAIDs and analgesics	ng/L	490	21	4.5	0.82
Dipyridamole	Other cardiovascular m.	ng/L	<1.1	<1.1	<0.67	<0.67
Emamectin	Veterinary medicines	ng/L	0.19	<0.09	<0.02	4.6
Enalapril	Antihypertensives	ng/L	<2.8	<2.8	N/A	N/A
Eprosartan	Antihypertensives	ng/L	3.82	<0.22	N/A	N/A
Erythromycin	Antibiotics	ng/L	N/A	N/A	11	<0.92
Estrone (E1)	Hormones	ng/L	<0.70	<0.70	<0.17	5.4
Fenbendazole	Veterinary medicines	ng/L	0.13	<0.07	<0.03	<0.03
Fexofenadine	Asthma and allergy med.	ng/L	7.4	1.3	N/A	N/A
Fluconazole	Antibiotics	ng/L	11	<0.05	0.25	0.30
Fluticasone	Asthma and allergy med.	ng/L	0.08	<0.06	<0.002	<0.002
Gabapentin	Antiepileptics	ng/L	450	60	N/A	N/A
Gemfibrozil	Metabolic disease med.	ng/L	11	<1.5	25	1.9
Irbesartan	Antihypertensives	ng/L	30	3.5	0.45	0.93
Ketoprofen	NSAIDs and analgesics	ng/L	2.78	<0.72	<0.38	<0.38
Levetiracetam	Antiepileptics	ng/L	12	5.47	<5.43	<5.43
Lincomycin	Antibiotics	ng/L	0.22	<0.10	0.05	<0.04
Losartan	Antihypertensives	ng/L	10.0	<0.14	<0.02	0.28
Mesalazine	Gastrointestinal disease m.	ng/L	N/A	N/A	2.3	100
Metformin	Metabolic disease medi.	ng/L	200	230	3.2	<0.12
Metoprolol	Other cardiovascular m.	ng/L	83	6.7	0.99	<0.35
Mometasone furoate	Asthma and allergy med.	ng/L	<1.3	<1.3	<0.29	<0.29
Naproxen	NSAIDs and analgesics	ng/L	30	<0.57	<0.47	<0.47
Nebivolol	Other cardiovascular m.	ng/L	0.40	0.23	0.02	4.3
Norethisterone	Hormones	ng/L	0.23	0.68	<0.04	<0.04
Ofloxacin	Antibiotics	ng/L	<10	<10	<4.2	<4.2
Oxazepam	Psycopharmaceuticals	ng/L	1.3	0.45	0.07	<0.03
Oxycodone	NSAIDs and analgesics	ng/L	1.1	<0.042	0.05	<0.03
Primidone	Antiepileptics	ng/L	19	5.9	0.83	1.3
Progesterone	Hormones	ng/L	0.41	<0.086	0.04	<0.03
Quetiapine	Psycopharmaceuticals	ng/L	0.35	<0.15	0.01	<0.01
Ramipril	Antihypertensives	ng/L	4.90	<0.72	N/A	N/A
Sertraline	Psycopharmaceuticals	ng/L	0.51	0.45	<0.03	<0.03
Simvastatin	Metabolic disease med.	ng/L	N/A	N/A	<0.02	<0.02
Sotalol	Other cardiovascular med.	ng/L	<0.89	<0.89	<0.68	<0.68
Sulfadiazine	Antibiotics	ng/L	<17	<17	N/A	N/A
Telmisartan	Antihypertensives	ng/L	160	24	N/A	N/A
Temazepam	Psycopharmaceuticals	ng/L	1.5	<0.36	<0.34	<0.34
Testosterone	Hormones	ng/L	0.42	<0.080	0.08	<0.05
Tetracycline / Doxycycline	Antibiotics	ng/L	<5.7	<5.7	<3.17	4.9
Tiamulin	Veterinary medicines	ng/L	0.13	<0.079	0.01	<0.01
Toltrazuril	Veterinary medicines	ng/L	<4.8	<4.8	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/L	21	6.5	0.55	1.2
Trimethoprim	Antibiotics	ng/L	3.5	<0.37	<0.17	<0.17
Tylosin	Veterinary medicines	ng/L	20	<3.7	2.38	<1.9
Valsartan	Antihypertensives	ng/L	510	21	N/A	N/A
Warfarin	Other cardiovascular m.	ng/L	<0.87	<0.87	<0.58	<0.58
Venlafaxine	Psycopharmaceuticals	ng/L	27	4.2	0.47	<0.03
Xylometazoline	Asthma and allergy medi.	ng/L	1.6	<0.05	<0.19	<0.19
Sum concentration		ng/L	2418	478	62	177
Number of detected / analysed APIs			46/58	24/58	29/53	18/53

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Latvia (1/3)		LV1	LV1	LV2	LV2	LV3	LV3	LV4	LV4
Surface water type		river	river	river	river	river	river	river	river
Date	dd.mm.yy	28.11.17	24.5.18	28.11.17	24.5.18	27.11.17	22.5.18	27.11.17	22.5.18
N coordinates	WGS84 DD	56.37543		56.27518		56.66733		56.68299	
E coordinates	WGS84 DD	24.62691		24.36051		23.71688		23.70381	
API	**Unit**	**Mēmele**		**Mūsa**		**Driksa1**		**Driksa2**	
Amlodipine	ng/L	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7	<7.74
Atenolol	ng/L	<12	<12	<12	<12	<12	<12	<12	<12
Atorvastatin	ng/L	<15	<15	<15	<15	30	<15	<15	<15
Bezafibrate	ng/L	<0.83	<0.83	<0.83	<0.83	<0.83	<0.83	<0.83	<0.83
Bisoprolol	ng/L	<0.52	<0.52	<0.52	<0.52	<0.52	<0.52	<0.52	1
Caffeine	ng/L	22	27	45	<0.75	72	28	52	33
Candesartan	ng/L	<0.68	5	<0.68	<0.68	<0.68	<0.68	<0.68	<0.68
Carbamazepine	ng/L	1	6.0	2.8	18	2.2	11	2.1	17
Carprofen	ng/L	4.4	<0.77	<0.77	<0.77	7.3	1.9	2.2	1.8
Cetirizine	ng/L	0.23	<0.11	0.73	<0.11	0.43	2.6	0.53	1.5
Ciprofloxacin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Citalopram	ng/L	0.24	<0.06	0.39	2.48	0.33	0.58	0.28	<0.06
Clarithromycin	ng/L	2.1	<1.0	12	<1.0	5.4	3.4	5.2	5.9
Codeine	ng/L	N/A	<0.07	N/A	<0.07	N/A	<0.07	N/A	<0.07
Diclofenac	ng/L	6.5	3.4	57	43	33	8.9	32	33
Dipyridamole	ng/L	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Emamectin	ng/L	0.21	<0.09	0.19	<0.09	0.29	<0.09	0.25	<0.09
Enalapril	ng/L	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8
Eprosartan	ng/L	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22
Erythromycin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Estrone (E1)	ng/L	<0.70	2.4	<0.70	<0.70	<0.70	2.0	<0.70	0.83
Fenbendazole	ng/L	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07
Fexofenadine	ng/L	<0.09	<0.09	0.14	<0.09	<0.09	<0.09	0.10	<0.09
Fluconazole	ng/L	0.48	<0.05	<0.05	7.4	1.4	0.75	<0.05	0.79
Fluticasone	ng/L	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Gabapentin	ng/L	9.8	24	36	92	30	77	28	128
Gemfibrozil	ng/L	7.7	22	5.1	<1.5	4.50	23	<1.5	13
Irbesartan	ng/L	<0.06	<0.06	0.32	<0.06	<0.06	<0.06	<0.06	<0.06
Ketoprofen	ng/L	<0.72	<0.72	2.5	<0.72	1.2	<0.72	1.0	1.3
Levetiracetam	ng/L	<3.52	<3.52	<3.52	99	5.5	<3.52	<3.52	<3.52
Lincomycin	ng/L	0.26	<0.10	3.72	<0.10	0.31	<0.10	0.31	<0.10
Losartan	ng/L	0.27	<0.14	1.40	<0.14	0.67	<0.14	0.77	<0.14
Mesalazine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	ng/L	19	<0.24	49	170	55	<0.24	52	430
Metoprolol	ng/L	0.55	<0.54	9.1	3.0	3.7	0.74	2.9	3.9
Mometasone furoate	ng/L	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3
Naproxen	ng/L	<0.57	0.76	3.1	5.1	2.3	2.0	3.1	<0.57
Nebivolol	ng/L	0.47	<0.052	0.48	<0.052	0.56	<0.052	0.51	<0.052
Norethisterone	ng/L	0.78	0.57	0.19	<0.080	<0.080	<0.080	0.49	0.53
Ofloxacin	ng/L	<10	<10	<10	<10	<10	<10	<10	<10
Oxazepam	ng/L	N/A	<0.033	N/A	2.29	N/A	0.65	N/A	1.09
Oxycodone	ng/L	N/A	<0.042	N/A	7.74	N/A	<0.042	N/A	<0.042
Primidone	ng/L	<1.37	<1.37	<1.37	<1.37	<1.37	<1.37	<1.37	<1.37
Progesterone	ng/L	0.11	<0.086	<0.086	<0.086	0.20	<0.086	0.16	<0.086
Quetiapine	ng/L	<0.15	<0.15	<0.15	<0.15	<0.15	0.33	<0.15	<0.15
Ramipril	ng/L	<0.72	<0.72	<0.72	<0.72	<0.72	<0.72	<0.72	<0.72
Sertraline	ng/L	<0.04	<0.04	<0.04	1.85	<0.04	<0.04	<0.04	<0.04
Simvastatin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sotalol	ng/L	<0.89	<0.89	<0.89	<0.89	<0.89	<0.89	<0.89	2.0
Sulfadiazine	ng/L	<17	<17	<17	<17	<17	<17	<17	<17
Telmisartan	ng/L	1.5	6.4	18	13	11	27	9.7	25
Temazepam	ng/L	N/A	<0.36	N/A	<0.36	N/A	<0.36	N/A	<0.36
Testosterone	ng/L	<0.080	<0.080	<0.080	<0.080	<0.080	<0.080	0.10	<0.080
Tetracycline / Doxycycline	ng/L	<5.7	<5.7	<5.7	<5.7	<5.7	<5.7	<5.7	<5.7
Tiamulin	ng/L	0.39	<0.079	0.43	<0.079	0.56	<0.079	0.51	<0.079
Toltrazuril	ng/L	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8
Tramadol	ng/L	0.18	0.19	0.93	8.3	0.57	1.3	0.51	2.6
Trimethoprim	ng/L	<0.37	<0.37	<0.37	3.9	<0.37	3.0	<0.37	1.1
Tylosin	ng/L	20	<3.7	20	<3.7	<3.7	<3.7	20	<3.7
Valsartan	ng/L	<6.4	<6.4	25	<6.4	7.50	14	8.20	15
Warfarin	ng/L	<0.87	<0.87	<0.87	<0.87	<0.87	<0.87	<0.87	<0.87
Venlafaxine	ng/L	0.07	<0.03	0.22	6.0	0.23	0.25	0.17	0.34
Xylometazoline	ng/L	1.8	<0.05	1.8	<0.05	1.8	<0.05	1.7	<0.05
Sum concentration	ng/L	100	98	296	483	278	208	225	719
Number of detected / analysed APIs		24/54	11/58	26/54	16/58	27/54	20/58	27/54	22/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Latvia (2/3)	LV5	LV5	LV6	LV6	LV7	LV7

	Surface water type		river	river	river	river	river	river
	Date	dd.mm.yy	1.12.17	21.5.18	27.11.17	21.5.18	27.11.17	22.5.18
	N cordinates	WGS84 DD	56.77263		56.77263		56.811603	
	E cordinates	WGS84 DD	23.91336		23.91336		23.578999	
API	**API group**	**unit**	**Pupla1**		**Pupla2**		**Lielupe**	
Amlodipine	Antihypertensives	ng/L	<7.7	<7.7	<7.7	<7.7	<0.038	<0.038
Atenolol	Other cardiovascular med.	ng/L	<12	<12	<12	<12	<0.82	<0.82
Atorvastatin	Metabolic disease m.	ng/L	<15	<15	1100	260	N/A	N/A
Bezafibrate	Metabolic disease m.	ng/L	<0.83	<0.83	<0.83	<0.83	<0.042	<0.042
Bisoprolol	Other cardiovascular m.	ng/L	<0.52	<0.52	13	22	<0.20	<0.20
Caffeine	Other	ng/L	26	<0.75	37	11	0.20	2.4
Candesartan	Antihypertensives	ng/L	<0.68	4	2	10	<0.027	<0.027
Carbamazepine	Antiepileptics	ng/L	<0.005	0	13	110	0.08	1.7
Carprofen	Veterinary medicines	ng/L	9.3	3.3	<0.77	2.6	<5.4	<5.4
Cetirizine	Asthma and allergy m.	ng/L	0.13	<0.11	2.5	15	<0.003	0.07
Ciprofloxacin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	<3.5	<3.5
Citalopram	Psycopharmaceuticals	ng/L	0.22	<0.06	1.2	8.8	<0.042	<0.042
Clarithromycin	Antibiotics	ng/L	1.7	<1.0	28	100	0.004	0.57
Codeine	NSAIDs and analgesics	ng/L	N/A	<0.07	N/A	2.4	<0.017	0.08
Diclofenac	NSAIDs and analgesics	ng/L	490	300	860	1100	<0.50	7.4
Dipyridamole	Other cardiovascular m.	ng/L	<1.1	<1.1	<1.1	<1.1	<0.78	<0.78
Emamectin	Veterinary medicines	ng/L	0.15	<0.09	0.14	0.37	<1.8	<1.8
Enalapril	Antihypertensives	ng/L	<2.8	<2.8	<2.8	<2.8	N/A	N/A
Eprosartan	Antihypertensives	ng/L	<0.22	<0.22	<0.22	<0.22	N/A	N/A
Erythromycin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	0.13	0.10
Estrone (E1)	Hormones	ng/L	<0.70	1.2	<0.70	<0.70	<0.91	<0.91
Fenbendazole	Veterinary medicines	ng/L	<0.07	<0.07	<0.07	<0.07	0.15	<0.036
Fexofenadine	Asthma and allergy m.	ng/L	<0.09	<0.09	<0.09	<0.09	N/A	N/A
Fluconazole	Antibiotics	ng/L	5.4	<0.05	7.0	12	<0.0034	<0.0034
Fluticasone	Asthma and allergy m.	ng/L	<0.06	<0.06	<0.06	0.06	<0.019	0.13
Gabapentin	Antiepileptics	ng/L	3.7	<0.88	160	420	N/A	N/A
Gemfibrozil	Metabolic disease m.	ng/L	1.9	<1.5	11	7.1	0.03	<0.025
Irbesartan	Antihypertensives	ng/L	<0.06	<0.06	0.26	<0.06	<0.25	<0.25
Ketoprofen	NSAIDs and analgesics	ng/L	<0.72	<0.72	12	35	<0.0021	<0.0021
Levetiracetam	Antiepileptics	ng/L	<3.52	<3.52	<3.52	50	<0.039	<0.039
Lincomycin	Antibiotics	ng/L	<0.10	<0.10	2.1	5.3	<0.057	0.97
Losartan	Antihypertensives	ng/L	0.33	<0.14	6.7	2.9	<0.026	<0.026
Mesalazine	Gastrointestinal disease	ng/L	N/A	N/A	N/A	N/A	0.04	0.12
Metformin	Metabolic disease m.	ng/L	1.5	13	160	2300	<0.94	<0.94
Metoprolol	Other cardiovascular m.	ng/L	<0.54	<0.54	43	140	<0.042	<0.042
Mometasone furoate	Asthma and allergy m.	ng/L	<1.3	<1.3	<1.3	<1.3	<0.0036	<0.0036
Naproxen	NSAIDs and analgesics	ng/L	<0.57	<0.57	6.0	45	N/A	N/A
Nebivolol	Other cardiovascular m.	ng/L	0.47	<0.052	0.76	1.9	<0.50	<0.50
Norethisterone	Hormones	ng/L	<0.080	<0.080	<0.080	<0.080	0.06	0.04
Ofloxacin	Antibiotics	ng/L	<10	<10	19	74	<0.43	<0.43
Oxazepam	Psycopharmaceuticals	ng/L	N/A	<0.033	N/A	15	<4.6	<4.6
Oxycodone	NSAIDs and analgesics	ng/L	N/A	<0.042	N/A	<0.042	<0.037	15
Primidone	Antiepileptics	ng/L	<1.37	<1.37	<1.37	<1.37	<0.032	<0.032
Progesterone	Hormones	ng/L	0.21	<0.086	0.11	<0.086	<0.080	<0.080
Quetiapine	Psycopharmaceuticals	ng/L	<0.15	<0.15	<0.15	0.46	<0.0083	<0.0083
Ramipril	Antihypertensives	ng/L	<0.72	<0.72	<0.72	0.99	N/A	N/A
Sertraline	Psycopharmaceuticals	ng/L	<0.04	<0.04	<0.04	1.1	<0.016	<0.016
Simvastatin	Metabolic disease med.	ng/L	N/A	N/A	N/A	N/A	0.07	0.08
Sotalol	Other cardiovascular m.	ng/L	<0.89	<0.89	31	31	<0.0021	0.03
Sulfadiazine	Antibiotics	ng/L	<17	<17	<17	<17	N/A	N/A
Telmisartan	Antihypertensives	ng/L	<1.4	<1.4	48	230	N/A	N/A
Temazepam	Psycopharmaceuticals	ng/L	N/A	<0.36	N/A	1.9	<0.070	0.66
Testosterone	Hormones	ng/L	0.16	<0.080	0.11	<0.080	0.74	0.43
Tetracycline / Doxycycline	Antibiotics	ng/L	<5.7	<5.7	<5.7	<5.7	<0.055	<0.055
Tiamulin	Veterinary medicines	ng/L	0.43	<0.079	0.73	0.73	0.02	0.02
Toltrazuril	Veterinary medicines	ng/L	<4.8	<4.8	<4.8	<4.8	<0.038	<0.038
Tramadol	NSAIDs and analgesics	ng/L	0.06	<0.038	8.6	82	0.24	2.9
Trimethoprim	Antibiotics	ng/L	<0.37	<0.37	25	58	<0.019	<0.019
Tylosin	Veterinary medicines	ng/L	20	<3.7	<3.7	<3.7	<0.20	<0.20
Valsartan	Antihypertensives	ng/L	<6.4	<6.4	<6.4	19	N/A	N/A
Warfarin	Other cardiovascular m.	ng/L	<0.87	<0.87	3.4	2.5	<0.062	0.07
Venlafaxine	Psycopharmaceuticals	ng/L	0.32	4.5	0.51	5.1	<0.031	<0.031
Xylometazoline	Asthma and allergy m.	ng/L	1.6	<0.05	2.5	2.5	<0.019	0.02
Sum concentration		ng/L	564	326	2604	5186	1.8	33
Number of detected / analysed APIs			20/54	7/58	32/54	39/58	12/52	20/52

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Latvia (3/3)	Site code		L-BSE	L-BSE	L-BSEs	L-BSE
	Surface water type & sampling depth		Sea 1-m	Sea 12-m	Sea 1-m	Sea 12-m
	Date	dd.mm.yy	5.12.17	5.12.17	23.5.18	23.5.18
	N cordinates	WGS84 DD	57.04395			
	E cordinates	WGS84 DD	23.96913			
API	**API group**	**unit**	**Riga-s**	**Riga-b**	**Riga-s**	**Riga-b**
Amlodipine	antihypertensives	ng/L	<0.038	<0.038	<0.038	<0.038
Atenolol	other cardiovascular m.	ng/L	<0.82	<0.82	<0.82	<0.82
Atorvastatin	metabolic disease m.	ng/L	N/A	N/A	N/A	N/A
Bezafibrate	metabolic disease m.	ng/L	0.11	0.06	<0.042	<0.042
Bisoprolol	other cardiovascular m.	ng/L	<0.20	<0.20	<0.20	<0.20
Caffeine	Other	ng/L	0.80	0.65	0.88	0.72
Candesartan	antihypertensives	ng/L	<0.027	<0.027	<0.027	<0.027
Carbamazepine	antiepileptics	ng/L	0.54	0.46	0.40	0.69
Carprofen	veterinary m.	ng/L	<5.4	<5.4	<5.4	<5.4
Cetirizine	asthma and allergy m.	ng/L	0.02	0.02	0.08	0.02
Ciprofloxacin	antibiotics	ng/L	<3.5	<3.5	<3.5	<3.5
Citalopram	psycopharmaceuticals	ng/L	<0.042	0.05	<0.042	<0.042
Clarithromycin	antibiotics	ng/L	0.08	0.05	0.08	0.066
Codeine	NSAIDs and analgesics	ng/L	0.03	<0.017	0.11	0.12
Diclofenac	NSAIDs and analgesics	ng/L	0.52	0.77	0.58	1.2
Dipyridamole	other cardiovascular m.	ng/L	<0.78	<0.78	<0.78	<0.78
Emamectin	veterinary m.	ng/L	2.1	<1.8	<1.8	<1.8
Enalapril	antihypertensives	ng/L	N/A	N/A	N/A	N/A
Eprosartan	antihypertensives	ng/L	N/A	N/A	N/A	N/A
Erythromycin	antibiotics	ng/L	6.2	0.06	0.13	0.09
Estrone (E1)	hormones	ng/L	<0.91	<0.91	<0.91	<0.91
Fenbendazole	veterinary m.	ng/L	<0.036	<0.036	<0.036	<0.036
Fexofenadine	asthma and allergy m.	ng/L	N/A	N/A	N/A	N/A
Fluconazole	antibiotics	ng/L	<0.0034	<0.0034	<0.0034	<0.0034
Fluticasone	asthma and allergy m.	ng/L	0.07	<0.019	0.30	0.18
Gabapentin	antiepileptics	ng/L	N/A	N/A	N/A	N/A
Gemfibrozil	metabolic disease m.	ng/L	<0.025	<0.025	<0.025	<0.025
Irbesartan	antihypertensives	ng/L	<0.25	<0.25	<0.25	<0.25
Ketoprofen	NSAIDs and analgesics	ng/L	<0.0021	<0.0021	<0.0021	0.01
Levetiracetam	antiepileptics	ng/L	0.14	<0.039	0.17	0.16
Lincomycin	antibiotics	ng/L	1.5	0.27	0.31	<0.057
Losartan	antihypertensives	ng/L	<0.026	<0.026	<0.026	<0.026
Mesalazine	gastrointestinal disease m.	ng/L	0.11	0.07	0.07	0.09
Metformin	metabolic disease m.	ng/L	<0.94	<0.94	<0.94	<0.94
Metoprolol	other cardiovascular m.	ng/L	<0.042	<0.042	<0.042	<0.042
Mometasone furoate	asthma and allergy m.	ng/L	<0.0036	0.16	0.13	0.24
Naproxen	NSAIDs and analgesics	ng/L	N/A	N/A	N/A	N/A
Nebivolol	other cardiovascular m.	ng/L	0.53	<0.50	<0.50	<0.50
Norethisterone	hormones	ng/L	0.03	0.03	0.05	0.07
Ofloxacin	antibiotics	ng/L	<0.43	<0.43	<0.43	<0.43
Oxazepam	psycopharmaceuticals	ng/L	<4.6	<4.6	<4.6	<4.6
Oxycodone	NSAIDs and analgesics	ng/L	<0.037	0.78	<0.037	<0.037
Primidone	antiepileptics	ng/L	<0.032	<0.032	<0.032	<0.032
Progesterone	hormones	ng/L	<0.080	<0.080	<0.080	<0.080
Quetiapine	psycopharmaceuticals	ng/L	<0.0083	<0.0083	<0.0083	<0.0083
Ramipril	antihypertensives	ng/L	N/A	N/A	N/A	N/A
Sertraline	psycopharmaceuticals	ng/L	<0.016	<0.016	<0.016	<0.016
Simvastatin	metabolic disease m.	ng/L	0.08	0.09	0.14	0.10
Sotalol	other cardiovascular m.	ng/L	0.12	<0.0021	<0.0021	<0.0021
Sulfadiazine	antibiotics	ng/L	N/A	N/A	N/A	N/A
Telmisartan	antihypertensives	ng/L	N/A	N/A	N/A	N/A
Temazepam	psycopharmaceuticals	ng/L	<0.070	<0.070	<0.070	<0.070
Testosterone	hormones	ng/L	2.2	0.19	5.8	1.6
Tetracycline/Doxycycline	antibiotics	ng/L	<0.055	<0.055	<0.055	<0.055
Tiamulin	veterinary m.	ng/L	0.02	0.03	0.02	0.02
Toltrazuril	veterinary m.	ng/L	<0.038	<0.038	<0.038	<0.038
Tramadol	NSAIDs and analgesics	ng/L	0.72	0.80	0.89	1.0
Trimethoprim	antibiotics	ng/L	0.08	0.11	<0.019	<0.019
Tylosin	veterinary m.	ng/L	<0.20	<0.20	<0.20	<0.20
Valsartan	antihypertensives	ng/L	N/A	N/A	N/A	N/A
Warfarin	other cardiovascular m.	ng/L	<0.062	<0.062	<0.062	<0.062
Venlafaxine	psycopharmaceuticals	ng/L	<0.031	<0.031	<0.031	<0.031
Xylometazoline	asthma and allergy m.	ng/L	0.02	<0.019	<0.019	0.01
Sum concentration		ng/L	16	4.6	10	6.4
Number of detected / analysed APIs			22/52	18/52	17/52	18/52

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Sweden (1/3)	Site code		SE1	SE1	SE2	SE2
	Surface water type		Lake	lake	lake	Lake
	Date	dd.mm.yy	19.12.17	7.6.18	19.12.17	7.6.18
	N cordinates	WGS84 DD	58.528349		58.553747	
	E cordinates	WGS84 DD	14.991961		15.278206	
API	**API group**	**unit**	**Vättern**		**Boren**	
Amlodipine	antihypertensives	ng/L	<7.7	<7.7	<7.7	<7.7
Atenolol	other cardiovascular m.	ng/L	<12	<12	<12	<12
Atorvastatin	metabolic disease m.	ng/L	<15	<15	<15	<15
Bezafibrate	metabolic disease m.	ng/L	<0.83	<0.83	<0.83	<0.83
Bisoprolol	other cardiovascular m.	ng/L	<0.52	<0.52	<0.52	<0.52
Caffeine	other	ng/L	21	15	23	38
Candesartan	antihypertensives	ng/L	<0.68	<0.68	<0.68	<0.68
Carbamazepine	antiepileptics	ng/L	1.1	0.8	1.8	1.5
Carprofen	veterinary m.	ng/L	<0.77	<0.77	<0.77	1.2
Cetirizine	asthma and allergy m.	ng/L	0.43	<0.11	1.8	<0.11
Ciprofloxacin	antibiotics	ng/L	N/A	N/A	N/A	N/A
Citalopram	psycopharmaceuticals	ng/L	0.60	5.9	0.2	10
Clarithromycin	antibiotics	ng/L	<1.0	<1.0	1.4	<1.0
Codeine	NSAIDs and analgesics	ng/L	0.10	<0.07	N/A	<0.07
Diclofenac	NSAIDs and analgesics	ng/L	<1.2	<1.2	1.6	<1.2
Dipyridamole	other cardiovascular m.	ng/L	<1.1	<1.1	<1.1	<1.1
Emamectin	veterinary m.	ng/L	0.33	0.43	0.10	<0.09
Enalapril	antihypertensives	ng/L	<2.8	<2.8	<2.8	<2.8
Eprosartan	antihypertensives	ng/L	<0.22	<0.22	<0.22	<0.22
Erythromycin	antibiotics	ng/L	N/A	N/A	N/A	N/A
Estrone (E1)	hormones	ng/L	<0.70	<0.70	<0.70	<0.70
Fenbendazole	veterinary m.	ng/L	0.22	<0.07	<0.07	<0.07
Fexofenadine	asthma and allergy m.	ng/L	0.13	<0.09	1.0	<0.09
Fluconazole	antibiotics	ng/L	0.75	1.5	1,2,	<0.05
Fluticasone	asthma and allergy m.	ng/L	0.08	<0.06	<0.06	<0.06
Gabapentin	antiepileptics	ng/L	23	14	39	35
Gemfibrozil	metabolic disease m.	ng/L	9.3	<1.5	<1.5	<1.5
Irbesartan	antihypertensives	ng/L	0.08	<0.06	<0.06	<0.06
Ketoprofen	NSAIDs and analgesics	ng/L	<0.72	<0.72	<0.72	<0.72
Levetiracetam	antiepileptics	ng/L	<3.52	<3.52	<3.52	<3.52
Lincomycin	antibiotics	ng/L	0.11	<0.10	<0.10	<0.10
Losartan	antihypertensives	ng/L	1.5	<0.14	4.2	0.88
Mesalazine	gastrointestinal disease m.	ng/L	N/A	N/A	N/A	N/A
Metformin	metabolic disease m.	ng/L	32	<0.24	33	100
Metoprolol	other cardiovascular m.	ng/L	0.75	<0.54	2.9	1.7
Mometasone furoate	asthma and allergy m.	ng/L	<1.3	<1.3	<1.3	<1.3
Naproxen	NSAIDs and analgesics	ng/L	<0.57	<0.57	2.92	<0.57
Nebivolol	other cardiovascular m.	ng/L	0.87	<0.052	0.27	<0.052
Norethisterone	hormones	ng/L	0.34	2.10	0.15	2.00
Ofloxacin	antibiotics	ng/L	39	15	<10	<9.96
Oxazepam	psycopharmaceuticals	ng/L	0.32	<0.033	N/A	0.90
Oxycodone	NSAIDs and analgesics	ng/L	0.10	0.77	N/A	1.6
Primidone	antiepileptics	ng/L	<1.37	<1.37	<1.37	<1.37
Progesterone	hormones	ng/L	0.23	0.64	<0.086	0.34
Quetiapine	psycopharmaceuticals	ng/L	<0.15	<0.15	<0.15	<0.15
Ramipril	antihypertensives	ng/L	<0.72	<0.72	<0.72	<0.72
Sertraline	psycopharmaceuticals	ng/L	0.79	8.0	<0.04	10.0
Simvastatin	metabolic disease m.	ng/L	N/A	N/A	N/A	N/A
Sotalol	other cardiovascular m.	ng/L	<0.89	<0.89	<0.89	<0.89
Sulfadiazine	antibiotics	ng/L	<17	<17	<17	<17
Telmisartan	antihypertensives	ng/L	<1.4	<1.4	<1.4	<1.4
Temazepam	psycopharmaceuticals	ng/L	<0.36	<0.36	N/A	<0.36
Testosterone	hormones	ng/L	0.42	<0.080	<0.080	<0.080
Tetracycline/Doxycycline	antibiotics	ng/L	<5.7	<5.7	<5.7	<5.7
Tiamulin	veterinary m.	ng/L	0.21	<0.079	0.36	<0.079
Toltrazuril	veterinary m.	ng/L	<4.8	<4.8	<4.8	<4.8
Tramadol	NSAIDs and analgesics	ng/L	1.2	1.0	2.9	2.5
Trimethoprim	antibiotics	ng/L	<0.37	1.4	<0.37	<0.37
Tylosin	veterinary m.	ng/L	<3.7	<3.7	<3.7	<3.7
Valsartan	antihypertensives	ng/L	<6.4	<6.4	<6.4	<6.4
Warfarin	other cardiovascular m.	ng/L	<0.87	<0.87	<0.87	<0.87
Venlafaxine	psycopharmaceuticals	ng/L	0.53	1.2	0.99	2.0
Xylometazoline	asthma and allergy m.	ng/L	0.4	<0.054	1.7	<0.054
Sum concentration		ng/L	136	68	119	208
Number of detected / analysed APIs			29/58	14/58	19/54	15/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Sweden (2/3)		SE3	SE3	SE4	SE4	SE5	SE5
Surface water type		river	river	river	river	river	River
Date	dd.mm.yy	19.12.17	7.6.18	19.12.17	7.6.18	19.12.17	7.6.18
N coordinates	WGS84 DD	58.288652		58.421394		58.44432	
E coordinates	WGS84 DD	15.114039		15.631321		15.622594	
API	**Unit**	**Svartån**		**Stångån upstr.**		**Stångån-Roxen**	
Amlodipine	ng/L	9.8	<7.7	<7.7	<7.7	<7.7	<7.7
Atenolol	ng/L	<12	<12	<12	<12	33	42
Atorvastatin	ng/L	700	<15	<15	<15	660	300
Bezafibrate	ng/L	<0.83	<0.83	<0.83	<0.83	2.2	4.0
Bisoprolol	ng/L	<0.52	<0.52	<0.52	<0.52	1.7	<0.52
Caffeine	ng/L	24	<0.75	17	68	30	160
Candesartan	ng/L	16	<0.68	6.6	<0.68	1.7	12
Carbamazepine	ng/L	3.7	1.9	1.1	2.4	4.8	72
Carprofen	ng/L	<0.77	<0.77	1.6	1.6	1.5	2.0
Cetirizine	ng/L	2.3	<0.11	0.58	<0.11	6.7	1.3
Ciprofloxacin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Citalopram	ng/L	2.2	13	0.1	2.2	1.7	28
Clarithromycin	ng/L	2.0	<1.0	1.3	<1.0	3.2	<1.0
Codeine	ng/L	0.19	<0.07	N/A	<0.07	N/A	0.29
Diclofenac	ng/L	1.9	1.5	<1.2	<1.2	27	160
Dipyridamole	ng/L	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Emamectin	ng/L	3.2	0.38	0.31	0.45	0.17	<0.09
Enalapril	ng/L	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8
Eprosartan	ng/L	<0.22	<0.22	<0.22	<0.22	0.79	<0.22
Erythromycin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Estrone (E1)	ng/L	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70
Fenbendazole	ng/L	0.63	<0.07	<0.07	<0.07	<0.07	<0.07
Fexofenadine	ng/L	0.79	<0.09	0.23	0.18	2.1	8.3
Fluconazole	ng/L	0.52	<0.05	1.1	0.28	4.2	18.33
Fluticasone	ng/L	0.21	<0.06	<0.06	<0.06	<0.06	<0.06
Gabapentin	ng/L	160	82	50	60	130	1700
Gemfibrozil	ng/L	23	<1.5	4.1	<1.5	12	<1.5
Irbesartan	ng/L	0.24	<0.06	0.08	0.07	1.6	3.8
Ketoprofen	ng/L	<0.72	<0.72	<0.72	<0.72	4.6	8.0
Levetiracetam	ng/L	<3.52	<3.52	<3.52	<3.52	<3.52	14.93
Lincomycin	ng/L	0.13	<0.10	0.18	<0.10	<0.10	<0.10
Losartan	ng/L	9.6	1.1	0.27	<0.14	39.90	95.24
Mesalazine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	ng/L	53	180	15	<0.24	29	980
Metoprolol	ng/L	5.2	3.7	0.7	1.1	18	190
Mometasone furoate	ng/L	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3
Naproxen	ng/L	<0.57	<0.57	1.09	<0.57	2.39	68
Nebivolol	ng/L	4.00	<0.052	0.55	<0.052	0.36	<0.052
Norethisterone	ng/L	2.10	0.69	0.70	1.50	0.53	<0.080
Ofloxacin	ng/L	210	<10	340	<10	46	<10
Oxazepam	ng/L	1.77	1.49	N/A	0.99	N/A	44
Oxycodone	ng/L	0.26	2.3	N/A	0.51	N/A	5.2
Primidone	ng/L	<1.37	<1.37	<1.37	<1.37	2.2	5.9
Progesterone	ng/L	0.44	<0.086	0.14	<0.086	0.11	<0.086
Quetiapine	ng/L	0.17	<0.15	<0.15	<0.15	<0.15	<0.15
Ramipril	ng/L	<0.72	<0.72	<0.72	<0.72	<0.72	<0.72
Sertraline	ng/L	4.1	5.9	<0.04	2.8	0.19	19
Simvastatin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Sotalol	ng/L	<0.89	<0.89	<0.89	<0.89	<0.89	1.8
Sulfadiazine	ng/L	<17	<17	<17	<17	<17	<17
Telmisartan	ng/L	<1.4	<1.4	<1.4	<1.4	<1.4	<1.4
Temazepam	ng/L	<0.36	<0.36	N/A	0.36	N/A	2.2
Testosterone	ng/L	0.48	<0.080	0.19	<0.080	<0.080	<0.080
Tetracycline/Doxycycline	ng/L	<5.7	<5.7	47	<5.7	<5.7	<5.7
Tiamulin	ng/L	0.69	<0.079	0.51	<0.079	0.41	<0.079
Toltrazuril	ng/L	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8
Tramadol	ng/L	4.4	4.0	0.5	1.3	6.4	110
Trimethoprim	ng/L	0.91	<0.37	0.51	<0.37	1.4	<0.37
Tylosin	ng/L	<3.7	<3.7	<3.7	<3.7	<3.7	<3.7
Valsartan	ng/L	<6.4	<6.4	<6.4	<6.4	10.0	60
Warfarin	ng/L	<0.87	<0.87	<0.87	<0.87	<0.87	2.6
Venlafaxine	ng/L	2.0	4.1	0.17	0.76	2.7	45
Xylometazoline	ng/L	2.5	<0.054	1.8	<0.054	1.9	<0.054
Sum concentration	ng/L	1243	302	493	144	1091	4164
Number of detected / analysed APIs		35/58	14/58	29/54	17/58	36/54	31/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Sweden (3/3)		SE6	SE6	SE7	SE7	SE-BSE	SE-BSE
Surface water type		lake	lake	lake	Lake	sea	sea
Date	dd.mm.yy	20.12.17	7.6.18	20.12.17	7.6.18	21.12.17	11.6.18
N coordinates	WGS84 DD	58.645406		58.59418		58.628369	
E coordinates	WGS84 DD	15.858221		16.12531		16.307817	
API	**unit**	**Dovern**		**Glan**		**Bråviken**	
Amlodipine	ng/L	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7
Atenolol	ng/L	<12	<12	<12	<12	<12.13	<12
Atorvastatin	ng/L	170	<15	<15	<15	44	<15
Bezafibrate	ng/L	<0.83	<0.83	<0.83	<0.83	<0.83	<0.83
Bisoprolol	ng/L	<0.52	<0.52	<0.52	<0.52	<0.52	<0.52
Caffeine	ng/L	49	33	22	55	16	140
Candesartan	ng/L	2.9	9.5	<0.68	8.4	<0.68	13
Carbamazepine	ng/L	0.8	3.6	3.3	4.0	1.5	5.4
Carprofen	ng/L	<0.77	5.7	<0.77	2.70	1.0	2.9
Cetirizine	ng/L	1.2	<0.11	3.5	0.71	1.0	1.7
Ciprofloxacin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Citalopram	ng/L	0.5	5.4	0.1	1.2	0.3	1.1
Clarithromycin	ng/L	1.22	<1.0	1.31	<1.0	1.37	<1.0
Codeine	ng/L	N/A	<0.07	N/A	0.14	N/A	0.24
Diclofenac	ng/L	5.2	5.8	4.4	3.4	2.8	2.1
Dipyridamole	ng/L	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Emamectin	ng/L	0.15	0.68	0.21	0.53	0.21	0.79
Enalapril	ng/L	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8
Eprosartan	ng/L	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22
Erythromycin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Estrone (E1)	ng/L	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70
Fenbendazole	ng/L	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07
Fexofenadine	ng/L	0.37	0.87	1.5	0.72	0.69	3.3
Fluconazole	ng/L	<0.05	1.3	2.5	1.2	<0.05	<0.05
Fluticasone	ng/L	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Gabapentin	ng/L	38	120	93	120	34	120
Gemfibrozil	ng/L	13	<1.5	<1.5	<1.5	4.4	<1.5
Irbesartan	ng/L	0.18	0.28	0.20	0.19	0.15	0.27
Ketoprofen	ng/L	0.95	<0.72	<0.72	<0.72	<0.72	<0.72
Levetiracetam	ng/L	<3.52	<3.52	<3.52	<3.52	<3.52	<3.52
Lincomycin	ng/L	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
Losartan	ng/L	10.30	5.4	3.4	1.3	4.8	1.8
Mesalazine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	ng/L	57	1300	20	400	23	230
Metoprolol	ng/L	4.0	11	2.2	4.2	1.9	4.5
Mometasone furoate	ng/L	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3
Naproxen	ng/L	3.08	1.41	9.65	5.15	16	5.28
Nebivolol	ng/L	0.36	0.22	0.43	<0.052	0.38	0.43
Norethisterone	ng/L	0.26	<0.080	0.36	1.20	0.53	<0.080
Ofloxacin	ng/L	35	<10	<10	<10	15	<10
Oxazepam	ng/L	N/A	3.70	N/A	2.20	N/A	2.70
Oxycodone	ng/L	N/A	<0.042	N/A	0.18	N/A	<0.042
Primidone	ng/L	<1.37	<1.37	1.6	1.4	<1.37	<1.37
Progesterone	ng/L	0.20	<0.086	0.11	<0.086	0.11	<0.086
Quetiapine	ng/L	<0.15	<0.15	<0.15	<0.15	<0.15	<0.15
Ramipril	ng/L	<0.72	<0.72	<0.72	<0.72	<0.72	<0.72
Sertraline	ng/L	<0.04	8.8	<0.04	1.8	<0.04	2.8
Simvastatin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Sotalol	ng/L	<0.89	<0.89	<0.89	<0.89	<0.89	<0.89
Sulfadiazine	ng/L	<17	<17	<17	<17	<17	<17
Telmisartan	ng/L	<1.4	<1.4	<1.4	<1.4	<1.4	<1.4
Temazepam	ng/L	N/A	<0.36	N/A	<0.36	N/A	0.58
Testosterone	ng/L	<0.080	<0.080	0.10	<0.080	0.13	<0.080
Tetracycline/Doxycycline	ng/L	<5.7	<5.7	<5.7	<5.7	23	<5.7
Tiamulin	ng/L	0.39	0.33	0.41	0.25	0.41	<0.079
Toltrazuril	ng/L	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8
Tramadol	ng/L	1.6	5.4	3.2	5.0	1.3	4.1
Trimethoprim	ng/L	<0.37	<0.37	<0.37	0.38	<0.37	<0.37
Tylosin	ng/L	<3.7	<3.7	<3.7	<3.7	<3.7	<3.7
Valsartan	ng/L	<6.4	<6.4	<6.4	<6.4	<6.4	<6.4
Warfarin	ng/L	<0.87	<0.87	<0.87	<0.87	<0.87	<0.87
Venlafaxine	ng/L	0.89	4.9	0.79	3.4	0.50	2.0
Xylometazoline	ng/L	1.7	<0.054	1.9	<0.054	1.6	<0.054
Sum concentration	ng/L	399	1527	176	625	196	545
Number of detected / analysed APIs		26/54	21/58	24/54	26/58	27/54	22/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Finland (1/4)	Site code		FI1	FI1	FI1	FI2	FI2	FI2
	Surface water type		River	River	River	River	River	River
	Date	dd.mm.yy	12.12.17	6.6.18	21.11.18	12.12.17	6.6.18	21.11.18
	N coordinates	WGS84	60.59269			60.56589		
	E coordinates	WGS84	24.87521			24.88894		
API	**API group**	**Unit**	**Vantaa1**			**Vantaa2**		
Amlodipine	antihypertensives	ng/L	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7
Atenolol	other cardiovascular m.	ng/L	<12	<12	<12	<12	19	<12
Atorvastatin	metabolic disease m.	ng/L	<15	245	100	44	<15	1500
Bezafibrate	metabolic disease m.	ng/L	<0.83	1.2	1.7	<0.83	1.5	2.7
Bisoprolol	other cardiovascular m.	ng/L	3.2	14	<0.52	7.2	70	<0.52
Caffeine	Other	ng/L	22	190	<0.75	19	110	<0.75
Candesartan	antihypertensives	ng/L	<0.68	12	<0.68	<0.68	17	<0.68
Carbamazepine	Antiepileptics	ng/L	1.3	59	20	2.7	130	28
Carprofen	veterinary m.	ng/L	3.8	6.5	<0.77	<0.77	2.6	<0.77
Cetirizine	asthma and allergy m.	ng/L	2.7	200	7.4	6.3	630	8.0
Ciprofloxacin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Citalopram	psycopharmaceuticals	ng/L	1.0	11	5.2	2.3	59	23
Clarithromycin	Antibiotics	ng/L	3.2	27	51	5.4	100	58
Codeine	NSAIDs and analgesics	ng/L	N/A	7.2	8.5	N/A	13	23
Diclofenac	NSAIDs and analgesics	ng/L	16	130	200	34	640	450
Dipyridamole	other cardiovascular m.	ng/L	<1.1	<1.1	<1.1	4.7	4.4	6.9
Emamectin	veterinary m.	ng/L	0.14	0.10	0.45	0.12	0.10	0.40
Enalapril	antihypertensives	ng/L	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8
Eprosartan	antihypertensives	ng/L	2.6	0.45	2.8	4.6	2.3	4.3
Erythromycin	Antibiotics	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Estrone (E1)	Hormones	ng/L	<0.70	6.7	8.3	<0.70	<0.70	6.7
Fenbendazole	veterinary m.	ng/L	<0.07	0.12	0.15	<0.07	0.33	<0.07
Fexofenadine	asthma and allergy m.	ng/L	1.4	180	5.9	3.4	320	5.7
Fluconazole	Antibiotics	ng/L	1.2	33	6.6	2.9	44	46
Fluticasone	asthma and allergy m.	ng/L	<0.06	0.23	0.13	<0.06	0.41	0.24
Gabapentin	Antiepileptics	ng/L	100	<0.88	850	190	<0.88	1600
Gemfibrozil	metabolic disease m.	ng/L	14	260	<1.5	13	210	<1.5
Irbesartan	antihypertensives	ng/L	<0.06	0.57	<0.06	<0.06	1.4	0.11
Ketoprofen	NSAIDs and analgesics	ng/L	0.81	<0.72	6.9	1.3	7.8	15
Levetiracetam	Antiepileptics	ng/L	<3.52	9.4	<3.52	<3.52	24	9.4
Lincomycin	Antibiotics	ng/L	<0.10	0.20	0.31	<0.10	0.57	0.44
Losartan	antihypertensives	ng/L	6.0	120	<0.14	16	200	<0.14
Mesalazine	gastrointestinal disease m.	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	metabolic disease m.	ng/L	51	180	160	62	280	630
Metoprolol	other cardiovascular m.	ng/L	4.3	88	34	7.5	200	67
Mometasone furoate	asthma and allergy m.	ng/L	<1.3	1.5	<1.3	<1.3	<1.3	<1.3
Naproxen	NSAIDs and analgesics	ng/L	4.1	<0.57	12	1.7	94	34
Nebivolol	other cardiovascular m.	ng/L	0.3	0.3	0.3	0.3	0.3	0.2
Norethisterone	Hormones	ng/L	<0.080	1.4	1.1	<0.080	0.83	0.65
Ofloxacin	Antibiotics	ng/L	13	<10	<10	14	<10	<10
Oxazepam	psycopharmaceuticals	ng/L	N/A	72	110	N/A	250	290
Oxycodone	NSAIDs and analgesics	ng/L	N/A	2.2	0.98	N/A	10	3.3
Primidone	Antiepileptics	ng/L	<1.37	1.6	<1.37	<1.37	1.5	<1.37
Progesterone	Hormones	ng/L	0.09	<0.086	<0.086	0.16	0.11	<0.086
Quetiapine	psycopharmaceuticals	ng/L	<0.15	0.25	<0.15	<0.15	1.1	<0.15
Ramipril	antihypertensives	ng/L	<0.72	1.6	0.83	<0.72	3.5	2.4
Sertraline	psycopharmaceuticals	ng/L	<0.04	0.27	1.1	0.14	2.9	2.4
Simvastatin	metabolic disease m.	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Sotalol	other cardiovascular m.	ng/L	<0.89	6.7	1.5	<0.89	17	4.6
Sulfadiazine	Antibiotics	ng/L	<17	<17	<17	<17	<17	<17
Telmisartan	antihypertensives	ng/L	5.4	220	7.4	17	610	22
Temazepam	psycopharmaceuticals	ng/L	N/A	30	55	N/A	100	180
Testosterone	Hormones	ng/L	0.11	0.37	<0.08	0.13	0.34	<0.08
Tetracycline / Doxycycline	Antibiotics	ng/L	<5.7	<5.7	20	<5.7	<5.7	20
Tiamulin	veterinary m.	ng/L	0.39	<0.079	0.11	0.39	<0.079	<0.079
Toltrazuril	veterinary m.	ng/L	<4.8	<4.8	5.1	<4.8	<4.8	<4.8
Tramadol	NSAIDs and analgesics	ng/L	1.9	65	28	4.5	220	46
Trimethoprim	Antibiotics	ng/L	1.2	32	9.7	2.9	83	34
Tylosin	veterinary m.	ng/L	<3.7	<3.7	<3.7	<3.7	<3.7	<3.7
Valsartan	antihypertensives	ng/L	19	45	38	68	120	170
Warfarin	other cardiovascular m.	ng/L	<0.87	1.3	<0.87	<0.87	2.6	<0.87
Venlafaxine	psycopharmaceuticals	ng/L	1.8	54	22	4.7	210	67
Xylometazoline	asthma and allergy m.	ng/L	1.6	0.53	0.31	1.7	1.7	0.32
Sum concentration		ng/L	284	2319	1783	542	4816	5361
Number of detected / analysed APIs			30/54	45/58	38/58	32/54	47/58	38/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Finland (2/4)		FI3	FI3	FI3	FI4	FI5	FI5	FI5
Surface water type		River	River	River	Tributary	River	River	River
Date	dd.mm.yy	12.12.17	6.6.18	21.11.18	21.11.18	12.12.17	6.6.18	21.11.18
N coordinates	WGS84	60.43332			60.36534	60.23736		
E coordinates	WGS84	24.85264			24.78238	024.98510		
API	**unit**	**Vantaa3**			**Luhtaj.**	**Vantaa4**		
Amlodipine	ng/L	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7	<7.7
Atenolol	ng/L	<12	<12	<12	<12	<12	<12	<12
Atorvastatin	ng/L	35	500	920	210	42	<15	140
Bezafibrate	ng/L	<0.83	0.97	2.7	1.6	<0.83	<0.83	1.1
Bisoprolol	ng/L	7.9	40	<0.52	<0.52	2.5	10	<0.52
Caffeine	ng/L	80	78	1.7	1.2	42	86	1.8
Candesartan	ng/L	<0.68	17	<0.68	1.4	<0.68	<0.68	<0.68
Carbamazepine	ng/L	2.6	96	32	19	1.4	22	8.8
Carprofen	ng/L	<0.77	6.1	<0.77	<0.77	<0.77	<0.77	<0.77
Cetirizine	ng/L	6.4	330	11	3.5	2.5	100	1.9
Ciprofloxacin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Citalopram	ng/L	2.0	25	19	17	0.6	2.8	3.0
Clarithromycin	ng/L	5.5	68	95	36	1.9	4.2	16
Codeine	ng/L	N/A	9.8	18	21	N/A	1.8	5.5
Diclofenac	ng/L	34	380	390	470	17	53	130
Dipyridamole	ng/L	1.7	1.4	<1.1	<1.1	<1.1	<1.1	<1.1
Emamectin	ng/L	0.12	0.10	0.42	0.39	0.12	<0.09	0.45
Enalapril	ng/L	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8	<2.8
Eprosartan	ng/L	4.5	0.82	4.8	1.1	1.6	0.25	0.94
Erythromycin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Estrone (E1)	ng/L	<0.70	6.9	10	6.0	<0.70	<0.70	5.9
Fenbendazole	ng/L	<0.07	0.18	<0.07	0.07	<0.07	<0.07	0.08
Fexofenadine	ng/L	3.9	220	8.7	0.95	1.3	70	2.4
Fluconazole	ng/L	<0.05	50	12	15	0.9	7.9	<0.05
Fluticasone	ng/L	<0.06	0.23	0.21	0.16	<0.06	<0.06	0.13
Gabapentin	ng/L	170	<0.88	1800	320	88	780	410
Gemfibrozil	ng/L	12	230	7.20	8.60	9.30	29	<1.5
Irbesartan	ng/L	<0.06	0.92	0.06	<0.06	<0.06	<0.06	<0.06
Ketoprofen	ng/L	1.3	1.9	11	4.3	<0.72	<0.72	2.4
Levetiracetam	ng/L	<3.52	12	26	9.1	<3.52	4.6	<3.52
Lincomycin	ng/L	<0.10	0.33	0.34	0.35	<0.10	<0.10	0.32
Losartan	ng/L	17	120	<0.14	<0.14	7.3	11	<0.14
Mesalazine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Metformin	ng/L	62	210	1300	260	39	350	340
Metoprolol	ng/L	6.8	110	68	44	3.0	15	17
Mometasone furoate	ng/L	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3	<1.3
Naproxen	ng/L	2.3	56	30	21	31	6.4	14
Nebivolol	ng/L	0.3	0.4	0.3	<0.05	0.4	1.3	0.3
Norethisterone	ng/L	<0.080	1.2	0.88	0.62	<0.080	<0.080	0.71
Ofloxacin	ng/L	<10	<10	<10	<10	<10	<10	<10
Oxazepam	ng/L	N/A	191	210	250	N/A	38	87
Oxycodone	ng/L	N/A	5.5	2.7	2.4	N/A	0.59	1.2
Primidone	ng/L	<1.37	<1.37	<1.37	<1.37	<1.37	<1.37	<1.37
Progesterone	ng/L	0.12	0.09	<0.086	<0.086	<0.086	<0.086	<0.086
Quetiapine	ng/L	<0.15	0.22	<0.15	<0.15	<0.15	<0.15	<0.15
Ramipril	ng/L	<0.72	1.9	2.5	<0.72	<0.72	0.74	<0.72
Sertraline	ng/L	0.06	0.55	1.7	8.6	<0.04	3.4	1.7
Simvastatin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sotalol	ng/L	<0.89	12	7.9	10.0	<0.89	4.8	1.7
Sulfadiazine	ng/L	<17	<17	<17	<17	<17	<17	<17
Telmisartan	ng/L	19	440	11	1.8	4.3	61	<1.4
Temazepam	ng/L	N/A	68	160	200	N/A	16	49
Testosterone	ng/L	<0.080	0.78	<0.08	<0.08	<0.080	<0.080	<0.08
Tetracycline/Doxycycline	ng/L	<5.7	<5.7	<5.7	20	<5.7	<5.7	20
Tiamulin	ng/L	0.36	0.09	<0.079	<0.079	0.36	<0.079	0.15
Toltrazuril	ng/L	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8	<4.8
Tramadol	ng/L	4.5	140	68	60	2.1	24	11
Trimethoprim	ng/L	2.5	41	26	19.0	1.0	9.1	5.4
Tylosin	ng/L	<3.7	<3.7	<3.7	<3.7	<3.7	<3.7	<3.7
Valsartan	ng/L	55	73	110	110	23	66	35
Warfarin	ng/L	<0.87	2.0	<0.87	<0.87	<0.87	<0.87	<0.87
Venlafaxine	ng/L	4.4	120	68	54	2.0	20	17
Xylometazoline	ng/L	1.7	1.1	0.50	<0.05	1.6	1.6	<0.05
Sum concentration	ng/L	543	3671	5438	2208	326	1801	1333
Detected / Analysed APIs		29/54	48/58	38/58	37/58	26/54	31/58	34/58

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Finland (3/4)	Site code		FI6	FI6	FI6	FI7	FI7
	Surface water type		Estuary	Estuary	Estuary	Estuary	Estuary
	Date	dd.mm.yy	6.3.18	6.6.18	21.11.18	6.3.18	4.6.18
	N coordinates	WGS84	60.21357			60.19587	
	E coordinates	WGS84	24.98403			24.99376	
API	**API group**	**unit**	**Matins**			**Vanhank.**	
Amlodipine	antihypertensives	ng/L	0.1	<0.003	<7.7	0.08	7.0
Atenolol	other cardiovascular m.	ng/L	<8.0	<8.0	<12	<8.0	<8.0
Atorvastatin	metabolic disease m.	ng/L	N/A	N/A	<15	N/A	N/A
Bezafibrate	metabolic disease m.	ng/L	0.54	<0.40	<0.83	0.51	<0.40
Bisoprolol	other cardiovascular m.	ng/L	5.1	5.3	<0.52	4.5	1.6
Caffeine	Other	ng/L	14	22	1.2	11	18
Candesartan	antihypertensives	ng/L	1.5	<0.22	<0.68	<0.22	<0.22
Carbamazepine	antiepileptics	ng/L	4.7	11	2.4	4.3	6.3
Carprofen	veterinary m.	ng/L	<0.58	<0.58	<0.77	0.79	<0.58
Cetirizine	asthma and allergy m.	ng/L	7.4	22	5.1	8.3	10
Ciprofloxacin	Antibiotics	ng/L	<35	<35	N/A	<35	<35
Citalopram	psycopharmaceuticals	ng/L	0.9	0.8	0.9	0.8	0.9
Clarithromycin	antibiotics	ng/L	1.7	1.5	7.3	1.6	1.0
Codeine	NSAIDs and analgesics	ng/L	1.9	0.91	0.87	1.6	0.47
Diclofenac	NSAIDs and analgesics	ng/L	20	30	19	22	11
Dipyridamole	other cardiovascular m.	ng/L	<0.67	<0.67	<1.1	<0.67	<0.67
Emamectin	veterinary m.	ng/L	<0.02	0.18	0.48	<0.02	0.73
Enalapril	antihypertensives	ng/L	N/A	N/A	<2.8	N/A	N/A
Eprosartan	antihypertensives	ng/L	N/A	N/A	0.24	N/A	N/A
Erythromycin	antibiotics	ng/L	9.0	<0.92	N/A	8.4	<0.92
Estrone (E1)	hormones	ng/L	0.37	<0.17	4.6	0.29	<0.17
Fenbendazole	veterinary m.	ng/L	<0.03	0.06	0.20	<0.03	0.16
Fexofenadine	asthma and allergy m.	ng/L	N/A	N/A	2.20	N/A	N/A
Fluconazole	antibiotics	ng/L	2.0	3.2	<0.05	2.0	2.3
Fluticasone	asthma and allergy m.	ng/L	0.03	0.03	0.10	0.03	<0.002
Gabapentin	antiepileptics	ng/L	N/A	N/A	82	N/A	N/A
Gemfibrozil	metabolic disease m.	ng/L	<0.02	<0.02	<1.5	2.1	7.2
Irbesartan	antihypertensives	ng/L	0.04	0.04	0.08	0.04	0.06
Ketoprofen	NSAIDs and analgesics	ng/L	1.3	<0.38	<0.72	0.95	<0.38
Levetiracetam	antiepileptics	ng/L	<5.43	<5.43	<3.52	<5.43	6.1
Lincomycin	antibiotics	ng/L	0.04	<0.04	0.37	<0.04	0.12
Losartan	antihypertensives	ng/L	7.7	0.72	<0.14	7.4	0.06
Mesalazine	gastrointestinal disease m.	ng/L	3.7	190	N/A	1.8	110
Metformin	metabolic disease m.	ng/L	30	25	120	26	16
Metoprolol	other cardiovascular m.	ng/L	6.0	5.3	3.0	5.4	2.3
Mometasone furoate	asthma and allergy m.	ng/L	<0.29	<0.29	<1.3	<0.29	<0.29
Naproxen	NSAIDs and analgesics	ng/L	5.3	<0.47	<0.57	5.1	0.7
Nebivolol	other cardiovascular m.	ng/L	0.0	0.2	0.4	0.0	1.5
Norethisterone	hormones	ng/L	0.19	0.27	0.45	<0.04	0.32
Ofloxacin	antibiotics	ng/L	<4.2	<4.2	<10	<4.2	<4.2
Oxazepam	psycopharmaceuticals	ng/L	10	17	12	9.4	11
Oxycodone	NSAIDs and analgesics	ng/L	0.35	0.5	0.37	0.3	0.25
Primidone	antiepileptics	ng/L	<0.71	<0.71	<1.37	<0.71	<0.71
Progesterone	hormones	ng/L	<0.03	<0.03	<0.086	0.03	0.24
Quetiapine	psycopharmaceuticals	ng/L	0.09	0.03	0.16	0.08	0.11
Ramipril	antihypertensives	ng/L	N/A	N/A	<0.72	N/A	N/A
Sertraline	psycopharmaceuticals	ng/L	0.09	<0.03	0.31	0.08	5.8
Simvastatin	metabolic disease m.	ng/L	0.04	<0.02	N/A	<0.02	<0.02
Sotalol	other cardiovascular m.	ng/L	2.3	3.4	<0.89	3.1	1.3
Sulfadiazine	antibiotics	ng/L	N/A	N/A	<17	N/A	N/A
Telmisartan	antihypertensives	ng/L	N/A	N/A	1.8	N/A	N/A
Temazepam	psycopharmaceuticals	ng/L	4.2	9.1	9.7	4.4	5.6
Testosterone	hormones	ng/L	0.06	<0.05	0.33	0.06	0.35
Tetracycline / Doxycycline	antibiotics	ng/L	<3.17	4.9	20	<3.17	11
Tiamulin	veterinary m.	ng/L	<0.01	<0.01	0.28	<0.01	<0.01
Toltrazuril	veterinary m.	ng/L	<3.60	<3.60	<4.8	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/L	5.7	11	5.4	5.5	4.9
Trimethoprim	antibiotics	ng/L	2.0	3.8	0.9	2.0	2.0
Tylosin	veterinary m.	ng/L	2.2	<1.9	<3.7	3.5	<1.9
Valsartan	antihypertensives	ng/L	N/A	N/A	6.7	N/A	N/A
Warfarin	other cardiovascular m.	ng/L	<0.58	<0.58	<0.87	<0.58	<0.58
Venlafaxine	psycopharmaceuticals	ng/L	5.3	9.6	3.5	4.8	3.9
Xylometazoline	asthma and allergy m.	ng/L	<0.19	<0.19	<0.05	<0.19	<0.19
Sum concentration		ng/L	155	378	312	148	244
Number of detected / analysed APIs			36/53	28/53	33/58	35/53	34/53

N/A: not analysed; Concentration lower than quantification limit (LOQ) are marked as "<" and LOQ

Finland (4/4)		FI-BSE1	FI-BSE2	FI-BSE2	FI-BSE2	FI-BSE2	FI-BSE2	FI-BSE2
Surface water type &		Sea	Sea	Sea	Sea	Sea	Sea	Sea
sampling depth		9-m	1-m	13-m	25-m	1-m	13-m	25-m
Date	dd.mm.yy	4.6.18	5.3.18	5.3.18	5.3.18	4.6.18	4.6.18	4.6.18
N cordinates	WGS84 DD	60.08613	60.09652					
E cordinates	WGS84 DD	24.91319	24.89046					
API	**unit**	**WWTP pipe**	**Katajaluoto surface**	**middle**	**bottom**	**Katajaluoto surface**	**middle**	**Bottom**
Amlodipine	ng/L	<0.003	0.17	0.04	<0.003	<0.003	<0.003	<0.003
Atenolol	ng/L	<8.0	<8.0	<8.0	<8.0	<8.0	<8.0	<8.0
Atorvastatin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bezafibrate	ng/L	0.54	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40
Bisoprolol	ng/L	4.3	1.2	0.46	0.26	0.42	<0.21	<0.21
Caffeine	ng/L	3.2	1.8	5.4	13	21	6.1	4.8
Candesartan	ng/L	3.0	1.4	<0.22	<0.22	<0.22	<0.22	<0.22
Carbamazepine	ng/L	2.8	0.64	0.6	2.6	0.87	0.96	0.89
Carprofen	ng/L	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Cetirizine	ng/L	13	1.5	0.6	0.23	0.41	0.2	0.27
Ciprofloxacin	ng/L	<35	<35	<35	<35	<35	<35	<35
Citalopram	ng/L	1.70	0.39	0.26	0.21	0.19	0.05	0.05
Clarithromycin	ng/L	1.20	0.59	<0.33	<0.33	<0.33	<0.33	<0.33
Codeine	ng/L	1.08	0.55	0.25	0.23	0.22	0.04	0.05
Diclofenac	ng/L	35	6.3	2.6	3.0	3.0	<0.34	0.43
Dipyridamole	ng/L	35	2.3	<0.67	<0.67	<0.67	<0.67	<0.67
Emamectin	ng/L	0.45	<0.02	<0.02	0.23	0.4	0.32	<0.02
Enalapril	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Eprosartan	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Erythromycin	ng/L	<0.92	7.80	20	<0.92	<0.92	<0.92	<0.92
Estrone (E1)	ng/L	0.51	0.6	1.0	<0.17	0.32	<0.17	0.43
Fenbendazole	ng/L	0.06	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Fexofenadine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fluconazole	ng/L	1.4	0.35	0.26	1.2	0.61	0.40	0.31
Fluticasone	ng/L	0.05	0.02	<0.002	<0.002	<0.002	<0.002	<0.002
Gabapentin	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gemfibrozil	ng/L	0.61	<0.02	40	<0.02	<0.02	<0.02	<0.02
Irbesartan	ng/L	0.27	<0.02	<0.02	0.04	0.02	<0.02	<0.02
Ketoprofen	ng/L	<0.38	<0.38	<0.38	<0.38	<0.38	<0.38	<0.38
Levetiracetam	ng/L	6.5	<5.43	<5.43	<5.43	<5.43	<5.43	<5.43
Lincomycin	ng/L	<0.04	<0.04	0.05	0.13	<0.04	<0.04	<0.04
Losartan	ng/L	3.8	3.4	<0.02	0.12	0.3	0.15	0.13
Mesalazine	ng/L	<0.82	0.82	<0.82	58	<0.82	<0.82	29
Metformin	ng/L	16	3.4	13	<0.12	18	<0.12	<0.12
Metoprolol	ng/L	2.2	0.45	0.46	0.41	<0.35	<0.35	<0.35
Mometasone furoate	ng/L	<0.29	<0.29	<0.29	<0.29	<0.29	<0.29	<0.29
Naproxen	ng/L	0.52	0.62	0.63	2.0	2.9	<0.47	1.7
Nebivolol	ng/L	0.28	0.02	0.02	0.75	0.29	0.22	0.19
Norethisterone	ng/L	0.35	0.39	0.21	<0.04	<0.04	0.11	<0.04
Ofloxacin	ng/L	<4.2	<4.2	<4.2	<4.2	<4.2	<4.2	<4.2
Oxazepam	ng/L	8.0	0.94	0.45	0.8	1.0	0.23	0.33
Oxycodone	ng/L	0.25	<0.03	<0.03	0.18	0.04	0.05	<0.03
Primidone	ng/L	<0.71	<0.71	<0.71	0.74	<0.71	<0.71	<0.71
Progesterone	ng/L	<0.03	0.03	0.03	0.09	<0.03	0.03	<0.03
Quetiapine	ng/L	0.14	0.39	0.06	0.17	0.01	<0.01	<0.01
Ramipril	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sertraline	ng/L	0.56	0.03	<0.03	5.1	0.58	<0.03	<0.03
Simvastatin	ng/L	<0.02	<0.02	<0.02	<0.02	<0.02	0.14	<0.02
Sotalol	ng/L	1.7	<0.68	<0.68	0.71	<0.68	<0.68	<0.68
Sulfadiazine	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Telmisartan	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Temazepam	ng/L	3.2	0.48	<0.34	0.61	0.66	<0.34	<0.34
Testosterone	ng/L	<0.05	0.05	0.06	<0.05	<0.05	0.06	<0.05
Tetracycline / Doxycycline	ng/L	5.2	<3.17	<3.17	11	5.2	<3.17	4.9
Tiamulin	ng/L	<0.01	0.01	0.01	<0.01	<0.01	<0.01	<0.01
Toltrazuril	ng/L	<3.60	<3.60	4.4	<3.60	<3.60	<3.60	<3.60
Tramadol	ng/L	2.9	0.31	0.24	0.64	0.69	0.15	0.12
Trimethoprim	ng/L	1.5	0.28	0.26	0.34	0.26	<0.17	<0.17
Tylosin	ng/L	<1.9	<1.9	<1.9	<1.9	<1.9	<1.9	<1.9
Valsartan	ng/L	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Warfarin	ng/L	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Venlafaxine	ng/L	4.8	0.6	0.35	0.59	1.2	0.15	0.14
Xylometazoline	ng/L	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19
Sum concentration	ng/L	162	38	92	103	59	9	44
Detected / Analysed APIs		35/53	31/53	26/53	28/53	24/53	17/53	16/53

Annex 4. APIs in river and estuary sediments

Country			Sweden	Sweden	Latvia	Latvia	Estonia	Estonia
Date (day/month/year)			19-12-2017	11-6-2018	5-12-2017	23-5-2018	13-12-2017	6-6-2018
Coordinate X			58.628369	58.628369	57,0429	57,04395	58,389707	58,355054
Coordinate Y			16.307817	16.307817	23,9681	23,96913	24,496484	24,42677
Coordinate system			WGS84	WGS84	WGS84	WGS84	L-Est 97	L-Est 97
Dry matter content			21%	13%	64%	67%	45%	53%
API	**API group**	**Unit**	**SE Bråviken**	**SE Bråviken**	**LV Riga coast**	**LV Riga coast**	**EE Pärnu river**	**EE Pärnu bay**
Atenolol	other cardiovascular medicines	µg/kg d.w.	<0.050	<0.050	<0.050	<0.050	<0.050	<0.050
Amlodipine	antihypertensives	µg/kg d.w.	<0.062	<0.062	0,65	<0.062	0,24	<0.062
Bezafibrate	metabolic disease medications	µg/kg d.w.	<0.076	0,20	<0.076	<0.076	<0.076	<0.076
Bisoprolol	other cardiovascular medicines	µg/kg d.w.	0,16	0,069	0,039	0,011	0,18	<0.011
Caffeine	other	µg/kg d.w.	3,4	2,4	0,73	2,4	11	2,4
Carbamazepine	antiepileptics	µg/kg d.w.	0,18	<0.099	<0.099	0,12	0,21	<0.099
Cetirizine	asthma and allergy medications	µg/kg d.w.	0,52	0,13	0,048	<0.014	0,17	<0.014
Ciprofloxacin	antibiotics	µg/kg d.w.	7,1	<1.9	12	14	34	<1.9
Citalopram	psycopharmaceuticals	µg/kg d.w.	3,7	1,6	<0.093	0,10	0,59	<0.093
Clarithromycin	antibiotics	µg/kg d.w.	0,19	<0.085	<0.085	0,27	1,7	<0.085
Codeine	NSAIDs and analgesics	µg/kg d.w.	<0.77	<0.77	<0.77	<0.77	<0.77	<0.77
Diclofenac	NSAIDs and analgesics	µg/kg d.w.	<0.10	<0.10	<0.10	<0.10	1,2	0,10
Dipyridamole	other cardiovascular medicines	µg/kg d.w.	1,2	0,24	0,23	<0.22	0,34	<0.22
Emamectin	veterinary medicines	µg/kg d.w.	<0.24	<0.24	0,31	<0.24	0,47	<0.24
Enalapril	antihypertensives	µg/kg d.w.	<0.047	<0.047	<0.047	<0.047	0,55	<0.047
Eprosartan	antihypertensives	µg/kg d.w.	<0.047	<0.047	<0.047	<0.047	<0.047	<0.047
Erythromycin	antibiotics	µg/kg d.w.	<16	<16	<16	<16	<16	<16
Estriol (E3)	hormones	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Estrone (E1)	hormones	µg/kg d.w.	<0.51	<0.51	3,8	1,8	<0.51	<0.51
Fenbendazole	veterinary medicines	µg/kg d.w.	1,8	0,42	<0.012	0,43	0,29	<0.012
Fexofenadine	asthma and allergy medications	µg/kg d.w.	1,5	0,50	0,043	<0.017	0,19	<0.017
Florfenicol	veterinary medicines	µg/kg d.w.	<0.010	0,25	0,029	<0.010	0,10	0,040
Fluconazole	antibiotics	µg/kg d.w.	0,12	<0.0041	0,032	<0.0041	0,088	<0.0041
Fluticasone	asthma and allergy medications	µg/kg d.w.	<0.60	<0.60	<0.60	<0.60	<0.60	<0.60
Gemfibrozil	metabolic disease medications	µg/kg d.w.	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18
Hydrochlorothiazide	antihypertensives	µg/kg d.w.	<10	<10	<10	22	<10	41
Irbesartan	antihypertensives	µg/kg d.w.	<0.013	N/A	<0.013	N/A	0,082	N/A
Ivermectin	veterinary medicines	µg/kg d.w.	<6.2	<6.2	<6.2	<6.2	<6.2	<6.2
Ketoprofen	NSAIDs and analgesics	µg/kg d.w.	0,6	<0.059	<0.059	0,40	0,61	0,35
Levetiracetam	antiepileptics	µg/kg d.w.	<0.47	<0.47	<0.47	7,6	<0.47	<0.47
Lincomycin	antibiotics	µg/kg d.w.	<0.0058	<0.0058	0,020	<0.0058	0,77	<0.0058
Metformin	metabolic disease medications	µg/kg d.w.	6,8	25	8,4	8,6	60	5,8
Metoprolol	other cardiovascular medicines	µg/kg d.w.	1,2	1,7	0,10	<0.050	0,84	<0.050
Mometasone	asthma and allergy medications	µg/kg d.w.	<0.75	<0.75	<0.75	<0.75	<0.75	<0.75
Naproxen	NSAIDs and analgesics	µg/kg d.w.	<0.52	2,5	<0.52	<0.52	1,5	<0.52
Nebivolol	other cardiovascular medicines	µg/kg d.w.	0,37	0,15	<0.099	0,15	0,37	<0.099
Norethisterone	hormones	µg/kg d.w.	<0.12	0,46	<0.12	N/A	0,71	N/A
Norfloxacin	antibiotics	µg/kg d.w.	7,8	15	8,9	20	17	<1.5
Ofloxacin	antibiotics	µg/kg d.w.	0,73	<0.60	<0.60	<0.60	16	<0.60
Olanzepine	psycopharmaceuticals	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Oxazepam	psycopharmaceuticals	µg/kg d.w.	1,2	0,41	0,066	0,039	0,19	0,10
Oxycodone	NSAIDs and analgesics	µg/kg d.w.	<0.065	<0.065	<0.065	<0.065	0,31	<0.065
Paracetamol	NSAIDs and analgesics	µg/kg d.w.	61	84	<0.25	3,9	22	<0.25
Primidone	antiepileptics	µg/kg d.w.	<0.057	<0.057	<0.057	<0.057	<0.057	<0.057
Progesterone	hormones	µg/kg d.w.	1,6	5,2	<0.092	0,17	8,8	0,39
Quetiapine	psycopharmaceuticals	µg/kg d.w.	<0.0084	<0.0084	0,041	<0.0084	0,14	<0.0084
Ramipril	antihypertensives	µg/kg d.w.	<0.052	<0.052	<0.052	<0.052	<0.052	<0.052
Risperidone	psycopharmaceuticals	µg/kg d.w.	1,3	0,17	0,73	0,27	0,73	0,27
Sertraline	psycopharmaceuticals	µg/kg d.w.	0,30	0,83	0,37	0,044	1,7	<0.038
Simvastatin	metabolic disease medications	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11	0,57	<0.11
Sotalol	other cardiovascular medicines	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11
Sulfamethoxazole	antibiotics	µg/kg d.w.	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12
Telmisartan	antihypertensives	µg/kg d.w.	1,1	N/A	<0.14	1,3	1,2	<0.14
Temazepam	psycopharmaceuticals	µg/kg d.w.	<0.087	<0.087	<0.087	<0.087	0,11	<0.087
Testosterone	hormones	µg/kg d.w.	1,1	0,60	<0.20	<0.20	0,61	<0.20
Tetracycline/Doxycycline	antibiotics	µg/kg d.w.	5,0	<1.6	<1.6	2,0	<1.6	3,4
Tiamulin	veterinary medicines	µg/kg d.w.	<0.044	<0.044	<0.044	<0.044	<0.044	<0.044
Toltrazuril	veterinary medicines	µg/kg d.w.	<4.6	<4.6	<4.6	<4.6	<4.6	<4.6
Tramadol	NSAIDs and analgesics	µg/kg d.w.	5,0	1,5	1,1	0,64	1,5	0,93
Trimethoprim	antibiotics	µg/kg d.w.	0,22	0,19	<0.050	0,095	0,36	0,086
Tylosin	veterinary medicines	µg/kg d.w.	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2
Valsartan	antihypertensives	µg/kg d.w.	<0.092	0,17	<0.092	<0.092	1,4	<0.092
Warfarin	other cardiovascular medicines	µg/kg d.w.	<0.0059	<0.0059	<0.0059	<0.0059	<0.0059	<0.0059
Venlafaxine	psycopharmaceuticals	µg/kg d.w.	0,33	0,32	0,069	<0.044	0,39	<0.044
Xylometazoline	asthma and allergy medications	µg/kg d.w.	<0.046	<0.046	<0.046	75	<0.046	48
	Number of analysed API		65	63	65	63	65	63
	Number of APIs above LOQ		28	24	21	24	41	13
	Detection rate (%)		43	38	32	38	63	21
	Sum concentration (µg/kg d.w.)		115	145	37	161	188	103

Annex 5. API concentrations in WWTP influents

Country			Estonia	Estonia	Estonia	Estonia	Estonia	Estonia
Date			06-12-2017	06-12-2017	12-12-2017	05-06-2018	05-06-2018	07-06-2018
Year			2017	2017	2017	2018	2018	2018
Month			12	12	12	6	6	6
Date			6	6	12	5	5	7
Name			Türi	Paide	Pärnu	Paide	Türi	Pärnu
Comments			24-h	24-h	24-h	24-h	24-h	24-h
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<13718	<13718	<13718	<13718	<13718	<13718
Amlodipine	antihypertensives	ng/l	<396	<396	<396	450	<396	<396
Atenolol	other cardiovascular medicines	ng/l	<211	<211	<211	<211	<211	<211
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	<27	<27	<27	<27	<27	53
Bisoprolol	other cardiovascular medicines	ng/l	<30	<30	<30	<30	<30	57
Caffeine	other	ng/l	249	385	253	8805	10830	3935
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	<17	<17	<17	2067	2464	1428
Carprofen	veterinary medicines	ng/l	<14	<14	<14	<14	31	<14
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	38	58	29	126	74	91
Clarithromycin	antibiotics	ng/l	529	1859	562	888	327	339
Codeine	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	2090	1608	1579
Diclofenac	NSAIDs and analgesics	ng/l	5407	7279	4421	8811	15730	2778
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	<185	581	590	1796
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	<167	<167	<167	<167	<167
Eprosartan	antihypertensives	ng/l	<10	<10	<10	<10	<10	162
Erythromycin	antibiotics	ng/l	<39	<39	<39	19040	9157	1463
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	<12	<12	<12	54	71	80
Estrone (E1)	hormones	ng/l	27	<26	296	41	59	1224
Fenbendazole	veterinary medicines	ng/l	<36	<36	<36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64	<64
Fluconazole	antibiotics	ng/l	<20	44	48	<20	<20	57
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415	607
Gabapentin	antiepileptics	ng/l	1667	2845	2733	5158	7954	8633
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	<165	611	<165	<165
Hydrochlorothiazide	antihypertensives	ng/l	2655	2152	2278	10121	21007	11860
Ibuprofen	NSAIDs and analgesics	ng/l	<2272	<2272	2331	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	<53	<53	<53	<53	<53	<53
Ketoprofen	NSAIDs and analgesics	ng/l	446	491	205	2119	1927	1127
Levetiracetam	antiepileptics	ng/l	1074	797	734	3772	3234	3508
Lincomycin	antibiotics	ng/l	<18	<18	<18	<18	<18	<18
Losartan	antihypertensives	ng/l	<508	<508	<508	<508	1062	<508
Mesalazine	gastrointestinal disease medications	ng/l	5562	5050	4360	13052	13685	<282
Metformin	metabolic disease medications	ng/l	14832	26315	16703	108975	99787	93169
Metoprolol	other cardiovascular medicines	ng/l	791	791	571	1585	2730	1814
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	2679	2089	1341	5508	11789	7082
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	<974	1452	1452	1542
Norethisterone	hormones	ng/l	<24	<24	<24	187	80	93
Norfloxacin	antibiotics	ng/l	13299	13365	13409	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	<417	<417	<417	<417	<417	<417
Olanzapine	psycopharmaceuticals	ng/l	<5.9	<5.9	<5.9	<5.9	<5.9	<5.9
Oxazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	36	67	73
Oxycodone	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	<263	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	98860	335776	145893	7573	8479	4411
Primidone	antiepileptics	ng/l	<35	<35	<35	<35	<35	<35
Progesterone	hormones	ng/l	<31	<31	<31	<31	33	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	687	<473
Ramipril	antihypertensives	ng/l	<32	<32	<32	<32	<32	<32
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	<20	<20	<20	45	31	49
Simvastatin	metabolic disease medications	ng/l	<1.4	<1.4	<1.4	98	5	<1.4
Sotalol	other cardiovascular medicines	ng/l	70	142	124	143	151	215
Sulfadiazine	antibiotics	ng/l	<590	<590	<590	<590	<590	<590
Sulfamethoxazole	antibiotics	ng/l	130	296	100	376	228	386
Telmisartan	antihypertensives	ng/l	<49	54	<49	6851	12021	189
Temazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	30	39	30
Testosterone	hormones	ng/l	<81	<81	<81	<81	<81	<81
Tetracycline/Doxycycl	antibiotics	ng/l	260	298	404	<239	<239	<239
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	<77	<77	<77	462	444	406
Trimethoprim	antibiotics	ng/l	123	197	103	323	158	237
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	<295	743	580	465	544	1383
Warfarin	other cardiovascular medicines	ng/l	<13	<13	<13	<13	14	14
Venlafaxine	psycopharmaceuticals	ng/l	<20	48	43	199	189	343
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	<51	<51	<51	<51
	Number of analysed API		71	71	71	74	74	74
	Number of APIs above LOQ		20	23	24	35	38	37
	Detection rate (%)		28	32	34	47	51	50

Country			Finland	Finland	Finland	Finland	Finland	Finland
Date			15-15-2017	29-8-2018	21-11-2018	12-12-2017	06-06-2018	21-11-2018
Year			2017	2018	2018	2017	2018	2018
Month			12	8	11	12	6	11
Date			15	29	21	12	6	21
Name			Viikki	Viikki	Viikki	Kalteva	Kalteva	Kalteva
Comments			24-h	24-h	24-h	24-h	24-h	24-h
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<13718	<13718	<13718	<13718	<13718	162899
Amlodipine	antihypertensives	ng/l	<396	<396	<396	<396	<396	<396
Atenolol	other cardiovascular medicines	ng/l	<211	<211	<211	<211	<211	<211
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	32	105	62	30	<27	44
Bisoprolol	other cardiovascular medicines	ng/l	301	<30	<30	697	665	<30
Caffeine	other	ng/l	938	9545	<17	1085	N/A	62
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	<17	222	104	<17	439	169
Carprofen	veterinary medicines	ng/l	23	<14	18	<14	26	<14
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	273	<2.2	318	295	429	647
Clarithromycin	antibiotics	ng/l	100	<31	70	290	52	<31
Codeine	NSAIDs and analgesics	ng/l	N/A	<42	2005	N/A	4177	4496
Diclofenac	NSAIDs and analgesics	ng/l	2796	2428	3613	4398	4165	5226
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	1144	<185	4976	4657
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	<167	<167	<167	<167	195
Eprosartan	antihypertensives	ng/l	215	<10	292	341	286	368
Erythromycin	antibiotics	ng/l	<39	<39	305	<39	<39	110
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	<12	250	<12	<12	<12	21
Estrone (E1)	hormones	ng/l	<26	59	<26	54	52	<26
Fenbendazole	veterinary medicines	ng/l	<36	<36	<36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64	<64
Fluconazole	antibiotics	ng/l	142	94	201	167	229	289
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415	<415
Gabapentin	antiepileptics	ng/l	9517	36968	10107	11246	68351	19072
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	<165	<165	232	<165
Hydrochlorothiazide	antihypertensives	ng/l	2624	1856	<7.5	3269	5834	4151
Ibuprofen	NSAIDs and analgesics	ng/l	3971	N/A	N/A	7995	N/A	N/A
Irbesartan	antihypertensives	ng/l	<53	<53	<53	<53	<53	<53
Ketoprofen	NSAIDs and analgesics	ng/l	154	251	186	261	335	310
Levetiracetam	antiepileptics	ng/l	4298	8363	9124	7308	11112	12938
Lincomycin	antibiotics	ng/l	<18	<18	<18	<18	<18	<18
Losartan	antihypertensives	ng/l	<508	1335	<508	<508	1873	<508
Mesalazine	gastrointestinal disease medications	ng/l	6828	14124	1317	5269	7576	2584
Metformin	metabolic disease medications	ng/l	46589	103739	107115	43350	343234	169888
Metoprolol	other cardiovascular medicines	ng/l	212	<14	238	474	<14	455
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	2024	1724	3185	3302	6878	4509
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	<974	<974	<974	<974
Norethisterone	hormones	ng/l	<24	<24	332	<24	1942	343
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	973	597	<417	431	711	510
Olanzapine	psycopharmaceuticals	ng/l	<5.9	<5.9	<5.9	<5.9	2218	<5.9
Oxazepam	psycopharmaceuticals	ng/l	N/A	827	1508	N/A	1395	3113
Oxycodone	NSAIDs and analgesics	ng/l	N/A	<263	<263	N/A	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	736802	4674	8248	395653	983013	12349
Primidone	antiepileptics	ng/l	<35	<35	<35	<35	<35	<35
Progesterone	hormones	ng/l	<31	<31	<31	<31	<31	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	<473	<473
Ramipril	antihypertensives	ng/l	<32	<32	<32	<32	<32	51
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	143	<20	82	85	928	295
Simvastatin	metabolic disease medications	ng/l	<1.4	7	<1.5	4	33	<1.7
Sotalol	other cardiovascular medicines	ng/l	39	<15	21	82	66	16
Sulfadiazine	antibiotics	ng/l	<590	<590	<591	<590	<590	<593
Sulfamethoxazole	antibiotics	ng/l	63	73	87	<42	208	187
Telmisartan	antihypertensives	ng/l	<49	<49	1364	<49	9824	1953
Temazepam	psycopharmaceuticals	ng/l	N/A	603	1213	N/A	616	2356
Testosterone	hormones	ng/l	<81	<81	<81	<81	<81	<81
Tetracycline/Doxycycl	antibiotics	ng/l	2463	<239	806	2479	577	801
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	<77	397	204	<77	908	670
Trimethoprim	antibiotics	ng/l	337	1393	382	563	598	659
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	2054	5485	3800	4480	5264	7784
Warfarin	other cardiovascular medicines	ng/l	<13	26	<13	<13	21	<13
Venlafaxine	psycopharmaceuticals	ng/l	472	1014	630	640	1036	1107
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	<51	<51	<51	<51
	Number of analysed API		71	74	74	71	73	74
	Number of APIs above LOQ		28	27	32	28	38	36
	Detection rate (%)		39	36	43	39	52	49

Country			Germany	Germany	Germany	Germany	Germany
Date			19-2-2018	07-02-2018	09-02-2018	19-03-2018	01-06-2018
Year			2018	2018	2018	2018	2018
Month			2	2	2	3	6
Date			19	7	9	19	1
Name			Wismar	Neubrandenburg	Greifswald	Rostock	Wismar
Comments			grap sample				
Info					Sample melted during delivery		Sample melted during delivery
API	**API group**	**Unit**					
Allopurinol	metabolic disease medications	ng/l	<13718	<13718	<13718	N/A	<13718
Amlodipine	antihypertensives	ng/l	<396	<396	<396	<396	430
Atenolol	other cardiovascular medicines	ng/l	583	<211	<211	239	491
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	1445	930	<27	1215	782
Bisoprolol	other cardiovascular medicines	ng/l	1097	1750	86	1055	1225
Caffeine	other	ng/l	N/A	N/A	N/A	4590	15938
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	1113	3513	559	875	1370
Carprofen	veterinary medicines	ng/l	<14	84	<14	20	50
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	469	658	437	237	479
Clarithromycin	antibiotics	ng/l	297	529	65	180	62
Codeine	NSAIDs and analgesics	ng/l	668	766	225	359	624
Diclofenac	NSAIDs and analgesics	ng/l	6432	15909	637	6913	6142
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	<185	<185	1076
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	236	<167	<167	<167
Eprosartan	antihypertensives	ng/l	723	997	13	706	601
Erythromycin	antibiotics	ng/l	1273	3121	446	307	13541
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	<12	<12	<12	15	76
Estrone (E1)	hormones	ng/l	81	85	<26	75	<26
Fenbendazole	veterinary medicines	ng/l	<36	36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64
Fluconazole	antibiotics	ng/l	186	183	72	133	115
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415
Gabapentin	antiepileptics	ng/l	46217	95419	12307	10220	17182
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	<165	<165	428
Hydrochlorothiazide	antihypertensives	ng/l	6966	<7.5	2580	7365	6624
Ibuprofen	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	1065	2962	1313	1505	2918
Ketoprofen	NSAIDs and analgesics	ng/l	58	104	19	114	164
Levetiracetam	antiepileptics	ng/l	16536	24511	3889	20820	20256
Lincomycin	antibiotics	ng/l	<18	<18	<18	<18	<18
Losartan	antihypertensives	ng/l	<508	<508	<508	569	664
Mesalazine	gastrointestinal disease medications	ng/l	6488	7507	2547	6514	15475
Metformin	metabolic disease medications	ng/l	480308	480308	55777	197864	182214
Metoprolol	other cardiovascular medicines	ng/l	<14	<14	<14	1656	4021
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	1634	1197	482	750	1067
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	<974	N/A	1448
Norethisterone	hormones	ng/l	581	865	2847	370	92
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	985	1217	693	702	<417
Olanzapine	psycopharmaceuticals	ng/l	2075	2079	2065	2361	<5.9
Oxazepam	psycopharmaceuticals	ng/l	38	45	41	34	29
Oxycodone	NSAIDs and analgesics	ng/l	<263	<263	<263	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	615723	834395	442074	N/A	1109
Primidone	antiepileptics	ng/l	317	751	<35	343	361
Progesterone	hormones	ng/l	<31	46	<31	<31	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	<473
Ramipril	antihypertensives	ng/l	123	168	<32	146	103
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	351	<20	652	61	124
Simvastatin	metabolic disease medications	ng/l	61	61	4	<1.4	60
Sotalol	other cardiovascular medicines	ng/l	23	39	<15	125	20
Sulfadiazine	antibiotics	ng/l	<590	<590	<590	<590	<590
Sulfamethoxazole	antibiotics	ng/l	160	368	43	149	706
Telmisartan	antihypertensives	ng/l	2831	9457	12745	2471	1650
Temazepam	psycopharmaceuticals	ng/l	27	76	<17	20	<17
Testosterone	hormones	ng/l	<81	198	115	<81	85
Tetracycline/Doxycycl	antibiotics	ng/l	<239	<239	<239	<239	<239
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	781	759	297	550	606
Trimethoprim	antibiotics	ng/l	180	200	179	462	756
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	10325	53753	1177	23391	7768
Warfarin	other cardiovascular medicines	ng/l	<13	<13	<13	<13	<13
Venlafaxine	psycopharmaceuticals	ng/l	760	1110	293	823	766
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	<51	<51	<51
	Number of analysed API		73	73	73	71	74
	Number of APIs above LOQ		38	40	32	40	44
	Detection rate (%)		52	55	44	56	59

Country			Germany	Germany	Germany	Germany	Germany
Date			27-11-2018	03-12-2018	19-06-2018	26-06-2018	21-06-2018
Year			2018	2018	2018	2018	2018
Month			11	12	6	6	6
Date			27	3	19	26	21
Name			Rostock	Greifswald	Neubrandenburg	Greifswald	Rostock
Comments							
Info					Sample melted during delivery		Sample melted during delivery
API	**API group**	**Unit**					
Allopurinol	metabolic disease medications	ng/l	<13718	77402.7	<13718	<13718	<13718
Amlodipine	antihypertensives	ng/l	<396	<396	<396	<396	452
Atenolol	other cardiovascular medicines	ng/l	<211	<211	<211	<211	298
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	464	301	567	468	1227
Bisoprolol	other cardiovascular medicines	ng/l	<30	<30	1809	1617	1114
Caffeine	other	ng/l	1899	5200	23530	21066	19918
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	217	797	3377	2325	1315
Carprofen	veterinary medicines	ng/l	<14	<14	<14	<14	39
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	269	254	810	461	526
Clarithromycin	antibiotics	ng/l	46	214	213	434	156
Codeine	NSAIDs and analgesics	ng/l	430	564	473	495	485
Diclofenac	NSAIDs and analgesics	ng/l	5868	12159	6481	6011	4934
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	1367	643	944
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	<167	<167	<167	<167
Eprosartan	antihypertensives	ng/l	136	73	483	256	650
Erythromycin	antibiotics	ng/l	265	965	11144	12913	11257
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	16	<12	<12	36	59
Estrone (E1)	hormones	ng/l	<26	70	50	101	83
Fenbendazole	veterinary medicines	ng/l	<36	<36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64
Fluconazole	antibiotics	ng/l	93	234	78	194	81
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415
Gabapentin	antiepileptics	ng/l	12809	21155	23216	20782	13173
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	334	368	779
Hydrochlorothiazide	antihypertensives	ng/l	4389	1110	10986	15335	10306
Ibuprofen	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	514	1079	4671	2456	2062
Ketoprofen	NSAIDs and analgesics	ng/l	53	60	106	80	154
Levetiracetam	antiepileptics	ng/l	12149	25651	23420	26997	22099
Lincomycin	antibiotics	ng/l	<18	<18	<18	<18	<18
Losartan	antihypertensives	ng/l	<508	<508	835	815	657
Mesalazine	gastrointestinal disease medications	ng/l	2565	3845	18353	16527	16885
Metformin	metabolic disease medications	ng/l	160885	199891	162964	117291	143330
Metoprolol	other cardiovascular medicines	ng/l	1013	1519	3311	2262	2668
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	444	1382	1538	2230	1225
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	1447	1450	1464
Norethisterone	hormones	ng/l	<24	<24	117	60	47
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	503	639	3783	2116	1992
Olanzapine	psycopharmaceuticals	ng/l	<5.9	<5.9	<5.9	<5.9	<5.9
Oxazepam	psycopharmaceuticals	ng/l	40	176	48	66	33
Oxycodone	NSAIDs and analgesics	ng/l	<263	<263	<263	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	2044	2734	1710	3044	1257
Primidone	antiepileptics	ng/l	73	146	607	385	326
Progesterone	hormones	ng/l	<31	<31	<31	58	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	<473
Ramipril	antihypertensives	ng/l	54	144	122	118	73
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	92	545	178	336	<20
Simvastatin	metabolic disease medications	ng/l	<1.8	<1.9	92	60	93
Sotalol	other cardiovascular medicines	ng/l	<15	<15	<15	54	106
Sulfadiazine	antibiotics	ng/l	<594	<595	<590	<590	<590
Sulfamethoxazole	antibiotics	ng/l	51	159	402	126	403
Telmisartan	antihypertensives	ng/l	309	968	1925	914	716
Temazepam	psycopharmaceuticals	ng/l	53	137	60	38	24
Testosterone	hormones	ng/l	<81	<81	82	194	143
Tetracycline/Doxycycl	antibiotics	ng/l	<239	284	<239	<239	<239
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	136	369	607	964	601
Trimethoprim	antibiotics	ng/l	160	442	153	430	383
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	10706	16487	30072	16507	19368
Warfarin	other cardiovascular medicines	ng/l	<13	<13	<13	<13	<13
Venlafaxine	psycopharmaceuticals	ng/l	501	776	1470	1314	1131
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	61	56	<51
	Number of analysed API		74	74	74	74	74
	Number of APIs above LOQ		34	35	43	46	46
	Detection rate (%)		46	47	58	62	62

Country			Latvia	Latvia	Latvia	Latvia	Latvia	Latvia
Date			01-12-2017	27-11-2017	07-12-2017	21-05-2018	21-05-2018	29-05-2018
Year			2017	2017	2017	2018	2018	2018
Month			12	11	12	5	5	5
Date			1	27	7	21	21	29
Name			WWTP 3	WWTP 1	WWTP 2	WWTP 3	WWTP 1	WWTP 2
Comments								
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<13718	21752	<13718	150363	<13718	<13718
Amlodipine	antihypertensives	ng/l	<396	<396	<396	<396	<396	<396
Atenolol	other cardiovascular medicines	ng/l	<211	<211	<211	<211	<211	<211
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	<27	<27	<27	<27	<27	<27
Bisoprolol	other cardiovascular medicines	ng/l	289	417	316	420	493	386
Caffeine	other	ng/l	<17	340	721	101	3772	2538
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	<17	<17	<17	492	1357	635
Carprofen	veterinary medicines	ng/l	<14	25	<14	<14	<14	<14
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	48	25	47	38	29	37
Clarithromycin	antibiotics	ng/l	521	693	878	936	845	507
Codeine	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	106	139	129
Diclofenac	NSAIDs and analgesics	ng/l	6092	3977	5346	4261	4103	4081
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	<185	<185	<185	<185
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	<167	<167	<167	<167	<167
Eprosartan	antihypertensives	ng/l	<10	<10	<10	<10	<10	<10
Erythromycin	antibiotics	ng/l	<39	<39	<39	283	436	351
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	<12	<12	<12	132	204	163
Estrone (E1)	hormones	ng/l	36	<26	30	<26	92	101
Fenbendazole	veterinary medicines	ng/l	<36	<36	<36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64	<64
Fluconazole	antibiotics	ng/l	127	55	223	60	73	136
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415	<415
Gabapentin	antiepileptics	ng/l	6888	10008	11215	7491	12582	7488
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	<165	<165	<165	<165
Hydrochlorothiazide	antihypertensives	ng/l	2396	2622	1811	2998	9997	4074
Ibuprofen	NSAIDs and analgesics	ng/l	2587	3964	3256	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	<53	<53	<53	<53	<53	<53
Ketoprofen	NSAIDs and analgesics	ng/l	387	290	483	403	680	414
Levetiracetam	antiepileptics	ng/l	<217	661	1687	1919	1804	2117
Lincomycin	antibiotics	ng/l	<18	<18	<18	<18	<18	<18
Losartan	antihypertensives	ng/l	<508	<508	<508	<508	<508	<508
Mesalazine	gastrointestinal disease medications	ng/l	2816	6266	6830	3664	5961	6439
Metformin	metabolic disease medications	ng/l	21924	29873	30167	92101	121479	49814
Metoprolol	other cardiovascular medicines	ng/l	556	431	583	421	404	388
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	1093	1301	1151	1010	1405	1020
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	<974	<974	<974	<974
Norethisterone	hormones	ng/l	<24	<24	<24	463	688	637
Norfloxacin	antibiotics	ng/l	13360	13439	13312	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	1470	<417	<417	1000	<417	<417
Olanzapine	psycopharmaceuticals	ng/l	<5.9	<5.9	<5.9	2371	2374	2385
Oxazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	74	104	81
Oxycodone	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	<263	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	272165	271908	396604	3249	<77	<77
Primidone	antiepileptics	ng/l	<35	<35	<35	<35	<35	<35
Progesterone	hormones	ng/l	70	45	<31	<31	71	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	<473	<473
Ramipril	antihypertensives	ng/l	<32	<32	<32	<32	<32	<32
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	28	<20	26	<20	<20	<20
Simvastatin	metabolic disease medications	ng/l	<1.4	<1.4	<1.4	<1.4	<1.4	<1.4
Sotalol	other cardiovascular medicines	ng/l	78	109	137	109	204	80
Sulfadiazine	antibiotics	ng/l	<590	<590	<590	<590	<590	<590
Sulfamethoxazole	antibiotics	ng/l	418	501	944	238	107	270
Telmisartan	antihypertensives	ng/l	52	<49	51	2888	3126	923
Temazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	<17	19	<17
Testosterone	hormones	ng/l	<81	<81	<81	<81	<81	<81
Tetracycline/Doxycycl	antibiotics	ng/l	1064	349	411	<239	<239	<239
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	<77	<77	<77	367	245	288
Trimethoprim	antibiotics	ng/l	661	457	562	378	269	266
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	522	646	1149	716	807	934
Warfarin	other cardiovascular medicines	ng/l	<13	<13	<13	<13	<13	<13
Venlafaxine	psycopharmaceuticals	ng/l	<20	30	50	<20	46	52
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	<51	<51	<51	<51
	Number of analysed API		71	71	71	74	74	74
	Number of APIs above LOQ		26	26	27	30	32	30
	Detection rate (%)		37	37	38	41	43	41

Country			Poland	Poland	Sweden	Sweden	Sweden	Sweden	Sweden	Sweden
Date			29-11-2017	18-07-2018	12-2017	12-2017	12-2017	11-06-2018	15-06-2018	07-06-2018
Year			2017	2018	2017	2017	2017	2018	2018	2018
Month			11	7	12	12	12	6	6	6
Date			29	18	18	18	18	11	15	7
Name			Błonie	Błonie WWTP	Motala	Linköping	Norrköping	Motala	Linköping	Norrköping
Comments										
Info			Sample melted during delivery							
API	**API group**	**Unit**								
Allopurinol	metabolic disease medications	ng/l	<13718	<13719	<13718	<13718	<13718	<13718	<13718	<13718
Amlodipine	antihypertensives	ng/l	<396	<396	<396	<396	<396	<396	<396	<396
Atenolol	other cardiovascular medicines	ng/l	<211	<211	2563	1223	1848	636	<211	259
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	<27	<27	91	213	261	N/A	N/A	N/A
Bisoprolol	other cardiovascular medicines	ng/l	242	450	56	46	90	<30	62	72
Caffeine	other	ng/l	597	1601	N/A	N/A	N/A	4345	1682	3739
Candesartan	antihypertensives	ng/l	<772	<772	<772	<772	<772	<772	<772	<772
Carbamazepine	antiepileptics	ng/l	26	1573	577	1188	473	617	322	389
Carprofen	veterinary medicines	ng/l	<14	<14	53	<14	<14	29	<14	<14
Cetirizine	asthma and allergy medications	ng/l	<3218	<3218	<3218	<3218	<3218	<3218	<3218	<3218
Ciprofloxacin	antibiotics	ng/l	<3136	<3136	<3136	<3136	<3136	<3136	<3136	<3136
Citalopram	psycopharmaceuticals	ng/l	80	58	273	280	290	<2.2	<2.2	<2.2
Clarithromycin	antibiotics	ng/l	719	340	37	41	<31	<31	<31	48
Codeine	NSAIDs and analgesics	ng/l	N/A	105	1520	1004	1059	1682	667	782
Diclofenac	NSAIDs and analgesics	ng/l	9718	4486	3217	2542	2969	3362	1736	2704
Dipyridamole	other cardiovascular medicines	ng/l	<185	<185	780	277	871	229	<185	<185
Emamectin	veterinary medicines	ng/l	<29	<29	<29	<29	<29	<29	<29	<29
Enalapril	antihypertensives	ng/l	<167	<167	188	235	237	<167	<167	<167
Eprosartan	antihypertensives	ng/l	<10	27	15	57	21	<10	<10	<10
Erythromycin	antibiotics	ng/l	<39	255	<39	<39	<39	491	789	1545
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441	<8441	<8441
Estriol	hormones	ng/l	<12	<12	<12	<12	<12	121	150	<12
Estrone (E1)	hormones	ng/l	<26	121	<26	58	<26	4255	11186	11804
Fenbendazole	veterinary medicines	ng/l	<36	<36	<36	<36	<36	<36	<36	<36
Fexofenadine	asthma and allergy medications	ng/l	<4255	<4255	<4255	<4255	<4255	<4255	<4255	<4255
Florfenicol	veterinary medicines	ng/l	<64	<64	<64	<64	<64	N/A	N/A	N/A
Fluconazole	antibiotics	ng/l	436	436	82	209	84	N/A	N/A	N/A
Fluticasone	asthma and allergy medications	ng/l	<415	<415	<415	<415	<415	<415	<415	<415
Gabapentin	antiepileptics	ng/l	3314	1608	26937	21217	28656	N/A	N/A	N/A
Gemfibrozil	metabolic disease medications	ng/l	<165	<165	219	254	<165	<165	<165	<165
Hydrochlorothiazide	antihypertensives	ng/l	2084	5549	7835	16789	6216	6120	1134	1232
Ibuprofen	NSAIDs and analgesics	ng/l	<2272	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	<53	<53	85	165	110	64	116	111
Ketoprofen	NSAIDs and analgesics	ng/l	2803	2134	508	475	495	N/A	N/A	N/A
Levetiracetam	antiepileptics	ng/l	16657	6292	11322	6370	5228	N/A	N/A	N/A
Lincomycin	antibiotics	ng/l	<18	22	<18	<18	<18	N/A	N/A	N/A
Losartan	antihypertensives	ng/l	<508	650	2169	1595	1600	3616	2274	2502
Mesalazine	gastrointestinal disease medications	ng/l	12313	8508	6314	2963	5505	775	<282	<282
Metformin	metabolic disease medications	ng/l	65213	119869	148042	95447	130323	103601	24508	64613
Metoprolol	other cardiovascular medicines	ng/l	792	469	<14	<14	15	N/A	N/A	N/A
Mometasone furoate	asthma and allergy medications	ng/l	<828	<828	<828	<828	<828	<828	<828	<828
Naproxen	NSAIDs and analgesics	ng/l	2688	2080	7570	6088	6322	N/A	N/A	N/A
Nebivolol	other cardiovascular medicines	ng/l	<974	<974	<974	<974	<974	<974	<974	<974
Norethisterone	hormones	ng/l	<24	479	1176	1727	1286	169	<24	<24
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437	<12437	N/A	N/A	N/A
Ofloxacin	antibiotics	ng/l	1178	<417	521	543	543	N/A	N/A	N/A
Olanzapine	psycopharmaceuticals	ng/l	<5.9	2418	2101	2102	2125	8	10	24
Oxazepam	psycopharmaceuticals	ng/l	N/A	<23	542	329	440	624	219	438
Oxycodone	NSAIDs and analgesics	ng/l	N/A	<263	<263	<263	<263	<263	<263	<263
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	178721	5803	955686	1039957	1007060	7252	7025	6836
Primidone	antiepileptics	ng/l	<35	<35	59	<35	<35	N/A	N/A	N/A
Progesterone	hormones	ng/l	<31	88	<31	32	33	<31	<31	<31
Quetiapine	psycopharmaceuticals	ng/l	<473	<473	<473	<473	<473	<473	<473	<473
Ramipril	antihypertensives	ng/l	<32	72	<32	<32	<32	N/A	N/A	N/A
Risperidone	psycopharmaceuticals	ng/l	<804	<804	<804	<804	<804	<804	<804	<804
Sertraline	psycopharmaceuticals	ng/l	70	<20	384	520	377	N/A	N/A	N/A
Simvastatin	metabolic disease medications	ng/l	<1.4	<1.4	3	<1.4	48	<1.4	<1.4	<1.4
Sotalol	other cardiovascular medicines	ng/l	48	271	88	64	52	<15	<15	<15
Sulfadiazine	antibiotics	ng/l	<590	<590	<590	<590	<590	<590	<590	<590
Sulfamethoxazole	antibiotics	ng/l	61	120	<42	279	90	N/A	N/A	N/A
Telmisartan	antihypertensives	ng/l	143	3667	115	131	77	<49	<49	<49
Temazepam	psycopharmaceuticals	ng/l	N/A	<17	<17	<17	20	19	<17	<17
Testosterone	hormones	ng/l	<81	<81	<81	93	92	<81	<81	<81
Tetracycline/Doxycycl	antibiotics	ng/l	581	700	473	1208	564	245	475	296
Tiamulin	veterinary medicines	ng/l	<38	<38	<38	<38	<38	<38	<38	<38
Toltrazuril	veterinary medicines	ng/l	<8992	<8992	<8992	<8992	<8992	<8992	<8992	<8992
Tramadol	NSAIDs and analgesics	ng/l	<77	806	1356	764	1029	1389	535	858
Trimethoprim	antibiotics	ng/l	205	115	180	220	140	N/A	N/A	N/A
Tylosin	veterinary medicines	ng/l	<316	<316	<316	<316	<316	<316	<316	<316
Valsartan	antihypertensives	ng/l	1238	7602	345	591	511	446	332	469
Warfarin	other cardiovascular medicines	ng/l	<13	<13	16	<13	<13	14	<13	<13
Venlafaxine	psycopharmaceuticals	ng/l	327	182	605	407	748	N/A	N/A	N/A
Xylometazoline	asthma and allergy medications	ng/l	<51	<51	<51	<51	<51	<51	<51	<51

Annex 6. API concentrations in WWTP effluents

Country			Estonia	Estonia	Estonia	Estonia	Estonia	Estonia
Year			2017	2017	2017	2018	2018	2018
Month			12	12	12	6	6	6
Date			6	12	6	5	5	7
Name			Paide	Pärnu	Türi	Paide	Türi	Pärnu
Comments			24-h	24-h	24-h	24-h	24-h	24-h
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<123	<123	<123	<123	<123	<123
Amlodipine	antihypertensives	ng/l	<113	<113	<113	<113	<113	<113
Atenolol	other cardiovascular medicines	ng/l	<106	<106	<106	<106	<106	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	<13	<13	<13	<13	<13	<13
Bisoprolol	other cardiovascular medicines	ng/l	<15	19.34412	<15	<15	24	33
Caffeine	other	ng/l	<871	<871	<871	<871	<871	<871
Candesartan	antihypertensives	ng/l	<11	<11	<11	<11	<11	<11
Carbamazepine	antiepileptics	ng/l	895	666	877	2501	1095	368
Carprofen	veterinary medicines	ng/l	<7.1	<7.1	<7.1	<7.1	<7.1	<7.1
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204	<1204	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	<1568	<1568	<1568	<1568
Citalopram	psycopharmaceuticals	ng/l	72	42	70	104	57	21
Clarithromycin	antibiotics	ng/l	2208	405	526	618	376	63
Codeine	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	287	62	16
Diclofenac	NSAIDs and analgesics	ng/l	5419	7902	6116	38175	12592	5961
Dipyridamole	other cardiovascular medicines	ng/l	<87	<87	<87	<87	<87	<87
Emamectin	veterinary medicines	ng/l	<11	<11	<11	39	<11	<11
Enalapril	antihypertensives	ng/l	<83	<83	<83	<83	<83	<83
Eprosartan	antihypertensives	ng/l	<5.2	<5.2	<5.2	<5.2	<5.2	7.3
Erythromycin	antibiotics	ng/l	3500	908	1748	5740	90	151
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	<13	<13	<13	<13	<13	<13
Fenbendazole	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572	<1572	<1572
Florfenicol	veterinary medicines	ng/l	<32	<32	<32	<32	<32	<32
Fluconazole	antibiotics	ng/l	28	68	<9.6	16	112	<9.6
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	1203	3128	1068	0	4461	3156
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	1391	1039	2670	2096	4444	2019
Ibuprofen	NSAIDs and analgesics	ng/l	4854	4211	9461	<1136	<1136	<1136
Irbesartan	antihypertensives	ng/l	<70	<70	<70	<70	<70	<70
Ketoprofen	NSAIDs and analgesics	ng/l	18	366	49	125	356	299
Levetiracetam	antiepileptics	ng/l	<108	570	<108	171	165	<108
Lincomycin	antibiotics	ng/l	<9.8	<9.8	<9.8	<9.8	<9.8	27
Losartan	antihypertensives	ng/l	<254	<254	<254	270	<254	<254
Mesalazine	gastrointestinal disease medications	ng/l	<63	85	<63	892	<63	<63
Metformin	metabolic disease medications	ng/l	217	<7.5	604	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	2433	3536	2609	7170	7265	3939
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	<5.4	283	23	840	458	65
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	34	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	<9.5	<9.5	95	<9.5
Norfloxacin	antibiotics	ng/l	13351	13309	13317	<12437	18787	<12437
Ofloxacin	antibiotics	ng/l	<208	<208	<208	<208	<208	<208
Olanzapine	psycopharmaceuticals	ng/l	<0.96	<0.96	<0.96	19	382	386
Oxazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	72	59	61
Oxycodone	NSAIDs and analgesics	ng/l	N/A	N/A	N/A	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	812	2501	612	<77	<77	3476
Primidone	antiepileptics	ng/l	<18	<18	<18	<18	<18	<18
Progesterone	hormones	ng/l	<12	<12	<12	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	<16	<16	<16	32	64	22
Risperidone	psycopharmaceuticals	ng/l	<10	<10	<10	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/l	<10	<10	<10	16	<10	26
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/l	123	238	151	184	195	177
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	<8.9	225	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	1753	813	2159	2158	4031	2178
Temazepam	psycopharmaceuticals	ng/l	N/A	N/A	N/A	55	38	<8.3
Testosterone	hormones	ng/l	<18	<18	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	155	132	131	550	<119	135
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<8952	<8952	<8952	<8952
Tramadol	NSAIDs and analgesics	ng/l	175	205	182	472	306	235
Trimethoprim	antibiotics	ng/l	188	51	82	156	131	<11
Tylosin	veterinary medicines	ng/l	<102	<102	124	<102	<102	139
Valsartan	antihypertensives	ng/l	<147	322	<147	343	362	481
Warfarin	other cardiovascular medicines	ng/l	<6.3	<6.3	<6.3	15	6.3	11
Venlafaxine	psycopharmaceuticals	ng/l	42	70	23	213	172	128
Xylometazoline	asthma and allergy medications	ng/l	<26	<26	<26	27	<26	<26
	Number of analysed API		71	71	71	75	75	75
	Number of APIs above LOQ		20	24	22	31	27	27
	Detection rate (%)		28	34	31	41	36	36

Country			Finland	Finland	Finland	Finland	Finland	Finland
Year			2017	2018	2018	2017	2018	2018
Month			12	8	11	12	6	11
Date			15	29	21	12	6	21
Name			Viikki	Viikki	Viikki	Kalteva	Kalteva	Kalteva
Comments			24-h	24-h	24-h	24-h	24-h	24-h
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<123	244	159	<123	<123	<123
Amlodipine	antihypertensives	ng/l	<113	<113	<113	<113	<113	<113
Atenolol	other cardiovascular medicines	ng/l	<106	<106	<106	<106	<106	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	35	39	32	20	<13	13
Bisoprolol	other cardiovascular medicines	ng/l	344	<15	<15	642	1063	<15
Caffeine	other	ng/l	<871	<871	<871	<871	<871	<871
Candesartan	antihypertensives	ng/l	<11	<11	<11	<11	<11	<11
Carbamazepine	antiepileptics	ng/l	150	227	173	221	387	282
Carprofen	veterinary medicines	ng/l	<7.1	<7.1	<7.1	<7.1	<7.1	<7.1
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204	1263	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	<1568	<1568	<1568	<1568
Citalopram	psycopharmaceuticals	ng/l	245	<1.1	249	234	250	242
Clarithromycin	antibiotics	ng/l	116	<16	94	282	181	94
Codeine	NSAIDs and analgesics	ng/l	N/A	<11	656	N/A	94	217
Diclofenac	NSAIDs and analgesics	ng/l	2255	2204	3903	3106	6834	3418
Dipyridamole	other cardiovascular medicines	ng/l	806	<87	681	<87	<87	160
Emamectin	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11
Enalapril	antihypertensives	ng/l	<83	<83	<83	<83	<83	<83
Eprosartan	antihypertensives	ng/l	<5.2	<5.2	<5.2	<5.2	29	<5.2
Erythromycin	antibiotics	ng/l	1113	<8.5	233	1284	3869	154
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	N/A	<8441	<8441	N/A
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	14	<13	55	36	<13	33
Fenbendazole	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572	<1572	<1572
Florfenicol	veterinary medicines	ng/l	<32	<32	<32	<32	<32	<32
Fluconazole	antibiotics	ng/l	105	128	201	100	67	184
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	4428	<911	7138	7667	N/A	6957
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	1242	13852	<106	2355	2114	1188
Ibuprofen	NSAIDs and analgesics	ng/l	17721	30406	N/A	<1136	N/A	N/A
Irbesartan	antihypertensives	ng/l	<70	<70	<70	<70	<70	<70
Ketoprofen	NSAIDs and analgesics	ng/l	133	213	205	80	<11	108
Levetiracetam	antiepileptics	ng/l	533	152	<108	162	<108	<108
Lincomycin	antibiotics	ng/l	<9.8	<9.8	<9.8	<9.8	<9.8	<9.8
Losartan	antihypertensives	ng/l	680	1080	<254	655	585	<254
Mesalazine	gastrointestinal disease medications	ng/l	334	109	<63	172	932	<63
Metformin	metabolic disease medications	ng/l	<7.5	21	<7.5	2639	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	748	794	1074	1504	1309	1492
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	573	379	374	154	178	140
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	<16	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	<9.5	<9.5	<9.5	<9.5
Norfloxacin	antibiotics	ng/l	13271	<12437	<12437	13406	<12437	<12437
Ofloxacin	antibiotics	ng/l	<208	<208	<208	<208	<208	<208
Olanzapine	psycopharmaceuticals	ng/l	<0.96	<0.96	<0.96	<0.96	14	<0.96
Oxazepam	psycopharmaceuticals	ng/l	N/A	602	1720	N/A	868	2711
Oxycodone	NSAIDs and analgesics	ng/l	N/A	<115	<115	N/A	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	N/A	<763	<763	N/A
Paracetamol	NSAIDs and analgesics	ng/l	1251	<77	254	5366	<77	246
Primidone	antiepileptics	ng/l	<18	<18	<18	<18	<18	<18
Progesterone	hormones	ng/l	<12	<12	<12	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	<16	<16	37	22	20	49
Risperidone	psycopharmaceuticals	ng/l	<10	<10	<10	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/l	12	<10	30	12	31	20
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	3	<1.5	<1.5	8
Sotalol	other cardiovascular medicines	ng/l	88	18	33	101	32	21
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	269	<8.9	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	549	1	519	970	83	880
Temazepam	psycopharmaceuticals	ng/l	N/A	412	1072	N/A	376	1814
Testosterone	hormones	ng/l	<18	<18	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	155	<119	<119	134	122	<119
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<8952	<8952	<8952	<8952
Tramadol	NSAIDs and analgesics	ng/l	203	363	421	516	791	704
Trimethoprim	antibiotics	ng/l	275	<11	356	396	467	471
Tylosin	veterinary medicines	ng/l	156	<102	<102	247	<102	<102
Valsartan	antihypertensives	ng/l	2364	3406	3502	3632	988	1749
Warfarin	other cardiovascular medicines	ng/l	<6.3	20	<6.3	8	14	<6.3
Venlafaxine	psycopharmaceuticals	ng/l	367	533	679	513	889	843
Xylometazoline	asthma and allergy medications	ng/l	<26	<26	<26	<26	<26	<26
	Number of analysed API		71	75	72	71	73	72
	Number of APIs above LOQ		30	23	27	31	28	27
	Detection rate (%)		42	31	38	44	38	38

Country			Germany	Germany	Germany	Germany
Year			2018	2018	2018	2018
Month			2	2	6	6
Date			7	9	1	19
Name			Neubrandenburg	Greifswald	Wismar	Neubrandenburg
Comments			24-h	24-h	24-h	24-h
Info				Sample melted during delivery	Sample melted during delivery	Sample melted during delivery
API	**API group**	**Unit**				
Allopurinol	metabolic disease medications	ng/l	166	433	<123	<123
Amlodipine	antihypertensives	ng/l	<113	<113	<113	<113
Atenolol	other cardiovascular medicines	ng/l	<106	<106	<106	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	394	99	31	90
Bisoprolol	other cardiovascular medicines	ng/l	1428	1194	277	984
Caffeine	other	ng/l	3274	<871	<871	<871
Candesartan	antihypertensives	ng/l	<11	<11	41	32
Carbamazepine	antiepileptics	ng/l	2112	407	1220	2231
Carprofen	veterinary medicines	ng/l	10	<7.1	9	<7.1
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	<1568	<1568
Citalopram	psycopharmaceuticals	ng/l	346	195	165	348
Clarithromycin	antibiotics	ng/l	615	850	35	101
Codeine	NSAIDs and analgesics	ng/l	76	99	26	17
Diclofenac	NSAIDs and analgesics	ng/l	26107	3712	4758	7299
Dipyridamole	other cardiovascular medicines	ng/l	<87	<87	<87	<87
Emamectin	veterinary medicines	ng/l	<11	<11	32	<11
Enalapril	antihypertensives	ng/l	<83	<83	<83	<83
Eprosartan	antihypertensives	ng/l	233	50	15	50
Erythromycin	antibiotics	ng/l	8270	6571	44	103
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	17	<13	<13	<13
Fenbendazole	veterinary medicines	ng/l	<11	<11	15	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572
Florfenicol	veterinary medicines	ng/l	<32	<32	<32	<32
Fluconazole	antibiotics	ng/l	74	21	290	133
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	N/A	N/A	<911	2107
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	1822	2101	7632	2876
Ibuprofen	NSAIDs and analgesics	ng/l	N/A	N/A	<1136	<1136
Irbesartan	antihypertensives	ng/l	<70	<70	626	1803
Ketoprofen	NSAIDs and analgesics	ng/l	16	<11	<11	17
Levetiracetam	antiepileptics	ng/l	343	346	<108	234
Lincomycin	antibiotics	ng/l	<9.8	<9.8	15	<9.8
Losartan	antihypertensives	ng/l	382	291	<254	<254
Mesalazine	gastrointestinal disease medications	ng/l	943	903	<63	<63
Metformin	metabolic disease medications	ng/l	<7.5	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	4279	1611	2628	4524
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	436	124	41	218
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	17	<9.5
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	<208	739	<208	<208
Olanzapine	psycopharmaceuticals	ng/l	13	13	432	383
Oxazepam	psycopharmaceuticals	ng/l	31	14	31	39
Oxycodone	NSAIDs and analgesics	ng/l	<115	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	<77	1928	<77	<77
Primidone	antiepileptics	ng/l	931	106	446	874
Progesterone	hormones	ng/l	<12	<12	12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	171	32	49	223
Risperidone	psycopharmaceuticals	ng/l	<10	<10	12	<10
Sertraline	psycopharmaceuticals	ng/l	13	39	18	10
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/l	22	14	75	26
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	710	65	1756	4480
Temazepam	psycopharmaceuticals	ng/l	54	10	23	57
Testosterone	hormones	ng/l	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	<119	133	<119	<119
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<8952	<8952
Tramadol	NSAIDs and analgesics	ng/l	772	320	588	680
Trimethoprim	antibiotics	ng/l	182	134	69	107
Tylosin	veterinary medicines	ng/l	<102	<102	173	324
Valsartan	antihypertensives	ng/l	21426	4582	242	3689
Warfarin	other cardiovascular medicines	ng/l	<6.3	<6.3	<6.3	<6.3
Venlafaxine	psycopharmaceuticals	ng/l	893	418	610	851
Xylometazoline	asthma and allergy medications	ng/l	99	52	61	55
	Number of analysed API		73	73	75	75
	Number of APIs above LOQ		34	33	36	32
	Detection rate (%)		47	45	48	43

Country			**Germany**	**Germany**	**Germany**	**Germany**
Year			2018	2018	2018	2018
Month			6	6	11	12
Date			26	21	27	3
Name			Greifswald	Rostock	Rostock	Greifswald
Comments			24-h	24-h	24-h	24-h
Info				Sample melted during delivery		
API	**API group**	**Unit**				
Allopurinol	metabolic disease medications	ng/l	<123	<123	138	206
Amlodipine	antihypertensives	ng/l	<113	<113	<113	<113
Atenolol	other cardiovascular medicines	ng/l	<106	<106	<106	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	72	365	265	65
Bisoprolol	other cardiovascular medicines	ng/l	1128	950	<15	42
Caffeine	other	ng/l	<871	<871	<871	<871
Candesartan	antihypertensives	ng/l	<11	<11	<11	<11
Carbamazepine	antiepileptics	ng/l	1891	823	1009	902
Carprofen	veterinary medicines	ng/l	<7.1	<7.1	<7.1	<7.1
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	<1568	<1568
Citalopram	psycopharmaceuticals	ng/l	207	227	221	94
Clarithromycin	antibiotics	ng/l	239	225	86	409
Codeine	NSAIDs and analgesics	ng/l	17	50	62	124
Diclofenac	NSAIDs and analgesics	ng/l	7485	3786	6773	7011
Dipyridamole	other cardiovascular medicines	ng/l	<87	<87	<87	<87
Emamectin	veterinary medicines	ng/l	<11	<11	<11	<11
Enalapril	antihypertensives	ng/l	<83	<83	<83	<83
Eprosartan	antihypertensives	ng/l	5	173	<5.2	<5.2
Erythromycin	antibiotics	ng/l	152	129	272	426
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	N/A	N/A
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	<13	<13	22	47
Fenbendazole	veterinary medicines	ng/l	<11	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572
Florfenicol	veterinary medicines	ng/l	<32	<32	<32	<32
Fluconazole	antibiotics	ng/l	512	95	145	131
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	2038	<911	1002	1858
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	8992	18760	246	1562
Ibuprofen	NSAIDs and analgesics	ng/l	<1136	<1136	N/A	N/A
Irbesartan	antihypertensives	ng/l	1481	919	1222	858
Ketoprofen	NSAIDs and analgesics	ng/l	29	28	34	28
Levetiracetam	antiepileptics	ng/l	<108	<108	<108	<108
Lincomycin	antibiotics	ng/l	<9.8	<9.8	<9.8	<9.8
Losartan	antihypertensives	ng/l	<254	<254	<254	<254
Mesalazine	gastrointestinal disease medications	ng/l	<63	<63	<63	<63
Metformin	metabolic disease medications	ng/l	<7.5	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	4895	2628	3980	3782
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	97	60	65	46
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	<9.5	<9.5
Norfloxacin	antibiotics	ng/l	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	<208	<208	<208	<208
Olanzapine	psycopharmaceuticals	ng/l	387	385	<0.96	<0.96
Oxazepam	psycopharmaceuticals	ng/l	54	22	69	118
Oxycodone	NSAIDs and analgesics	ng/l	<115	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	N/A	N/A
Paracetamol	NSAIDs and analgesics	ng/l	<77	<77	382	486
Primidone	antiepileptics	ng/l	490	302	207	143
Progesterone	hormones	ng/l	<12	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	286	89	91	112
Risperidone	psycopharmaceuticals	ng/l	<10	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/l	15	<10	<10	19
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/l	113	71	44	15
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	2692	1417	638	790
Temazepam	psycopharmaceuticals	ng/l	33	14	92	91
Testosterone	hormones	ng/l	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	<119	<119	<119	<119
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<8952	<8952
Tramadol	NSAIDs and analgesics	ng/l	881	399	644	699
Trimethoprim	antibiotics	ng/l	194	153	70	171
Tylosin	veterinary medicines	ng/l	353	210	<102	<102
Valsartan	antihypertensives	ng/l	842	5781	2217	2351
Warfarin	other cardiovascular medicines	ng/l	<6.3	<6.3	<6.3	<6.3
Venlafaxine	psycopharmaceuticals	ng/l	874	623	955	557
Xylometazoline	asthma and allergy medications	ng/l	47	48	49	52
	Number of analysed API		75	75	72	72
	Number of APIs above LOQ		30	28	28	30
	Detection rate (%)		40	37	39	42

Country			Latvia	Latvia	Latvia	Latvia	Latvia	Latvia	Poland	Poland
Year			2017	2017	2017	2018	2018	2018	2017	2018
Month			11	12	12	5	5	5	11	7
Date			27	8	1	21	21	30	29	18
Name			WWTP 1	WWTP 2	WWTP 3	WWTP 3	WWTP 1	WWTP 2	Błonie	Błonie
Comments										
Info									Sample melted during delivery	
API	**API group**	**Unit**								
Allopurinol	metabolic disease medications	ng/l	<123	<123	7332	<123	<123	<123	189	<123
Amlodipine	antihypertensives	ng/l	<113	<113	N/A	<113	<113	<113	<113	<113
Atenolol	other cardiovascular medicines	ng/l	<106	<106	<106	<106	<106	<106	<106	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	17075	<10405	<10405	<10405	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	<13	<13	N/A	<13	<13	<13	<13	<13
Bisoprolol	other cardiovascular medicines	ng/l	196	333.54	<15	298	372	331	366	94
Caffeine	other	ng/l	<871	<871	32227	<871	<871	<871	<871	<871
Candesartan	antihypertensives	ng/l	<11	<11	<11	<11	<11	<11	<11	<11
Carbamazepine	antiepileptics	ng/l	835	499	390	<7.7	1137	671	2014	1692
Carprofen	veterinary medicines	ng/l	<7.1	<7.1	<7.1	<7.1	<7.1	<7.1	<7.1	8
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204	<1204	<1204	<1204	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	N/A	<1568	<1568	<1568	<1568	<1568
Citalopram	psycopharmaceuticals	ng/l	21	27	20	23	22	23	39	51
Clarithromycin	antibiotics	ng/l	377	874	210	288	198	231	885	121
Codeine	NSAIDs and analgesics	ng/l	N/A	N/A	129	<11	52	68	39	<11
Diclofenac	NSAIDs and analgesics	ng/l	4884	5038	5000	2254	3402	3819	16229	3083
Dipyridamole	other cardiovascular medicines	ng/l	<87	<87	<87	<87	<87	<87	<87	<87
Emamectin	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11	<11	<11
Enalapril	antihypertensives	ng/l	<83	<83	N/A	<83	<83	<83	<83	<83
Eprosartan	antihypertensives	ng/l	<5.2	<5.2	N/A	<5.2	<5.2	<5.2	<5.2	<5.2
Erythromycin	antibiotics	ng/l	2534	3784	439	<8.5	171	253	6185	117
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441	<8441	<8441
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	<13	<13	10565	<13	<13	<13	<13	<13
Fenbendazole	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572	<1572	<1572	<1572	1776
Florfenicol	veterinary medicines	ng/l	<32	<32	N/A	<32	<32	<32	<32	<32
Fluconazole	antibiotics	ng/l	90	137	71	<9.6	49	157	152	327
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	1993	8575	7294	<911	1641	<911	N/A	5823
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	1473	3279	4821	7211	4070	3044	3788	7021
Ibuprofen	NSAIDs and analgesics	ng/l	17966	44305	N/A	<1136	<1136	<1136	N/A	<1136
Irbesartan	antihypertensives	ng/l	<70	<70	<70	<70	<70	<70	<70	<70
Ketoprofen	NSAIDs and analgesics	ng/l	215	333	N/A	72	260	294	115	14
Levetiracetam	antiepileptics	ng/l	<108	<108	N/A	<108	<108	<108	154	<108
Lincomycin	antibiotics	ng/l	39	33	<9.8	<9.8	33	63	14	33
Losartan	antihypertensives	ng/l	<254	<254	<254	<254	<254	<254	366	<254
Mesalazine	gastrointestinal disease medications	ng/l	131	181	70	<63	<63	<63	891	<63
Metformin	metabolic disease medications	ng/l	1045	1384	<7.5	<7.5	<7.5	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	1318	2118	N/A	1099	1229	1610	1257	808
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	31	51	N/A	46	59	147	116	5.0
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	<16	<16	<16	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	<9.5	112	<9.5	<9.5	<9.5	<9.5
Norfloxacin	antibiotics	ng/l	13383	13541	<12437	<12437	<12437	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	553	<208	N/A	295	<208	<208	<208	<208
Olanzapine	psycopharmaceuticals	ng/l	<0.96	<0.96	1.3	387	390	390	13	400
Oxazepam	psycopharmaceuticals	ng/l	N/A	N/A	60	1.3	79	88	25	19
Oxycodone	NSAIDs and analgesics	ng/l	N/A	N/A	<115	<115	<115	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	1690	2763	1373	1148	<77	<77	<77	<77
Primidone	antiepileptics	ng/l	19	<18	N/A	<18	23	<18	43	<18
Progesterone	hormones	ng/l	<12	<12	29	29	<12	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	<16	<16	N/A	<16	21	20	43	<16
Risperidone	psycopharmaceuticals	ng/l	<10	<10	<10	<10	<10	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/l	20	<10	N/A	<10	<10	<10	10	<10
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/l	134	237	18	74	217	241	174	128
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	<8.9	<8.9	<8.9	<8.9	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	944	750	597	105	2399	1813	1963	4695
Temazepam	psycopharmaceuticals	ng/l	N/A	N/A	<8.3	<8.3	14	13	24	15
Testosterone	hormones	ng/l	<18	<18	<18	32	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	284	166	<119	<119	<119	<119	127	<119
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<LOQ	<8952	<8952	<8952	<8952	<8952
Tramadol	NSAIDs and analgesics	ng/l	206	289	229	<38	217	329	993	671
Trimethoprim	antibiotics	ng/l	300	272	N/A	261	240	72	192	58
Tylosin	veterinary medicines	ng/l	141	198	126	<102	144	183	<102	130
Valsartan	antihypertensives	ng/l	<147	272	381	<147	297	356	332	106
Warfarin	other cardiovascular medicines	ng/l	<6.3	<6.3	8	<6.3	<6.3	12	<6.3	<6.3
Venlafaxine	psycopharmaceuticals	ng/l	34	43	N/A	<10	37	47	266	169
Xylometazoline	asthma and allergy medications	ng/l	<26	31	<26	<26	<26	<26	<26	<26
	Number of analysed API		71	71	58	75	75	75	73	75
	Number of APIs above LOQ		28	28	23	18	26	25	30	25
	Detection rate (%)		39	39	40	24	35	33	41	33

Country			Sweden	Sweden	Sweden	Sweden	Sweden	Sweden
Year			2017	2017	2017	2018	2018	2018
Month			12	12	12	6	6	6
Date			18	18	18	11	15	7
Name			Motala	Linköping	Norrköping	Motala	Linköping	Norrköping
Comments								
Info								
API	**API group**	**Unit**						
Allopurinol	metabolic disease medications	ng/l	<123	160	<123	153.1622	<123	<123
Amlodipine	antihypertensives	ng/l	<113	<113	<113	N/A	N/A	N/A
Atenolol	other cardiovascular medicines	ng/l	492	487	541	<106	109	<106
Atorvastatin	metabolic disease medications	ng/l	<10405	<10405	15976	<10405	<10405	<10405
Bezafibrate	metabolic disease medications	ng/l	84	144	104	N/A	N/A	N/A
Bisoprolol	other cardiovascular medicines	ng/l	123	106	138	<15	<15	<15
Caffeine	other	ng/l	<871	1599	<871	<871	2829	2956
Candesartan	antihypertensives	ng/l	<11	<11	22	<11	<11	<11
Carbamazepine	antiepileptics	ng/l	343	384	342	521	454	533
Carprofen	veterinary medicines	ng/l	<7.1	<7.1	<7.1	<7.1	<7.1	<7.1
Cetirizine	asthma and allergy medications	ng/l	<1204	<1204	<1204	<1204	<1204	<1204
Ciprofloxacin	antibiotics	ng/l	<1568	<1568	<1568	N/A	N/A	N/A
Citalopram	psycopharmaceuticals	ng/l	169	149	250	111	90	179
Clarithromycin	antibiotics	ng/l	95	96	64	<16	35	48
Codeine	NSAIDs and analgesics	ng/l	529	372	N/A	496	207	192
Diclofenac	NSAIDs and analgesics	ng/l	4173	2221	2494	3263	1395	3019
Dipyridamole	other cardiovascular medicines	ng/l	<87	<87	<87	<87	<87	<87
Emamectin	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11
Enalapril	antihypertensives	ng/l	<83	<83	<83	N/A	N/A	N/A
Eprosartan	antihypertensives	ng/l	33	48	<5.2	N/A	N/A	N/A
Erythromycin	antibiotics	ng/l	4514	4195	1649	334	385	644
Esomeprazole	gastrointestinal disease medications	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estriol (E3)	hormones	ng/l	<8441	<8441	<8441	<8441	<8441	<8441
Estrone (E1)	hormones	ng/l	<13	<13	<13	<13	<13	<13
Fenbendazole	veterinary medicines	ng/l	<11	<11	<11	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/l	<1572	<1572	<1572	<1572	<1572	<1572
Florfenicol	veterinary medicines	ng/l	<32	<32	<32	N/A	N/A	N/A
Fluconazole	antibiotics	ng/l	28	34	99	134	76	100
Fluticasone	asthma and allergy medications	ng/l	<147	<147	<147	<147	<147	<147
Gabapentin	antiepileptics	ng/l	N/A	N/A	7027	13594	4765	12025
Gemfibrozil	metabolic disease medications	ng/l	<100	<100	<100	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/l	1470	1672	5877	5611	9697	5054
Ibuprofen	NSAIDs and analgesics	ng/l	N/A	N/A	3673	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/l	<70	<70	73	74	<70	104
Ketoprofen	NSAIDs and analgesics	ng/l	107	125	337	N/A	N/A	N/A
Levetiracetam	antiepileptics	ng/l	1223	563	250	N/A	N/A	N/A
Lincomycin	antibiotics	ng/l	31	<9.8	<9.8	<9.8	<9.8	23
Losartan	antihypertensives	ng/l	3305	2353	2560	4160	2101	2649
Mesalazine	gastrointestinal disease medications	ng/l	928	940	198	<63	79	78
Metformin	metabolic disease medications	ng/l	<7.5	<7.5	<7.5	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/l	3373	3061	5877	N/A	N/A	N/A
Mometasone furoate	asthma and allergy medications	ng/l	<27	<27	<27	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/l	1187	1310	950	N/A	N/A	N/A
Nebivolol	other cardiovascular medicines	ng/l	<16	<16	<16	<16	<16	<16
Norethisterone	hormones	ng/l	<9.5	<9.5	<9.5	<9.5	13	10
Norfloxacin	antibiotics	ng/l	<12437	<12437	13297	<12437	<12437	<12437
Ofloxacin	antibiotics	ng/l	<208	<208	<208	N/A	N/A	N/A
Olanzapine	psycopharmaceuticals	ng/l	13	13	<0.96	1.3	1.2	1.2
Oxazepam	psycopharmaceuticals	ng/l	419	214	N/A	583	210	540
Oxycodone	NSAIDs and analgesics	ng/l	<115	<115	N/A	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/l	<763	<763	<763	<763	<763	<763
Paracetamol	NSAIDs and analgesics	ng/l	<77	729	859	3385	1164	1777
Primidone	antiepileptics	ng/l	75	57	31	N/A	N/A	N/A
Progesterone	hormones	ng/l	<12	<12	<12	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/l	<116	<116	<116	<116	<116	<116
Ramipril	antihypertensives	ng/l	<16	<16	<16	N/A	N/A	N/A
Risperidone	psycopharmaceuticals	ng/l	<10	<10	<10	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/l	151	33	52	N/A	N/A	N/A
Simvastatin	metabolic disease medications	ng/l	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/l	48	33	47	11	10	<7.7
Sulfadiazine	antibiotics	ng/l	<295	<295	<295	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/l	<8.9	<8.9	<8.9	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/l	<11	<11	17	17	<11	<11
Temazepam	psycopharmaceuticals	ng/l	11	12	N/A	18	9.0	30
Testosterone	hormones	ng/l	<18	<18	<18	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/l	<119	<119	145	<119	<119	<119
Tiamulin	veterinary medicines	ng/l	<19	<19	<19	<19	<19	<19
Toltrazuril	veterinary medicines	ng/l	<8952	<8952	<8952	<LOQ	<LOQ	<8952
Tramadol	NSAIDs and analgesics	ng/l	1308	745	924	1506	520	1220
Trimethoprim	antibiotics	ng/l	146	174	96	N/A	N/A	N/A
Tylosin	veterinary medicines	ng/l	<102	<102	160	131	<102	159
Valsartan	antihypertensives	ng/l	476	616	559	484	276	733
Warfarin	other cardiovascular medicines	ng/l	12	10	<6.3	10	<6.3	9
Venlafaxine	psycopharmaceuticals	ng/l	517	313	517	N/A	N/A	N/A
Xylometazoline	asthma and allergy medications	ng/l	39	34	39	<26	<26	<26
	Number of analysed API		73	73	71	58	58	58
	Number of APIs above LOQ		31	33	34	21	21	23
	Detection rate (%)		42	45	48	36	36	40

Annex 7. Average efficiency of API treatment according to wastewater influent and effluent data (%)

		Estonia			Finland		Germany			Latvia			Poland	Sweden			
API	API group	Paide	Pärnu	Türi	Kalteva	Viikki	Greifswald	Neubrandenburg	Rostock	WWTP 1	WWTP 2	WWTP 3	Błonie WWTP	Linköping	Motala	Norrköping	Average
Atenolol	other cardiovascular medicines													60	82	71	71
Allopurinol	metabolic disease medications				100		100			99		100					100
Bezafibrate	metabolic disease medications					63	82	58	43					33	8	60	49
Bisoprolol	other cardiovascular medicines				-26	-14	30	18		39	4	62	79			-54	17
Caffeine	other	90		92		91	90										91
Carbamazepine	antiepileptics	-21	74	56	-27	-35	3	40	-364	16	-6	98	-8	13	28	-5	-6
Carprofen	veterinary medicines							88							87		87
Citalopram	psycopharmaceuticals	-3	14	-29	42	16	59	47	18	20	40	49	12	47	38	14	26
Clarithromycin	antibiotics	6	55	-7	3	-16	-23	-16		61	27	64	64				22
Codeine	NSAIDs and analgesics	86	99	96	96	67	87	90	86	63	47	90	90	66	68	75	80
Diclofenac	NSAIDs and analgesics	-154	-97	3	0	7	9	-64	-15	-3	6	33	31	16	-13	2	-14
Dipyridamole	other cardiovascular medicines	85	95	85	97	41	86								89	90	84
Eprosartan	antihypertensives		96		96	98	95	77	96				81	16			82
Erythromycin	antibiotics	70	90	99	-40	24	77	-165	-2	61	28	97	54	51	32	58	37
Estrone (E1)	hormones		97				60	80		86	87		89	100	100	100	89
Fluconazole	antibiotics		83		49	-3	-60	59	-56	-15	12	64	25	84	66	-18	22
Gabapentin	antiepileptics	100	63	44	48	60	91		92	84	56	41				75	68
Gemfibrozil	metabolic disease medications	84															84
Hydrochlorothiazide	antihypertensives	57	69	39	54	-297	0		94	52	-28	-121	-27	-333	45	-152	-39
Ibuprofen	NSAIDs and analgesics				86												86
Irbesartan	antihypertensives						30	98	-138								-3
Ketoprofen	NSAIDs and analgesics	95	-2	85	77	6	59	85		44	30	82	99	74	79	32	60
Levetiracetam	antiepileptics	91	60	92	99	95	100	99	99	89	94	94	98	91	89	95	92
Losartan	antihypertensives				69	19								-20	-34	-33	0
Mesalazine	gastrointestinal disease medicatic	96	98	99	94	97	99	87	98	98	98	98	99	68	89	96	95
Metformin	metabolic disease medications	100	100	98	98	100	100	100	100	98	98	100	100	100	100	100	99
Metoprolol	other cardiovascular medicines	-280	-318	-198	-222	-302	-133		-293	-205	-289	-161	-72				-224
Naproxen	NSAIDs and analgesics	92	89	98	97	79	96	64	85	97	91	95	100	78	84	85	89
Nebivolol	other cardiovascular medicines	98	99	99			99										99
Norethisterone	hormones	95	90	-18	98	97	84	99		99	99	76	98	99	97	99	87
Ofloxacin	antibiotics						90	83									87
Olanzepine	psycopharmaceuticals				99			99		84	84	84	83	94	92	97	90
Oxazepam	psycopharmaceuticals		16	13	25	7	26			24	-8	98		20	15	-23	21
Paracetamol	NSAIDs and analgesics	99	60	99	99	98	90	100	81	99	99	82	99	92	77	87	91
Primidone	antiepileptics						-13	-24									-18
Progesterone	hormones									83		59	86				75
Ramipril	antihypertensives						-60	-1									-31
Quetiapine	psycopharmaceuticals			83													83
Sertraline	psycopharmaceuticals				92	77	96		89					94	61	86	85
Simvastatin	metabolic disease medications	98			95		98	98								97	97
Sotalol	other cardiovascular medicines	-8	-37	-72	14	-127	-108	44		-15	-136	55	53	49	45	10	-18
Sulfamethoxazole	antibiotics	97	94	11	95	-31	94	98	82	95	98	97	93	97		90	80
Telmisartan	antihypertensives	69	-1049	66	77	62	-88	92	-107	23	-96	96	-28	92	90	79	-38
Temazepam	psycopharmaceuticals				31	22	34	29	-74								8
Testosterone	hormones						91	91						80		80	85
Tetracycline/Doxycycline	antibiotics				90	89						89	83	90			88
Tramadol	NSAIDs and analgesics	-2	42	31	4	-49	-40	-2		11	-14	90	17	3	-2	-16	7
Trimethoprim	antibiotics	28	73	25	27	41	58	9	56	23	62	31	50	21	19	31	37
Valsartan	antihypertensives	80	65		59	10	90	60	79	63	69		99				67
Venlafaxine	psycopharmaceuticals	-7	63	9	19	21	31	20	-91		11		7	23	15	31	12

Annex 8. APIs in WWTP sludge samples

Country			**Estonia**	**Estonia**	**Estonia**	**Estonia**	**Estonia**	**Estonia**	**Finland**	**Finland**	**Finland**
Date (dd-mm-yyyy)			06-12-2017	12-12-2017	06-12-2017	05-06-2018	05-06-2018	07-06-2018	15-12-2017	29-08-2018	06-06-2018
WWTP			Paide	Pärnu	Türi	Türi	Paide	Pärnu	Viikki	Viikki	Kalteva
Sludge type			dewatered	dewatered	dewatered	dewatered	dewatered	dewatered	treated, ready for transport from WWTP	treated, ready for transport from WWTP	treated sludge
Dry matter content		%	18	22	15	59	37	26	29	18	2.5
API	**API group**	**Unit**									
Bisoprolol	other cardiovascular medicines	µg/kg dw	0.62	2.2	0.45	<0.099	<0.099	0.47	8.6	25	38
Caffeine	other	µg/kg dw	75	77	60	5.3	23	160	29	68	150
Carbamazepine	antiepileptics	µg/kg dw	93	89	130	17	180	63	26	46	37
Citalopram	psycopharmaceuticals	µg/kg dw	61	55	45	8.8	30	52	130	510	150
Codeine	NSAIDs and analgesics	µg/kg dw	<3.7	27	23	<3.7	<3.7	<3.7	<3.7	8.4	43
Diclofenac	NSAIDs and analgesics	µg/kg dw	210	120	440	30	2.3	700	61	110	340
Enalapril	antihypertensives	µg/kg dw	<0.39	1.4	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39
Fluconazole	antibiotics	µg/kg dw	0.49	0.31	0.15	0.22	0.21	0.93	0.81	2.1	6.2
Gabapentin	antiepileptics	µg/kg dw	2.3	51	<0.32	<0.32	<0.32	<0.32	<0.32	<0.32	<0.32
Irbesartan	antihypertensives	µg/kg dw	0.21	1.0	0.13	<0.085	<0.085	0.73	1.5	2.7	0.58
Ketoprofen	NSAIDs and analgesics	µg/kg dw	0.95	<0.17	1.2	0.73	<0.17	9.4	2.6	<0.17	2.3
Levetiracetam	antiepileptics	µg/kg dw	11	13	<0.16	<0.16	3.2	<0.16	<0.16	10	31
Lincomycin	antibiotics	µg/kg dw	<0.042	0.24	<0.042	<0.042	<0.042	0.11	<0.042	0.28	0.18
Metformin	metabolic disease medications	µg/kg dw	300	120	170	9.0	8.5	510	55	57	200
Metoprolol	other cardiovascular medicines	µg/kg dw	44	150	67	16	110	190	30	65	42
Naproxen	NSAIDs and analgesics	µg/kg dw	6.0	3.7	17	<1.5	<1.5	16	<1.5	2.6	42
Ofloxacin	antibiotics	µg/kg dw	2.4	3.1	<1.8	8.1	2.8	<1.8	35	89	8600
Olanzapine	psycopharmaceuticals	µg/kg dw	5.0	7.6	<4.4	<4.4	<4.4	7.2	10	26	4.8
Oxazepam	psycopharmaceuticals	µg/kg dw	23	25	4.6	3.1	<0.027	21	21	140	91
Oxycodone	NSAIDs and analgesics	µg/kg dw	<0.26	16	1.4	<0.26	2.3	100	0.89	1.4	1.0
Primidone	antiepileptics	µg/kg dw	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	2.4	4.4
Ramipril	antihypertensives	µg/kg dw	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46
Risperidone	psycopharmaceuticals	µg/kg dw	1.7	3.2	<0.078	3.9	<0.078	6.0	4.6	<0.078	N/A
Sertraline	psycopharmaceuticals	µg/kg dw	120	100	130	29	99	920	280	720	330
Telmisartan	antihypertensives	µg/kg dw	8700	7100	3500	1900	4800	<1.4	450	1000	1100
Temazepam	psycopharmaceuticals	µg/kg dw	21	12	17	3.3	9.2	23	88	310	260
Toltrazuril	veterinary medicines	µg/kg dw	<17	<17	<17	<17	<17	<17	<17	<17	<17
Tramadol	NSAIDs and analgesics	µg/kg dw	38	18	22	7.2	10	<0.047	6.2	23	44
Trimethoprim	antibiotics	µg/kg dw	2.4	41	1.1	<0.16	<0.16	<0.16	14	0.26	<0.16
Tylosin	veterinary medicines	µg/kg dw	<53	<53	<53	<53	<53	<53	<53	<53	<53
Venlafaxine	psycopharmaceuticals	µg/kg dw	4.7	2.7	1.9	1.9	5.5	13	58	53	41
	Number of analysed API		31	31	31	31	31	31	31	31	30
	Number of APIs above LOQ		23	26	20	16	15	19	21	24	24
	Detection rate (%)		74	84	65	52	48	61	68	77	80

Country			**Germany**	**Germany**	**Germany**	**Germany**	**Germany**	**Latvia**	**Latvia**	**Latvia**	**Latvia**
Date (dd-mm-yyyy)			26-06-2018	21-06-2018	09-02-2018	27-11-2018	03-12-2018	21-11-2017	07-12-2017	21-05-2018	12-06-2018
WWTP			Greifswald	Rostock	Greifswald	Rostock	Greifswald	WWTP 1	WWTP 2	WWTP 1	WWTP 2
Sludge type			Dewatered and digested.	Dewatered and digested.	Dewatered and digested.	Dewatered and digested.	Dewatered and digested.	No info	No info	No info	No info
Info			Sample melted during delivery	Sample melted during delivery	Sample melted during delivery	-	-	-	-	-	-
Dry matter content		%	20	26	22	23	20	19	24	19	28
API	**API group**	**Unit**									
Bisoprolol	other cardiovascular medicines	µg/kg dw	70	27	48	123	82	6.8	21	15	5.3
Caffeine	other	µg/kg dw	53	12	16	2.2	0.59	110	31	97	15
Carbamazepine	antiepileptics	µg/kg dw	280	41	240	30	16	55	43	76	58
Citalopram	psycopharmaceuticals	µg/kg dw	140	49	170	340	450	24	34	27	55
Codeine	NSAIDs and analgesics	µg/kg dw	<3.7	<3.7	<3.7	18	<3.7	<3.7	12	<3.7	3.8
Diclofenac	NSAIDs and analgesics	µg/kg dw	250	270	240	630	190	300	150	220	140
Enalapril	antihypertensives	µg/kg dw	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39
Fluconazole	antibiotics	µg/kg dw	1.9	0.48	1.6	0.86	0.30	1.3	1.2	0.84	1.1
Gabapentin	antiepileptics	µg/kg dw	<0.32	0.92	<0.32	<0.32	<0.32	43	36	<0.32	<0.32
Irbesartan	antihypertensives	µg/kg dw	40	36	51	N/A	N/A	4.0	2.7	2.3	0.76
Ketoprofen	NSAIDs and analgesics	µg/kg dw	<0.17	26	4.0	3.5	<0.17	3.4	<0.17	4.0	1.9
Levetiracetam	antiepileptics	µg/kg dw	<0.16	<0.16	<0.16	<0.16	<0.16	<0.16	<0.16	<0.16	<0.16
Lincomycin	antibiotics	µg/kg dw	2.2	<0.042	0.52	0.17	<0.042	0.32	1.7	0.26	1.5
Metformin	metabolic disease medications	µg/kg dw	200	22	26	17	19	366	34	380	27
Metoprolol	other cardiovascular medicines	µg/kg dw	150	200	150	300	360	38	130	44	110
Naproxen	NSAIDs and analgesics	µg/kg dw	5.6	<1.5	<1.5	<1.5	11	5.0	<1.5	4.6	<1.5
Ofloxacin	antibiotics	µg/kg dw	180	32	<1.8	<1.8	38	<1.8	14	9.9	9.5
Olanzapine	psycopharmaceuticals	µg/kg dw	<4.4	<4.4	14	<4.4	<4.4	6.1	4.9	14	9.9
Oxazepam	psycopharmaceuticals	µg/kg dw	21	2.9	3.3	22	13	68	17	26	4.2
Oxycodone	NSAIDs and analgesics	µg/kg dw	0.5	8.4	0.73	32	21	35	5.4	17	1.9
Primidone	antiepileptics	µg/kg dw	<0.39	3.0	2.0	1.1	<0.39	<0.39	<0.39	<0.39	<0.39
Ramipril	antihypertensives	µg/kg dw	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46
Risperidone	psycopharmaceuticals	µg/kg dw	6.6	0.37	3.2	4.6	3.8	0.59	3.4	2.0	1.1
Sertraline	psycopharmaceuticals	µg/kg dw	290	250	510	270	1100	15	71	34	66
Telmisartan	antihypertensives	µg/kg dw	1600	580	<1.4	N/A	N/A	1900	1100	<1.4	<1.4
Temazepam	psycopharmaceuticals	µg/kg dw	6.3	1.9	7.5	62	36	23	11	11	23
Toltrazuril	veterinary medicines	µg/kg dw	<17	<17	<17	<17	<17	<17	<17	<17	<17
Tramadol	NSAIDs and analgesics	µg/kg dw	19	21.9	12	8.2	<0.047	51	11	17	4.9
Trimethoprim	antibiotics	µg/kg dw	<0.16	<0.16	<0.16	<0.16	<0.16	0.59	0.39	<0.16	<0.16
Tylosin	veterinary medicines	µg/kg dw	<53	<53	<53	<53	<53	<53	<53	<53	<53
Venlafaxine	psycopharmaceuticals	µg/kg dw	86	130	54	98	75	9.3	7.8	3.8	5.7
	Number of analysed API		31	31	31	29	29	31	31	31	31
	Number of APIs above LOQ		20	21	20	19	16	23	23	21	21
	Detection rate (%)		65	68	65	66	55	74	74	68	68

Country			**Poland**	**Poland**	**Sweden**	**Sweden**	**Sweden**	**Sweden**	**Sweden**	**Sweden**	**Sweden**	**Sweden**
Date (dd-mm-yyyy)			17-11-2017	18-07-2018	12-2017	12-2017	12-2017	12-2017	06-2018	15-06-2018	15-06-2018	06-2018
WWTP			Błonie	Błonie	Motala	Linköping	Linköping	Norrköping	Motala	Linköping	Linköping	Norrköping
Sludge type			Fermentation tank	Fermentation tank	Dewatered	Dewatered	Dewatered and digested	Dewatered	Dewatered	Dewatered	Dewatered and digested	Dewatered
Info			Melted during delivery	-	-	-	-	-	-	-	-	-
Dry matter content		%	1.6	2.3	25	29	2.6	26	40	24	3.1	24
API	**API group**	**Unit**										
Bisoprolol	other cardiovascular medicines	µg/kg dw	69	53	1.3	0.60	3.6	8.2	4.0	1.2	7.1	8.0
Caffeine	other	µg/kg dw	39	60	22	29	52	5.1	17	8.2	13	8.2
Carbamazepine	antiepileptics	µg/kg dw	600	350	93	44	370	110	52	38	49	130
Citalopram	psycopharmaceuticals	µg/kg dw	63	76	250	31	120	390	400	67	46	350
Codeine	NSAIDs and analgesics	µg/kg dw	4.8	4.0	<3.7	<3.7	<3.7	<3.7	18	<3.7	14	20
Diclofenac	NSAIDs and analgesics	µg/kg dw	860	960	100	74	280	35	110	65	130	150
Enalapril	antihypertensives	µg/kg dw	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	<0.39	0.45
Fluconazole	antibiotics	µg/kg dw	34	24	0.64	<0.016	<0.016	0.27	1.3	<0.016	5.0	1.1
Gabapentin	antiepileptics	µg/kg dw	<0.32	<0.32	<0.32	<0.32	<0.32	25	<0.32	<0.32	<0.32	<0.32
Irbesartan	antihypertensives	µg/kg dw	0.63	0.42	2.0	N/A	8.2	12	13	N/A	18	12
Ketoprofen	NSAIDs and analgesics	µg/kg dw	79	49	<0.17	0.66	16	0.8	<0.17	<0.17	8.7	<0.17
Levetiracetam	antiepileptics	µg/kg dw	<0.16	<0.16	<0.16	8.1	7.7	1.8	<0.16	<0.16	<0.16	<0.16
Lincomycin	antibiotics	µg/kg dw	0.75	0.43	0.28	0.52	0.97	0.36	1.3	0.44	<0.042	0.55
Metformin	metabolic disease medications	µg/kg dw	97	31	71	21	83	20	22	8.6	100	41
Metoprolol	other cardiovascular medicines	µg/kg dw	160	130	270	230	410	380	85	240	300	330
Naproxen	NSAIDs and analgesics	µg/kg dw	12	5.0	7.6	1.6	8.4	2.4	4.3	4.3	6.9	4.8
Ofloxacin	antibiotics	µg/kg dw	45	42	<1.8	<1.8	34	3	<1.8	<1.8	35	18
Olanzapine	psycopharmaceuticals	µg/kg dw	<4.4	176	15	<4.4	5.2	<4.4	15	<4.4	<4.4	10
Oxazepam	psycopharmaceuticals	µg/kg dw	20	7.0	6.4	4.6	24	110	88	7.1	33	110
Oxycodone	NSAIDs and analgesics	µg/kg dw	8.6	5.9	1.3	<0.26	<0.26	<0.26	2.8	<0.26	7.7	1.0
Primidone	antiepileptics	µg/kg dw	1.6	<0.39	<0.39	<0.39	<0.39	<0.39	3.9	5.1	<0.39	4.1
Ramipril	antihypertensives	µg/kg dw	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46	<0.46
Risperidone	psycopharmaceuticals	µg/kg dw	8.4	4.3	<0.078	1.2	4.3	1.9	3.7	1.8	6.7	2.7
Sertraline	psycopharmaceuticals	µg/kg dw	270	370	1200	1400	1400	1200	45	1300	790	1300
Telmisartan	antihypertensives	µg/kg dw	3700	<1.4	30	10	17	52	52	<1.4	5	68
Temazepam	psycopharmaceuticals	µg/kg dw	38	11	4.1	1.8	7.3	<0.77	5.9	1.0	2.9	8.0
Toltrazuril	veterinary medicines	µg/kg dw	<17	31	<17	<17	<17	<17	<17	<17	<17	<17
Tramadol	NSAIDs and analgesics	µg/kg dw	71	54	4.6	3.0	29	25	37	6.9	58	38
Trimethoprim	antibiotics	µg/kg dw	0.35	<0.16	0.17	<0.16	0.34	<0.16	0.76	3.1	0.32	30
Tylosin	veterinary medicines	µg/kg dw	<53	<53	<53	<53	<53	<53	<53	<53	<53	<53
Venlafaxine	psycopharmaceuticals	µg/kg dw	11	26	140	33	47	21	58	17	30	58
	Number of analysed API		31	31	31	30	31	31	31	30	31	31
	Number of APIs above LOQ		24	23	20	18	22	21	23	17	22	25
	Detection rate (%)		77	74	65	60	71	68	74	57	71	81

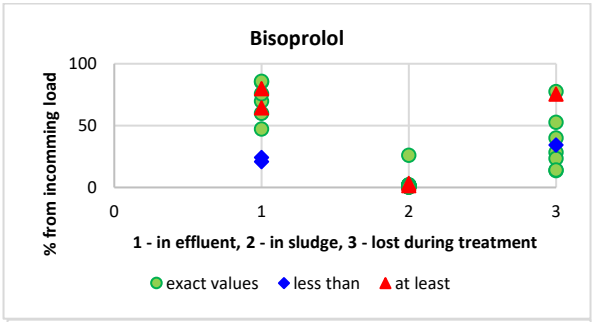
Annex 9. Partitioning of APIs at WWTPs.

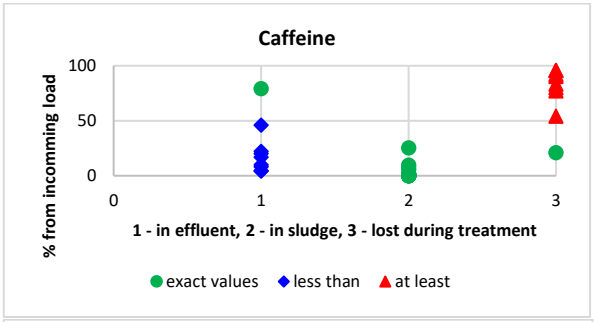
Symbology in graphs:

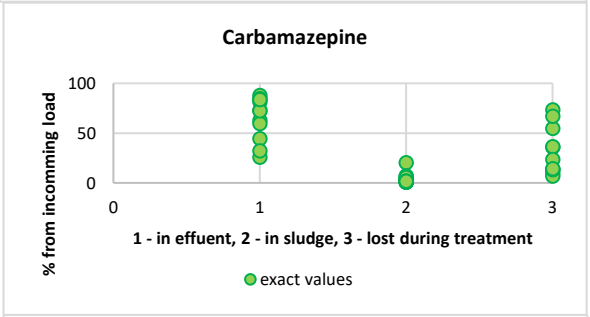
▲ = At least – the amount (%) partitioning in effluent or sludge, or transformed during the treatment is likely more than the point in the graph. For example, if the concentration in influent was above LOQ, but effluent < LOQ, the amount of API transformed during the treatment process could more than the calculated value (i.e. influent concentration minus effluent LOQ);

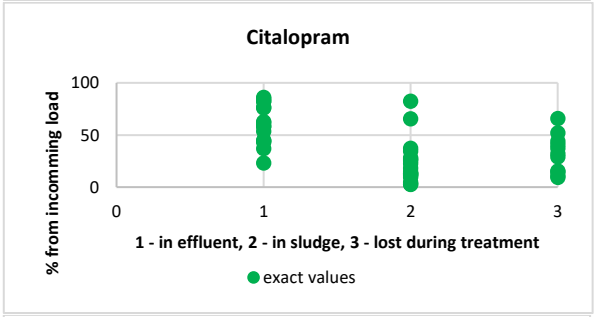
◆ = Less than – the amount (%) partitioning in effluent or sludge, or transformed during the treatment is likely less than the point in the graph. For example, if the concentration in influent was < LOQ, but the concentration in effluent > LOQ, the amount of API transformed during the treatment process could less than the calculated value (i.e. influent LOQ minus effluent concentration);

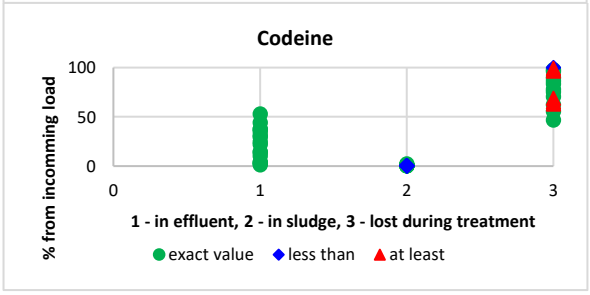
● = Exact value – calculation based on of detected concentrations.

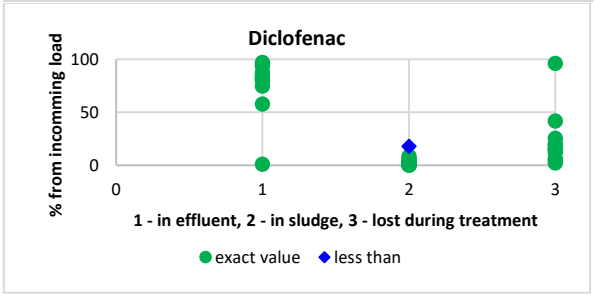


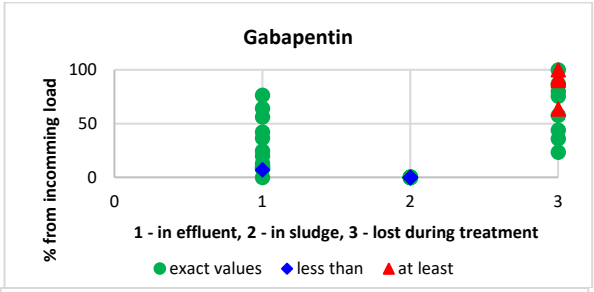


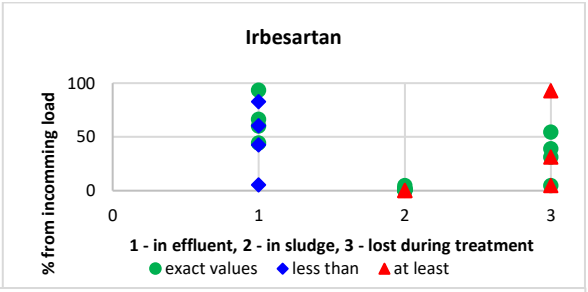


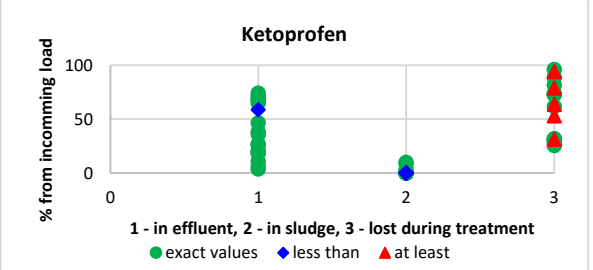


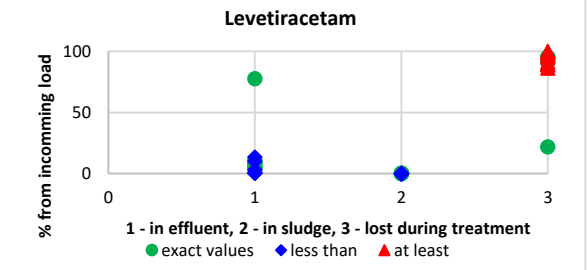


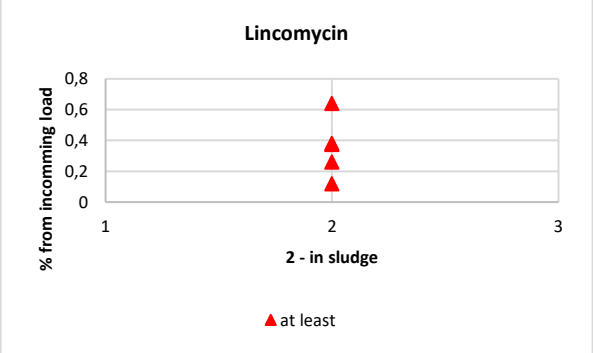


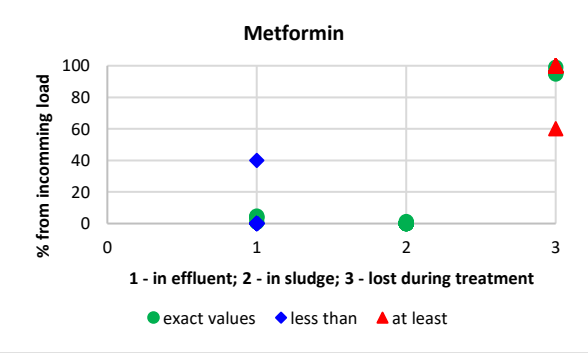

Gabapentin
% from incomming load
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

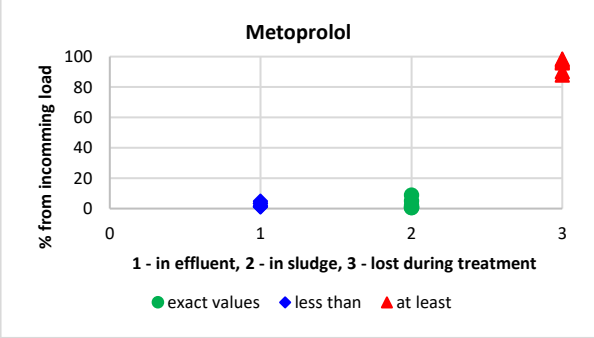

Irbesartan
% from incomming load
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

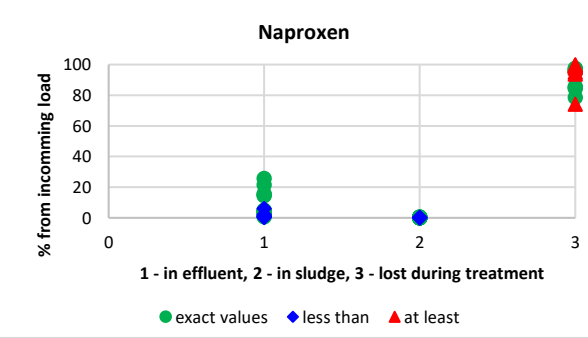

Ketoprofen
% from incomming load
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

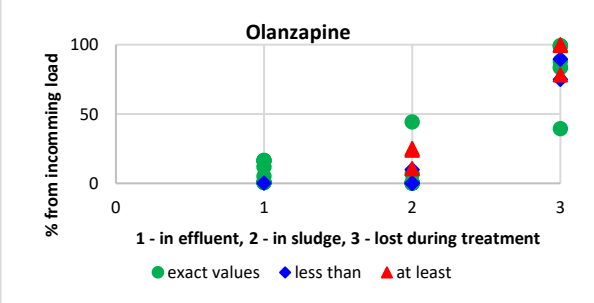

Levetiracetam
% from incomming load
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

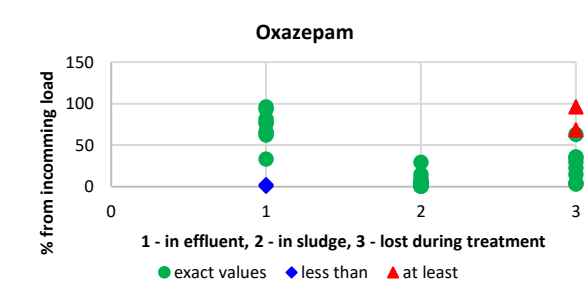

Lincomycin
% from incomming load
0,8
0,6
0,4
0,2
0
1
2
3
2 - in sludge
at least

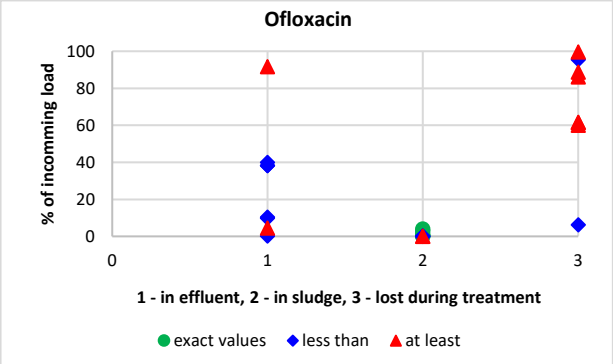

Metformin
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent; 2 - in sludge; 3 - lost during treatment
exact values
less than
at least

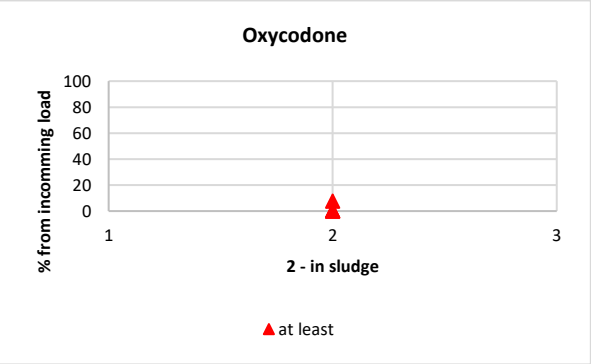

Metoprolol
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

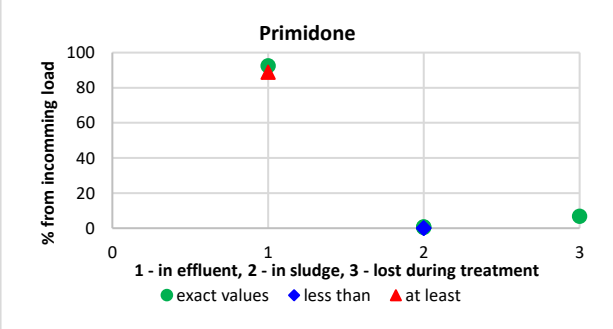

Naproxen
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

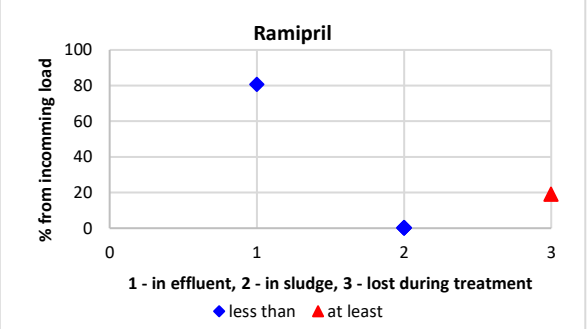

Olanzapine
% from incomming load
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

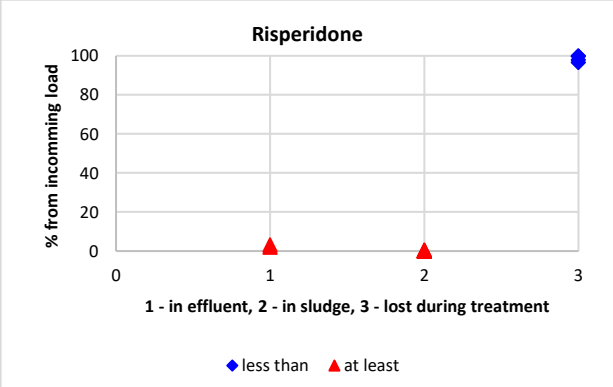

Oxazepam
% from incomming load
150
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

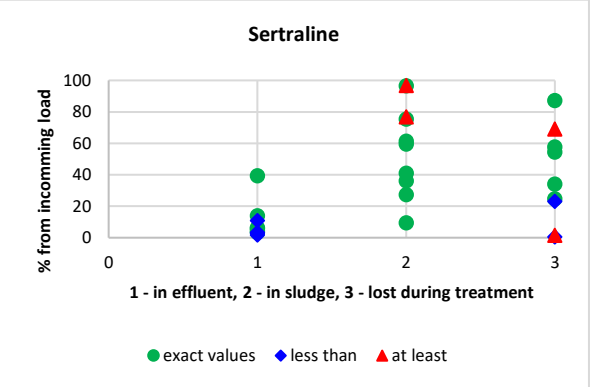

Ofloxacin
% of incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

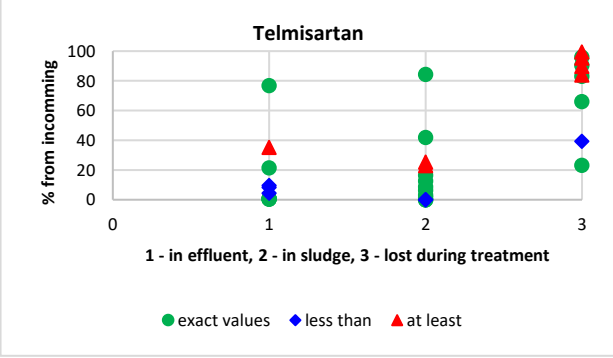

Oxycodone
% from incomming load
100
80
60
40
20
0
1
2
3
2 - in sludge
at least

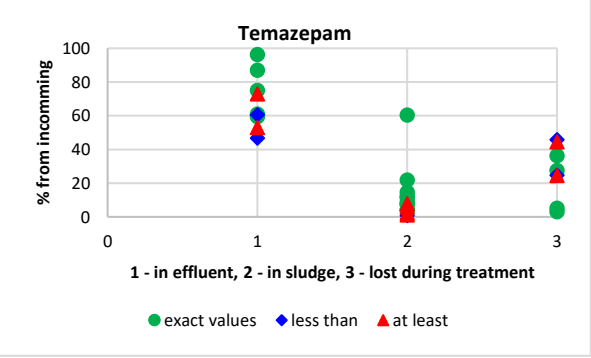

Primidone
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least

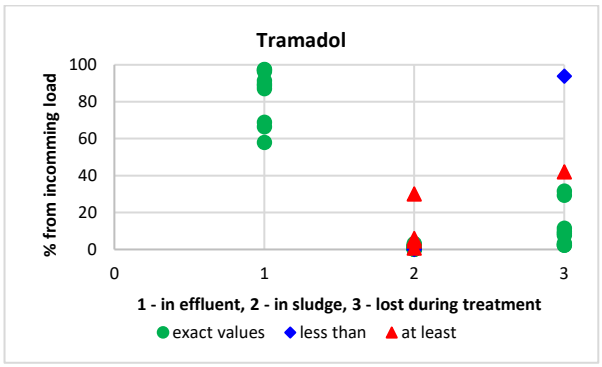

Ramipril
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
less than
at least

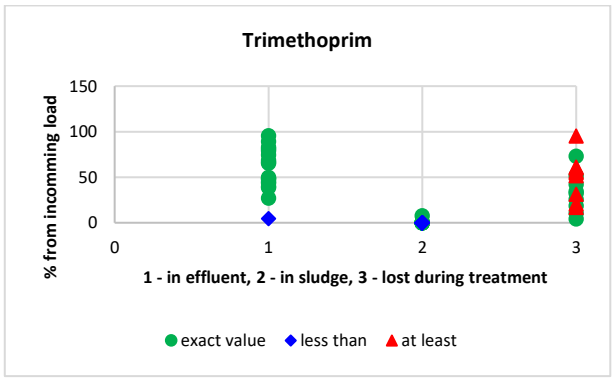

Risperidone
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
less than
at least

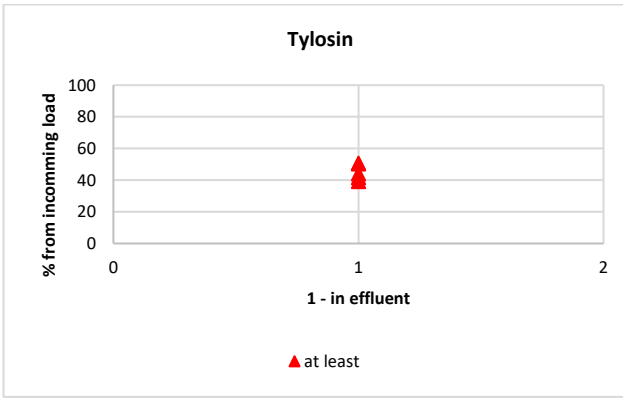

Sertraline
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least


Telmisartan
% from incomming
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least


Temazepam
% from incomming
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least


Tramadol
% from incomming load
100
80
60
40
20
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact values
less than
at least


Trimethoprim
% from incomming load
150
100
50
0
0
1
2
3
1 - in effluent, 2 - in sludge, 3 - lost during treatment
exact value
less than
at least


Tylosin
% from incomming load
100
80
60
40
20
0
0
1
2
1 - in effluent
at least

Annex 10. API concentrations at landfill WWTP

Country			Finland	Finland	Finland	Finland	Finland	Finland
Year			2018	2018	2018	2018	2018	2018
Month			3	6	11	3	6	11
Date			6	6	21	6	6	21
Comments			grab sample	grab sample	grab sample	24-h	24-h	24-h

API	API group	Unit	Influent			Effluent		
Allopurinol	metabolic disease medications	ng/L	<14000	<14000	<14000	<120	<120	<120
Amlodipine	antihypertensives	ng/L	<400	<400	<400	<110	<110	<110
Atenolol	other cardiovascular medicines	ng/L	<210	<210	<210	<110	<110	<110
Atorvastatin	metabolic disease medications	ng/L	<10000	<10000	<10000	<10000	<10000	<10000
Bezafibrate	metabolic disease medications	ng/L	<27	<27	<27	<13	<13	<13
Bisoprolol	other cardiovascular medicines	ng/L	<30	<30	<30	<15	<15	31
Caffeine	other	ng/L	21	N/A	<17	<870	8800	<870
Candesartan	antihypertensives	ng/L	<770	<770	<770	<11	<11	<11
Carbamazepine	antiepileptics	ng/L	250	230	43	200	215	65
Carprofen	veterinary medicines	ng/L	<14	<14	<14	<7.1	<7.1	93
Cetirizine	asthma and allergy medications	ng/L	<3200	<3200	<3200	<1200	<1200	<1200
Ciprofloxacin	antibiotics	ng/L	<3100	<3100	<3100	<1600	<1600	<1600
Citalopram	psycopharmaceuticals	ng/L	<2.2	9.1	5.9	2.0	3.6	<1.1
Clarithromycin	antibiotics	ng/L	<31	<31	<31	<16	<16	<16
Codeine	NSAIDs and analgesics	ng/L	<42	<42	<42	<11	<11	<11
Diclofenac	NSAIDs and analgesics	ng/L	140	252	300	415	230	167
Dipyridamole	other cardiovascular medicines	ng/L	571	<185	<185	<87	<87	<87
Emamectin	veterinary medicines	ng/L	<29	<29	<29	<11	17	<11
Enalapril	antihypertensives	ng/L	<167	<167	<167	<83	<83	<83
Eprosartan	antihypertensives	ng/L	20	30	<10	<5.2	<5.2	<5.2
Erythromycin	antibiotics	ng/L	2493	<39	<39	1833	1598	<8.5
Esomeprazole	gastrointestinal disease medications	ng/L	<8400	<8400	<8400	<8400	<8400	N/A
Estriol (E3)	hormones	ng/L	84	<12	<12	<8400	<8400	<8400
Estrone (E1)	hormones	ng/L	57	<26	<26	<13	<13	653
Fenbendazole	veterinary medicines	ng/L	<36	<36	<36	<11	<11	<11
Fexofenadine	asthma and allergy medications	ng/L	<4300	<4300	<4300	<1600	<1600	<1600
Florfenicol	veterinary medicines	ng/L	<64	<64	<64	<32	<32	<32
Fluconazole	antibiotics	ng/L	40	77	49	22	29	27
Fluticasone	asthma and allergy medications	ng/L	<415	<415	<415	<150	<150	<150
Gabapentin	antiepileptics	ng/L	1860	6960	1253	N/A	N/A	<910
Gemfibrozil	metabolic disease medications	ng/L	302	353	<165	<100	<100	<100
Hydrochlorothiazide	antihypertensives	ng/L	23000	79000	<7.5	4400	3300	<100
Ibuprofen	NSAIDs and analgesics	ng/L	N/A	N/A	N/A	N/A	N/A	N/A
Irbesartan	antihypertensives	ng/L	<53	<53	<53	<70	<70	<70
Ketoprofen	NSAIDs and analgesics	ng/L	1700	1400	540	13	<11	<11
Levetiracetam	antiepileptics	ng/L	970	760	480	<110	<110	<110
Lincomycin	antibiotics	ng/L	<18	<18	<18	13	<9.8	<9.8
Losartan	antihypertensives	ng/L	<510	<510	<510	<250	<250	<250
Mesalazine	gastrointestinal disease medications	ng/L	<280	3300	680	950	920	<63

API	API group	Unit	Influent			Effluent		
Metformin	metabolic disease medications	ng/L	930	2600	<250	<7.5	<7.5	<7.5
Metoprolol	other cardiovascular medicines	ng/L	29	<14	17	43	<29	<29
Mometasone furoate	asthma and allergy medications	ng/L	<830	<830	<830	<27	<27	<27
Naproxen	NSAIDs and analgesics	ng/L	83	230	150	<5.4	<5.4	16
Nebivolol	other cardiovascular medicines	ng/L	1400	<970	<970	<16	<16	<16
Norethisterone	hormones	ng/L	<24	<24	<24	<9.5	<9.5	<9.5
Norfloxacin	antibiotics	ng/L	<12000	<12000	<12000	<12000	<12000	<12000
Ofloxacin	antibiotics	ng/L	<420	<420	<420	<210	<210	<210
Olanzapine	psycopharmaceuticals	ng/L	<5.9	2100	<5.9	13	15	<0.96
Oxazepam	psycopharmaceuticals	ng/L	<23	<23	<23	4.3	<11	<11
Oxycodone	NSAIDs and analgesics	ng/L	<260	<260	<260	<115	<115	<115
Pantoprazole	gastrointestinal disease medications	ng/L	<760	<760	<760	<760	<760	N/A
Paracetamol	NSAIDs and analgesics	ng/L	<77	74000	<77	<77	<77	<77
Primidone	antiepileptics	ng/L	66	81	<35	69	73	19
Progesterone	hormones	ng/L	<31	<31	<31	<12	<12	<12
Quetiapine	psycopharmaceuticals	ng/L	<470	<470	<470	<120	<120	<120
Ramipril	antihypertensives	ng/L	<32	<32	<32	<16	<16	<16
Risperidone	psycopharmaceuticals	ng/L	<800	<800	<800	<10	<10	<10
Sertraline	psycopharmaceuticals	ng/L	<20	<20	<20	<10	<10	<10
Simvastatin	metabolic disease medications	ng/L	<1.4	<1.4	<1.6	<1.5	<1.5	<1.5
Sotalol	other cardiovascular medicines	ng/L	<15	<15	<15	<7.7	<7.7	<7.7
Sulfadiazine	antibiotics	ng/L	<590	<590	<590	<295	<295	<295
Sulfamethoxazole	antibiotics	ng/L	<42	<42	<42	<8.9	<8.9	<8.9
Telmisartan	antihypertensives	ng/L	<49	77	<49	<11	<11	<11
Temazepam	psycopharmaceuticals	ng/L	<17	<17	<17	<8.3	<8.3	<8.3
Testosterone	hormones	ng/L	<81	<81	<81	<18	<18	<18
Tetracycline/Doxycycline	antibiotics	ng/L	<240	<240	<240	<120	<120	<120
Tiamulin	veterinary medicines	ng/L	<38	<38	<38	<19	<19	<19
Toltrazuril	veterinary medicines	ng/L	<9000	<9000	<9000	<9000	<9000	<9000
Tramadol	NSAIDs and analgesics	ng/L	<77	84	<77	71	64	<38
Trimethoprim	antibiotics	ng/L	<22	<22	<22	<11	<11	<11
Tylosin	veterinary medicines	ng/L	<320	<320	<320	<100	<100	<100
Valsartan	antihypertensives	ng/L	<300	<300	<300	<150	<150	<150
Warfarin	other cardiovascular medicines	ng/L	23	<13	<13	<6.3	<6.3	<6.3
Venlafaxine	psycopharmaceuticals	ng/L	<20	<20	<20	<10	6.5	<10
Xylometazoline	asthma and allergy medications	ng/L	<51	<51	<51	<26	<26	<26
	Number of analysed APIs		74	73	74	73	73	72
	Number of APIs above LOQ		20	18	10	14	13	8
	Detection rate (%)		27	25	14	19	18	11

Annex 11. Concentration of APIs in wastewater effluents of hospitals

Country			Estonia	Estonia	Germany	Germany	Sweden	Sweden
Date (day/month/year)			12-12-2017	7-6-2018	19-2-2018	1-6-2018	15-6-2018	8-6-2018
API	**API group**	**Unit**	**Pärnu hospital**	**Pärnu hospital**	**Wismar hospital**	**Wismar hospital**	**Linköping hospital**	**Norrköping hospital**
Allopurinol	metabolic disease medications	µg/l	22	<14	<14	18	<14	<14
Amlodipine	antihypertensives	µg/l	<0,40	0,41	<0,40	<0,40	<0,40	<0,40
Atenolol	other cardiovascular medicines	µg/l	<0,21	<0,21	<0,21	<0,21	0,22	0,25
Atorvastatin	metabolic disease medications	µg/l	<10	<10	<10	<10	<10	<10
Bezafibrate	metabolic disease medications	µg/l	<0,027	<0,027	0,071	0,163	N/A	N/A
Bisoprolol	other cardiovascular medicines	µg/l	0,038	0,052	0,82	0,064	0,078	0,146
Caffeine	other	µg/l	0,97	27	N/A	11	12	29
Candesartan	antihypertensives	µg/l	<0,77	<0,77	<0,77	<0,77	<0,77	<0,77
Carbamazepine	antiepileptics	µg/l	0,038	0,31	0,25	0,067	2,3	0,61
Carprofen	veterinary medicines	µg/l	<0,014	<0,014	0,026	0,042	<0,014	<0,014
Cetirizine	asthma and allergy medications	µg/l	<3,2	<3,2	<3,2	<3,2	<3,2	<3,2
Ciprofloxacin	antibiotics	µg/l	<3,1	14	<3,1	<3,1	<3,1	<3,1
Citalopram+escitalopram (SUM)	psycopharmaceuticals	µg/l	0,24	0,16	0,72	0,18	<0,0022	<0,0022
Clarithromycin	antibiotics	µg/l	3,5	0,21	0,34	0,31	<0,031	<0,031
Codeine	NSAIDs and analgesics	µg/l	N/A	14	0,16	<0,042	0,79	2,4
Diclofenac	NSAIDs and analgesics	µg/l	9,6	3,2	0,63	0,25	0,71	1,7
Dipyridamole	other cardiovascular medicines	µg/l	<0,19	0,52	<0,19	0,53	<0,19	<0,19
Emamectin	veterinary medicines	µg/l	<0,029	<0,029	<0,029	<0,029	<0,029	<0,029
Enalapril	antihypertensives	µg/l	<0,17	<0,17	<0,17	<0,17	<0,17	<0,17
Eprosartan	antihypertensives	µg/l	<0,010	<0,010	0,17	<0,010	<0,010	<0,010
Erythromycin	antibiotics	µg/l	<0,039	7,4	0,51	5,3	1,4	5,4
Esomeprazole	gastrointestinal disease medications	µg/l	<8,4	<8,4	<8,4	<8,4	<8,4	<8,4
Estriol	hormones	µg/l	<0,012	0,055	<0,012	0,029	0,248	0,266
Estrone (E1)	hormones	µg/l	0,054	0,088	0,081	<0,026	<0,026	9,1
Fenbendazole	veterinary medicines	µg/l	<0,036	<0,036	<0,036	<0,036	<0,036	<0,036
Fexofenadien	asthma and allergy medications	µg/l	<4,3	<4,3	<4,3	<4,3	<4,3	<4,3
Florfenicol	veterinary medicines	µg/l	<0,064	<0,064	<0,064	<0,064	N/A	N/A
Fluconazole	antibiotics	µg/l	3,2	1,8	<0,02	<0,02	N/A	N/A
Fluticasone	asthma and allergy medications	µg/l	<0,42	<0,42	<0,42	<0,42	<0,42	<0,42
Gabapentin	antiepileptics	µg/l	103	44	2,1	<0,91	N/A	N/A
Gemfibrozil	metabolic disease medications	µg/l	<0,17	1,3	<0,17	<0,17	<0,17	<0,17
Hydrochlorothiazide	antihypertensives	µg/l	2,8	16	8,3	13	1,9	2,6
Ibuprofen	NSAIDs and analgesics	µg/l	2,8	N/A	N/A	N/A	N/A	N/A
Irbesartan	antihypertensives	µg/l	<0,053	<0,053	<0,053	<0,053	<0,053	<0,053
Ketoprofen	NSAIDs and analgesics	µg/l	4,4	4,5	<0,018	<0,018	N/A	N/A
Levetiracetam	antiepileptics	µg/l	0,85	<0,22	22	<0,22	N/A	N/A
Lincomycin	antibiotics	µg/l	0,065	0,13	<0,018	<0,018	N/A	N/A
Losartan	antihypertensives	µg/l	<0,51	<0,51	0,94	<0,51	1,4	1,6
Mesalazine	gastrointestinal disease medications	µg/l	6,1	14	11	13	0,66	2,5
Metformin	metabolic disease medications	µg/l	124	167	314	3,8	62	158
Metoprolol	other cardiovascular medicines	µg/l	2,0	2,7	<0,014	0,73	N/A	N/A
Mometasone furoate	asthma and allergy medications	µg/l	<0,83	<0,83	<0,83	<0,83	<0,83	<0,83
Naproxen	NSAIDs and analgesics	µg/l	6,3	54	1,0	<0,011	N/A	N/A
Nebivolol	other cardiovascular medicines	µg/l	<0,97	1,4	<0,97	1,5	<0,97	<0,97
Norethisterone	hormones	µg/l	<0,024	0,10	0,41	0,055	<0,024	<0,024
Norfloxacin	antibiotics	µg/l	13	<12	<12	<12	N/A	N/A
Ofloxacin	antibiotics	µg/l	<0,42	<0,42	1,2	1,8	N/A	N/A

Country			Estonia	Estonia	Germany	Germany	Sweden	Sweden
Date (day/month/year)			12-12-2017	7-6-2018	19-2-2018	1-6-2018	15-6-2018	8-6-2018
API	**API group**	**Unit**	**Pärnu hospital**	**Pärnu hospital**	**Wismar hospital**	**Wismar hospital**	**Linköping hospital**	**Norrköping hospital**
Olanzepine	psycopharmaceuticals	µg/l	<0,0059	1,8	2,0	<0,0059	0,012	0,014
Oxazepam	psycopharmaceuticals	µg/l	N/A	0,24	0,053	<0,023	0,81	3,7
Oxycodone	NSAIDs and analgesics	µg/l	N/A	<0,263	0,58	0,40	0,34	0,56
Pantoprazole	gastrointestinal disease medications	µg/l	<0,76	<0,76	<0,76	<0,76	<0,76	<0,76
Paracetamol	NSAIDs and analgesics	µg/l	908	<0,077	601	<0,077	6,8	4,6
Primidone	antiepileptics	µg/l	<0,035	<0,035	<0,035	<0,035	N/A	N/A
Progesterone	hormones	µg/l	<0,031	<0,031	<0,031	<0,031	<0,031	<0,031
Quetiapine	psycopharmaceuticals	µg/l	<0,47	3,3	<0,47	<0,47	<0,47	<0,47
Ramipril	antihypertensives	µg/l	0,049	0,069	0,11	0,037	N/A	N/A
Risperidone	psycopharmaceuticals	µg/l	<0,80	<0,80	<0,80	<0,80	<0,80	<0,80
Sertraline	psycopharmaceuticals	µg/l	0,10	0,11	0,52	0,13	N/A	N/A
Simvastatin	metabolic disease medications	µg/l	<0,0014	<0,0014	0,0086	0,028	<0,0014	<0,0014
Sotalol	other cardiovascular medicines	µg/l	0,12	0,87	<0,015	<0,015	<0,015	<0,015
Sulfadiazine	antibiotics	µg/l	<0,59	<0,59	<0,59	<0,59	<0,59	<0,59
Sulfamethoxazole	antibiotics	µg/l	2,3	11	0,31	2,5	N/A	N/A
Telmisartan	antihypertensives	µg/l	0,32	7,8	2,8	<0,049	0,30	<0,049
Temazepam	psycopharmaceuticals	µg/l	N/A	0,17	<0,017	<0,017	<0,017	0,14
Testosterone	hormones	µg/l	<0,081	0,16	<0,081	<0,081	<0,081	<0,081
Tetracycline+doxycycline (SUM)	antibiotics	µg/l	0,35	<0,24	<0,24	<0,24	0,84	0,28
Tiamulin	veterinary medicines	µg/l	<0,038	<0,038	<0,038	<0,038	<0,038	<0,038
Toltrazuril	veterinary medicines	µg/l	<9,0	<9,0	<9,0	<9,0	<9,0	<9,0
Tramadol	NSAIDs and analgesics	µg/l	<0,077	3,6	<0,077	<0,077	0,35	1,0
Trimethoprim	antibiotics	µg/l	2,7	11	0,49	2,4	N/A	N/A
Tylosin	veterinary medicines	µg/l	<0,32	<0,32	<0,32	<0,32	<0,32	<0,32
Valsartan	antihypertensives	µg/l	<0,30	<0,30	2,1	0,62	<0,30	0,78
Warfarin	other cardiovascular medicines	µg/l	0,018	0,034	<0,013	<0,013	<0,013	0,021
Venlafaxine	psycopharmaceuticals	µg/l	0,48	0,33	0,37	0,077	N/A	N/A
Xylometazoline	asthma and allergy medications	µg/l	<0,051	<0,051	0,41	<0,051	<0,051	<0,051
	Number of analysed API		71	74	73	74	57	57
	Number of APIs above LOQ		30	39	33	28	19	22
	Detection rate (%)		42	53	45	38	33	39
	Sum concentration (µg/l)		915	40	610	6	9	11

Annex 12. API load from hospitals and comparison with total load to WWTPs

The tables show the load of APIs (g/day) in hospital effluents and in the connected wastewater treatment plant, and the % of APIs from hospital effluents compared to total load of APIs in WWTP influents. APIs below LOQ in both hospital effluents and WWTP influents are excluded. * indicates that it was not possible to calculate the % of APIs from hospitals because the API was below LOQ in either hospital effluents or WWTP influents.

		February 2018			June 2018		
API	Group of API	Wismar hospital (g/day)	Wismar WWTP infl. (g/day)	% from Wismar hospital	Wismar hospital (g/day)	Wismar WWTP infl. (g/day)	% from Wismar hospital
Clarithromycin	antibiotics	0,029	2,9	0,97	0,023	0,64	3,6
Erythromycin		0,043	13	0,34	0,40	139	0,28
Ofloxacin		0,099	9,8	1,0	0,14	<LOQ	*
Sulfamethoxazole		0,026	1,6	1,7	0,19	7,3	2,6
Trimethoprim		0,041	1,8	2,3	0,18	7,8	2,3
Carbamazepine	antiepileptics	0,022	11	0,20	0,0050	14	0,036
Gabapentin		0,17	458	0,038	<LOQ	<LOQ	<LOQ
Levetiracetam		1,8	164	1,1	<LOQ	<LOQ	<LOQ
Eprosartan	antihyper-tensives	0,014	7,2	0,20	<LOQ	<LOQ	<LOQ
Hydrochlorothiazide		0,70	69	1,0	0,96	68	1,4
Losartan		0,080	<LOQ	*	<LOQ	<LOQ	<LOQ
Ramipril		0,0092	1,2	0,75	0,0028	1,1	0,26
Telmisartan		0,24	28	0,84	<LOQ	<LOQ	<LOQ
Valsartan		0,18	102	0,18	0,047	80	0,06
Xylometazoline	asthma and allergy med.	0,035	<LOQ	*	<LOQ	<LOQ	<LOQ
Caffeine	caffeine	<LOQ	<LOQ	<LOQ	0,83	164	0,51
Estriol	hormones	<LOQ	<LOQ	<LOQ	0,0022	0,78	0,28
Estrone (E1)		0,0069	0,80	0,86	<LOQ	<LOQ	<LOQ
Norethisterone		0,035	5,8	0,60	0,0042	0,95	0,44
Mesalazine	gastrointestinal disease medications	0,93	64	1,4	0,95	159	0,60
Allopurinol	metabolic disease med.	<LOQ	<LOQ	<LOQ	1,3	<LOQ	*
Bezafibrate		0,0060	14	0,042	0,012	8,1	0,15
Metformin		27	4756	0,56	0,28	1876	0,015
Simvastatin		0,00073	0,60	0,12	0,0021	0,62	0,34
Codeine	NSAIDs and analgesics	0,013	6,6	0,20	<LOQ	<LOQ	<LOQ
Diclofenac		0,054	64	0,084	0,019	63	0,029
Naproxen		0,086	16	0,53	<LOQ	<LOQ	<LOQ
Oxycodone		0,049	<LOQ	*	0,030	<LOQ	*
Paracetamol		51	6097	0,83	<LOQ	<LOQ	<LOQ
Bisoprolol	other cardiovascular med.	0,070	11	0,64	0,0048	13	0,038
Dipyridamole		<LOQ	<LOQ	<LOQ	0,040	11	0,36
Metoprolol		<LOQ	<LOQ	<LOQ	0,055	41	0,13
Nebivolol		<LOQ	<LOQ	<LOQ	0,11	15	0,74
Citalopram+escitalopram (SUM)	psyco-pharmaceuticals	0,061	4,6	1,3	0,013	4,9	0,27
Olanzepine		0,17	21	0,84	<LOQ	<LOQ	<LOQ
Oxazepam		0,0045	0,38	1,2	<LOQ	<LOQ	<LOQ
Sertraline		0,044	3,5	1,3	0,010	1,3	0,77
Venlafaxine		0,031	7,5	0,41	0,0058	7,9	0,07
Carprofen	veterinary medicines	0,0022	<LOQ	*	0,0031	0,52	0,60
		Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital	Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital
		82	11 941	0,69	6	2 686	0,21
		Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital	Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital
		84,6	9 902	0,85	75,2	10 297	0,73

		December 2017			June 2018		
API	**Group of API**	**Pärnu hospital (g/day)**	**Pärnu WWTP infl. (g/day)**	**% from Pärnu hospital**	**Pärnu hospital (g/day)**	**Pärnu WWTP infl. (g/day)**	**% from Pärnu hospital**
Ciprofloxacin	antibiotics	<LOQ	<LOQ	<LOQ	1,1	<LOQ	*
Clarithromycin		0,29	22	1,3	0,017	3,6	0,47
Erythromycin		<LOQ	<LOQ	<LOQ	0,61	16	3,9
Fluconazole		0,27	1,9	14	0,15	0,62	24
Lincomycin		0,0054	<LOQ	*	0,011	<LOQ	*
Norfloxacin		1,1	528	0,21	<LOQ	<LOQ	<LOQ
Sulfamethoxazole		0,19	4,0	4,8	0,89	4,2	21
Tetracycline+doxycycline (SUM)		0,029	16	0,18	<LOQ	<LOQ	<LOQ
Trimethoprim		0,22	4,1	5,4	0,90	2,6	35
Carbamazepine	antiepileptics	0,0032	<LOQ	*	0,025	15	0,17
Gabapentin		8,6	108	8,0	3,7	93	4,0
Levetiracetam		0,07	29	0,24	<LOQ	<LOQ	<LOQ
Amlodipine	antihyper-tensives	<LOQ	<LOQ	<LOQ	0,034	<LOQ	*
Hydrochlorothiazide		0,23	90	0,26	1,3	128	1,1
Ramipril		0,0041	<LOQ	*	0,0058	<LOQ	*
Telmisartan		0,026	<LOQ	*	0,65	2,0	32
Caffeine	caffeine	0,080	10,0	0,81	2,2	42	5,3
Estriol	hormones	<LOQ	<LOQ	<LOQ	0,0046	0,87	0,53
Estrone (E1)		0,0045	12	0,039	0,0073	13	0,055
Norethisterone		<LOQ	<LOQ	<LOQ	0,0085	1,0	0,86
Testosterone		<LOQ	<LOQ	<LOQ	0,013	<LOQ	*
Mesalazine	gastrointestinal disease med.	0,51	172	0,29	1,2	<LOQ	*
Allopurinol	metabolic disease med.	1,8	<LOQ	*	<LOQ	<LOQ	<LOQ
Gemfibrozil		<LOQ	<LOQ	<LOQ	0,11	<LOQ	*
Metformin		10	658	1,6	14	1002	1,4
Codeine	NSAIDs and analgesics	<LOQ	<LOQ	<LOQ	1,2	17	7,1
Diclofenac		0,80	174	0,46	0,27	30	0,90
Naproxen		0,52	53	1,0	4,5	76	5,9
Ibuprofen		0,23	92	0,25	<LOQ	<LOQ	<LOQ
Ketoprofen		0,36	8,1	4,5	0,37	12	3,1
Paracetamol		75	5745	1,3	<LOQ	<LOQ	<LOQ
Tramadol		<LOQ	<LOQ	<LOQ	0,30	4,4	6,8
Bisoprolol	other cardiovascular med.	0,0031	<LOQ	*	0,0043	0,62	0,70
Dipyridamole		<LOQ	<LOQ	<LOQ	0,043	19	0,22
Metoprolol		0,17	22	0,74	0,22	20	1,1
Nebivolol		<LOQ	<LOQ	<LOQ	0,12	17	0,72
Sotalol		0,010	4,9	0,21	0,072	2,3	3,1
Warfarin		0,0015	<LOQ	*	0,0029	0,15	1,9
citalopram+escitalopram (SUM)	psyco-pharmaceuticals	0,20	1,1	18	0,013	1,0	1,3
Olanzepine		<LOQ	<LOQ	<LOQ	0,15	<LOQ	*
Oxazepam		<LOQ	<LOQ	<LOQ	0,020	0,78	2,5
Quetiapine		<LOQ	<LOQ	<LOQ	0,27	<LOQ	*
Sertraline		0,0087	<LOQ	*	0,0091	0,53	1,7
Temazepam		<LOQ	<LOQ	<LOQ	0,014	0,32	4,3
Venlafaxine		0,040	1,7	2,4	0,027	3,7	0,74
		Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital	Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital
		101	7 754	1,3	34	1 529	2,3
		Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital	Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital
		83	39 375	0,21	83	10 759	0,77

Annex 13. APIs in wastewater effluents of a pharmaceutical manufacturer

		June 2018			June 2018		
API	**Group of API**	**Linköping hospital (g/day)**	**Linköping WWTP infl. (g/day)**	**% from Linköping hospital**	**Norrköping hospital (g/day)**	**Norrköping WWTP infl. (g/day)**	**% from Norrköping hospital**
Erythromycin	antibiotics	0,80	32	2,5	1,1	60	1,8
Tetracycline+doxycycline (SUM)		0,49	19	2,6	0,054	11	0,47
Hydrochlorothiazide	antihyper-tensives	1,1	45	2,4	0,50	48	1,1
Losartan		0,82	91	0,90	0,31	97	0,32
Telmisartan		0,17	<LOQ	*	<LOQ	<LOQ	<LOQ
Valsartan		<LOQ	<LOQ	<LOQ	0,15	18	0,84
Carbamazepine	antiepileptics	1,3	13	10	0,12	15	0,79
Caffeine	caffeine	6,6	67	9,9	5,7	144	3,9
Mesalazine	gastrointestinal disease med.	0,38	<LOQ	*	0,48	<LOQ	*
Estriol	hormones	0,14	6,0	2,4	0,052	<LOQ	*
Estrone (E1)		<LOQ	<LOQ	<LOQ	1,8	456	0,39
Atenolol	metabolic disease	0,13	<LOQ	*	0,050	10	0,50
Metformin	med.	36	981	3,7	31	2497	1,2
Codeine	NSAIDs and	0,45	27	1,7	0,47	30	1,6
Diclofenac	analgesics	0,41	70	0,59	0,33	105	0,32
Oxycodone		0,20	<LOQ	*	0,11	<LOQ	*
Paracetamol		3,9	281	1,4	0,90	264	0,34
Tramadol		0,20	21	0,95	0,20	33	0,61
Bisoprolol	other	0,045	2,5	1,8	0,028	2,8	1,0
Warfarin	cardiovascular	<LOQ	<LOQ	<LOQ	0,0042	<LOQ	<LOQ
Olanzepine	psyco-	0,0068	0,40	1,7	0,0027	0,94	0,28
Oxazepam	pharmaceuticals	0,47	8,8	5,3	0,72	17	4,2
Temazepam		<LOQ	<LOQ	<LOQ	0,028	<LOQ	*
		Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital	Sum of APIs (g/day)	Sum of APIs (g/day)	% APIs from hospital
		54	1 665	3,2	44	3 809	1,1
		Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital	Hospital effluent (m3/day)	Influent WWTP (m3/day)	% water flow from hospital
		577	40 043	1,4	195	38 650	0,50

Country			**Latvia**	**Latvia**
Date (day/month/year)			7.12.2017	28.5.2018
API	API group	Unit		
Allopurinol	metabolic disease medications	µg/L	<0.12	4.8
Amlodipine	antihypertensives	µg/L	<0.11	N/A
Atenolol	other cardiovascular medicines	µg/L	<0.11	<0.11
Atorvastatin	metabolic disease medications	µg/L	<10.4	<10.4
Bezafibrate	metabolic disease medications	µg/L	<0.013	N/A
Bisoprolol	other cardiovascular medicines	µg/L	<0.015	<0.015
Caffeine	other	µg/L	<0.87	8.8
Candesartan	antihypertensives	µg/L	<0.011	<0.011
Carbamazepine	antiepileptics	µg/L	<0.008	<0.008
Carprofen	veterinary medicines	µg/L	<0.007	<0.007
Cetirizine	asthma and allergy medications	µg/L	<1.2	<1.2
Ciprofloxacin	antibiotics	µg/L	<1.6	N/A
Citalopram	psychopharmaceuticals	µg/L	0.022	<0.001
Clarithromycin	antibiotics	µg/L	<0.016	0.018
Codeine	NSAIDs and analgesics	µg/L	<0.011	<0.011
Diclofenac	NSAIDs and analgesics	µg/L	0.042	0.022
Dipyridamole	other cardiovascular medicines	µg/L	<0.087	<0.087
Emamectin	veterinary medicines	µg/L	<0.011	<0.011
Enalapril	antihypertensives	µg/L	<0.083	N/A

Eprosartan	antihypertensives	µg/L	<0.005	N/A
Erythromycin	antibiotics	µg/L	<0.009	<0.009
Esomeprazole	gastrointestinal disease	µg/L	<8.4	<8.4
Estriol (E3)	hormones	µg/L	<8.4	<8.4
Estrone (E1)	hormones	µg/L	0.031	5.5
Fenbendazole	veterinary medicines	µg/L	<0.011	<0.011
Fexofenadine	asthma and allergy medications	µg/L	<1.6	<1.6
Florfenicol	veterinary medicines	µg/L	<0.032	N/A
Fluconazole	antibiotics	µg/L	<0.01	<0.01
Fluticasone	asthma and allergy medications	µg/L	<0.14	<0.14
Gabapentin	antiepileptics	µg/L	<0.91	<0.91
Gemfibrozil	metabolic disease medications	µg/L	<0.10	<0.10
Hydrochlorothiazide	antihypertensives	µg/L	6.9	1.2
Ibuprofen	NSAIDs and analgesics	µg/L	<1.1	N/A
Irbesartan	antihypertensives	µg/L	<0.07	<0.07
Ketoprofen	NSAIDs and analgesics	µg/L	0.86	N/A
Levetiracetam	antiepileptics	µg/L	<0.11	N/A
Lincomycin	antibiotics	µg/L	<0.01	<0.01
Losartan	antihypertensives	µg/L	<0.25	<0.25
Mesalazine	gastrointestinal disease	µg/L	<0.063	<0.063
Metformin	metabolic disease medications	µg/L	<0.008	<0.008
Mometasone furotate	asthma and allergy medications	µg/L	<0.027	<0.027
Naproxen	NSAIDs and analgesics	µg/L	0.069	N/A
Nebivolol	other cardiovascular medicines	µg/L	<0.016	<0.016
Norethisterone	hormones	µg/L	0.018	<0.01
Norfloxacin	antibiotics	µg/L	<12	<12
Ofloxacin	antibiotics	µg/L	<0.21	N/A
Olanzepine	psychopharmaceuticals	µg/L	0.39	<0.001
Oxazepam	psychopharmaceuticals	µg/L	<0.011	0.004
Oxycodone	NSAIDs and analgesics	µg/L	<0.12	<0.12
Pantoprazole	gastrointestinal disease	µg/L	<0.76	<0.76
Paracetamol	NSAIDs and analgesics	µg/L	4.5	16
Primidone	antiepileptics	µg/L	<0.018	N/A
Progesterone	hormones	µg/L	<0.012	<0.012
Quetiapine	psychopharmaceuticals	µg/L	<0.12	<0.12
Ramipril	antihypertensives	µg/L	<0.016	N/A
Risperidone	psychopharmaceuticals	µg/L	<0.01	0.072
Sertraline	psychopharmaceuticals	µg/L	<0.01	N/A
Simvastatin	metabolic disease medications	µg/L	<0.002	<0.002
Sotalol	other cardiovascular medicines	µg/L	<0.008	<0.008
Sulfadiazine	antibiotics	µg/L	0.58	<0.30
Sulfamethoxazole	antibiotics	µg/L	<0.009	<0.009
Telmisartan	antihypertensives	µg/L	0.021	0.022
Temazepam	psychopharmaceuticals	µg/L	<0.008	<0.008
Testosterone	hormones	µg/L	0.031	<0.018
Tetracycline+doxycycline	antibiotics	µg/L	0.20	<0.12
Tiamulin	veterinary medicines	µg/L	<0.019	<0.019
Toltrazuril	veterinary medicines	µg/L	<9.0	<9.0
Tramadol	NSAIDs and analgesics	µg/L	<0.038	0.077
Trimethoprim	antibiotics	µg/L	<0.011	N/A
Tylosin	veterinary medicines	µg/L	<0.10	<0.10
Valsartan	antihypertensives	µg/L	0.59	<0.15
Venlafaxine	psychopharmaceuticals	µg/L	0.25	N/A
Warfarin	other cardiovascular medicines	µg/L	2.0	0.068
Xylometazoline	asthma and allergy medications	µg/L	0.028	<0.026
	Number of analysed APIs		74	58
	Number of APIs above LOQ		17	12
	Detection rate (%)		23	21

Annex 14. APIs in surface water at fishfarms

Country			Estonia	Estonia	Finland	Finland	Finland	Finland	Finland
			Roosna-Alliku fish farm, effluent	Roosna-Alliku fish farm, effluent	CWP2 - 1	CWP3 - 1	CPW2 - 4.5	CWP1 - 5.3 A	CWP1- 1 A
Sampling			06/12/2017	06/06/2018	21/08/2018	22/08/2018	23/08/2018	24/08/2018	25/08/2018
Coordinate X					60.2674	60.2676	60.2674	60.2676	60.2676
Coordinate Y					21.4112	21.4185	21.4113	21.4093	21.4093
Coordinate system			L-Est 97	L-Est 97	WGS84	WGS84	WGS84	WGS84	WGS84
API	**API group**	**Unit**							
Amlodipine	antihypertensives	ng/l	<0.003	1.57	1.57	1.49	1.37	1.79	<0.003
Atenolol	other cardiovascular medicines	ng/l	<8.00	<8.00	<8.00	<8.00	<8.00	<8.00	<8.00
Bezafibrate	metabolic disease medications	ng/l	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40
Bisoprolol	other cardiovascular medicines	ng/l	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21
Caffeine	other	ng/l	6.04	4.31	2.83	3.40	1.46	0.57	0.75
Candesartan	antihypertensives	ng/l	<0.22	<0.22	<0.22	<0.22	<0.22	1.29	<0.22
Carbamazepine	antiepileptics	ng/l	0.63	1.15	0.82	0.80	0.91	2.34	2.52
Carprofen	veterinary medicines	ng/l	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Cetirizine	asthma and allergy medications	ng/l	0.38	<0.03	<0.03	<0.03	<0.03	0.24	0.17
Ciprofloxacin	antibiotics	ng/l	<34.8	<34.8	<34.8	<34.8	<34.8	<34.8	<34.8
Citalopram	psycopharmaceuticals	ng/l	0.06	<0.04	<0.04	<0.04	<0.04	0.05	<0.04
Clarithromycin	antibiotics	ng/l	<0.33	<0.33	<0.33	<0.33	<0.33	<0.33	<0.33
Codeine	NSAIDs and analgesics	ng/l	<0.01	<0.01	<0.01	<0.01	<0.01	0.04	<0.01
Diclofenac	NSAIDs and analgesics	ng/l	1.32	0.92	<0.34	<0.34	<0.34	<0.34	<0.34
Dipyridamole	other cardiovascular medicines	ng/l	<0.67	<0.67	<0.67	<0.67	<0.67	0.67	<0.67
Emamectin	veterinary medicines	ng/l	0.08	0.53	0.59	0.61	<0.02	0.29	0.30
Erythromycin	antibiotics	ng/l	<0.92	<0.92	<0.92	<0.92	<0.92	<0.92	<0.92
Estrone (E1)	hormones	ng/l	1.10	9.82	1.49	1.08	2.07	<0.17	<0.17
Fenbendazole	veterinary medicines	ng/l	<0.03	<0.03	<0.03	<0.03	<0.03	0.29	0.16
Fluconazole	antibiotics	ng/l	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	0.25
Fluticasone	asthma and allergy medications	ng/l	<0.002	<0.002	<0.002	<0.002	<0.002	0.14	0.10
Gemfibrozil	metabolic disease medications	ng/l	0.58	<0.02	6.62	<0.02	8.55	2.74	2.62
Irbesartan	antihypertensives	ng/l	0.07	<0.02	<0.02	<0.02	<0.02	0.14	0.04
Ketoprofen	NSAIDs and analgesics	ng/l	<0.38	<0.38	<0.38	<0.39	<0.38	<0.38	<0.38
Levetiracetam	antiepileptics	ng/l	<5.43	<5.43	<5.43	<5.43	<5.43	<5.43	<5.43
Lincomycin	antibiotics	ng/l	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Losartan	antihypertensives	ng/l	0.02	<0.02	0.17	0.18	0.19	0.16	0.13
Mesalazine	gastrointestinal disease medications	ng/l	59.76	71.40	35.80	28.57	32.72	<0.82	<0.82
Metformin	metabolic disease medications	ng/l	1.98	N/A	<0.12	<0.12	<0.12	<0.12	<0.12
Metoprolol	other cardiovascular medicines	ng/l	<0.35	<0.36	<0.35	<0.35	<0.35	<0.35	<0.35
Mometasone	asthma and allergy medications	ng/l	<0.29	<0.29	<0.29	<0.29	<0.29	<0.29	<0.29
Naproxen	NSAIDs and analgesics	ng/l	<0.47	0.14	<0.47	<0.47	<0.47	<0.47	<0.47
Nebivolol	other cardiovascular medicines	ng/l	0.22	1.52	1.71	1.40	0.75	0.83	0.18
Norethisterone	hormones	ng/l	8.12	<0.04	0.39	<0.04	<0.04	0.33	<0.04
Ofloxacin	antibiotics	ng/l	<4.16	<4.16	<4.16	<4.16	<4.16	<4.16	<4.16
Oxazepam	psycopharmaceuticals	ng/l	0.19	<0.03	<0.03	<0.03	<0.03	0.68	<0.03
Oxycodone	NSAIDs and analgesics	ng/l	0.04	<0.03	<0.03	<0.03	<0.03	0.24	<0.03
Primidone	antiepileptics	ng/l	1.17	<0.71	0.32	0.26	0.29	<0.71	<0.71
Progesterone	hormones	ng/l	0.04	<0.03	<0.03	<0.03	<0.03	0.17	<0.03
Quetiapine	psycopharmaceuticals	ng/l	<0.01	<0.01	<0.01	<0.01	<0.01	0.12	0.08
Sertraline	psycopharmaceuticals	ng/l	<0.03	<0.03	<0.03	<0.03	<0.03	2.83	0.21
Simvastatin	metabolic disease medications	ng/l	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Sotalol	other cardiovascular medicines	ng/l	<0.68	<0.68	<0.68	<0.68	<0.68	<0.68	<0.68
Temazepam	psycopharmaceuticals	ng/l	<0.34	<0.34	<0.34	<0.34	<0.34	0.72	0.57
Testosterone	hormones	ng/l	0.13	3.48	<0.05	<0.05	<0.05	<0.05	<0.05
Tetracycline/Doxycy	antibiotics	ng/l	4.95	<3.17	5.58	5.45	3.26	3.67	<3.17
Tiamulin	veterinary medicines	ng/l	<0.01	<0.01	0.19	0.15	<0.01	0.30	0.13
Toltrazuril	veterinary medicines	ng/l	<3.60	<3.60	<3.60	<3.60	<3.60	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/l	0.16	<0.02	<0.02	<0.02	<0.02	0.46	0.40
Trimethoprim	antibiotics	ng/l	<0.17	<0.17	1.42	1.54	1.69	2.07	1.97
Tylosin	veterinary medicines	ng/l	<1.91	<1.91	<1.91	<1.91	<1.91	<1.91	<1.91
Warfarin	other cardiovascular medicines	ng/l	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Venlafaxine	psycopharmaceuticals	ng/l	0.10	<0.03	<0.03	<0.03	<0.03	<0.35	<0.35
Xylometazoline	asthma and allergy medications	ng/l	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19
	Number of analysed API		54	54	54	54	54	54	54
	Number of APIs above LOQ		22	10	14	12	11	26	17
	Detection rate (%)		41	19	26	22	20	48	31
	Sum concentration (ng/l)		87.14	94.84	59.49	44.93	53.26	23.18	10.58

Country			Finland	Finland	Finland	Finland	Finland	Finland	Finland
			CWP3 -5.7 A	CWP3 - 1 B	CWP1 - 1 B	CWP2 -1 B	CWP1 - 5.2 B	CWP3 - 6.4 B	CWP2 - 4.1 B
Sampling			26/08/2018	18/09/2018	18/09/2018	18/09/2018	18/09/2018	18/09/2018	18/09/2018
Coordinate X			60.2667	60.2677	60.2678	60.2677	60.2678	60.2677	60.2677
Coordinate Y			21.4184	21.4113	21.4094	21.4182	21.4094	21.4182	21.4132
Coordinate system			WGS84	WGS84	WGS84	WGS84	WGS84	WGS84	WGS84
API	**API group**	**Unit**							
Amlodipine	antihypertensives	ng/l	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003
Atenolol	other cardiovascular medicines	ng/l	<8.00	<8.00	<8.00	<8.00	<8.00	<8.00	<8.00
Bezafibrate	metabolic disease medications	ng/l	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40
Bisoprolol	other cardiovascular medicines	ng/l	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21
Caffeine	other	ng/l	0.57	1.87	0.53	0.58	0.44	0.76	0.62
Candesartan	antihypertensives	ng/l	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22
Carbamazepine	antiepileptics	ng/l	2.19	2.11	1.72	1.90	1.78	1.82	1.67
Carprofen	veterinary medicines	ng/l	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Cetirizine	asthma and allergy medications	ng/l	0.19	0.16	0.15	0.14	0.14	0.15	0.11
Ciprofloxacin	antibiotics	ng/l	<34.8	<34.8	<34.8	<34.8	<34.8	<34.8	<34.8
Citalopram	psycopharmaceuticals	ng/l	0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Clarithromycin	antibiotics	ng/l	<0.33	<0.33	<0.33	<0.33	<0.33	<0.33	<0.33
Codeine	NSAIDs and analgesics	ng/l	<0.01	<0.01	<0.01	0.06	0.09	<0.01	0.07
Diclofenac	NSAIDs and analgesics	ng/l	<0.34	<0.34	<0.34	<0.34	<0.34	<0.34	<0.34
Dipyridamole	other cardiovascular medicines	ng/l	<0.67	<0.67	<0.67	<0.67	<0.67	<0.67	<0.67
Emamectin	veterinary medicines	ng/l	0.32	0.19	0.17	0.15	0.17	0.16	0.14
Erythromycin	antibiotics	ng/l	<0.92	<0.92	<0.92	<0.92	<0.92	<0.92	<0.92
Estrone (E1)	hormones	ng/l	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17
Fenbendazole	veterinary medicines	ng/l	0.13	<0.03	0.08	<0.03	<0.03	<0.03	<0.03
Fluconazole	antibiotics	ng/l	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25	<0.25
Fluticasone	asthma and allergy medications	ng/l	0.08	<0.002	0.09	<0.002	<0.002	<0.002	<0.002
Gemfibrozil	metabolic disease medications	ng/l	3.94	<0.02	3.37	2.52	3.02	3.35	3.84
Irbesartan	antihypertensives	ng/l	<0.02	0.03	0.02	<0.02	0.02	0.01	<0.02
Ketoprofen	NSAIDs and analgesics	ng/l	<0.38	<0.38	<0.38	<0.38	<0.38	<0.38	<0.38
Levetiracetam	antiepileptics	ng/l	<5.43	<5.43	<5.43	<5.43	<5.43	<5.43	<5.43
Lincomycin	antibiotics	ng/l	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Losartan	antihypertensives	ng/l	0.11	0.07	0.10	<0.02	<0.02	0.08	<0.02
Mesalazine	gastrointestinal disease medications	ng/l	<0.82	<0.82	<0.82	<0.82	<0.82	<0.82	<0.82
Metformin	metabolic disease medications	ng/l	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12
Metoprolol	other cardiovascular medicines	ng/l	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
Mometasone	asthma and allergy medications	ng/l	<0.29	<0.29	<0.29	<0.29	<0.29	<0.29	0.66
Naproxen	NSAIDs and analgesics	ng/l	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47
Nebivolol	other cardiovascular medicines	ng/l	0.19	0.09	0.06	0.09	0.07	<0.01	0.06
Norethisterone	hormones	ng/l	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Ofloxacin	antibiotics	ng/l	<4.16	<4.16	<4.16	<4.16	<4.16	<4.16	<4.16
Oxazepam	psycopharmaceuticals	ng/l	0.54	<0.03	<0.03	<0.03	<0.03	<0.03	0.23
Oxycodone	NSAIDs and analgesics	ng/l	0.08	<0.03	<0.03	0.11	<0.03	<0.03	<0.03
Primidone	antiepileptics	ng/l	<0.71	<0.71	<0.71	<0.71	<0.71	<0.71	<0.71
Progesterone	hormones	ng/l	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Quetiapine	psycopharmaceuticals	ng/l	0.10	0.09	0.06	0.06	0.06	0.05	0.05
Sertraline	psycopharmaceuticals	ng/l	0.17	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Simvastatin	metabolic disease medications	ng/l	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Sotalol	other cardiovascular medicines	ng/l	<0.68	<0.68	<0.68	<0.68	<0.68	<0.68	<0.68
Temazepam	psycopharmaceuticals	ng/l	0.51	<0.34	<0.34	<0.34	0.48	<0.34	<0.34
Testosterone	hormones	ng/l	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Tetracycline/Doxycy	antibiotics	ng/l	<3.17	<3.17	<3.17	<3.17	<3.17	<3.17	<3.17
Tiamulin	veterinary medicines	ng/l	0.13	<0.01	0.07	0.07	0.05	0.06	<0.01
Toltrazuril	veterinary medicines	ng/l	<3.60	<3.60	<3.60	<3.60	<3.60	<3.60	<3.60
Tramadol	NSAIDs and analgesics	ng/l	0.39	0.31	0.31	0.30	0.28	0.28	0.29
Trimethoprim	antibiotics	ng/l	3.73	0.31	0.30	0.26	0.26	0.27	0.24
Tylosin	veterinary medicines	ng/l	<1.91	<1.91	<1.91	<1.91	<1.91	<1.91	<1.91
Warfarin	other cardiovascular medicines	ng/l	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
Venlafaxine	psycopharmaceuticals	ng/l	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
Xylometazoline	asthma and allergy medications	ng/l	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19	<0.19
	Number of analysed API		54	54	54	54	54	54	54
	Number of APIs above LOQ		18	10	14	12	13	11	12
	Detection rate (%)		33	19	26	22	24	20	22
	Sum concentration (ng/l)		13.40	5.23	7.04	6.23	6.88	7.00	7.98

Annex 15. APIs in sediments at fishfarms

Country			Estonia	Finland	Finland	Finland
			Roosna-Alliku fishfarm			
Sampling			06/12/2017	17/09/2018	17/09/2018	17/09/2019
Coordinate X			59.022195	60.2676	60.2673	60.2654
Coordinate Y			25.698521	21.4084	21.4208	21.4256
Coordinate system			L-Est 97	WGS84	WGS84	WGS84
Comments			ca 5 cm top layer	2-4 top layer	~3 cm top layer	~4 cm top layer
Dry matter content		%	68.6	34.6	67.7	18.3
API	**API group**	**Unit**				
Atenolol	other cardiovascular medicines	µg/kg d.w.	<0.050	<0.050	<0.050	<0.050
Amlodipine	antihypertensives	µg/kg d.w.	<0.062	<0.062	<0.062	<0.062
Bezafibrate	metabolic disease medications	µg/kg d.w.	<0.076	<0.076	0.14	<0.076
Bisoprolol	other cardiovascular medicines	µg/kg d.w.	0.07	<0.011	0.02	<0.011
Caffeine	other	µg/kg d.w.	2.95	40.90	<0.46	1.97
Carbamazepine	antiepileptics	µg/kg d.w.	0.18	0.39	<0.099	0.72
Cetirizine	asthma and allergy medications	µg/kg d.w.	0.06	<0.014	0.03	0.05
Ciprofloxacin	antibiotics	µg/kg d.w.	7.86	4.79	<1.93	7.46
Citalopram	psycopharmaceuticals	µg/kg d.w.	<0.093	0.39	<0.093	0.45
Clarithromycin	antibiotics	µg/kg d.w.	<0.085	<0.085	<0.085	<0.085
Codeine	NSAIDs and analgesics	µg/kg d.w.	<0.77	<0.77	<0.77	<0.77
Diclofenac	NSAIDs and analgesics	µg/kg d.w.	<0.10	<0.10	<0.10	<0.10
Dipyridamole	other cardiovascular medicines	µg/kg d.w.	<0.22	<0.22	<0.22	1.32
Emamectin	veterinary medicines	µg/kg d.w.	0.34	<0.24	<0.24	<0.24
Enalapril	antihypertensives	µg/kg d.w.	0.08	<0.047	<0.047	<0.047
Eprosartan	antihypertensives	µg/kg d.w.	<0.047	<0.047	<0.047	<0.047
Erythromycin	antibiotics	µg/kg d.w.	<16	<16	<16	<16
Estriol (E3)	hormones	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1
Estrone (E1)	hormones	µg/kg d.w.	<0.51	9.60	<0.51	1.28
Fenbendazole	veterinary medicines	µg/kg d.w.	0.04	1.02	0.44	2.64
Fexofenadine	asthma and allergy medications	µg/kg d.w.	0.07	0.07	0.06	0.11
Florfenicol	veterinary medicines	µg/kg d.w.	0.13	<0.010	<0.010	<0.010
Fluconazole	antibiotics	µg/kg d.w.	<0.0041	<0.0041	<0.0041	0.10
Fluticasone	asthma and allergy medications	µg/kg d.w.	<0.60	<0.60	<0.60	<0.60
Gemfibrozil	metabolic disease medications	µg/kg d.w.	<0.18	<0.18	<0.18	<0.18
Hydrochlorothiazide	antihypertensives	µg/kg d.w.	<10	113.30	17.08	38.26
Irbesartan	antihypertensives	µg/kg d.w.	0.03	<0.013	N/A	<0.013
Ivermectin	veterinary medicines	µg/kg d.w.	<6.2	<6.2	<6.2	<6.2
Ketoprofen	NSAIDs and analgesics	µg/kg d.w.	0.09	0.38	0.25	<0.059
Levetiracetam	antiepileptics	µg/kg d.w.	<0.47	<0.47	<0.47	<0.47
Lincomycin	antibiotics	µg/kg d.w.	0.07	0.02	<0.0058	<0.0058
Metformin	metabolic disease medications	µg/kg d.w.	37.73	2.99	3.00	11.35
Metoprolol	other cardiovascular medicines	µg/kg d.w.	<0.050	<0.050	<0.050	0.26
Mometasone	asthma and allergy medications	µg/kg d.w.	<0.75	<0.75	<0.75	<0.75
Naproxen	NSAIDs and analgesics	µg/kg d.w.	<0.52	0.83	<0.52	<0.52
Nebivolol	other cardiovascular medicines	µg/kg d.w.	0.10	0.38	<0.099	<0.099
Norethisterone	hormones	µg/kg d.w.	<0.12	N/A	<0.12	<0.12
Norfloxacin	antibiotics	µg/kg d.w.	<1.5	<1.5	12.74	<1.5
Ofloxacin	antibiotics	µg/kg d.w.	<0.60	2.38	<0.60	<0.60
Olanzepine	psycopharmaceuticals	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1
Oxazepam	psycopharmaceuticals	µg/kg d.w.	0.23	<0.0080	0.03	0.04
Oxycodone	NSAIDs and analgesics	µg/kg d.w.	0.08	0.36	<0.065	0.20
Paracetamol	NSAIDs and analgesics	µg/kg d.w.	17.48	<0.25	17.41	517.89
Primidone	antiepileptics	µg/kg d.w.	<0.057	<0.057	<0.057	<0.057
Progesterone	hormones	µg/kg d.w.	0.67	0.82	0.34	1.44
Quetiapine	psycopharmaceuticals	µg/kg d.w.	0.07	<0.0084	<0.0084	<0.0084
Ramipril	antihypertensives	µg/kg d.w.	<0.052	<0.052	<0.052	<0.052
Risperidone	psycopharmaceuticals	µg/kg d.w.	0.46	0.43	0.24	0.34
Sertraline	psycopharmaceuticals	µg/kg d.w.	<0.038	0.06	<0.038	0.11
Simvastatin	metabolic disease medications	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11
Sotalol	other cardiovascular medicines	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11
Sulfamethoxazole	antibiotics	µg/kg d.w.	<0.12	<0.12	<0.12	<0.12
Telmisartan	antihypertensives	µg/kg d.w.	0.36	1.57	N/A	3.29
Temazepam	psycopharmaceuticals	µg/kg d.w.	<0.087	<0.087	<0.087	<0.087
Testosterone	hormones	µg/kg d.w.	0.31	<0.20	<0.20	<0.20
Tetracycline/Doxycycline	antibiotics	µg/kg d.w.	2.65	<1.6	<1.6	3.96
Tiamulin	veterinary medicines	µg/kg d.w.	<0.044	<0.044	<0.044	<0.044
Toltrazuril	veterinary medicines	µg/kg d.w.	<4.6	<4.6	<4.6	<4.6
Tramadol	NSAIDs and analgesics	µg/kg d.w.	1.16	2.08	0.37	1.24
Trimethoprim	antibiotics	µg/kg d.w.	0.12	0.18	<0.050	0.08
Tylosin	veterinary medicines	µg/kg d.w.	<3.2	<3.2	<3.2	<3.2
Valsartan	antihypertensives	µg/kg d.w.	0.17	<0.092	0.15	<0.092
Warfarin	other cardiovascular medicines	µg/kg d.w.	<0.0059	<0.0059	<0.0059	0.027
Venlafaxine	psycopharmaceuticals	µg/kg d.w.	0.05	<0.044	<0.044	0.13
Xylometazoline	asthma and allergy medications	µg/kg d.w.	<0.046	88.53	<0.046	<0.046
	Number of analysed API		65	65	65	65
	Number of APIs above LOQ		28	22	15	25
	Detection rate (%)		43	34	23	38
	Sum concentration (µg/kg d.w.)		73.6	271.5	52.3	594.7

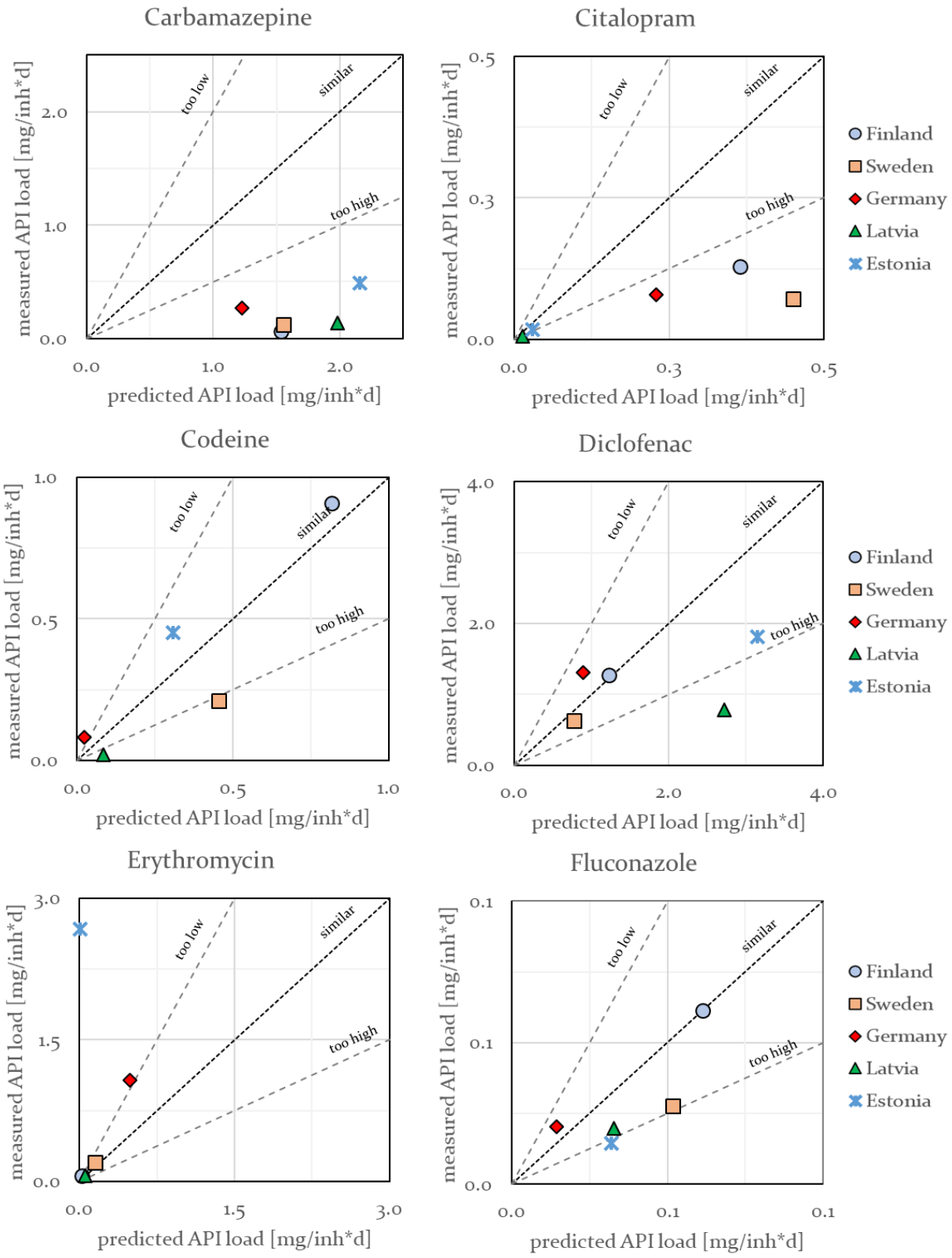
Annex 16. API concentrations near pig and poultry farms

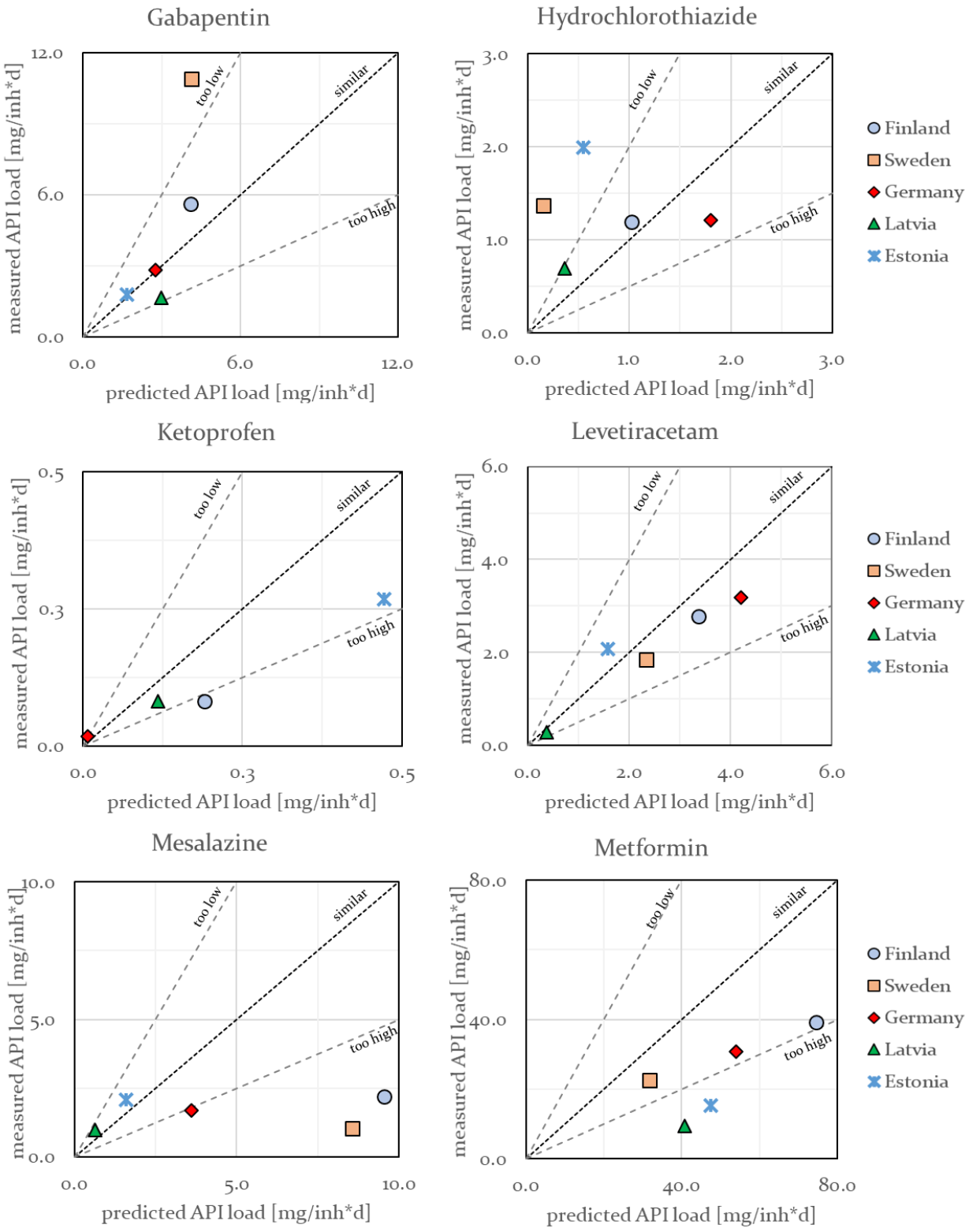
Country			Latvia	Latvia	Latvia	Latvia
Sample			Pig farm Pg	Poultry farm Py	Pig farm Pg	Poultry farm Py
		Sampling date	29.11.2017.	28.11.2017.	22.05.2018.	25.05.2018.
API name	**API's group**	**Unit**				
Amlodipine	Antihypertensives	ng/l	<7.7	<7.7	<7.7	<7.7
Atenolol	Other cardiovascular medicines	ng/l	<12	<12	<12	<12
Atorvastatin	Metabolic disease medications	ng/l	<15	<15	<15	<15
Bezafibrate	Metabolic disease medications	ng/l	<0.83	<0.83	<0.83	<0.83
Bisoprolol	Other cardiovascular medicines	ng/l	<0.52	<0.52	<0.52	<0.52
Caffeine	Other	ng/l	140	94	590	2.2
Candesartan	Antihypertensives	ng/l	<0.68	<0.68	<0.68	<0.68
Carbamazepine	Antiepileptics	ng/l	0.020	0.16	<0.005	1.1
Carprofen	Veterinary medicines	ng/l	<0.77	2.2	0.86	<0.77
Cetirizine	Asthma and allergy medications	ng/l	0.13	0.15	<0.11	<0.11
Citalopram	Psycopharmaceuticals	ng/l	0.17	0.18	<0.060	<0.060
Clarithromycin	Antibiotics	ng/l	1.6	1.6	<1.0	0.45
Codeine	NSAIDs and analgesics	ng/l	N/A	N/A	<0.070	<0.070
Diclofenac	NSAIDs and analgesics	ng/l	0.89	4.9	4.9	7.7
Dipyridamole	Other cardiovascular medicines	ng/l	<1.1	<1.1	<1.1	<1.1
Emamectin	Veterinary medicines	ng/l	0.15	0.14	<0.090	<0.090
Enalapril	Antihypertensives	ng/l	<2.8	<2.8	<2.8	<2.8
Eprosartan	Antihypertensives	ng/l	<0.22	<0.22	<0.22	<0.22
Estrone (E1)	Hormones	ng/l	<0.70	<0.70	<0.70	1.3
Fenbendazole	Veterinary medicines	ng/l	0.12	<0.070	<0.070	<0.070
Fexofenadien	Asthma and allergy medications	ng/l	3.0	<0.090	3.2	<0.090
Fluconazole	Antibiotics	ng/l	<0.050	<0.050	<0.050	<0.050
Fluticasone	Asthma and allergy medications	ng/l	<0.060	<0.060	<0.060	<0.060
Gabapentin	Antiepileptics	ng/l	7.3	25	<0.88	40
Gemfibrozil	Metabolic disease medications	ng/l	<1.5	3.2	<1.5	<1.5
Irbesartan	Antihypertensives	ng/l	<0.060	<0.060	<0.060	<0.060
Ketoprofen	NSAIDs and analgesics	ng/l	<0.72	5.1	<0.72	<0.72
Levetiracetam	Antiepileptics	ng/l	<3.5	<3.5	<3.5	<3.5
Lincomycin	Antibiotics	ng/l	<0.10	<0.10	<0.10	<0.10
Losartan	Antihypertensives	ng/l	<0.14	0.27	<0.14	<0.14
Metformin	Metabolic disease medications	ng/l	5.6	15	<0.24	191
Metoprolol	Other cardiovascular medicines	ng/l	0.66	0.24	5.0	0.42
Mometasone furoate	Asthma and allergy medications	ng/l	<1.3	<1.3	<1.3	<1.3
Naproxen	NSAIDs and analgesics	ng/l	<0.57	<0.57	<0.57	26
Nebivolol	Other cardiovascular medicines	ng/l	0.37	0.38	<0.052	<0.052
Norethisterone	Hormones	ng/l	<0.080	<0.080	<0.080	<0.080
Ofloxacin	Antibiotics	ng/l	<10	<10	<10	<10
Oxazepam	Psycopharmaceuticals	ng/l	N/A	N/A	<0.033	<0.033
Oxycodone	NSAIDs and analgesics	ng/l	N/A	N/A	<0.042	<0.042
Primidone	Antiepileptics	ng/l	<1.4	<1.4	<1.4	<1.4
Progesterone	Hormones	ng/l	0.25	0.16	<0.086	<0.086
Quetiapine	Psycopharmaceuticals	ng/l	<0.15	<0.15	<0.15	<0.15
Ramipril	Antihypertensives	ng/l	<0.72	<0.72	<0.72	<0.72
Sertraline	Psycopharmaceuticals	ng/l	<0.040	<0.040	<0.040	<0.040
Sotalol	Other cardiovascular medicines	ng/l	<0.89	<0.89	<0.89	<0.89
Sulfadiazine	Antibiotics	ng/l	<17	<17	<17	<17
Telmisartan	Antihypertensives	ng/l	<1.4	<1.4	<1.4	<1.4
Temazepam	Psycopharmaceuticals	ng/l	N/A	N/A	<0.36	<0.36
Testosterone	Hormones	ng/l	<0.080	<0.080	<0.080	<0.080
Tetracycline/Doxycycline	Antibiotics	ng/l	<5.7	<5.7	<5.7	<5.7
Tiamulin	Veterinary medicines	ng/l	18	1.3	7.3	1.7
Toltrazuril	Veterinary medicines	ng/l	10	<4.8	7.6	<4.8
Tramadol	NSAIDs and analgesics	ng/l	0.040	0.070	<0.038	<0.038
Trimethoprim	Antibiotics	ng/l	<0.37	<0.37	<0.37	<0.37
Tylosin	Veterinary medicines	ng/l	23	20	<3.7	<3.7
Valsartan	Antihypertensives	ng/l	<6.4	<6.4	<6.4	<6.4
Warfarin	Other cardiovascular medicines	ng/l	<0.87	<0.87	<0.87	<0.87
Venlafaxine	Psycopharmaceuticals	ng/l	0.030	0.040	<0.030	0.47
Xylometazoline	Asthma and allergy medications	ng/l	1.6	1.7	<0.054	<0.054
	Number of analysed API		55	55	59	59
	Number of APIs above LOQ		20	20	7	11
	Detection rate (%)		36	36	12	19
	Sum concentration (ng/L)		212.6	176.9	618.9	272.6

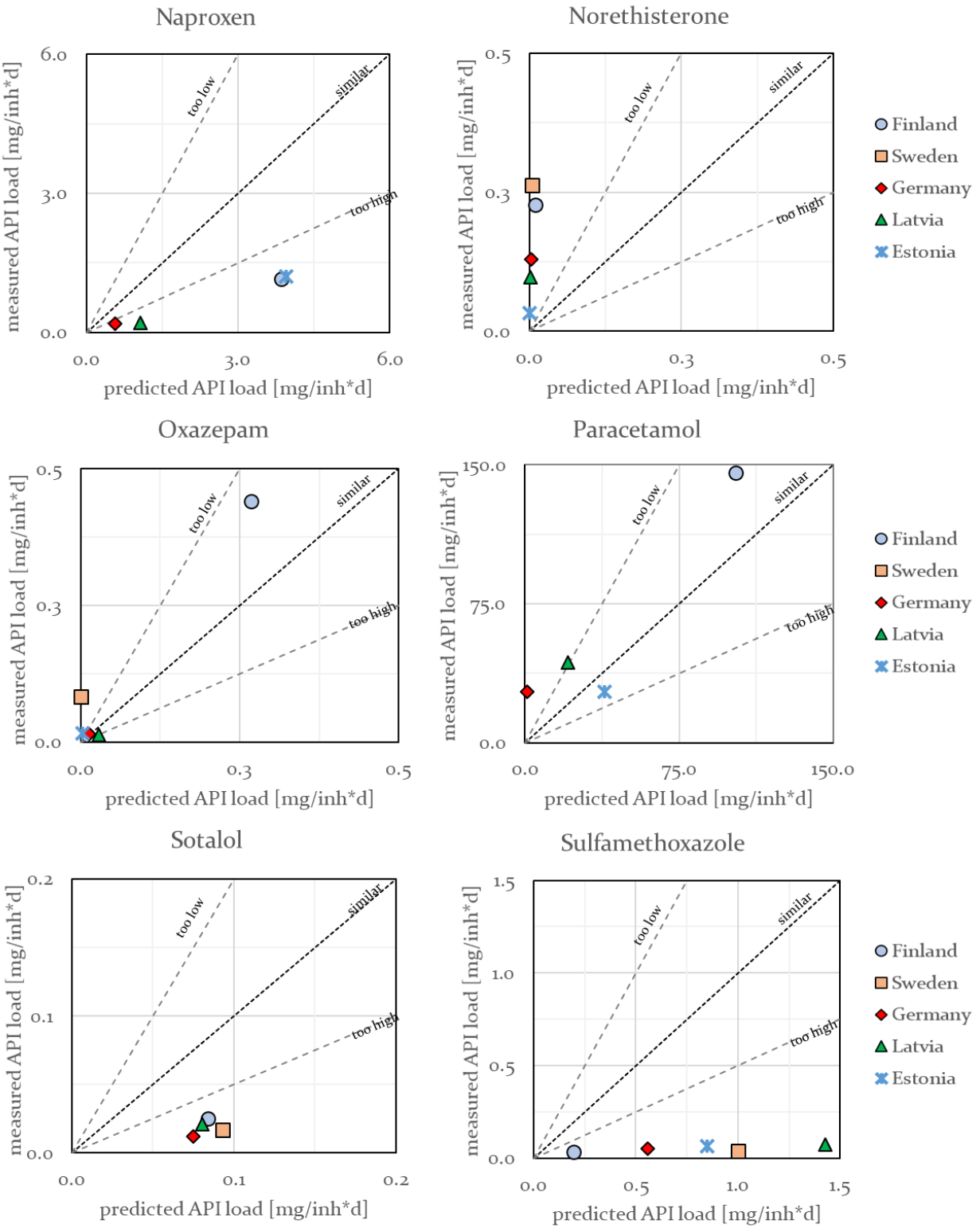
Annex 17. API concentrations in soil

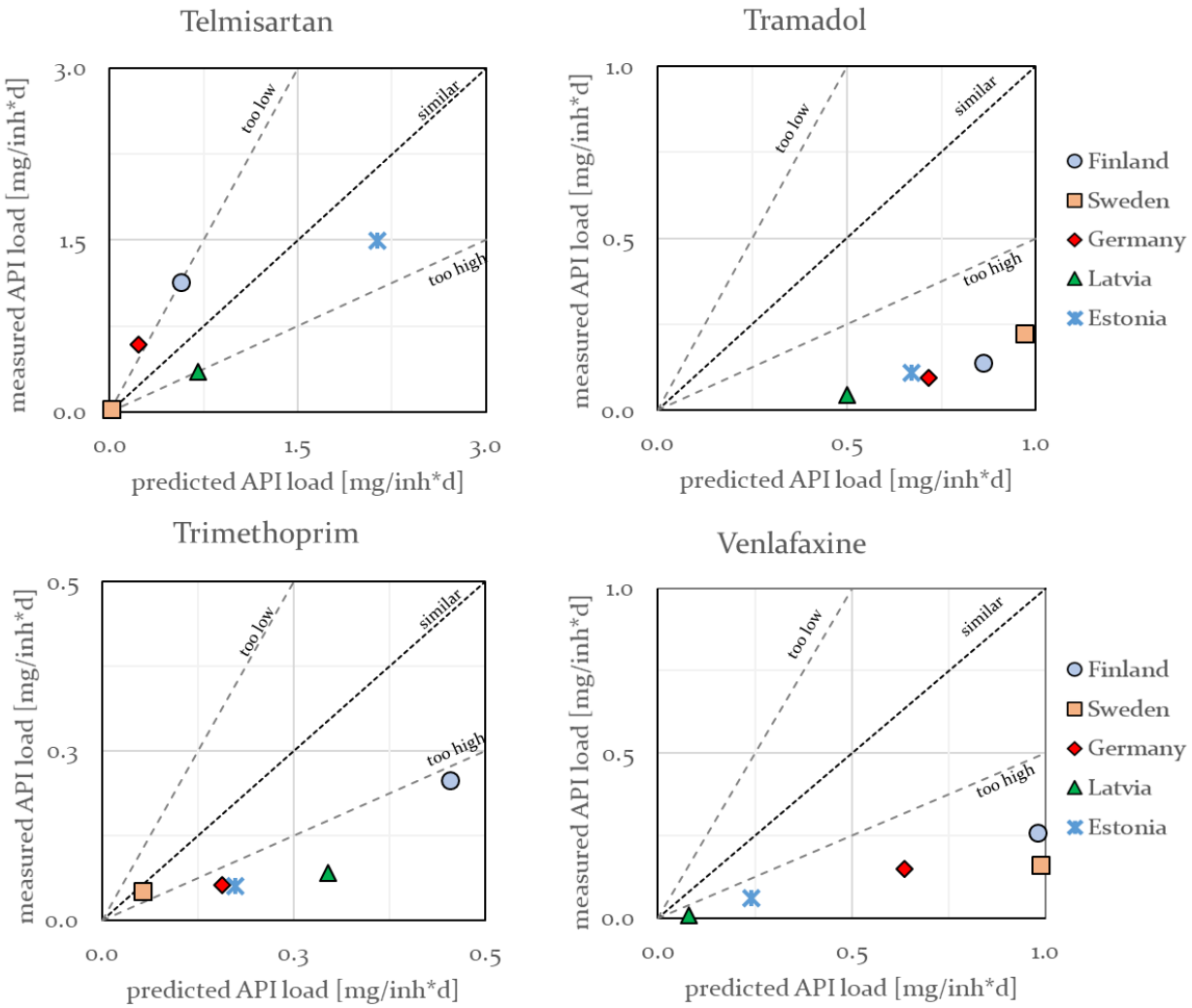
Country			Estonia		Germany	Latvia	Sweden	
Date (DD.MM.YYYY)			17/10/2018	17/10/2018	24/05/2018	12/06/2018	6.2018	6.2018
Name in diagram			*EST 1	^EST 2	*DE 1	*LV 1	*SWE 1	^SWE 2
Dry matter content		%	78	80	94	84	93	96
API	**Group of API**	**Unit**						
Amlodipine	Antihypertensives	µg/kg d.w.	<0.062	<0.062	<0.062	<0.062	<0.062	<0.062
Atenolol	Other cardiovascular medicines	µg/kg d.w.	<0.050	<0.050	<0.050	<0.050	<0.050	<0.050
Bezafibrate	Metabolic disease medications	µg/kg d.w.	<0.076	0.18	<0.076	0.17	0.16	0.18
Bisoprolol	Other cardiovascular medicines	µg/kg d.w.	<0.011	0.012	<0.011	0.049	0.012	0.012
Caffeine	Other	µg/kg d.w.	0.46	<0.46	1.0	1.1	1.3	<0.46
Carbamazepine	Antiepileptics	µg/kg d.w.	<0.099	<0.099	<0.099	<0.099	<0.099	<0.099
Cetirizine	Asthma and allergy medications	µg/kg d.w.	<0.014	0.018	<0.014	0.10	0.017	0.041
Ciprofloxacin	Antibiotics	µg/kg d.w.	<1.9	<1.9	4.7	<1.9	<1.9	<1.9
Citalopram	Psycopharmaceuticals	µg/kg d.w.	<0.093	<0.093	<0.093	0.19	<0.093	<0.093
Clarithromycin	Antibiotics	µg/kg d.w.	<0.085	<0.085	<0.085	<0.085	<0.085	<0.085
Codeine	NSAIDs and analgesics	µg/kg d.w.	<0.77	<0.77	<0.77	<0.77	<0.77	<0.77
Diclofenac	NSAIDs and analgesics	µg/kg d.w.	<0.10	0.43	<0.10	<0.10	<0.10	<0.10
Dipyridamole	Other cardiovascular medicines	µg/kg d.w.	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22
Emamectin	Veterinary medicines	µg/kg d.w.	<0.24	<0.24	<0.24	<0.24	<0.24	<0.24
Enalapril	Antihypertensives	µg/kg d.w.	<0.047	<0.047	<0.047	<0.047	<0.047	<0.047
Eprosartan	Antihypertensives	µg/kg d.w.	<0.047	<0.047	<0.047	<0.047	<0.047	<0.047
Erythromycin	Antibiotics	µg/kg d.w.	<16	<16	<16	<16	<16	<16
Estriol (E3)	Hormones	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Estrone (E1)	Hormones	µg/kg d.w.	<0.51	<0.51	16	<0.51	<0.51	<0.51
Fenbendazole	Veterinary medicines	µg/kg d.w.	1.0	0.51	0.46	1.7	0.40	0.41
Fexofenadine	Asthma and allergy medications	µg/kg d.w.	<0.017	0.065	0.018	0.18	0.021	0.045
Florfenicol	Veterinary medicines	µg/kg d.w.	0.063	0.028	<0.010	0.19	<0.010	<0.010
Fluconazole	Antibiotics	µg/kg d.w.	<0.004	<0.004	0.007	<0.004	<0.004	<0.004
Fluticasone	Asthma and allergy medications	µg/kg d.w.	<0.60	<0.60	<0.60	<0.60	<0.60	<0.60
Gemfibrozil	Metabolic disease medications	µg/kg d.w.	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18
Hydrochlorothiazide	Antihypertensives	µg/kg d.w.	<10	17	32	110	<10	15
Irbesartan	Antihypertensives	µg/kg d.w.	N/A	N/A	N/A	N/A	N/A	N/A
Ivermectin	Veterinary medicines	µg/kg d.w.	<6.2	<6.2	<6.2	<6.2	<6.2	11
Ketoprofen	NSAIDs and analgesics	µg/kg d.w.	0.97	0.40	0.69	<0.059	0.50	0.39
Levetiracetam	Antiepileptics	µg/kg d.w.	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47
Lincomycin	Antibiotics	µg/kg d.w.	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006
Metformin	Metabolic disease medications	µg/kg d.w.	<0.004	0.53	3.1	0.47	1.5	0.47
Metoprolol	Other cardiovascular medicines	µg/kg d.w.	0.094	<0.050	<0.050	0.14	0.16	<0.050
Mometasone furoate	Asthma and allergy medications	µg/kg d.w.	<0.75	<0.75	<0.75	<0.75	<0.75	<0.75
Naproxen	NSAIDs and analgesics	µg/kg d.w.	<0.52	<0.52	<0.52	<0.52	<0.52	<0.52
Nebivolol	Other cardiovascular medicines	µg/kg d.w.	<0.099	0.14	0.11	0.41	<0.099	0.11
Norethisterone	Hormones	µg/kg d.w.	N/A	<0.12	N/A	<0.12	<0.12	<0.12
Norfloxacin	Antibiotics	µg/kg d.w.	<1.5	15	<1.5	18	14	16
Ofloxacin	Antibiotics	µg/kg d.w.	<0.60	<0.60	0.91	<0.60	<0.60	<0.60
Olanzepine	Psycopharmaceuticals	µg/kg d.w.	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1
Oxazepam	Psycopharmaceuticals	µg/kg d.w.	0.045	<0.008	0.065	0.42	<0.008	0.024
Oxycodone	NSAIDs and analgesics	µg/kg d.w.	0.26	0.066	0.067	0.45	<0.065	<0.065
Paracetamol	NSAIDs and analgesics	µg/kg d.w.	6.6	4.5	1.4	27	2.4	2.3
Primidone	Antiepileptics	µg/kg d.w.	<0.057	<0.057	<0.057	<0.057	<0.057	<0.057
Progesterone	Hormones	µg/kg d.w.	0.30	<0.092	<0.092	0.22	<0.092	<0.092
Quetiapine	Psycopharmaceuticals	µg/kg d.w.	<0.008	<0.008	<0.008	<0.008	<0.008	<0.008
Ramipril	Antihypertensives	µg/kg d.w.	<0.052	<0.052	<0.052	<0.052	<0.052	<0.052
Risperidone	Psycopharmaceuticals	µg/kg d.w.	0.079	0.18	0.21	0.40	0.088	0.096
Sertraline	Psycopharmaceuticals	µg/kg d.w.	0.044	0.10	<0.038	<0.038	<0.038	0.044
Simvastatin	Metabolic disease medications	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11
Sotalol	Other cardiovascular medicines	µg/kg d.w.	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11
Sulfamethoxazole	Antibiotics	µg/kg d.w.	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12
Telmisartan	Antihypertensives	µg/kg d.w.	0.65	N/A	0.28	N/A	N/A	N/A
Temazepam	Psycopharmaceuticals	µg/kg d.w.	<0.087	<0.087	<0.087	0.36	0.14	0.13
Testosterone	Hormones	µg/kg d.w.	<0.20	<0.20	<0.20	<0.20	<0.20	<0.20
Tetracycline/Doxycycli	Antibiotics	µg/kg d.w.	<1.6	<1.6	<1.6	<1.6	<1.6	<1.6
Tiamulin	Veterinary medicines	µg/kg d.w.	<0.044	<0.044	<0.044	4.9	<0.044	<0.044
Toltrazuril	Veterinary medicines	µg/kg d.w.	<4.6	<4.6	<4.6	<4.6	<4.6	<4.6
Tramadol	NSAIDs and analgesics	µg/kg d.w.	0.92	0.34	0.80	1.5	0.31	0.34
Trimethoprim	Antibiotics	µg/kg d.w.	0.15	0.074	0.060	0.25	0.059	0.059
Tylosin	Veterinary medicines	µg/kg d.w.	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2
Valsartan	Antihypertensives	µg/kg d.w.	<0.092	<0.092	<0.092	0.21	0.17	<0.092
Venlafaxine	Psycopharmaceuticals	µg/kg d.w.	0.093	<0.044	0.080	0.20	<0.044	0.12
Warfarin	Other cardiovascular medicines	µg/kg d.w.	0.018	<0.006	<0.006	0.048	<0.006	<0.006
Xylometazoline	Asthma and allergy medications	µg/kg d.w.	2.3	<0.046	7.2	<0.046	<0.046	<0.046
	Number of analysed API		63	63	63	63	63	63
	Number of APIs above LOQ		17	18	20	24	16	19
	Detection rate (%)		27	29	32	38	25	30
	Sum concentration (µg/kg d.w.)		13.6	38.9	68.1	167.4	20.1	47.1

Annex 18. Predicted vs. measured API loads in WWTP influents




Gabapentin
Hydrochlorothiazide
Ketoprofen
Levetiracetam
Mesalazine
Metformin
measured API load [mg/inh*d]
predicted API load [mg/inh*d]
too low
similar
too high
Finland
Sweden
Germany
Latvia
Estonia

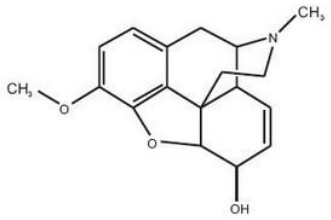

Naproxen
Norethisterone
Oxazepam
Paracetamol
Sotalol
Sulfamethoxazole
measured API load [mg/inh*d]
predicted API load [mg/inh*d]
too low
similar
too high
Finland
Sweden
Germany
Latvia
Estonia


Telmisartan
Tramadol
Trimethoprim
Venlafaxine
measured API load [mg/inh*d]
predicted API load [mg/inh*d]
too low
similar
too high
Finland
Sweden
Germany
Latvia
Estonia
0.0
1.5
3.0
0.5
1.0
0.3

Annex 19. API descriptions

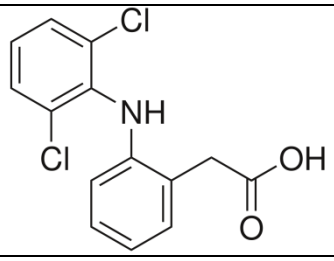
NSAIDs and analgesics

Codeine

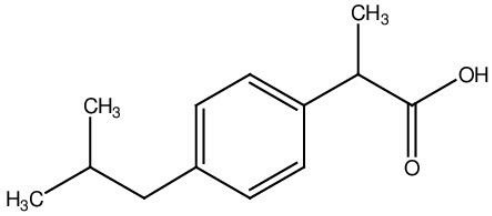
CAS number	76-57-3
ATC code	N02AA
ATC name (2nd level, therapeutic subgroup)	ANALGESICS (N02)
ATC name (4th level, chemical substance)	Natural opium alkaloids (N02AA), Opioids in combination with non-opioid analgesics (N02AJ)
Uses	Relief of mild to moderately severe pain.
Mechanism of action	Codeine selectively binds to mu-opioid receptors, which are involved in the transmission of pain throughout the body and central nervous system. The analgesic properties of codeine are thought to arise from its conversion to Morphine, although the exact mechanism of analgesic action is unknown at this time.
Metabolism/Excretion	Approximately 70 to 80% of the ingested dose of codeine is metabolized in the liver by conjugation, O-demethylation and N-demethylation. About 90% of the total dose of codeine is excreted by the kidneys. **Approximately 10% of the drug excreted by the kidneys is unchanged codeine.**
Molecular weight	299.37
Molecular formula	C18H21NO3
SMILES	CN1CCC23C4C1CC5=C2C(=C(C=C5)OC)OC3C(C=C4)O
Water solubility:	0.03 M (PubMed)
Log Kow	1.19 (PubChem)
Structure	

Diclofenac

CAS number	15307-86-5
ATC code	M01AB05
ATC name (2nd level, therapeutic subgroup)	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)
ATC name (4th level, chemical substance)	Acetic acid derivatives and related substances (M01AB)
Uses	Used to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis.
Mechanism of action	Inhibits cyclooxygenase-1 and -2, the enzymes responsible for production of prostaglandin (PG) G2 which is the precursor to other PGs.
Metabolism/Excretion	Undergoes oxidative metabolism to hydroxy metabolites as well as conjugation to glucuronic acid, sulfate, and taurine in the liver. Diclofenac is mainly eliminated via metabolism. **Little or no free unchanged diclofenac is excreted in the urine.** Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites.

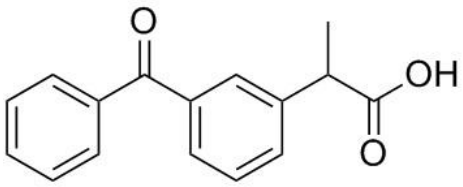
Molecular weight	295.017
Molecular formula	C14H11Cl2NO2
SMILES	C1=CC=C(C(=C1)CC(=O)O)NC2=C(C=CC=C2Cl)Cl
Water solubility:	2.37 mg/L at 25 deg C (PubChem)
Log Kow	4.51 (PubChem)
Structure	

Ibuprofen

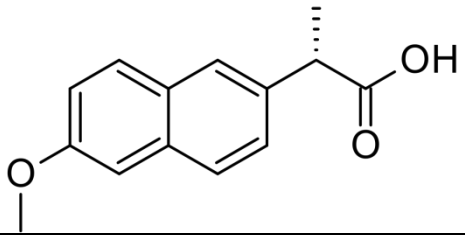
CAS number	15687-27-1
ATC code	M01AE01
ATC name (2nd level, therapeutic subgroup)	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)
ATC name (4th level, chemical substance)	Propionic acid derivatives (M01AE)
Uses	Used to reduce fever and treat pain or inflammation caused by many conditions such as headache, toothache, back pain, arthritis, menstrual cramps, or minor injury.
Mechanism of action	Non-selective inhibitor of cyclooxygenase, which is an enzyme involved in prostaglandin (mediators of pain and fever) and thromboxane (stimulators of blood clotting) synthesis via the arachidonic acid pathway.
Metabolism/Excretion	Metabolized and biotransformed in the liver to the formation of major metabolites which are the hydroxylated and carboxylated derivatives. Excreted as metabolites or their conjugates. **Ibuprofen is almost completely metabolized, with little to no unchanged drug found in the urine.** The elimination of ibuprofen is not impaired by old age or the presence of renal impairment.
Molecular weight	206.285
Molecular formula	C13H18O2
SMILES	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O
Water solubility:	21 mg/L (at 25 °C) (DrugBank)
Log Kow	3.97 (PubChem)
Structure	

Ketoprofen

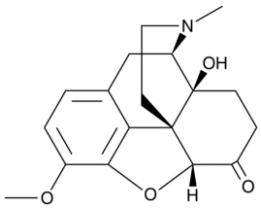
CAS number	22071-15-4
ATC code	M01AE03
ATC name (2nd level, therapeutic subgroup)	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)
ATC name (4th level, chemical substance)	Propionic acid derivatives (M01AE)

Uses	Used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and alleviate moderate pain.
Mechanism of action	Inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation.
Metabolism/Excretion	Rapidly and extensively metabolized in the liver, primarily via conjugation to glucuronic acid. No active metabolites have been identified. In a 24 hour period, approximately 80% of an administered dose of ketoprofen is excreted in the urine, primarily as the glucuronide metabolite. **Virtually no drug is eliminated unchanged.**
Molecular weight	254.285
Molecular formula	C16H14O3
SMILES	CC(C1=CC=CC(=C1)C(=O)C2=CC=CC=C2)C(=O)O
Water solubility:	2.13e-02 g/L (PubChem)
Log Kow	3.12 (SANGSTER (1993))
Structure	

Naproxen

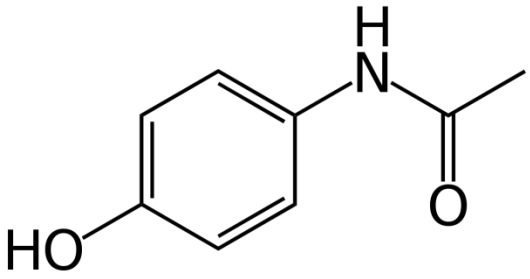
CAS number	22204-53-1
ATC code	M01AE02
ATC name (2nd level, therapeutic subgroup)	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)
ATC name (4th level, chemical substance)	Propionic acid derivatives (M01AE)
Uses	Used to treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps.
Mechanism of action	Clinical effects by blocking COX-1 and COX-2 enzymes leading to decreased prostaglandin synthesis.
Metabolism/Excretion	Heavily metabolized in the liver and undergoes both Phase I and Phase II metabolism. Approximately 95% of the Naproxen from any dose is **excreted in the urine,** primarily as **Naproxen (<1%), 6-0-desmethyl Naproxen (<1%) or their conjugates (66% to 92%).**
Molecular weight	230.263
Molecular formula	C14H14O3
SMILES	CC(C1=CC2=C(C=C1)C=C(C=C2)OC)C(=O)O
Water solubility:	15.9 mg/L at 25 deg C (PubChem)
Log Kow	3.18 (PubChem)
Structure	

Oxycodone

CAS number	76-42-6
ATC code	N02AA05
ATC name (2nd level, therapeutic subgroup)	ANALGESICS (N02)
ATC name (4th level, chemical substance)	Natural opium alkaloids (N02AA)
Uses	Used to treat moderate to severe pain.
Mechanism of action	Binding to a receptor, inhibition of adenylyl-cyclase and hyperpolarisation of neurons, and decreased excitability.
Metabolism/Excretion	Metabolism is hepatic. Metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone. Noroxycodone is a weaker opioid agonist than the parent compound, but the presence of this active metabolite increases the potential for interactions with other drugs metabolized by the CYP3A4 pathway. Oxycodone is mainly eliminated in the urine. Approximately 72% of an oxycodone dose is excreted in the urine; 8% as oxycodone, 47% as oxidative metabolites and 18% as reduced metabolites. 97% of excreted oxycodone is unconjugated. Of the oxidative metabolites, 93% of oxymorphone is excreted in its glucuronidated form, while noroxycodone is mostly unconjugated when excreted. When oxymorphone is administered directly to a subject, only 50% of the dose is excreted in the urine. 44% of the original dose is excreted as oxymorphone-3-glucuronide with the remaining 6% excreted as unchanged oxymorphone or as reduced metabolites. **Oxycodone** and its metabolites primarily undergo urinary excretion with **less than 10% of the parent compound excreted unchanged.**
Molecular weight	315.4
Molecular formula	C18H21NO4
SMILES	CN1CCC23C4C(=O)CCC2(C1CC5=C3C(=C(C=C5)OC)O4)O
Water solubility:	166mg/mL (DrugBank)
Log Kow	0.66 (est) (PubChem)
Structure	

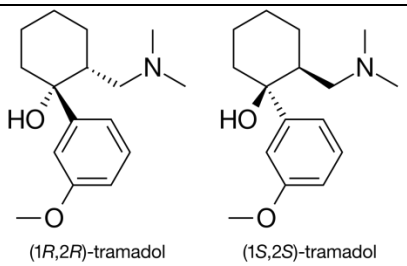
Paracetamol

CAS number	103-90-2
ATC code	N02BE01
ATC name (2nd level, therapeutic subgroup)	ANALGESICS (N02)
ATC name (4th level, chemical substance)	Anilides (N02BE)
Uses	Used to treat many conditions such as headache, muscle aches, arthritis, backache, toothaches, colds, and fevers.
Mechanism of action	Categorized as an NSAID (a nonsteroidal anti-inflammatory drug) due to that fact that it inhibits the cyclooxygenase (COX) pathways, and it is

	thought to exert central actions which ultimately lead to the alleviation of pain symptoms
Metabolism/Excretion	Acetaminophen is the major metabolite of *phenacetin* and *acetanilid*. Acetaminophen is mainly metabolized in the liver by first-order kinetics and its metabolism. Metabolites are excreted through the kidneys in the urine. **Only 2-5% of the dose is excreted in an unchanged form in the urine.** As a consequence of its short elimination half-life (1-3h), 24 hours after the ingestion of a single dose of paracetamol, 98% of the dose is eliminated.
Molecular weight	151.166
Molecular formula	C8H9NO2
SMILES	CC(=O)NC1=CC=C(C=C1)O
Water solubility:	14,000 mg/L at 25 deg C (PubChem)
Log Kow	0.46 (PubChem)
Structure	

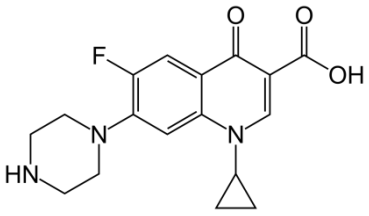
Tramadol

CAS number	27203-92-5
ATC code	N02AX02
ATC name (2nd level, therapeutic subgroup)	ANALGESICS (N02)
ATC name (4th level, chemical substance)	Other opioids (N02AX)
Uses	Used to help relieve moderate to moderately severe pain.
Mechanism of action	Tramadol is a centrally acting μ-opioid receptor agonist and SNRI. Tramadol exists as a racemic mixture consisting of two pharmacologically active enantiomers that both contribute to its analgesic property through different mechanisms.
Metabolism/Excretion	Undergoes extensive first-pass metabolism in the liver by N- and O-demethylation and conjugation. From the extensive metabolism, there have been identified at least 23 metabolites. **Approximately 30% of the dose is excreted in the urine as unchanged drug**, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites.
Molecular weight	263.381
Molecular formula	C16H25NO2
SMILES	CN(C)CC1CCCCC1(C2=CC(=CC=C2)OC)O
Water solubility:	1151 mg/L at 25 deg C (est) (PubChem)
Log Kow	3.01 (est) (PubChem)

Structure	 (1*R*,2*R*)-tramadol (1*S*,2*S*)-tramadol

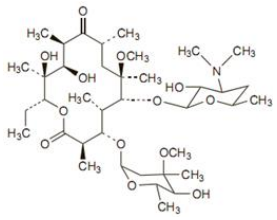
Antibiotics

Ciprofloxacin

CAS number	85721-33-1
ATC code	J01MA02
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Fluoroquinolones (J01MA)
Uses	An antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others.
Mechanism of action	Ciprofloxacin acts on bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Ciprofloxacin's targeting of the alpha subunits of DNA gyrase prevents it from supercoiling the bacterial DNA which prevents DNA replication.
Metabolism/Excretion	Ciprofloxacin is primarily metabolized in liver by CYP1A2. Converted into metabolites oxociprofloxacin and sulociprofloxacin and 2 minor metabolites desethylene ciprofloxacin and formylciprofloxacin. **Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug.**
Molecular weight	331.347
Molecular formula	C17H18FN3O3
SMILES	C1CC1N2C=C(C(=O)C3=CC(=C(C=C32)N4CCNCC4)F)C(=O)O
Water solubility:	30,000 mg/L at 20 deg C (PubChem)
Log Kow	0.28 (non-ionized) (PubChem)
Structure	

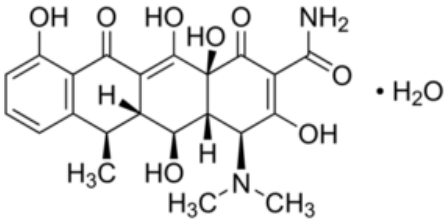
Clarithromycin

CAS number	81103-11-9
ATC code	J01FA01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level,	Macrolides (J01FA)

chemical substance)	
Uses	Used to treat many different types of bacterial infections affecting the skin and respiratory system.
Mechanism of action	Prevents bacteria from multiplying by acting as a protein synthesis inhibitor. It binds to 23S rRNA, a component of the 50S subunit of the bacterial ribosome, thus inhibiting the translation of peptides.
Metabolism/ Excretion	Partially hepatic metabolism via CYP3A4. Clarithromycin is converted to 14-OH clarithromycin (active metabolite); undergoes extensive first-pass metabolism. **Excreted primarily in the urine (20% to 40% as unchanged drug;** additional 10% to 15% as metabolite); feces (29% to 40% mostly as metabolites).
Molecular weight	748
Molecular formula	C38H69NO13
SMILES	CCC1C(C(C(C(=O)C(CC(C(C(C(C(C(=O)O1)C)OC2CC(C(C(O2)C)O)(C)OC)C)OC3C(C(CC(O3)C)N(C)C)O)(C)OC)C)C)O)(C)O
Water solubility:	1.693 mg/L at 25 deg C (est) (PubChem)
Log Kow	3.16 (PubChem)
Structure	

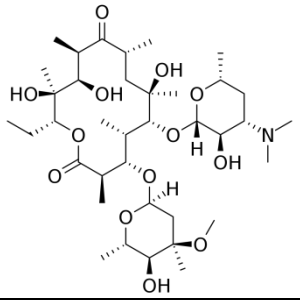
Doxycycline

CAS number	564-25-0
ATC code	J01AA02
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Tetracyclines (J01AA)
Uses	Used to treat many different bacterial infections, such as acne, urinary tract infections, intestinal infections, respiratory infections, eye infections, gonorrhea, chlamydia, syphilis, periodontitis (gum disease), and others.
Mechanism of action	Inhibits translation by binding to the 16S rRNA portion of the ribosome, preventing binding of tRNA to the RNA-30S bacterial ribosomal subunit, which is necessary for the delivery of amino acids for protein synthesis. As a result, the initiation of protein synthesis by polyribosome formation is blocked. This stops the replication of bacteria and produces a bacteriostatic effect.
Metabolism/Excretion	Metabolized in the liver and gastrointestinal tract and concentrated in bile. **Mainly eliminated via urine and feces as active and unchanged drug.** Between 40% and 60% of an administered dose can be accounted for in the urine by 92 hours, and approximately 30% can be accounted for in the feces.
Molecular weight	444.44

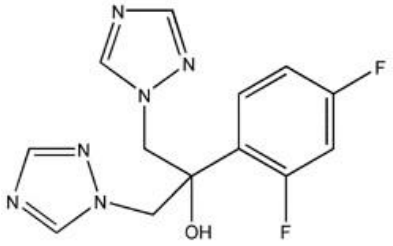
Molecular formula	C22H24N2O8
SMILES	CC1C2C(C3C(C(=O)C(=C(C3(C(=O)C2=C(C4=C1C=CC=C4O)O)O)O)C(=O)N)N(C)C)O
Water solubility:	50 mg/mL (DrugBank)
Log Kow	0.63 (PubChem)
Structure	

Erythromycin

CAS number	114-07-8
ATC code	J01FA01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Macrolides (J01FA)
Uses	Used to treat certain infections caused by bacteria, such as infections of the respiratory tract (bronchitis, pneumonia, Legionnaires' disease, pertussis); diphtheria; sexually transmitted diseases, including syphilis; and ear, intestine, gynecological, urinary tract, and skin infections. Also used to prevent recurrent rheumatic fever.
Mechanism of action	Erythromycin acts by inhibition of protein synthesis by binding to the 23S ribosomal RNA molecule in the 50S subunit of ribosomes in susceptible bacterial organisms. It stops bacterial protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.
Metabolism/ Excretion	Hepatic first-pass metabolism. Erythromycin concentrates in the liver and is then excreted in the bile. **Under 5% of the orally administered dose of erythromycin is found excreted in the urine.** A high percentage of absorbed erythromycin is not accounted for, but is likely metabolized.
Molecular weight	733.937
Molecular formula	C37H67NO13
SMILES	CCC1C(C(C(C(=O)C(CC(C(C(C(C(C(=O)O1)C)OC2CC(C(C(O2)C)O)(C)OC)C)OC3C(C(CC(O3)C)N(C)C)O)(C)O)C)C)O)(C)O
Water solubility:	4.2 mg/L at 25 deg C (est) (PubChem)
Log Kow	3.06 (PubChem)

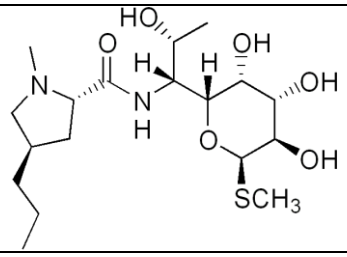
Structure	

Fluconazole

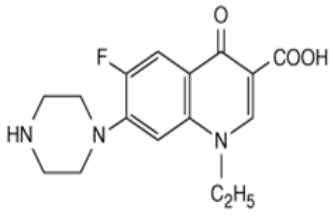
CAS number	86386-73-4
ATC code	J02AC01
ATC name (2nd level, therapeutic subgroup)	ANTIMYCOTICS FOR SYSTEMIC USE (J02)
ATC name (4th level, chemical substance)	Triazole derivatives (J02AC)
Uses	Used to prevent and treat a variety of fungal and yeast infections.
Mechanism of action	Fluconazole is a very selective inhibitor of fungal cytochrome P450 dependent enzyme *lanosterol 14-α-demethylase*. This enzyme normally works to convert *lanosterol* to *ergosterol*, which is necessary for fungal cell wall synthesis.
Metabolism/Excretion	Fluconazole is metabolized minimally in the liver. Fluconazole is cleared primarily by renal excretion, with **approximately 80% of the administered dose measured in the urine as unchanged drug.** About 11% of the dose is excreted in the urine as metabolites.
Molecular weight	306.277
Molecular formula	C13H12F2N6O
SMILES	OC(CN1C=NC=N1)(CN1C=NC=N1)C1=C(F)C=C(F)C=C1
Water solubility:	4,363 mg/L at 25 deg C (est) (PubChem)
Log Kow	0.25 at 25 deg C (est) (PubChem)
Structure	

Lincomycin

CAS number	154-21-2
ATC code	J01FF02
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Lincosamides (J01FF)
Uses	Used in the treatment of staphylococcal, streptococcal, and Bacteroides fragilis infections.
Mechanism of action	Lincomycin inhibits protein synthesis in susceptible bacteria by binding to the 50 S subunits of bacterial ribosomes and preventing peptide bond formation upon transcription. It is usually considered bacteriostatic, but may be bactericidal in high concentrations or when used against highly susceptible organisms.

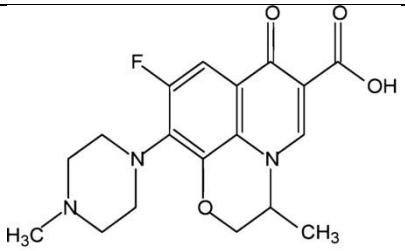
Metabolism/Excretion	Presumed hepatic, however metabolites have not been fully characterized. **Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3 percent).** Biliary excretion is also an important route of excretion.
Molecular weight	406.538
Molecular formula	C18H34N2O6S
SMILES	CCCC1CC(N(C1)C)C(=O)NC(C2C(C(C(C(O2)SC)O)O)O)C(C)O
Water solubility:	927 mg/L at 25 deg C (est) (PubChem)
Log Kow	0.20 (PubChem)
Structure	

Norfloxacin

CAS number	70458-96-7
ATC code	J01MA06
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Fluoroquinolones (J01MA)
Uses	Used to treat different bacterial infections of the prostate or urinary tract (bladder and kidneys). Norfloxacin is also used to treat gonorrhea.
Mechanism of action	Inhibits bacterial DNA gyrase. Norfloxacin is a broad-spectrum antibiotic agent that is shown to be effective against various Gram-positive and Gram-negative bacterial species.
Metabolism/Excretion	Metabolism in the liver and kidney. Norfloxacin is eliminated mainly through renal excretion. In the first 24 hours, 33 to 48% is recovered in the urine as norfloxacin. Six active metabolites of norfloxacin (5 to 8%) of lesser antimicrobial potency are also recovered in the urine. **The parent compound accounts for over 70% of total excretion.**
Molecular weight	319.336
Molecular formula	C16H18FN3O3
SMILES	CCN1C=C(C(=O)C2=CC(=C(C=C21)N3CCNCC3)F)C(=O)O
Water solubility:	0.28 mg/mL at 25 deg C. Solubility in water is pH dependent, increasing sharply at pH<5 or pH >10 (PubChem)
Log Kow	0.46 (PubChem)
Structure	

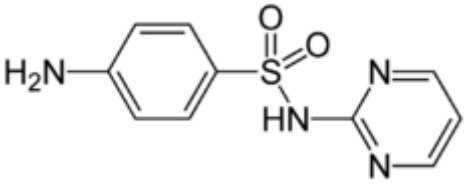
Ofloxacin

CAS number	82419-36-1
ATC code	J01MA01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)

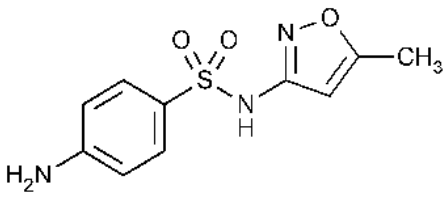
ATC name (4th level, chemical substance)	Fluoroquinolones (J01MA)
Uses	Used to treat bacterial infections of the skin, lungs, prostate, or urinary tract (bladder and kidneys). Ofloxacin is also used to treat pelvic inflammatory disease and Chlamydia and/or gonorrhea.
Mechanism of action	Inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replication.
Metabolism/Excretion	Hepatic. Ofloxacin is mainly eliminated by renal excretion, where **between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via urine** within 48 hours of dosing. About 4-8% of an ofloxacin dose is excreted in the feces and the drug is minimally subject to biliary excretion.
Molecular weight	361.373
Molecular formula	C18H20FN3O4
SMILES	CC1COC2=C3N1C=C(C(=O)C3=CC(=C2N4CCN(CC4)C)F)C(=O)O
Water solubility:	1.08X10+4 mg/L at 25 deg C (est) (PubChem)
Log Kow	-0.39 (PubChem)
Structure	

Sulfadiazine

CAS number	68-35-9
ATC code	J01EC02
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Intermediate-acting sulfonamides (J01EC)
Uses	Short-acting sulfonamides used in combination with pyrimethamine to treat toxoplasmosis in patients with acquired immunodeficiency syndrome and in newborns with congenital infections.
Mechanism of action	Sulfadiazine is a competitive inhibitor of the bacterial enzyme dihydropteroate synthetase. This enzyme is needed for the proper processing of para-aminobenzoic acid (PABA) which is essential for folic acid synthesis. The inhibited reaction is necessary in these organisms for the synthesis of folic acid.
Metabolism/Excretion	Metabolized partially in the liver. **Both unchanged drug and metabolites are excreted primarily in urine** by glomerular filtration and, to a lesser extent, renal tubular secretion; some drug appears in breast milk. Urine solubility of unchanged drug increases as urine pH increases.
Molecular weight	250.276
Molecular formula	C10H10N4O2S
SMILES	C1=CN=C(N=C1)NS(=O)(=O)C2=CC=C(C=C2)N
Water solubility:	77 mg/L (at 25 °C) (PubChem)
Log Kow	-0.09 (PubChem)

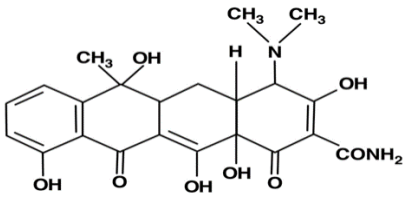
Structure	

Sulfamethoxazole

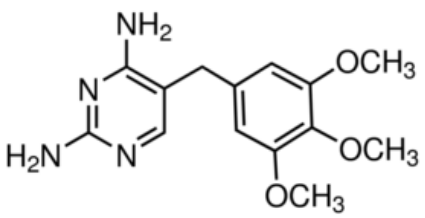
CAS number	723-46-6
ATC code	J01EC01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Intermediate-acting sulfonamides (J01EC)
Uses	Used to treat a wide variety of bacterial infections (such as middle ear, urine, respiratory, and intestinal infections). It is also used to prevent and treat a certain type of pneumonia (pneumocystis-type).
Mechanism of action	Bacteriostatic antibacterial agent that interferes with folic acid synthesis in susceptible bacteria. Its broad spectrum of activity has been limited by the development of resistance.
Metabolism/Excretion	The metabolism of sulfamethoxazole occurs predominately by N4-acetylation, although the glucuronide conjugate has been identified. **About 20% of the sulfamethoxazole in the urine is unchanged drug**, about 15 to 20% is the N-glucuronide conjugate, and about 50 to 70% is the acetylated metabolite. Sulfamethoxazole is also excreted in human milk.
Molecular weight	253.276
Molecular formula	C10H11N3O3S
SMILES	CC1=CC(=NO1)NS(=O)(=O)C2=CC=C(C=C2)N
Water solubility:	610 mg/L at 37 deg C (PubChem)
Log Kow	0.89 (PubChem)
Structure	

Tetracycline

CAS number	60-54-8
ATC code	J01AA07
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Tetracyclines (J01AA)
Uses	Used to treat a wide variety of infections, including acne.
Mechanism of action	Exerts a bacteriostatic effect on bacteria by binding reversible to the bacterial 30S ribosomal subunit and blocking incoming aminoacyl tRNA from binding to the ribosome acceptor site. It also binds to some extent to

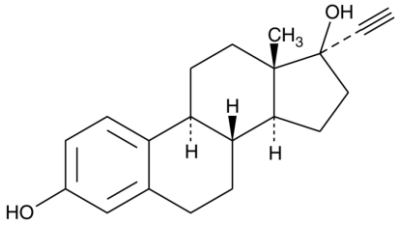
	the bacterial 50S ribosomal subunit and may alter the cytoplasmic membrane causing intracellular components to leak from bacterial cells.
Metabolism/Excretion	Metabolism is negligible. 40-55% of tetracycline is excreted from the body primarily by the kidney, the less part is excreted by the liver followed by reabsorption from the gastrointestinal tract. **About 60% is excreted unchanged in the urine during 24 h.**
Molecular weight	444.44
Molecular formula	C22H24N2O8
SMILES	CC1(C2CC3C(C(=O)C(=C(C3(C(=O)C2=C(C4=C1C=CC=C4O)O)O)O)C(=O)N)N(C)C)O
Water solubility:	231 mg/l at 25 deg C (PubChem)
Log Kow	-1.37 (PubChem)
Structure	

Trimethoprim

CAS number	738-70-5
ATC code	J01EA01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (J01)
ATC name (4th level, chemical substance)	Combinations of sulfonamides and trimethoprim, incl. Derivatives (J01EE)
Uses	Eliminates bacteria that cause urinary tract infections. It is used in combination with other drugs to treat certain types of pneumonia. It also is used to treat traveler's diarrhea.
Mechanism of action	Inhibits dihydrofolate reductase. This inhibition prevents the conversion of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF) in the thymidine synthesis pathway.
Metabolism/Excretion	Hepatic metabolism to oxide and hydroxylated metabolites. 10 to 20% of trimethoprim is metabolized, primarily in the liver; **approximately 60% to 80% of an administered dose of trimethoprim is excreted unchanged in the urine** via tubular secretion within 24 hours. The remainder of the drug is excreted by the kidney in one of four oxide or hydroxyl derivatives. The urinary metabolites are bacteriologically inactive.
Molecular weight	290.323
Molecular formula	C14H18N4O3
SMILES	COC1=CC(=CC(=C1OC)OC)CC2=CN=C(N=C2N)N
Water solubility:	400 mg/L (at 25 °C) (PubChem)
Log Kow	0.91 (PubChem)
Structure	

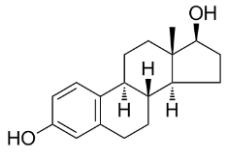
Hormones

17-α-ethinyl estradiol (EE2)

CAS number	57-63-6
ATC code	G03CA01 (ethinylestradiol)
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Natural and semisynthetic estrogens, plain (G03CA)
Uses	Used widely in birth control pills in combination with progestins.
Mechanism of action	Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) from the anterior pituitary. This cascade is initiated by initially binding to the estrogen receptors. The combination of an estrogen with a progestin suppresses the hypothalamic-pituitary system, decreasing the secretion of gonadotropin-releasing hormone (GnRH).
Metabolism/Excretion	Hepatic. Route of elimination not availible. The majority of estrogen elimination occurs through the kidneys in the form of sulfate or glucuronide conjugates.
Molecular weight	296.41
Molecular formula	C20H24O2
SMILES	CC12CCC3C(C1CCC2(C#C)O)CCC4=C3C=CC(=C4)O
Water solubility:	11.3 mg/L at 27 °C (DrugBank)
Log Kow	3.67 (DrugBank)
Structure	

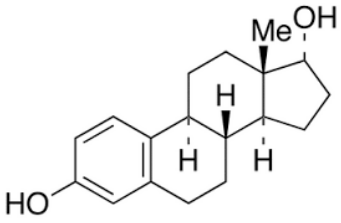
17-β-estradiol (E2)

CAS number	50-28-2
ATC code	G03CA03 (estradiol)
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Natural and semisynthetic estrogens, plain (G03CA)
Uses	Used in hormone therapy products for managing conditions associated with reduced estrogen production such as menopausal and peri-menopausal symptoms as well as hypoestrogenism. It is also used in transgender hormone therapy, as a component of oral contraceptive pills for preventing pregnancy (most commonly as Ethinylestradiol, a synthetic form of estradiol), and is sometimes used for the palliative treatment of some hormone-sensitive cancers like breast and prostate cancer.
Mechanism of action	When the estrogen receptor has bound its ligand it can enter the nucleus of the target cell, and regulate gene transcription which leads to formation of messenger RNA. The mRNA interacts with ribosomes to produce specific proteins that express the effect of estradiol upon the target cell. Estrogens increase the hepatic synthesis of sex hormone

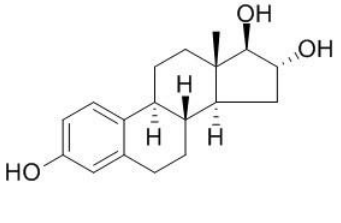
	binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) from the anterior pituitary.
Metabolism/Excretion	Exogenous estrogens are metabolized using the same mechanism as endogenous estrogens. Estrogens are partially metabolized by CYP450. Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.
Molecular weight	272.38
Molecular formula	C18H24O2
SMILES	CC12CCC3C(C1CCC2O)CCC4=C3C=CC(=C4)O
Water solubility:	3.90 mg/L at 27 °C (DrugBank)
Log Kow	4.01 (DrugBank)
Structure	

α-Estradiol

CAS number	57-91-0
ATC code	G03CA03 (estradiol)
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Natural and semisynthetic estrogens, plain (G03CA)
Uses	Used as a medication, primarily in hormone therapy for menopausal symptoms as well as transgender hormone replacement therapy.
Mechanism of action	Estrogen mediates its effects across the body through potent agonism of the Estrogen Receptor (ER), which is located in various tissues including in the breasts, uterus, ovaries, skin, prostate, bone, fat, and brain. Estradiol binds to both subtypes of the Estrogen Receptor. When the estrogen receptor has bound its ligand it can enter the nucleus of the target cell, and regulate gene transcription which leads to formation of messenger RNA. Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) from the anterior pituitary.
Metabolism/Excretion	Exogenous estrogens are metabolized using the same mechanism as endogenous estrogens. Estrogens are partially metabolized by CYP450. Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.
Molecular weight	272.388
Molecular formula	C18H24O2
SMILES	CC12CCC3C(C1CCC2O)CCC4=C3C=CC(=C4)O
Water solubility:	3.6 mg/L (at 27 °C) (PubChem)
Log Kow	4.01 (PubChem)

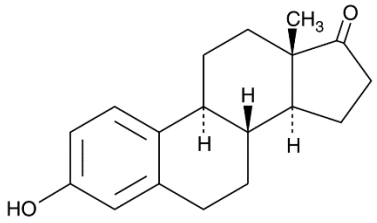
Structure	

Estriol (E3)

CAS number	50-27-1
ATC code	G03CA04
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Natural and semisynthetic estrogens, plain (G03CA)
Uses	Used for the treatment of post-menopausal hot flashes.
Mechanism of action	When the estrogen receptor has bound its ligand it can enter the nucleus of the target cell, and regulate gene transcription which leads to formation of messenger RNA. The mRNA interacts with ribosomes to produce specific proteins that express the effect of estriol upon the target cell. Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) from the anterior pituitary.
Metabolism/Excretion	In the liver, it is non-specifically metabolized by CYP1A2, CYP3A4, and CYP2C9 via 2-hydroxylation into 2-hydroxyestradiol, and by CYP2C9, CYP2C19, and CYP2C8 via 17β-hydroxy dehydrogenation into estrone, with various other CYP450 enzymes and metabolic transformations also being involved. Estriol is excreted more than 95% in urine.
Molecular weight	288.173
Molecular formula	C18H24O3
SMILES	CC12CCC3C(C1CC(C2O)O)CCC4=C3C=CC(=C4)O
Water solubility:	27.34 mg/L at 25 °C (est) (DrugBank)
Log Kow	2.45 (DrugBank)
Structure	

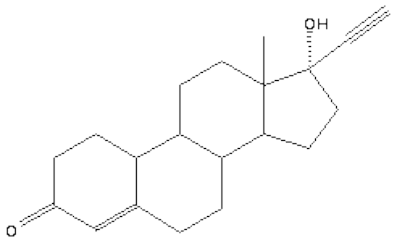
Estrone (E1)

CAS number	53-16-7
ATC code	G03CA07
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Natural and semisynthetic estrogens, plain (G03CA)

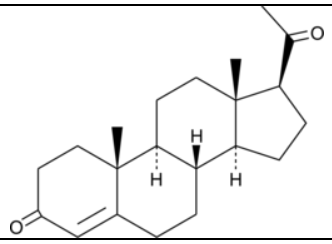
Uses	Used as an estrogen in the treatment of symptoms of low estrogen levels such as hot flashes and vaginal atrophy in postmenopausal or ovariectomized women.
Mechanism of action	Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) release from the anterior pituitary.
Metabolism/Excretion	Estrone is conjugated into estrogen conjugates such as estrone sulfate and estrone glucuronide by sulfotransferases and glucuronidases, and can also be hydroxylated by cytochrome P450 enzymes into catechol estrogens such as 2-hydroxyestrone and 4-hydroxyestrone or into estriol. Excreted in urine in the form of estrogen conjugates such as estrone sulfate.
Molecular weight	270.372
Molecular formula	C18H22O2
SMILES	CC12CCC3C(C1CCC2=O)CCC4=C3C=CC(=C4)O
Water solubility:	0.003 g/100 mL at 25 °C (PubChem)
Log Kow	3.13 (PubChem)
Structure	

Norethisterone

CAS number	68-22-4
ATC code	G03DC02
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Estren derivatives (G03DC)
Uses	Used for the treatment of amenorrhea; abnormal uterine bleeding; endometriosis; and for the prevention of pregnancy.
Mechanism of action	Norethisterone is a progestin, or a synthetic progestogen, and hence is an agonist of the progesterone receptor, the biological target of progestogens like progesterone. It has weak androgenic and estrogenic activity, mostly at high dosages, and no other important hormonal activity.
Metabolism/Excretion	Metabolized in the liver via hydroxylation as well, mainly by CYP3A4. Approximately 60% of the administered dose is excreted as metabolites in urine and faeces.
Molecular weight	298.426
Molecular formula	C20H26O2
SMILES	CC12CCC3C(C1CCC2(C#C)O)CCC4=CC(=O)CCC34
Water solubility:	7.04 mg/L water at 25 °C (PubChem)
Log Kow	2.97 (PubChem)

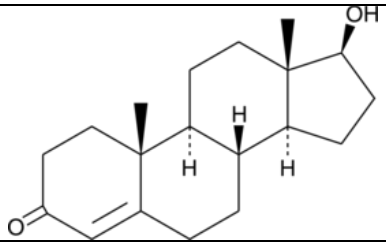
Structure	

Progesterone

CAS number	57-83-0
ATC code	G03DA04
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	Pregnen-(4) derivatives (**G03DA)**
Uses	Used to cause menstrual periods in women who have not yet reached menopause but are not having periods due to a lack of progesterone in the body. It is also used to prevent overgrowth in the lining of the uterus in postmenopausal women who are receiving estrogen hormone replacement therapy.
Mechanism of action	Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. During implantation and gestation, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy. Progesterone decreases contractility of the uterine smooth muscle.
Metabolism/Excretion	Metabolism occurs mainly in the liver, though enzymes that metabolize progesterone are also expressed widely in the brain, skin, and various other extrahepatic tissues. Metabolites are excreted mainly by the kidneys. Progesterone metabolites, excreted in the bile, may undergo enterohepatic recycling or may be found excreted in the feces.
Molecular weight	314.469
Molecular formula	C21H30O2
SMILES	CC(=O)C1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C
Water solubility:	8.81 mg/L at 25 °C (PubChem)
Log Kow	3.87 (PubChem)
Structure	

Testosterone

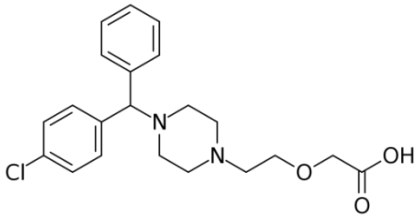
CAS number	58-22-0
ATC code	G03BA03
ATC name (2nd level, therapeutic subgroup)	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)
ATC name (4th level, chemical substance)	3-oxoandrosten-(4) derivatives (**G03BA)**
Uses	Used primarily to treat symptoms of sexual dysfunction in men and women and hot flashes in women. Potential benefits include improved libido, increased bone mass, and increased sense of well-being.

Mechanism of action	Testosterone and its androgenic metabolite, dihydrotestosterone, exert biological effects directly through binding to the androgen receptor and indirectly through aromatization of testosterone to estradiol, which allows action via binding to the estrogen receptor (ER).
Metabolism/Excretion	Testosterone is metabolized to 17-keto steroids through two different pathways. The major active metabolites are estradiol and dihydrotestosterone (DHT). Testosterone can be hydroxylated at a number of positions by CYP3A4, CYP2B6, CYP2C9, and CYP2C19. Androstenedione undergoes metabolism by aromatase to form estrone, which undergoes a reversible reaction to form estradiol. 90% of an intramuscular dose is eliminated in urine, mainly as glucuronide and sulfate conjugates. 6% is eliminated in feces, mostly as unconjugated metabolites.
Molecular weight	288.431
Molecular formula	C19H28O2
SMILES	CC12CCC3C(C1CCC2O)CCC4=CC(=O)CCC34C
Water solubility:	23.4 mg/L at 25 °C (PubChem)
Log Kow	3.32 (PubChem)
Structure	

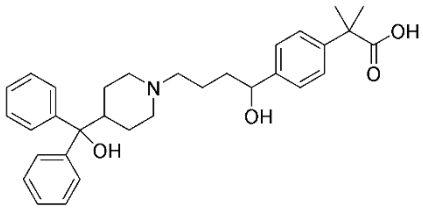
Asthma and allergy medications

Cetirizine

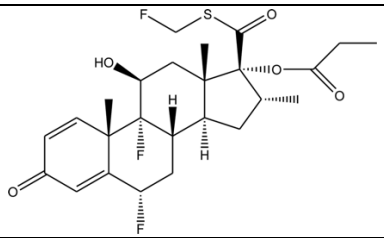
CAS number	83881-51-0
ATC code	R06AE07
ATC name (2nd level, therapeutic subgroup)	ANTIHISTAMINES FOR SYSTEMIC USE (R06)
ATC name (4th level, chemical substance)	Piperazine derivatives (R06AE)
Uses	Used in the treatment of various allergic symptoms, such as sneezing, coughing, nasal congestion, hives, and other symptoms.
Mechanism of action	Cetirizine, a metabolite of *hydroxyzine*, is an antihistamine drug. Its main effects are achieved through selective inhibition of peripheral H1 receptors.
Metabolism/Excretion	Cetirizine is metabolized partially by oxidative O-dealkylation to a metabolite with insignificant antihistaminic activity. Mainly eliminated in the urine. Between 70 – 85% of an orally administered dose can be found in the urine and 10 – 13% in the feces. **About 50 or 60% of cetirizine eliminated in the urine is unchanged.**
Molecular weight	388.9
Molecular formula	C21H25ClN2O3
SMILES	OC(=O)COCCN1CCN(CC1)C(C1=CC=CC=C1)C1=CC=C(Cl)C=C1
Water solubility:	6.96X10+4 mg/L at 25 deg C (est) (PubChem)
Log Kow	1.70 (PubChem)

Structure	

Fexofenadine

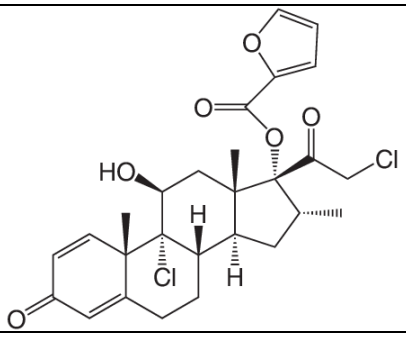
CAS number	83799-24-0
ATC code	R06AX26
ATC name (2nd level, therapeutic subgroup)	ANTIHISTAMINES FOR SYSTEMIC USE (R06)
ATC name (4th level, chemical substance)	Other antihistamines for systemic use (R06AX)
Uses	Used to relieve allergy symptoms such as watery eyes, runny nose, itching eyes/nose, sneezing, hives, and itching.
Mechanism of action	Competes with free histamine for binding at H1-receptors in the GI tract, large blood vessels, and bronchial smooth muscle. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms (eg. nasal congestion, watery eyes) brought on by histamine.
Metabolism/Excretion	Approximately 5% of the total dose is metabolized, by cytochrome P450 3A4 and by intestinal microflora. **Most of the substance is eliminated unchanged via the faeces (80%) and urine (11–12%).**
Molecular weight	501.288
Molecular formula	C32H39NO4
SMILES	CC(C)(C1=CC=C(C=C1)C(CCCN2CCC(CC2)C(C3=CC=CC=C3)(C4=CC=CC=C4)O)O)C(=O)O
Water solubility:	2.4X10-2 mg/L at 25 deg C (est) (PubChem)
Log Kow	5.6 (PubChem)
Structure	

Fluticasone

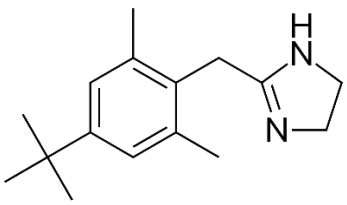
CAS number	80474-14-2
ATC code	R03BA05
ATC name (2nd level, therapeutic subgroup)	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03)
ATC name (4th level, chemical substance)	Glucocorticoids (R03BA)
Uses	Used to relieve seasonal and year-round allergic and non-allergic nasal symptoms, such as stuffy/runny nose, itching, and sneezing. It can also help relieve allergy eye symptoms such as itchy, watery eyes.
Mechanism of action	Synthetic glucocorticoid available as 2 esters. Fluticasone furoate and Fluticasone propionate work through an unknown mechanism to affect the action of various cell types and mediators of inflammation.
Metabolism/Excretion	Cleared from hepatic metabolism by cytochrome P450 3A4. Fluticasone propionate administered orally majority of the dose (87%-100%) is **excreted in the faeces, with up to 75% as unchanged drug**, depending on the dose administered. Between 1% and 5% of the dose is excreted as metabolites in urine.
Molecular weight	444.509
Molecular formula	C22H27F3O4S
SMILES	CC1CC2C3CC(C4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)SCF)O)C)O)F)C)F
Water solubility:	102 mg/L at 25 deg C (est) (PubChem)
Log Kow	1.40 (est) (PubChem)
Structure	

Mometasone

CAS number	105102-22-5
ATC code	R03BA07
ATC name (2nd level, therapeutic subgroup)	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03)
ATC name (4th level, chemical substance)	Glucocorticoids (R03BA)
Uses	Used to treat skin conditions such as eczema, psoriasis, allergies, and rash. Mometasone decreases swelling (inflammation), itching, and redness.
Mechanism of action	Unbound corticosteroids cross cell membranes and bind with high affinity to specific cytoplasmic receptors. Inflammation is decreased by diminishing the release of leukocytic acid hydrolases, prevention of macrophage accumulation at inflamed sites, interference with leukocyte adhesion to the capillary wall, reduction of capillary membrane permeability, reduction of complement components, inhibition of histamine and kinin release, and interference with the formation of scar

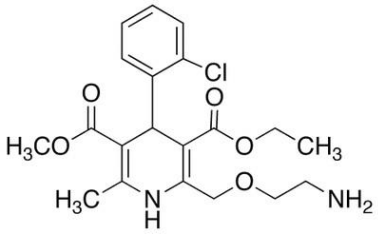
	tissue. The antiinflammatory actions of corticosteroids are thought to involve phospholipase A_2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.
Metabolism/Excretion	Hepatic. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.
Molecular weight	427.362
Molecular formula	C22H28Cl2O4
SMILES	CC1CC2C3CCC4=CC(=O)C=CC4(C3(C(CC2(C1(C(=O)CCl)O)C)O)Cl)C
Water solubility:	5.23e-03 g/L (PubChem)
Log Kow	2.1 (PubChem)
Structure	

Xylometazoline

CAS number	526-36-3
ATC code	R01AA07
ATC name (2nd level, therapeutic subgroup)	NASAL PREPARATIONS (R01)
ATC name (4th level, chemical substance)	Sympathomimetics, plain (R01AA)
Uses	Used to treat stuffy nose caused by allergies, sinus irritation, or the common cold.
Mechanism of action	Sympathomimetic drug, which acts on alpha-adrenergic receptors in the arterioles of the nasal mucosa. This activates the adrenal system to yield systemic vasoconstrction. In producing vasoconstriction, the result is a decrease in blood flow in the nasal passages and consequently decreased nasal congestion.
Metabolism/Excretion	Imidazoline compounds undergo some hepatic metabolism but **large proportions of the ingested dose may be excreted unchanged in the urine**.
Molecular weight	244.382
Molecular formula	C16H24N2
SMILES	CC1=CC(=CC(=C1CC2=NCCN2)C)C(C)(C)C
Water solubility:	0.00893 mg/mL (DrugBank)
Log Kow	3.2 (PubChem)
Structure	

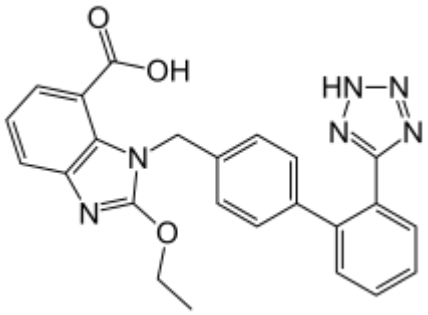
Antihypertensives

Amlodipine

CAS number	88150-42-9
ATC code	C08CA01
ATC name (2nd level, therapeutic subgroup)	CALCIUM CHANNEL BLOCKERS (C08)
ATC name (4th level, chemical substance)	Dihydropyridine derivatives (C08CA)
Uses	Used to treat high blood pressure.
Mechanism of action	Dihydropyridine L-type calcium channel blocker that selectively inhibits calcium influx in cardiac and vascular smooth muscle. Acting as a vasodilator, amlodipine reduces blood pressure by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance.
Metabolism/Excretion	Extensively (about 90%) converted to inactive metabolites via hepatic metabolism with **10% of the parent compound** and 60% of the metabolites **excreted in urine**.
Molecular weight	408.88
Molecular formula	C20H25ClN2O5
SMILES	CCOC(=O)C1=C(NC(=C(C1C2=CC=CC=C2Cl)C(=O)OC)C)COCCN
Water solubility:	5.3 mg/L at 25 deg C (est) (PubChem)
Log Kow	3.00 (PubChem)
Structure	

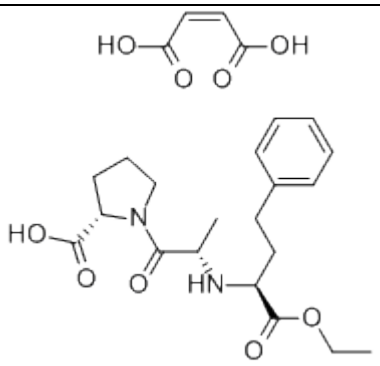
Candesartan

CAS number	139481-59-7
ATC code	C09CA06
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (C09CA)
Uses	Used to treat high blood pressure.
Mechanism of action	Candesartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II.
Metabolism/Excretion	The prodrug candesartan cilexetil undergoes rapid and complete ester hydrolysis in the intestinal wall to form the active drug, candesartan. Elimination of candesartan is primarily as unchanged drug in the urine and, by the biliary route, in the feces. Minor hepatic metabolism of candesartan (<20%) occurs by O-deethylation via cytochrome P450 2C9 to form an inactive metabolite. Candesartan undergoes N-glucuronidation in the tetrazole ring by uridine diphosphate glucuronosyltransferase 1A3 (UGT1A3). O-glucuronidation may also occur. **75% of candesartan is excreted as unchanged drug in urine and feces.**

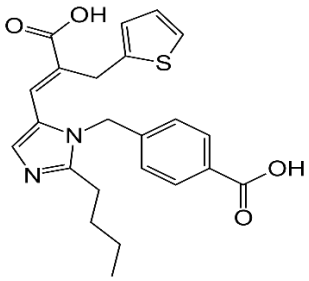
Molecular weight	440.5
Molecular formula	C24H20N6O3
SMILES	CCOC1=NC2=CC=CC(=C2N1CC3=CC=C(C=C3)C4=CC=CC=C4C5=NNN=N5)C(=O)O
Water solubility:	1.4X10-1 mg/L at 25 deg C (est) (PubChem)
Log Kow	4.79 (est) (PubChem)
Structure	

Enalapril maleate salt

CAS number	75847-73-3
ATC code	C09AA02
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	**ACE inhibitors, plain (C09AA)**
Uses	Used to treat high blood pressure in adults and children who are at least 1 month old. Enalapril is also used to treat congestive heart failure (CHF).
Mechanism of action	The active metabolite of enalapril competitively inhibits the ACE to hinder the production of angiotensin II, a key component of the renin-angiotensin-aldosterone system that promotes vasoconstriction and renal reabsorption of sodium ions in the kidneys. Ultimately, enalaprilat works to reduce blood pressure and blood fluid volume.
Metabolism/Excretion	About 60% of the absorbed dose is extensively hydrolyzed to enalaprilat via de-esterification mediated by hepatic esterases. Mainly eliminated through renal excretion, where **approximately 94% of the total dose is excreted via urine or feces as either enalaprilat or unchanged parent compound**. About 61% and 33% of the total dose can be recovered in the urine and feces, respectively. In the urine, about 40% of the recovered dose is in the form of enalaprilat.
Molecular weight	376.2
Molecular formula	C20H28N2O5
SMILES	CCOC(=O)C(CCC1=CC=CC=C1)NC(C)C(=O)N2CCCC2C(=O)O
Water solubility:	1.64E+004 mg/L (PubChem)
Log Kow	0.07 at pH 4.9 (DrugBank)

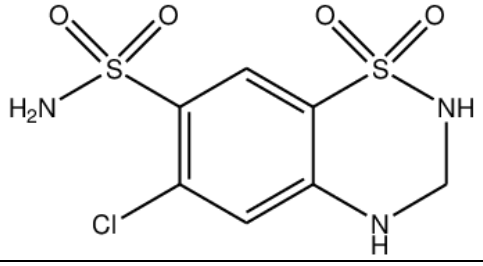
Structure	

Eprosartan

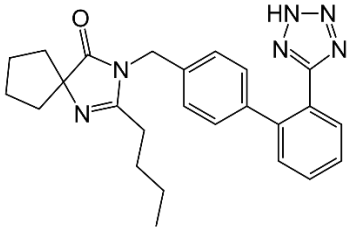
CAS number	133040-01-4
ATC code	C09CA02
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (**C09CA)**
Uses	Used to treat high blood pressure.
Mechanism of action	Blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland).
Metabolism/Excretion	Eprosartan is **not metabolized** by the cytochrome P450 system. It is **mainly eliminated as unchanged drug.** Less than 2% of an oral dose is excreted in the urine as a glucuronide.
Molecular weight	424.513
Molecular formula	C23H24N2O4S
SMILES	CCCCC1=NC=C(N1CC2=CC=C(C=C2)C(=O)O)C=C(CC3=CC=CS3)C(=O)O
Water solubility:	1.9X10-2 mg/L at 25 deg C (est) (PubChem)
Log Kow	6.37 (est) (PubChem)
Structure	

Hydrochlorothiazide

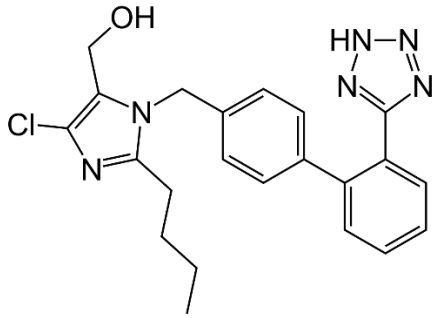
CAS number	58-93-5
ATC code	C03AA03
ATC name (2nd level, therapeutic subgroup)	DIURETICS (C03)
ATC name (4th level, chemical substance)	Thiazides, plain (C03AA)
Uses	Used to treat high blood pressure (hypertension). Hydrochlorothiazide is also used to treat fluid retention (edema) in people with congestive

	heart failure, cirrhosis of the liver, or kidney disorders, or edema caused by taking steroids or estrogen.
Mechanism of action	Hydrochlorothiazide acts on the distal convoluted tubules and inhibits the sodium chloride co-transporter system. This action leads to a diuretic action and loss of potassium in the urine.
Metabolism/Excretion	Hydrochlorothiazide is **not metabolized**. Hydrochlorothiazide is **eliminated in the urine as unchanged hydrochlorothiazide.**
Molecular weight	297.728
Molecular formula	C7H8ClN3O4S2
SMILES	C1NC2=CC(=C(C=C2S(=O)(=O)N1)S(=O)(=O)N)Cl
Water solubility:	722 mg/L at 25 deg C (PubChem)
Log Kow	-0.07 (PubChem)
Structure	

Irbesartan

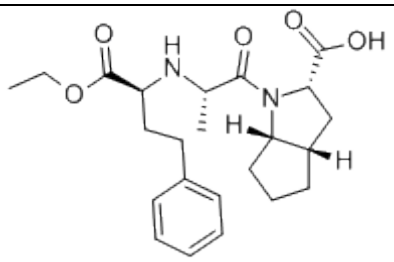
CAS number	138402-11-6
ATC code	C09CA04
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (C09CA)
Uses	Used to treat high blood pressure (hypertension) and to help protect the kidneys from damage due to diabetes.
Mechanism of action	Irbesartan's prevention of angiotensin II binding causes vascular smooth muscle relaxation and prevents the secretion of aldosterone, lowering blood pressure
Metabolism/Excretion	Largely metabolized by glucuronidation and oxidation in the liver. 20% of a radiolabelled oral dose of irbesartan is recovered in urine, and the rest is recovered in the feces. **<2% of the dose is recovered in urine as the unchanged drug**.
Molecular weight	428.54
Molecular formula	C25H28N6O
SMILES	CCCCC1=NC2(CCCC2)C(=O)N1CC3=CC=C(C=C3)C4=CC=CC=C4C5=NNN=N5
Water solubility:	5.9X10-2 mg/L at 25 deg C (est) (PubChem)
Log Kow	5.31 (est) (PubChem)
Structure	

Losartan

CAS number	114798-26-4
ATC code	C09CA01
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (C09CA)
Uses	Used to treat high blood pressure (hypertension).
Mechanism of action	Losartan reversibly and competitively prevents angiotensin II binding to the AT_1 receptor in tissues like vascular smooth muscle and the adrenal gland. This causes vascular smooth muscle relaxation, lowering blood pressure.
Metabolism/Excretion	Metabolized by the liver via the cytochrome P450 system. After single doses of losartan administered orally, **about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite.** Oral radiolabelled losartan is 35% recovered in urine and 60% in feces.
Molecular weight	422.917
Molecular formula	C22H23ClN6O
SMILES	CCCCC1=NC(=C(N1CC2=CC=C(C=C2)C3=CC=CC=C3C4=NNN=N4)CO)Cl
Water solubility:	8.22 mg/L at 25 deg C (est) (PubChem)
Log Kow	4.01 (est) (PubChem)
Structure	

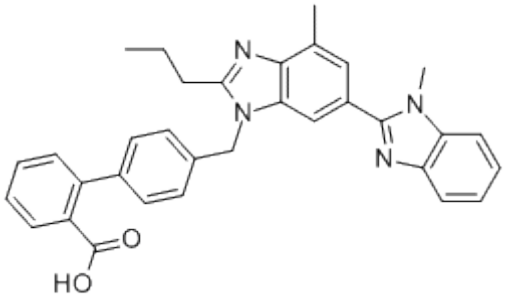
Ramipril

CAS number	87333-19-5
ATC code	C09AA05
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	ACE inhibitors, plain (**C09AA)**
Uses	Used to treat high blood pressure (hypertension) or congestive heart failure, and to improve survival after a heart attack.
Mechanism of action	Angiotensin converting enzyme is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.
Metabolism/Excretion	Hepatic metabolism accounts for 75% of total ramipril metabolism. 25% of hepatic metabolism produces the active metabolite ramiprilat via

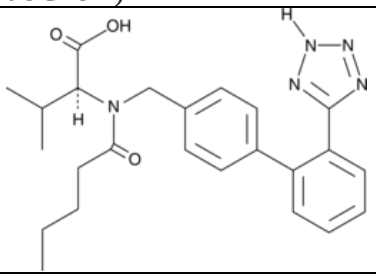
	liver esterase enzymes. 100% of renal metabolism converts ramipril to ramiprilat. Other metabolites, diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, are inactive. 60% of the parent drug and its metabolites are eliminated in the urine with the remaining 40% eliminated in the feces. **Less than 2% is excreted in urine as unchanged drug.**
Molecular weight	416.5
Molecular formula	C23H32N2O5
SMILES	CCOC(=O)C(CCC1=CC=CC=C1)NC(C)C(=O)N2C3CCCC3CC2C(=O)O
Water solubility:	11.2 mg/L at 25 °C (est)
Log Kow	3.32 (est)
Structure	

Telmisartan

CAS number	144701-48-4
ATC code	C09CA07
ATC name (2nd level, therapeutic subgroup)	Agents acting on the renin–angiotensin system (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (C09CA)
Uses	Used to treat high blood pressure (hypertension).
Mechanism of action	Interferes with the binding of angiotensin II to the angiotensin II AT1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance.
Metabolism/Excretion	Minimally metabolized by conjugation to form a pharmacologically inactive acylglucuronide. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. **Eliminated unchanged in faeces via biliary excretion (>97%); only minute amounts were found in the urine.**
Molecular weight	514.629
Molecular formula	C33H30N4O2
SMILES	CCCC1=NC2=C(C=C(C=C2N1CC3=CC=C(C=C3)C4=CC=CC=C4C(=O)O)C5=NC6=CC=CC=C6N5C)C
Water solubility:	2.8X10-6 mgL at 25 deg C (est) (PubChem)
Log Kow	8.42 (est) (PubChem)

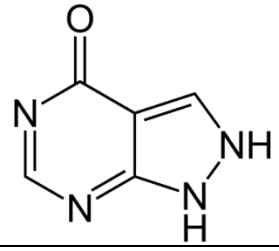
Structure	

Valsartan

CAS number	137862-53-4
ATC code	C09CA03
ATC name (2nd level, therapeutic subgroup)	AGENTS ACTING ON THE RENIN–ANGIOTENSIN SYSTEM (C09)
ATC name (4th level, chemical substance)	Angiotensin II receptor blockers (ARBs), plain (C09CA)
Uses	Used to treat high blood pressure and congestive heart failure.
Mechanism of action	Blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure. The drug binds to angiotensin type I receptors (AT1), working as an antagonist.
Metabolism/Excretion	Valsartan undergoes minimal liver metabolism and is not biotransformed to a high degree, as only approximately 20% of a single dose is recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. **Valsartan** is eliminated mostly by non-renal routes. It **is only slightly metabolized and excreted mainly unchanged in bile (<80%) and urine (20%)**
Molecular weight	435.528
Molecular formula	C24H29N5O3
SMILES	CCCCC(=O)N(CC1=CC=C(C=C1)C2=CC=CC=C2C3=NNN=N3)C(C(C)C)C(=O)O
Water solubility:	1.406 mg/L at 25 °C (est) (PubChem)
Log Kow	4.00 (average value) (PubChem)
Structure	

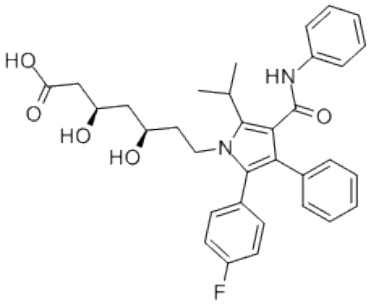
Metabolic disease medications

Allopurinol

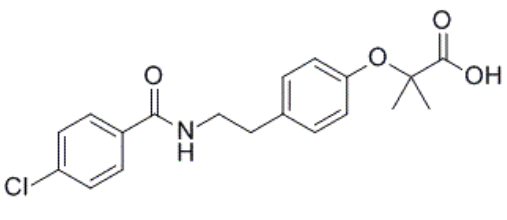
CAS number	315-30-0
ATC code	M04AA01
ATC name (2nd level, therapeutic subgroup)	ANTIGOUT PREPARATIONS (M04)
ATC name (4th level, chemical substance)	Preparations inhibiting uric acid production (M04AA)
Uses	Used to treat gout and certain types of kidney stones. It is also used to prevent increased uric acid levels in patients receiving cancer chemotherapy.
Mechanism of action	Allopurinol and its active metabolite inhibit xanthine oxidase, the enzyme that converts hypoxanthine to xanthine and xanthine to uric acid. The end result is decreased urine and serum uric acid concentrations, which decreases the incidence of gout symptoms.
Metabolism/Excretion	Rapidly metabolized to oxipurinol (alloxanthine). Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with **less than 10% of the unchanged drug excreted in the urine**. About 20% of ingested allopurinol is excreted in the feces.
Molecular weight	136.114
Molecular formula	C5H4N4O
SMILES	C1=C2C(=NC=NC2=O)NN1
Water solubility:	Solubility in water at 37°C is 80.0 mg/dL and is greater in an alkaline solution (DrugBank)
Log Kow	-0.55 (DrugBank)
Structure	

Atorvastatin

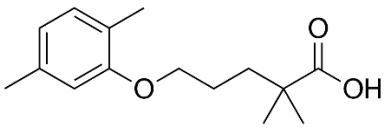
CAS number	110862-48-1
ATC code	C10AA05
ATC name (2nd level, therapeutic subgroup)	LIPID MODIFYING AGENTS (C10)
ATC name (4th level, chemical substance)	HMG CoA reductase inhibitors (C10AA)
Uses	Used to treat high cholesterol, and to lower the risk of stroke, heart attack, or other heart complications in people with type 2 diabetes, coronary heart disease, or other risk factors.
Mechanism of action	Lipid-lowering drug belonging to the statin class of medications. By inhibiting the endogenous production of cholesterol within the liver, statins lower abnormal cholesterol and lipid levels and ultimately reduce the risk of cardiovascular disease. More specifically, statin medications competitively

	inhibit the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) Reductase,8 which catalyzes the conversion of HMG-CoA to mevalonic acid.
Metabolism/Excretion	Extensively metabolized to its ortho- and para-hydroxylated derivatives, and to various beta oxidation products. **Less than 2% of a dose of atorvastatin is excreted in urine** following oral administration.
Molecular weight	558.6
Molecular formula	C33H35FN2O5
SMILES	CC(C)C1=C(C(=C(N1CCC(CC(CC(=O)O)O)O)C2=CC=C(C=C2)F)C3=CC=CC=C3)C(=O)NC4=CC=CC=C4
Water solubility:	0.00063 mg/mL (PubChem)
Log Kow	6.36 (est) (PubChem)
Structure	

Bezafibrate

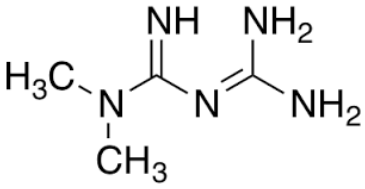
CAS number	41859-67-0
ATC code	C10AB02
ATC name (2nd level, therapeutic subgroup)	LIPID MODIFYING AGENTS (C10)
ATC name (4th level, chemical substance)	Fibrates (**C10AB**)
Uses	Used as a lipid-lowering agent to treat hyperlipidaemia.
Mechanism of action	Antilipemic agent that lowers cholesterol and triglycerides. It decreases low density lipoproteins and increases high density lipoproteins.
Metabolism/Excretion	Hepatic. Bezafibrate is rapidly and almost entirely eliminated via the kidneys, some of it in metabolised form. A study in volunteers showed that following oral administration, 95% of active 14C-labelled bezafibrate is excreted in the urine and 3% in the faeces within 48 hours. **50% of the administered dose appears in urine as unchanged bezafibrate**, 20% in the form of glucuronides.
Molecular weight	361.8
Molecular formula	C19H20ClNO4
SMILES	CC(C)(C(=O)O)OC1=CC=C(C=C1)CCNC(=O)C2=CC=C(C=C2)Cl
Water solubility:	0.00155 mg/mL (DrugBank)
Log Kow	
Structure	

Gemfibrozil

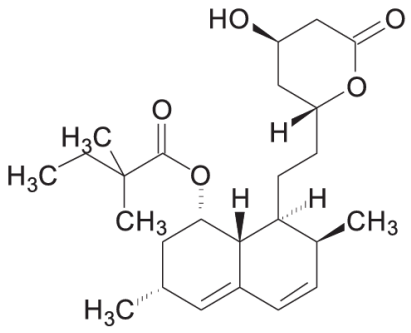
CAS number	25812-30-0
ATC code	C10AB04
ATC name (2nd level, therapeutic subgroup)	LIPID MODIFYING AGENTS (C10)
ATC name (4th level, chemical substance)	Fibrates (C10AB)
Uses	Used to treat very high cholesterol and triglyceride levels in people with pancreatitis and is also used to lower the risk of stroke, heart attack, or other heart complications in people with high cholesterol and triglycerides who have not been helped by other treatments.
Mechanism of action	Gemfibrozil activates peroxisome proliferator-activated receptor-α (PPARα), which alters lipid metabolism. This activation leads to increased HDL, apo AI, apo AII, lipoprotein lipase (LPL), inhibition of apo B synthesis, peripheral lipolysis, decreased removal of free fatty acids by the liver, and increased clearance of apoB.
Metabolism/Excretion	Gemfibrozil undergoes hydroxylation at the 5'-methyl and 4' positions to form the M1 and M2 metaolites respectively. Gemfibrozil also undergoes O-glucuronidation to form gemfibrozil 1-beta glucuronide, an inhibitor of CYP2C8. Approximately 70% of a dose of gemfibrozil is eliminated **in the urine**. The majority of a dose is eliminated as a glucuronide conjugate and **<2% is eliminated as the unmetabolized drug**. 6% of a dose is eliminated in the feces.
Molecular weight	250.338
Molecular formula	C15H22O3
SMILES	CC1=CC(=C(C=C1)C)OCCCC(C)(C)C(=O)O
Water solubility:	11 mg/L at 25 deg C (est) (PubChem)
Log Kow	4.77 (est) (PubChem)
Structure	

Metformin

CAS number	657-24-9
ATC code	A10BA02
ATC name (2nd level, therapeutic subgroup)	DRUGS USED IN DIABETES (A10)
ATC name (4th level, chemical substance)	Biguanides (A10BA)
Uses	Used together with diet and exercise to improve blood sugar control in adults with type 2 diabetes mellitus. Metformin is sometimes used together with insulin or other medications, but it is not for treating type 1 diabetes.
Mechanism of action	Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
Metabolism/Excretion	**Metformin is not metabolized**. It is cleared from the body by tubular secretion and **excreted unchanged in the urine**.

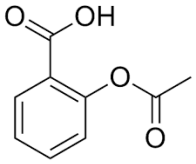
Molecular weight	129.167
Molecular formula	C4H11N5
SMILES	CN(C)C(=N)N=C(N)N
Water solubility:	1.06X10+6 mg/L (miscible) at 25 °C (est) (PubChem)
Log Kow	-2.64 at 25 °C (est) (PubChem)
Structure	

Simvastatin

CAS number	79902-63-9
ATC code	C10AA01
ATC name (2nd level, therapeutic subgroup)	LIPID MODIFYING AGENTS (C10)
ATC name (4th level, chemical substance)	HMG CoA reductase inhibitors (C10AA)
Uses	Used along with a proper diet to help lower "bad" cholesterol and fats (such as LDL, triglycerides) and raise "good" cholesterol (HDL) in the blood.
Mechanism of action	Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol.
Metabolism/Excretion	Administered as the inactive lactone derivative that is then metabolically activated to its β-hydroxyacid form. Oxidative metabolism in the liver is primarily mediated by CYP3A4 and CYP3A5, with the remaining metabolism occurring through CYP2C8 and CYP2C9. Following an oral dose of 14C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces.
Molecular weight	418.574
Molecular formula	C25H38O5
SMILES	CCC(C)(C)C(=O)OC1CC(C=C2C1C(C(C=C2)C)CCC3CC(CC(=O)O3)O)C
Water solubility:	3.0X10-2 mg/L (DrugBank)
Log Kow	4.68 (DrugBank)
Structure	

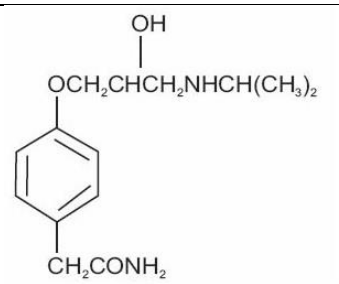
Other cardiovascular medicines

Acetylsalicylic acid

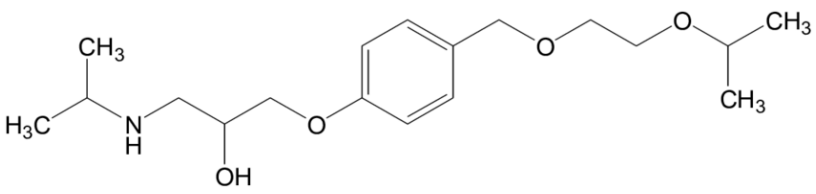
CAS number	50-78-2
ATC code	B01AC06
ATC name (2nd level, therapeutic subgroup)	ANTITHROMBOTIC AGENTS (B01)
ATC name (4th level, chemical substance)	Platelet aggregation inhibitors excl. Heparin (B01AC)
Uses	Used in the prevention of blood clots stroke, and myocardial infarction (MI)
Mechanism of action	Blocks prostaglandin synthesis. It is non-selective for COX-1 and COX-2 enzymes. Inhibition of COX-1 results in the inhibition of platelet aggregation. The acetyl group of acetylsalicylic acid binds with a serine residue of the cyclooxygenase-1 (COX-1) enzyme, leading to irreversible inhibition. This stops the conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent inducer of platelet aggregation.
Metabolism/Excretion	Acetylsalicylic acid is hydrolyzed in the plasma to salicylic acid. Salicylate is mainly metabolized in the liver. Elimination mainly through the kidney, by the processes of glomerular filtration and tubular excretion, in the form of free salicylic acid, salicyluric acid, and, additionally, phenolic and acyl glucuronides. Salicylate can be found in the urine soon after administration, however, the entire dose takes about 48 hours to be completely eliminated. The rate of salicylate is often variable, ranging from 10% to 85% in the urine, and heavily depends on urinary pH. Acidic urine generally aids in reabsorption of salicylate by the renal tubules, while alkaline urine increases excretion.
Molecular weight	180.159
Molecular formula	C9H8O4
SMILES	CC(=O)OC1=CC=CC=C1C(=O)O
Water solubility:	1.19 (PubChem)
Log Kow	4,600 mg/L at 25 °C (PubChem)
Structure	

Atenolol

CAS number	29122-68-7
ATC code	C07AB03
ATC name (2nd level, therapeutic subgroup)	BETA BLOCKING AGENTS (C07)
ATC name (4th level, chemical substance)	Beta blocking agents, selective (C07AB)
Uses	Used with or without other medications to treat high blood pressure.
Mechanism of action	Selectively binds to the β1-adrenergic receptor as an antagonist.
Metabolism/Excretion	Hydrophilic drug, which is predominantly eliminated via the kidneys, only about 5% of the atenolol is metabolised by the liver. **About 40%**

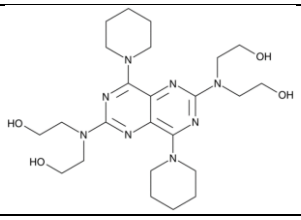
	to 50% of a given dose is excreted unchanged in urine; remainder is excreted as unchanged drug and metabolites in feces.
Molecular weight	266.34
Molecular formula	C14H22N2O3
SMILES	CC(C)NCC(COC1=CC=C(C=C1)CC(=O)N)O
Water solubility:	13.3 mg/mL at 25 °C (PubChem)
Log Kow	0.16 (PubChem)
Structure	

Bisoprolol

CAS number	66722-44-9
ATC code	C07AB07
ATC name (2nd level, therapeutic subgroup)	BETA BLOCKING AGENTS (C07)
ATC name (4th level, chemical substance)	Beta blocking agents, selective (C07AB)
Uses	Cardioselective β1-adrenergic blocking agent used to treat high blood pressure.
Mechanism of action	Bisoprolol reduces cardiac workload by decreasing contractility and the need for oxygen through competitive inhibition of β1-adrenergic receptors.
Metabolism/Excretion	About 50% of a single bisoprolol dose is metabolized mainly by the enzyme CYP3A4 to inactive metabolites. Bisoprolol is eliminated equally by both renal and hepatic pathways. **About 50% of an oral dose is excreted unchanged in the urine** with the remainder of the dose excreted as inactive bisoprolol metabolites. Under 2% of the ingested dose is found to be excreted in the feces.
Molecular weight	325.443
Molecular formula	C18H31NO4
SMILES	CC(C)NCC(COC1=CC=C(C=C1)COCCOC(C)C)O
Water solubility:	2.24X10+3 mg/L at 25 deg C (est) (PubChem)
Log Kow	1.87 (PubChem)
Structure	

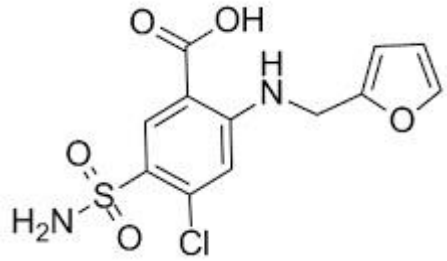
Dipyridamole

CAS number	58-32-2
ATC code	B01AC07
ATC name (2nd level, therapeutic subgroup)	ANTITHROMBOTIC AGENTS (B01)

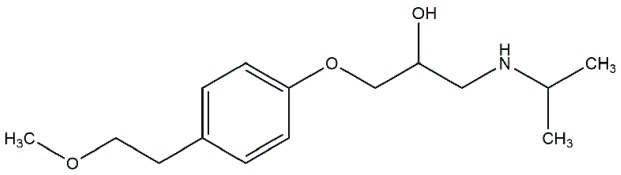
ATC name (4th level, chemical substance)	Platelet aggregation inhibitors excl. Heparin (B01AC)
Uses	Used to prevent blood clots after heart valve replacement surgery.
Mechanism of action	Likely inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function. This elevation in cAMP blocks the release of arachidonic acid from membrane phospholipids and reduces thromboxane A2 activity. Dipyridamole also directly stimulates the release of prostacyclin, which induces adenylate cyclase activity, thereby raising the intraplatelet concentration of cAMP and further inhibiting platelet aggregation.
Metabolism/Excretion	Dipyridamole is highly protein-bound, averaging 91 to 99%. undergoes hepatic metabolism, primarily glucuronidation, and these glucuronide conjugates are eliminated mainly in the feces, although enterohepatic circulation can occur. **A small amount of dipyridamole and its conjugates may be excreted in the urine.**
Molecular weight	504.636
Molecular formula	C24H40N8O4
SMILES	C1CCN(CC1)C2=NC(=NC3=C2N=C(N=C3N4CCCCC4)N(CCO)CCO)N(CCO)CCO
Water solubility:	10.7 ug/mL (PubChem)
Log Kow	1.5 (DrugBank)
Structure	

Furosemide

CAS number	54-31-9
ATC code	C03CA01
ATC name (2nd level, therapeutic subgroup)	DIURETICS (C03)
ATC name (4th level, chemical substance)	Sulfonamides, plain (C03CA)
Uses	Used to treat fluid retention (edema) in people with congestive heart failure, liver disease, or a kidney disorder such as nephrotic syndrome.
Mechanism of action	Furosemide is a loop diuretic (water pill) that prevents your body from absorbing too much salt. This allows the salt to instead be passed in your urine.
Metabolism/Excretion	Mainly occurs in the kidneys and in the liver to a smaller extent. The kidneys are responsible for 85% of total furosemide total clearance, where about 43% of the drug undergoes renal excretion. **Approximately 65% of furosemide is excreted unchanged in the urine**, and the remainder is conjugated to glucuronic acid in the kidney. Two major metabolites of furosemide are furosemide glucuronide and saluamine (CSA). Furosemide glucuronide is an active metabolite that also mediates a diuretic effect.
Molecular weight	330.008
Molecular formula	C12H11ClN2O5S
SMILES	C1=COC(=C1)CNC2=CC(=C(C=C2C(=O)O)S(=O)(=O)N)C
Water solubility:	73.1 mg/L (at 30 °C) (DrugBank)

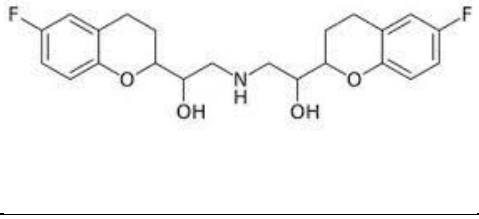
Log Kow	2.03 (DrugBank)
Structure	

Metoprolol

CAS number	51384-51-1
ATC code	C07AB02
ATC name (2nd level, therapeutic subgroup)	BETA BLOCKING AGENTS (C07)
ATC name (4th level, chemical substance)	Beta blocking agents, selective (C07AB)
Uses	Used with or without other medications to treat high blood pressure (hypertension).
Mechanism of action	Beta-1-adrenergic receptor inhibitor specific to cardiac cells with negligible effect on beta-2 receptors. This inhibition decreases cardiac output by producing negative chronotropic and inotropic effects without presenting activity towards membrane stabilization nor intrinsic sympathomimetics.
Metabolism/Excretion	Metoprolol goes through significant first-pass hepatic metabolism which covers around 50% of the administered dose. Mainly excreted via the kidneys. From the eliminated dose, **less than 5% is recovered unchanged**.
Molecular weight	267.369
Molecular formula	C15H25NO3
SMILES	CC(C)NCC(COC1=CC=C(C=C1)CCOC)O
Water solubility:	0.06 M (PubChem)
Log Kow	1.88 (PubChem)
Structure	

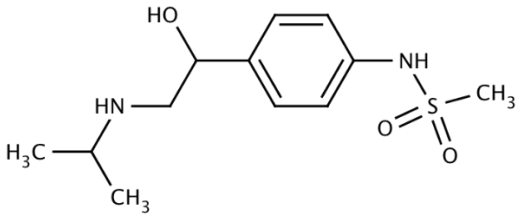
Nebivolol

CAS number	118457-14-0
ATC code	C07AB12
ATC name (2nd level, therapeutic subgroup)	BETA BLOCKING AGENTS (C07)
ATC name (4th level, chemical substance)	Beta blocking agents, selective (C07AB)
Uses	Is used alone or in combination with other medications to treat high blood pressure

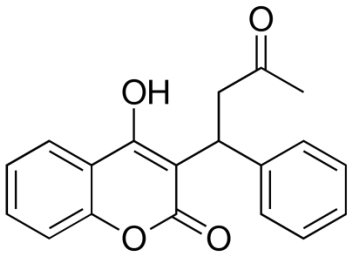
Mechanism of action	Selective β1-receptor antagonist. Activation of β1-receptors by epinephrine increases the heart rate and the blood pressure, and the heart consumes more oxygen. Nebivolol blocks these receptors which reverses the effects of epinephrine, lowering the heart rate and blood pressure. In addition, beta blockers prevent the release of renin, which is a hormone produced by the kidneys which leads to constriction of blood vessels.
Metabolism/Excretion	Metabolized mainly by glucuronidation and CYP2D6 mediated hydroxylation. In extensive CYP2D6 metabolizers, 38% is eliminated in the urine and 44% in the feces. In poor CYP2D6 metabolizers, 67% is eliminated in the urine and 13% in the feces. **<1% of a dose is excreted as the unmetabolized drug**.
Molecular weight	405.442
Molecular formula	C22H25F2NO4
SMILES	C1CC2=C(C=CC(=C2)F)OC1C(CNCC(C3CCC4=C(O3)C=CC(=C4)F)O)O
Water solubility:	0.091g/100mL (DrugBank)
Log Kow	4.04 (PubChem)
Structure	

Sotalol

CAS number	3930-20-9
ATC code	C07AA07
ATC name (2nd level, therapeutic subgroup)	BETA BLOCKING AGENTS (C07)
ATC name (4th level, chemical substance)	Beta blocking agents, non-selective (C07AA)
Uses	Used to treat ventricular tachycardia. It is also used to treat certain fast/irregular heartbeats (atrial fibrillation/flutter) in patients with severe symptoms such as weakness and shortness of breath.
Mechanism of action	Inhibits beta-1 adrenoceptors in the myocardium as well as rapid potassium channels to slow repolarization, lengthen the QT interval, and slow and shorten conduction of action potentials through the atria.
Metabolism/Excretion	**Not metabolized. 80-90%** of a given **dose is excreted in the urine as unchanged sotalol.** A small fraction of the doses is excreted in the feces as unchanged sotalol.
Molecular weight	272.363
Molecular formula	C12H20N2O3S
SMILES	CC(C)NCC(C1=CC=C(C=C1)NS(=O)(=O)C)O
Water solubility:	0.782 mg/mL (DrugBank)
Log Kow	0.85 (DrugBank)

Structure	

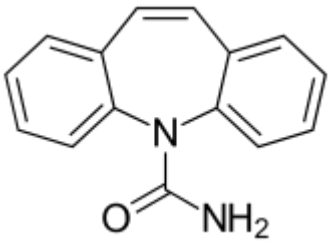
Warfarin

CAS number	81-81-2
ATC code	B01AA03
ATC name (2nd level, therapeutic subgroup)	ANTITHROMBOTIC AGENTS (B01)
ATC name (4th level, chemical substance)	Vitamin K antagonists (B01AA)
Uses	Used to treat or prevent blood clots in veins or arteries, which can reduce the risk of stroke, heart attack, or other serious conditions. Warfarin is an anticoagulant (blood thinner).
Mechanism of action	Warfarin reduces the formation of blood clots.
Metabolism/Excretion	Warfarin occurs as a pair of enantiomers that are differentially metabolized by human cytochromes P450. The elimination of warfarin is almost entirely by metabolism with a **small amount excreted unchanged**. 80% of the total dose is excreted in the urine with the remaining 20% appearing in the feces.
Molecular weight	308.333
Molecular formula	C19H16O4
SMILES	CC(=O)CC(C1=CC=CC=C1)C2=C(C3=CC=CC=C3OC2=O)O
Water solubility:	17 mg/L at 20 °C (DrugBank)
Log Kow	2.70 (DrugBank)
Structure	

Antiepileptics

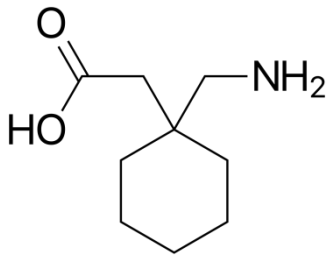
Carbamazepine

CAS number	298-46-4
ATC code	N03AF01
ATC name (2nd level, therapeutic subgroup)	ANTIEPILEPTICS (N03)
ATC name (4th level, chemical substance)	Carboxamide derivatives (N03AF)

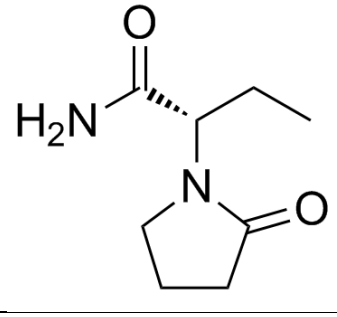
Uses	Anticonvulsant drug and analgesic drug used to control seizures and to treat pain resulting from trigeminal neuralgia.
Mechanism of action	Carbamazepine exerts its anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation. Its analgesic activity is not understood; however, carbamazepine is commonly used to treat pain associated with trigeminal neuralgia.
Metabolism/Excretion	Carbamazepine can induce its own metabolism. It is metabolized in the liver to an epoxide and several other metabolites. Carbamazepine and its metabolites are excreted in the urine. After oral administration, 72% of the dose is excreted in the urine and 28% is eliminated in the faeces. **Only about 1 to 3% of the drug is excreted unchanged in the urine**.
Molecular weight	236.27
Molecular formula	C15H12N2O
SMILES	C1=CC=C2C(=C1)C=CC3=CC=CC=C3N2C(=O)N
Water solubility:	0.152 mg/mL (DrugBank)
Log Kow	2.45 (PubChem)
Structure	

Gabapentin

CAS number	60142-96-3
ATC code	N03AX12
ATC name (2nd level, therapeutic subgroup)	ANTIEPILEPTICS (N03)
ATC name (4th level, chemical substance)	Other antiepileptics (N03AX)
Uses	Used with other medications to prevent and control seizures. It is also used to relieve nerve pain following shingles (a painful rash due to herpes zoster infection) in adults.
Mechanism of action	Gabapentin was designed to mimic the neurotransmitter GABA. It does not, however, bind to GABA receptors. Its mechanism of action as an antiepileptic agent likely involves its inhibition of the alpha 2-delta subunit of voltage-gated calcium channels.
Metabolism/Excretion	Gabapentin is **not appreciably metabolized in humans** - in humans, metabolites account for less than 1% of an administered dose, with the **remainder being excreted as unchanged parent drug in the urine.**
Molecular weight	171.24
Molecular formula	C9H17NO2
SMILES	C1CCC(CC1)(CC(=O)O)CN
Water solubility:	4.49X10+3 mg/L at 25 C (PubChem)
Log Kow	1.10 (PubChem)

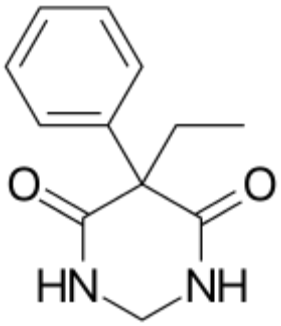
Structure	

Levetiracetam

CAS number	102767-28-2
ATC code	N03AX14
ATC name (2nd level, therapeutic subgroup)	ANTIEPILEPTICS (N03)
ATC name (4th level, chemical substance)	Other antiepileptics (N03AX)
Uses	Used in combination with other medications to treat seizure disorders (epilepsy).
Mechanism of action	Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release.
Metabolism/Excretion	Levetiracetam is minimally metabolized within the body - the major metabolic pathway appears to be the enzymatic hydrolysis of its acetamide group which produces an inactive carboxylic acid metabolite, L057, which accounts for approximately 24% of the total administered dose. **Approximately 66% of the administered dose of levetiracetam is excreted in the urine as unchanged drug**, while only 0.3% of the total dose is excreted via the feces.
Molecular weight	170.212
Molecular formula	C8H14N2O2
SMILES	CCC(C(=O)N)N1CCCC1=O
Water solubility:	104.0 g/100 mL (PubChem)
Log Kow	-0.49 (est) (PubChem)
Structure	

Primidone

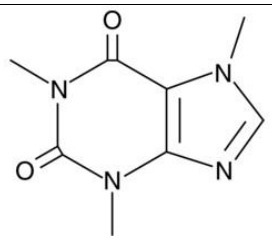
CAS number	125-33-7
ATC code	N03AA03
ATC name (2nd level, therapeutic subgroup)	ANTIEPILEPTICS (N03)
ATC name (4th level, chemical substance)	Barbiturates and derivatives (N03AA)
Uses	Used alone or with other medications for treating grand mal, psychomotor, or focal epileptic seizures.
Mechanism of action	Primidone is a GABA receptor agonist. The mechanism of Primidone's antiepileptic action is not known.

Metabolism/Excretion	Primidone undergoes hepatic oxidation and is **excreted in the urine as unchanged primidone, phenylethylmalonamide (PEMA) and phenobarbital.**
Molecular weight	218.256
Molecular formula	C12H14N2O2
SMILES	CCC1(C(=O)NCNC1=O)C2=CC=CC=C2
Water solubility:	480 mg/L at 30 °C (PubChem)
Log Kow	0.91 (PubChem)
Structure	

Other

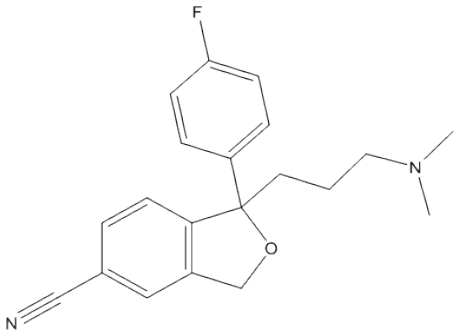
Caffeine

CAS number	1958-08-02
ATC code	N06BC01
ATC name (2nd level, therapeutic subgroup)	PSYCHOANALEPTICS (N06)
ATC name (4th level, chemical substance)	Xanthine derivatives (N06BC)
Uses	Central nervous system stimulant, increasing alertness and producing agitation. It also relaxes smooth muscle, stimulates cardiac muscle, stimulates diuresis, and appears to be useful in the treatment of some types of headache.
Mechanism of action	Mechanism of action of the methylxanthine is the antagonism at the level of adenosine receptors. Caffeine increases energy metabolism throughout the brain but decreases at the same time cerebral blood flow, inducing a relative brain hypoperfusion. Caffeine activates noradrenaline neurons and seems to affect the local release of dopamine. Many of the alerting effects of caffeine may be related to the action of the methylxanthine on serotonin neurons.
Metabolism/Excretion	Metabolized in the liver into three dimethylxanthines. Caffeine is readily reabsorbed by the renal tubules, once it is filtered by the glomeruli only a **small percentage is excreted unchanged in the urine.**
Molecular weight	194.2
Molecular formula	C8H10N4O2
SMILES	CN1C=NC2=C1C(=O)N(C(=O)N2C)C
Water solubility:	2.16E+004 mg/L (at 25 °C) (PubChem)
Log Kow	-0.07 (PubChem)

Structure	

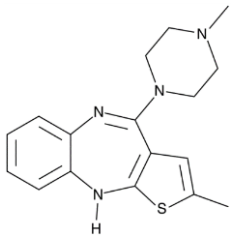
Psycopharmaceuticals

Citalopram

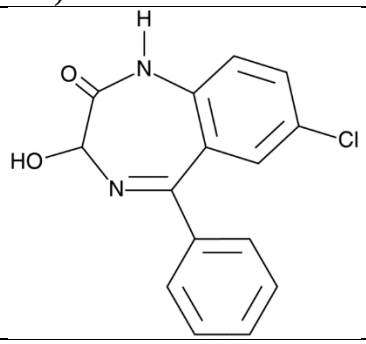
CAS number	59729-33-8
ATC code	N06AB04
ATC name (2nd level, therapeutic subgroup)	PSYCHOANALEPTICS (N06)
ATC name (4th level, chemical substance)	Selective serotonin reuptake inhibitors (N06AB)
Uses	Used to treat depression.
Mechanism of action	Inhibits neuronal reuptake of serotonin.
Metabolism/Excretion	Citalopram is metabolized mainly in the liver via *N*-demethylation to its main metabolite, *demethylcitalopram* by CYP2C19 and CYP3A4. **12-23% of an oral dose of citalopram is found unchanged in the urine,** while 10% of the dose is found in the faeces.
Molecular weight	324.4
Molecular formula	C20H21FN2O
SMILES	CN(C)CCCC1(OCC2=C1C=CC(=C2)C#N)C1=CC=C(F)C=C1
Water solubility:	31.09 mg/L at 25 deg C (est) (PubChem)
Log Kow	3.74 (est) (PubChem)
Structure	

Olanzapine

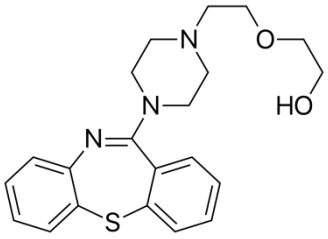
CAS number	132539-06-1
ATC code	N05AH03
ATC name (2nd level, therapeutic subgroup)	PSYCHOLEPTICS (N05)
ATC name (4th level, chemical substance)	Diazepines, oxazepines, thiazepines and oxepines (N05AH)
Uses	Used to treat certain mental/mood conditions (such as schizophrenia, bipolar disorder). It may also be used in combination with other medication to treat depression.
Mechanism of action	The exact mechanism of action of olanzapine is not known. It may work by blocking receptors for several neurotransmitters (chemicals that nerves use to communicate with each other) in the brain. It binds to

	alpha-1, dopamine, histamine H-1, muscarinic, and serotonin type 2 (5-HT2) receptors.
Metabolism/Excretion	Greatly metabolized in the liver, which represents around 40% of the administered dose, mainly by the activity of glucuronide enzymes and by the CYP450 system. Mainly eliminated through metabolism and hence, **only 7% of the eliminated drug can be found as the unchanged form.** It is mainly excreted in the urine which represents around 53% of the excreted dose followed by the feces that represent about 30%.
Molecular weight	312.435
Molecular formula	C17H20N4S
SMILES	CC1=CC2=C(S1)NC3=CC=CC=C3N=C2N4CCN(CC4)C
Water solubility:	39.88 mg/L at 25 °C (est) (PubChem)
Log Kow	3.00 (PubChem)
Structure	

Oxazepam

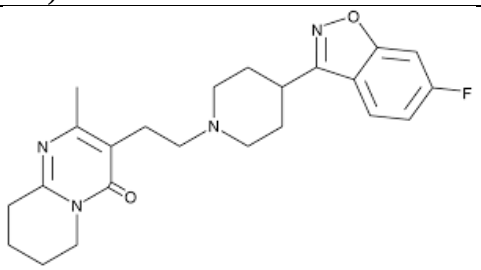
CAS number	604-75-1
ATC code	N05BA04
ATC name (2nd level, therapeutic subgroup)	PSYCHOLEPTICS (N05)
ATC name (4th level, chemical substance)	Benzodiazepine derivatives (**N05BA)**
Uses	Used to treat anxiety and also acute alcohol withdrawal.
Mechanism of action	Mechanism of action appears to be via potentiation of gamma aminobutyric acid (GABA)-receptor–mediated effects in the CNS.
Metabolism/Excretion	Oxazepam is one of the active products of metabolism from diazepam. It is hepatically metabolized and undergoes glucuronidation. It is metabolized in the liver to inactive metabolites. Metabolites are excreted in urine as glucuronide conjugates.
Molecular weight	286.71
Molecular formula	C15H11ClN2O2
SMILES	C1=CC=C(C=C1)C2=NC(C(=O)NC3=C2C=C(C=C3)Cl)O
Water solubility:	0.02 g/L at 22 °C (PubChem)
Log Kow	2.24 at pH 7.4 (PubChem)
Structure	

Quetiapine

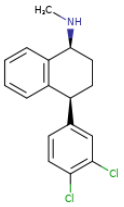
CAS number	111974-69-7
ATC code	N05AH04
ATC name (2nd level, therapeutic subgroup)	PSYCHOLEPTICS (N05)
ATC name (4th level, chemical substance)	Diazepines, oxazepines, thiazepines and oxepines (N05AH)
Uses	Used to treat certain mental/mood conditions (such as schizophrenia, bipolar disorder, sudden episodes of mania or depression associated with bipolar disorder).
Mechanism of action	Although the mechanism of action of quetiapine is not fully understood, several proposed mechanisms exist. In schizophrenia, its actions could occur from the antagonism of dopamine type 2 (D2) and serotonin 2A (5HT2A) receptors. In bipolar depression and major depression, quetiapine's actions may be attributed to the binding of this drug or its metabolite to the norepinephrine transporter.
Metabolism/Excretion	The metabolism of quetiapine occurs mainly in the liver. Sulfoxidation and oxidation are the main metabolic pathways of this drug. After an oral dose of radiolabeled quetiapine, **less than 1% of unchanged drug was detected in the urine**, suggesting that quetiapine is heavily metabolized. About 73% of a dose was detected in the urine, and about 20% in the feces.
Molecular weight	383.51
Molecular formula	C21H25N3O2S
SMILES	C1CN(CCN1CCOCCO)C2=NC3=CC=CC=C3SC4=CC=CC=C42
Water solubility:	0.5869 mg/L at 25 °C (est) (PubChem)
Log Kow	3.17 (est) (PubChem)
Structure	

Risperidone

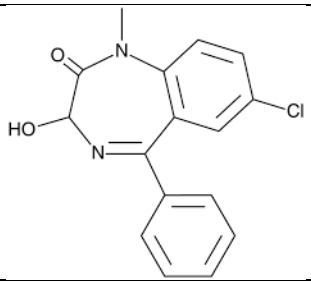
CAS number	106266-06-2
ATC code	N05AX08
ATC name (2nd level, therapeutic subgroup)	PSYCHOLEPTICS (N05)
ATC name (4th level, chemical substance)	**Other antipsychotics (N05AX)**
Uses	Used to treat certain mental/mood disorders (such as schizophrenia, bipolar disorder, irritability associated with autistic disorder). This medication can help you to think clearly and take part in everyday life.
Mechanism of action	Has a higher affinity for 5-HT2A receptors than for D2 receptors). According to the dopamine theory of schizophrenia, the mechanism of action of risperidone might involve a reduction of dopaminergic neurotransmission in the mesolimbic pathway.
Metabolism/Excretion	Extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyrisperidone, which has approximately the same receptor binding affinity as risperidone. Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces.

	Unchanged risperidone was excreted mainly in urine (4–30% depending on the subject's metabolism activities). Trace (~ 1%) of unchanged drug recovered in feces.
Molecular weight	410.493
Molecular formula	C23H27FN4O2
SMILES	CC1=C(C(=O)N2CCCCC2=N1)CCN3CCC(CC3)C4=NOC5=C4C=CC(=C5)F
Water solubility:	2.16 mg/L at 25 °C (est) (PubChem)
Log Kow	3.49 (est) (PubChem)
Structure	

Sertraline

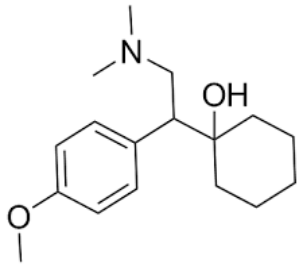
CAS number	79617-96-2
ATC code	N06AB06
ATC name (2nd level, therapeutic subgroup)	PSYCHOANALEPTICS (N06)
ATC name (4th level, chemical substance)	Selective serotonin reuptake inhibitors (N06AB)
Uses	Used to treat depression, panic attacks, obsessive compulsive disorder, post-traumatic stress disorder, social anxiety disorder (social phobia), and a severe form of premenstrual syndrome (premenstrual dysphoric disorder).
Mechanism of action	Selectively inhibits the reuptake of serotonin (5-HT) at the presynaptic membrane. This results in an increased synaptic concentration of serotonin in the CNS, which leads to numerous functional changes associated with enhanced serotonergic neurotransmission.
Metabolism/Excretion	Heavily metabolized in the liver and has one active metabolite. It undergoes N-demethylation to form N-desmethylsertraline, which is much less potent in its pharmacological activity. These metabolites are then conjugated and excreted in equal amounts in the urine and faeces; a **small amount of unchanged drug (less than 0.2 %) is excreted in the urine.**
Molecular weight	306.229
Molecular formula	C17H17Cl2N
SMILES	CNC1CCC(C2=CC=CC=C12)C3=CC(=C(C=C3)Cl)Cl
Water solubility:	3.8mg/L (DrugBank)
Log Kow	5.51 (DrugBank)
Structure	

Temazepam

CAS number	846-50-4
ATC code	N05CD07
ATC name (2nd level, therapeutic subgroup)	PSYCHOLEPTICS (N05)
ATC name (4th level, chemical substance)	Benzodiazepine derivatives (N05CD)
Uses	Used to treat insomnia symptoms, such as trouble falling asleep or staying asleep.
Mechanism of action	Increase the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor. This causes sedation, motor impairment, ataxia, anxiolysis, an anticonvulsant effect, muscle relaxation, and a reinforcing effect.
Metabolism/Excretion	Principally metabolized in the liver where most of the unchanged drug is directly conjugated to glucuronide and excreted in the urine. Less than 5% of the drug is demethylated to oxazepam and subsequently eliminated as the glucuronide. Glucuronides of temazepam have no demonstrable CNS activity and it is believed that no active metabolites are formed in general. Excreted in urine (80% to 90% as inactive metabolites).
Molecular weight	300.74
Molecular formula	C16H13ClN2O2
SMILES	CN1C2=C(C=C(C=C2)Cl)C(=NC(C1=O)O)C3=CC=CC=C3
Water solubility:	164 mg/L (PubChem)
Log Kow	2.19 (PubChem)
Structure	

Venlafaxine

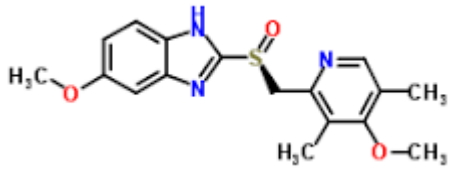
CAS number	93413-69-5
ATC code	N06AX16
ATC name (2nd level, therapeutic subgroup)	PSYCHOANALEPTICS (N06)
ATC name (4th level, chemical substance)	Other antidepressants (N06AX)
Uses	Affects chemicals in the brain that may be unbalanced in people with depression. Venlafaxine is used to treat major depressive disorder, anxiety and panic disorder.
Mechanism of action	Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), inhibit the reuptake of both serotonin and norepinephrine with a potency greater for the 5-HT than for the NE reuptake process.
Metabolism/Excretion	Undergoes extensive first pass metabolism in the liver to its major, active metabolite, ODV and two minor, less active metabolites, N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine. Formation of ODV is catalyzed by CYP450 2D6, whereas N-demethylation is catalyzed by CYP3A4, 2C19 and 2C9. ODV possesses antidepressant activity that is comparable to that of venlfaxine. Renal elimination of

	venlafaxine and its metabolites is the primary route of excretion. Approximately 87% of a venlafaxine dose is recovered **in the urine** within 48 hours as either **unchanged venlafaxine (5%),** unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%).
Molecular weight	277.408
Molecular formula	C17H27NO2
SMILES	CN(C)CC(C1=CC=C(C=C1)OC)C2(CCCCC2)O
Water solubility:	267 mg/L at 25 °C (est) (PubChem)
Log Kow	3.20 (PubChem)
Structure	

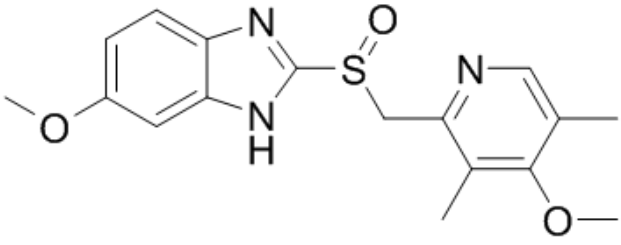
Gastrointestinal disease medications

Esomeprazole

CAS number	119141-88-7
ATC code	A02BC05
ATC name (2nd level, therapeutic subgroup)	DRUGS FOR ACID RELATED DISORDERS (A02)
ATC name (4th level, chemical substance)	Proton pump inhibitors (A02BC)
Uses	Used to treat symptoms of gastroesophageal reflux disease (GERD) and other conditions involving excessive stomach acid such as Zollinger-Ellison syndrome. Esomeprazole is also used to promote healing of erosive esophagitis (damage to your esophagus caused by stomach acid).
Mechanism of action	Suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell.
Metabolism/Excretion	Extensively metabolized in the liver by the CYP450 enzyme system. The metabolites of esomeprazole lack antisecretory activity. **Less than 1% of parent drug is excreted in the urine.** Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.
Molecular weight	345.417
Molecular formula	C17H19N3O3S
SMILES	CC1=CN=C(C(=C1OC)C)CS(=O)C2=NC3=C(N2)C=C(C=C3)OC
Water solubility:	1.4X10+4 mg/L at 25 °C (est) (PubChem)
Log Kow	3.40 (est) (PubChem)

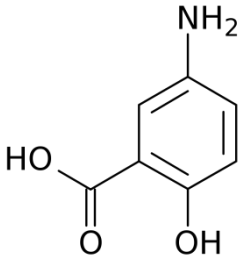
Structure	

Omeprazole

CAS number	73590-58-6
ATC code	A02BC01
ATC name (2nd level, therapeutic subgroup)	DRUGS FOR ACID RELATED DISORDERS (A02)
ATC name (4th level, chemical substance)	Proton pump inhibitors (A02BC)
Uses	Used to treat certain stomach and esophagus problems (such as acid reflux, ulcers). It works by decreasing the amount of acid your stomach makes. It relieves symptoms such as heartburn, difficulty swallowing, and persistent cough.
Mechanism of action	Suppresses stomach acid secretion by specific inhibition of the H^+/K^+-ATPase system found at the secretory surface of gastric parietal cells.
Metabolism/Excretion	Completely metabolized by the cytochrome P450 system, mainly in the liver. Identified metabolites are the sulfone, the sulfide, and hydroxy-omeprazole, which exert no significant effect on acid secretion. Most of the dose (about 77%) was eliminated in urine as at least six different metabolites, **little if any unchanged drug was excreted in urine.** The remainder of the dose was found in the feces. This suggests significant biliary excretion of omeprazole metabolites.
Molecular weight	345.417
Molecular formula	C17H19N3O3S
SMILES	CC1=CN=C(C(=C1OC)C)CS(=O)C2=NC3=C(N2)C=C(C=C3)OC
Water solubility:	82.3 mg/L at 25 °C /Estimated/ (PubChem)
Log Kow	2.23 (PubChem)
Structure	

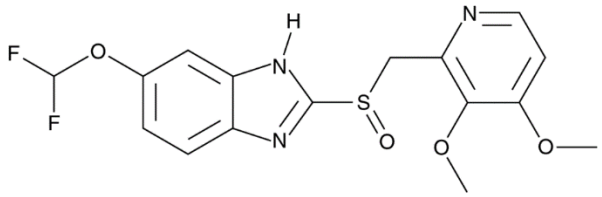
Mesalazine

CAS number	89-57-6
ATC code	A07EC02
ATC name (2nd level, therapeutic subgroup)	ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS (A07)
ATC name (4th level, chemical substance)	Aminosalicylic acid and similar agents (A07EC)
Uses	Used in the treatment of ulcerative colitis, a condition characterized by swelling and scarring of the colon and rectum. It is also used to control the symptoms of ulcerative colitis such as stomach pain, diarrhea, and rectal bleeding.

Mechanism of action	Not fully understood, it is believed to possess a topical anti-inflammatory effect on colonic epithelial cells.
Metabolism/Excretion	The primary metabolite of mesalazine (5-aminosalicylic acid) is predominantly N-acetyl-5-aminosalicylic acid (Ac-5-ASA). This metabolite is generated via N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, largely by NAT-1, in particular. Elimination of mesalazine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). After the oral administration of the extended-release formulation of mesalazine, of the approximately 21% to 22% of the drug absorbed, **less than 8% of the dose was excreted unchanged in the urine** after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid.
Molecular weight	153.135
Molecular formula	C7H7NO3
SMILES	C1=CC(=C(C=C1N)C(=O)O)O
Water solubility:	122 mg/L at 25 deg C (est) (PubChem)
Log Kow	0.98 (est) (PubChem)
Structure	

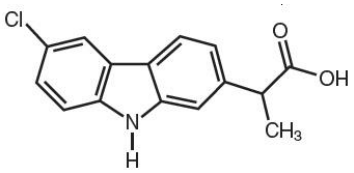
Pantoprazole

CAS number	102625-70-7
ATC code	A02BC02
ATC name (2nd level, therapeutic subgroup)	DRUGS FOR ACID RELATED DISORDERS (A02)
ATC name (4th level, chemical substance)	Proton pump inhibitors (A02BC)
Uses	Used to treat erosive esophagitis (damage to the esophagus from stomach acid caused by gastroesophageal reflux disease, or GERD) in adults and children who are at least 5 years old.
Mechanism of action	Inhibits the final step in gastric acid production. In the gastric parietal cell of the stomach, pantoprazole covalently binds to the H+/K+ ATP pump to inhibit gastric acid and basal acid secretion.
Metabolism/Excretion	Heavily metabolized in the liver by the CYP450 system. There is no evidence that any of the pantoprazole metabolites are pharmacologically active. About 71% of the dose was excreted in the urine, with 18% excreted in the feces by biliary excretion. There was **no renal excretion of unchanged pantoprazole.**
Molecular weight	383.37
Molecular formula	C16H15F2N3O4S
SMILES	COC1=C(C(=NC=C1)CS(=O)C2=NC3=C(N2)C=C(C=C3)OC(F)F)OC
Water solubility:	48 mg/L at 25 °C /Estimated/ (PubChem)
Log Kow	2.05 (PubChem)

Structure	

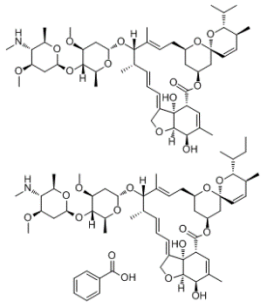
Veterinary medicines

Carprofen

CAS number	53716-49-7
ATC code	QM01AE91
ATC name (2nd level, therapeutic subgroup)	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (QM01)
ATC name (4th level, chemical substance)	Propionic acid derivatives (QM01AE)
Uses	Used by veterinarians as a supportive treatment for the relief of arthritic symptoms in geriatric dogs.
Mechanism of action	Believed to be associated with the inhibition of cyclooxygenase activity. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity.
Metabolism/Excretion	Hepatic. Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70–80%) and urine (10–20%). Some enterohepatic circulation of the drug is observed.
Molecular weight	273.716
Molecular formula	C15H12ClNO2
SMILES	CC(C1=CC2=C(C=C1)C3=C(N2)C=CC(=C3)Cl)C(=O)O
Water solubility:	0.00379 ng/L (PubChem)
Log Kow	3.8 (DrugBank)
Structure	

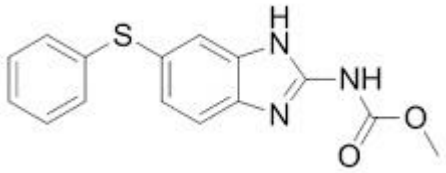
Emamectin benzoate

CAS number	155569-91-8
ATC code	QP54AA06
ATC name (2nd level, therapeutic subgroup)	Antiparasitic products, insecticides & repellents: Endectocides (QP54)

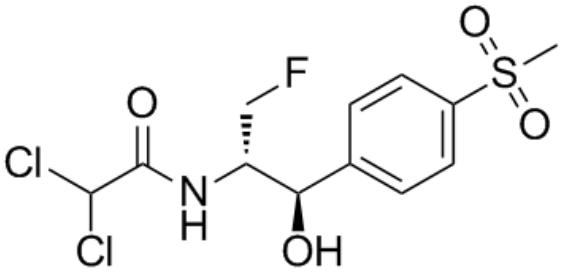
ATC name (4th level, chemical substance)	Avermectins (QP54AA)
Uses	Pesticide
Mechanism of action	Non-systemic, acts by causing insect paralysis by suppressing muscle contraction. Chloride channel activator.
Metabolism/Excretion	Relatively large molecule (actually a mixture of four closely related molecules) which is not completely absorbed on oral administration, is poorly absorbed by the dermal administration, and rapidly eliminated in the feces with whole-body half-lives of about 1.5 days. Thus, emamectin benzoate will not substantially accumulate over periods of long-term dosing. While emamectin benzoate is not extensively metabolized in mammals, the limited information on the metabolites of emamectin benzoate suggests that metabolism does not result in the detoxification of emamectin benzoate. One plant metabolite of emamectin benzoate is somewhat more toxic than emamectin benzoate itself.
Molecular weight	1008.256
Molecular formula	C56H81NO15
SMILES	CCC(C)C1C(C=CC2(O1)CC3CC(O2)CC=C(C(C(C=CC=C4COC5C4(C(C=C(C5O)C)C(=O)O3)O)C)OC6CC(C(C(O6)C)OC7CC(C(C(O7)C)[NH2+]C)OC)OC)C)C.C1=CC=C(C=C1)C(=O)[O-]
Water solubility:	0.024 g/L at 25 °C (pH 7)
Log Kow	5.0 at pH 7
Structure	

Fenbendazole

CAS number	43210-67-9
ATC code	QP52AC13
ATC name (2nd level, therapeutic subgroup)	ANTHELMINTICS (QP52)
ATC name (4th level, chemical substance)	Benzimidazoles and related substances (QP52AC)
Uses	Used to treat common helminth infections, including ascarids, hookworms, whipworms, and a single species of tapeworm, Taenia pisiformis.
Mechanism of action	Acts by binding to tubulin, an essential structural protein of microtubules. By blocking the microtubuless in worms the uptake of glucose is blocked which eventually depletes glycogen reserves.
Metabolism/Excretion	Metabolized in the liver to oxfendazole, which is anthelmintic too; oxfendazole partially gets reduced back to fenbendazole in the liver and rumen. Also, fenbendazole itself is an active metabolite of another anthelmintic drug, febantel. Elimination of fenbendazole is predominantly by the faecal route.
Molecular weight	299.348

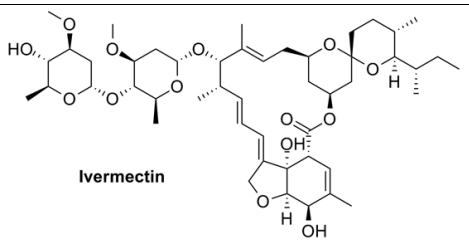
Molecular formula	C15H13N3O2S
SMILES	COC(=O)NC1=NC2=C(N1)C=C(C=C2)SC3=CC=CC=C3
Water solubility:	0.9 ug/mL (PubChem)
Log Kow	3.85 (Veterinary Substance DataBase)
Structure	

Florfenicol

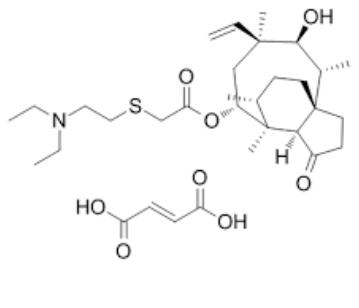
CAS number	73231-34-2
ATC code	QJ51BA90
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR INTRAMAMMARY USE (QJ51)
ATC name (4th level, chemical substance)	Amphenicols (QJ51BA)
Uses	Used in the treatment of bovine respiratory disease (also called BRD) and foot rot.
Mechanism of action	Bacteriostatic. Inhibits the protein synthesis of susceptible bacteria by combining simultaneously with the 50S and 70S subunits in the ribosome to abolish the activity of peptidyl transferase (5, 7).
Metabolism/Excretion	In most species, these drugs are eliminated by renal excretion of parent drug and by hepatic glucuronide conjugation and elimination in feces.
Molecular weight	358.205
Molecular formula	C12H14Cl2FNO4S
SMILES	CS(=O)(=O)C1=CC=C(C=C1)C(C(CF)NC(=O)C(Cl)Cl)O
Water solubility:	1.32 g/L at pH 7 (Aquaflor® Environmental Assessment)
Log Kow	0.37 (Aquaflor® Environmental Assessment)
Structure	

Ivermectin

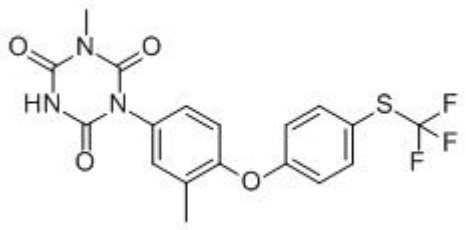
CAS number	70288-86-7
ATC code	P02CF01
ATC name (2nd level, therapeutic subgroup)	ANTHELMINTICS (P02)
ATC name (4th level, chemical substance)	Avermectines (P02CF)
Uses	Used to treat many types of parasite infestations. This includes head lice, scabies, river blindness (onchocerciasis), strongyloidiasis, trichuriasis, and lymphatic filariasis.
Mechanism of action	Binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria. This binding causes an increase in the permeability of the cell

	membrane to chloride ions and results in hyperpolarization of the cell, leading to paralysis and death of the parasite.
Metabolism/Excretion	Metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine.
Molecular weight	875.106
Molecular formula	C48H74O14
SMILES	CCC(C)C1C(CCC2(O1)CC3CC(O2)CC=C(C(C(C=CC=C4COC5C4(C(C=C(C5O)C)C(=O)O3)O)C)OC6CC(C(C(O6)C)OC7CC(C(C(O7)C)O)OC)OC)C)C
Water solubility:	Insoluble (DrugBank)
Log Kow	5.83 (DrugBank)
Structure	 Ivermectin

Tiamulin hydrogen fumarate

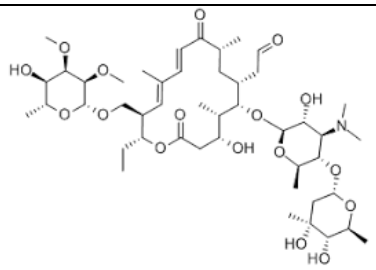
CAS number	55297-96-6
ATC code	QJ01XQ01
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (QJ01)
ATC name (4th level, chemical substance)	Pleuromutilins (QJ01XQ)
Uses	For treatment and prevention, when the disease is present at herd level,of swine dysentery caused by Brachyspira hyodysenteriae sensitive to tiamulin.The presence of disease in the herd should be established before use.
Mechanism of action	Binds with the rRNA in the peptidyl transferase slot on the ribosome, in which it prevents the correct positioning of the CCA ends of tRNA for peptide transferase and subsequent protein production.
Metabolism/Excretion	Following absorption, it is rapidly metabolised and excreted.
Molecular weight	609.819
Molecular formula	C32H51NO8S
SMILES	CCN(CC)CCSCC(=O)OC1CC(C(C(C23CCC(C1(C2C(=O)CC3)C)C)C)O)(C)C=C.C(=CC(=O)O)C(=O)O
Water solubility:	64.9 ug/mL (PubChem)
Log Kow	4.75 (est) (PubChem)
Structure	

Toltrazuril

CAS number	69004-03-1
ATC code	QP51AJ01
ATC name (2nd level, therapeutic subgroup)	ANTIPROTOZOALS (QP51)
ATC name (4th level, chemical substance)	Triazines (QP51AJ)
Uses	Used for the treatment of coccidiosis in chickens and turkeys.
Mechanism of action	Leads to a reduction of enzymes of the respiratory chain of the parasites. The biochemical mode of action of toltrazuril which causes obstruction of the wallforming bodies of Eimerian macrogamonts can not be explained up to now.
Metabolism/Excretion	Absorbed was rapidly converted to the short-lived intermediary metabolite toltrazuril sulfoxide (TZR-SO), and then metabolized to the reactive toltrazuril sulfone (TZR-SO2). Toltrazuril is slowly eliminated in both urine and faeces.
Molecular weight	425.382
Molecular formula	C18H14F3N3O4S
SMILES	CC1=C(C=CC(=C1)N2C(=O)NC(=O)N(C2=O)C)OC3=CC=C(C=C3)SC(F)(F)F
Water solubility:	1.04 mg.L-1 (HPRA Publicly Available Assessment Report for a Veterinary Medicinal Product)
Log Kow	2.49 (HPRA Publicly Available Assessment Report for a Veterinary Medicinal Product)
Structure	

Tylosin

CAS number	1401-69-0
ATC code	QJ01FA90
ATC name (2nd level, therapeutic subgroup)	ANTIBACTERIALS FOR SYSTEMIC USE (QJ01)
ATC name (4th level, chemical substance)	Macrolides (QJ01FA)
Uses	Used in veterinary medicine to treat bacterial infections in a wide range of species and has a high margin of safety. It has also been used as a growth promotant in some species, and as a treatment for colitis in companion animals.
Mechanism of action	Like other macrolides, tylosin has a bacteriostatic effect on susceptible organisms, caused by inhibition of protein synthesis through binding to the 50S subunit of the bacterial ribosome.
Metabolism/Excretion	Primary metabolism of tylosin occurs within the liver, similar metabolic pathways in rats, pigs and cattle, although quantitative differences in the amounts of produced metabolites were observed. Excretion rates in urine and faeces dependant on species of animal.

Molecular weight	916.112
Molecular formula	C46H77NO17
SMILES	CCC1C(C=C(C=CC(=O)C(CC(C(C(C(CC(=O)O1)O)C)OC2C(C(C(O2)C)OC3CC(C(C(O3)C)O)(C)O)N(C)C)O)CC=O)C)C)COC4C(C(C(C(O4)C)O)OC)OC
Water solubility:	5 mg/mL at 25 °C (PubChem)
Log Kow	1.63 (PubChem)
Structure	

Annex 20. Predicted no-effect concentrations in surface water

Ecotoxicological data used for deriving PNEC values are available at an external repository: https://helda.helsinki.fi/handle/10138/317151.

Antibiotics

Ciprofloxacin
50 test results were found for ciprofloxacin in the literature. These covered acute and chronic LC(EC)50 and NOEC values for crustacean, algae, bacteria, fish and rotifer.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0.00000511 mg/L

Clarithromycin
13 test results were found for clarithromycin in the literature. These covered acute and chronic LC(EC)50 and NOEC values for crustacean, algae, bacteria, fish, ciliate, cyanobacteria and higher plants.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0.00000391 mg/L

Doxycycline
Seven test results were found for doxycycline in literature. Higher plant and fungus EC(LC)50 values were available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0.0000369 mg/L

Erythromycin
26 test results were found for erythromycin in the literature. These covered acute and chronic LC(EC)50 and NOEC values for crustacean, algae, fish, cyanobacteria and higher plants.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0.0000835 mg/L

Fluconazole
26 test results were found for fluconazole in the literature. These covered acute and chronic LC(EC)50 and NOEC values for crustacean, algae, bacteria, fish, rotifier, cyanobacteria and higher plants.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0.0150 mg/L

Lincomycin
Ten test results were found for lincomycin in the literature. These covered acute and chronic LC(EC)50 and NOEC values for algae, bacteria, crustacean, fish, higher plant and rotifer.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0.00129 mg/L

Norfloxacin
19 test results were found in literature for norfloxacin. These covered acute and chronic algae, bacteria, cyanobacteria and higher plant LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,000481 mg/L

Ofloxacin
23 test results were found in literature for ofloxacin. These covered acute and chronic algae, bacteria, cyanobacteria, crustacean and higher plant LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0000204 mg/L

Sulfadiazine
6 test results were found in literature for sulfadiazine. Crustacean, cyanobacteria and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000135 mg/L

Sulfamethoxazole
21 test results were found in literature for sulfmetaxazole. These covered acute and chronic algae, bacteria, cyanobacteria, crustacean, rotifier, fish, faltworm and higher plant LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0000438 mg/L

Tetracycline
8 test results were found in literature for tetracycline. These covered acute and chronic algae, crustacean and faltworm LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00173 mg/L

Trimethoprim
17 test results were found in literature for trimetoprim. These covered acute and chronic algae, crustacean, faltworm and higher plant LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,508 mg/L

Antiepileptics

Carbamazepine
66 test results were found in literature for carbamazepine. These covered acute and chronic algae, crustacean, ciliate, cyanobacteria, higher plant, fish, fungus, hydrozoa, bacteria, insects, mollusks and rotifer LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00128 mg/L

Gabapentin
4 test results were found in literature for gabapentin. Crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Levetiracetam
3 test results were found in literature for levetiracetam. Crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Primidone
2 test results were found in literature for primidone. Crustacean and fish EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Antihypertensives

Amlodipine
19 test results were found in literature for amodipine. These covered acute and chronic algae, crustacean, fish and hydrozoa LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0000995 mg/L

Candesartan
6 test results were found in literature for candesartan. Crustacean, algae and fish LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000421 mg/L

Enalapril
7 test results were found in literature for candesartan. Crustacean, algae and fish LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,044736 mg/L

Eprosartan
Single test result was found in literature for eprosartan. Algae EC50 value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Hydrochlorothiazide
4 test results were found in literature for hydrochlorothiazide. Crustacean, algae and fish LC(EC)50 and NOEC values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 1 mg/L

Irbesartan
4 test results were found in literature for irbesartan. Crustacean and algae LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Losartan
3 test results were found in literature for losartan. Higher plant LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0.0078 mg/L

Ramipril
FASS database $PNEC_{water}$ value for ramipril was directly used for further assessment.
PNEC= 0.1 mg/L

Telmisartan
Single test result was found in literature for telmisartan. Algae EC50 value is available.

PNEC was derived using assessment factor (AF) method.
PNEC= 0,00988 mg/L

Valsartan
6 test results were found in literature for valsartan. These covered acute and chronic crustacean, algae and sea urchin LC(EC)50 and NOEC values.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,125 mg/L

Asthma and allergy medications

Cetirizine
No literature data were found for cetirizine. Own studies were conducted with algae, bacteria and crustacean.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,07862 mg/L

Fexofenadine
Single test results were found in literature for fexofenadine. Algae EC50 value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,2 mg/L

Fluticasone
Single test result was found in literature for fexofenadine. Crustacean EC50 value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00055 mg/L

Mometasone
FASS database $PNEC_{water}$ value for mometasone was directly used for further assessment.
PNEC= 0,000014 mg/L

Xylometazoline
FASS database $PNEC_{water}$ value for xylometazoline was directly used for further assessment.
PNEC= 0,00203 mg/L

Gastrointestinal disease medications

Esomeprazole
3 test results were found in literature for esomeprazole. Crustacean, fish and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Mesalazine
Single test result was found in literature for mesalazine. Fish NOEC value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,911 mg/L

Omeprazole
2 test results were found in literature for omeprazole. Crustacean and bacteria EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.

PNEC= 0,00176 mg/L

Pantoprazole
3 test results were found in literature for pantoprazole. Crustacean, fish and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,048 mg/L

Hormones

17-α-ethinyl estradiol (EE2)
76 test results were found in literature for EE2. These covered acute and chronic algae, bacteria, ciliate, fish, crustacean, fungus, insecta and rotifier LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,000000408 mg/L

17-β-estradiol (E2)
76 test results were found in literature for E2. These covered acute and chronic fish, crustacean, and fungus LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0000000323 mg/L

α-Estradiol
19 test results were found in literature for α-Estradiol. These covered acute and chronic fish LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,000000853 mg/L

Estriol (E3)
Single test result was found in literature for E3. Fish EC50 value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00000075 mg/L

Estrone (E1)
4 test results were found in literature for E1. Crustacean, and fish NOEC values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000000008 mg/L

Norethisterone
6 test results were found in literature for norethisterone. Crustacean, algae, bacteria and fish LC(EC)50 and NOEC values are available.
PNEC was derived using assessment factor (AF) method.

Progesterone
$PNEC_{water}$ value for progesterone (Orias & Perrodin 2013) was directly used for further assessment.
PNEC= 0.002 mg/L

Testosterone
Single test result was found in literature for testosterone. Crustacean NOEC value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,0015 mg/L

Metabolic disease medications

Allopurinol
4 test results were found in literature for allopurinol. Fish, crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,1 mg/L

Atorvastatin
37 test results were found in literature for atorvastatin. These covered acute and chronic crustacean, fungus, higher plant and insecta LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0021 mg/L

Bezafibrate
37 test results were found in literature for benzafibrate. These covered acute and chronic crustacean, molusca, hydrozoa and rotifier LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00126 mg/L

Gemfibrozil
23 test results were found in literature for gemfibrozil. These covered acute and chronic algae, crustacean, fish, rotifier, hydrozoa and bacteria LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,000825 mg/L

Metformin
5 test results were found in literature for metformin. Crustacean, higher plant and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00135 mg/L

Simvastatin
Single test result was found in literature for simvastatin. Algae EC50 value is available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,0228 mg/L

NSAIDs and analgesics

Acetylsalicylic acid
11 test results were found in literature for acetylsalicylic acid. These covered mostly acute crustacean, algae, bacteria, flatworm and rotifers LC(EC)50 values. PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,142 mg/L

Codeine
3 test results were found in literature for codeine. Fish, crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,016 mg/L

Diclofenac
48 test results were found in literature for diclofenac. These covered mostly chronic crustacean, algae, bacteria, fish, ciliate, molluscs, higher plants, cyanobacteria and rotifers NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0000852 mg/L

Ibuprofen
51 test results were found in literature for ibuprofen. These covered acute and chronic crustacean, algae, bacteria, fish, ciliate, molluscs LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,000000118 mg/L
Ketoprofen
3 test results were found in literature for ketoprofen. Bacteria, crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,002 mg/L

Naproxen
38 test results were found in literature for naproxen. These covered mostly chronic crustacean, algae, bacteria, fish, insects, molluscs, higher plants, cyanobacteria and rotifers NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00498 mg/L

Oxycodone
3 test results were found in literature for oxycodone. Algae, crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,003304 mg/L

Paracetamol
50 test results were found in literature for paracetamol. These covered acute and chronic crustacean, algae, bacteria, fish, rotifers, ciliate, molluscs, higher plants, cyanobacteria and rotifers LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00102 mg/L

Tramadol
2 test results were found in literature for tramadol. Bacteria and crustacean EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,17 mg/L

Other

Caffeine
ECHA registration $PNEC_{water}$ value for caffeine was directly used for further assessment.
PNEC= 0,087 mg/L

Other cardiovascular medicines

Atenolol
36 test results were found in literature for atenolol. These covered acute and chronic algae, crustacean, fish, bacteria, higher plant and hydrozoa LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,194 mg/L

Bisoprolol
4 test results were found in literature for bisoprolol. Crustacean, algae and fish LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,008 mg/L

Dipyridamole
3 test results were found in literature for bisoprolol. Crustacean, algae and fish LC(EC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00236 mg/L

Furosemide
8 test results were found in literature for furosemide. These covered acute and chronic crustacean, hydrozoa, rotifer and bacteria LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0159 mg/L

Metoprolol
23 test results were found in literature for metoprolol. These covered acute and chronic algae, crustacean, fish, higher plant and bacteria LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00438 mg/L

Nebivolol
No literature data were found for nebivolol. Own studies were conducted with algae, bacteria and crustacean.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000377 mg/L

Sotalol
3 test results were found in literature for sotalol. Bacteria, crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,3 mg/L

Warfarin
8 test results were found in literature for warfarin. These covered acute and chronic crustacean, fish, bacteria and rotifer LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0676 mg/L

Psychopharmaceuticals

Citalopram
8 test results were found in literature for citaloparm. These covered acute and chronic crustacean, and algae LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0154 mg/L

Quetiapine
FASS database $PNEC_{water}$ value for quetiapine was directly used for further assessment.
PNEC= 0,01 mg/L

Olanzapine
8 test results were found in literature for citaloparm. These covered acute and chronic crustacean, fish and algae LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0012 mg/L

Oxazepam
For oxazepam $PNEC_{water}$ calculated by RIMV (Smit 2015) was directly used for further environmental risk assessment.
PNEC= 0,00081 mg/L

Risperidone
FASS database $PNEC_{water}$ value for risperidone was directly used for further assessment.
PNEC= 0,0058 mg/L

Sertraline
8 test results were found in literature for sertraline. These covered acute and chronic crustacean, fish, algae, hydrozoa and mollusc LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,00107 mg/L

Temazepan
For temazepan $PNEC_{water}$ calculated by RIMV (Smit, 2015) was directly used for further environmental risk assessment.
PNEC= 0,00093 mg/L

Venlafaxine
3 test results were found in literature for venlafaxine. Crustacean and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00322 mg/L

Veterinary medication

Carprofen
4 test results were found in literature for carprofen. Crustacean, fish and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,03727 mg/L

Emamectin
4 test results were found in literature for emamectin. Crustacean, fish and insecta EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,0000010 mg/L

Fenbendazole
6 test results were found in literature for fenbendazole. Crustacean and fish EC(LC)50 and NOEC values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000015 mg/L

Florfenicol
8 test results were found in literature for florfenicol. These covered acute and chronic crustacean, fish, algae, higher plant, bacteria and mollusc LC(EC)50 and NOEC values.
PNEC was derived using species sensitivity distribution (SSD) method.
PNEC= 0,0409 mg/L

Ivermectin
4 test results were found in literature for ivermectin. Crustacean and nematode EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000000025 mg/L

Tiamulin
3 test results were found in literature for tiamulin. Crustacean, fish and algae EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000165 mg/L

Toltrazuril
7 test results were found in literature for toltrazuril. Crustacean, fish, higher plant and mollusks EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,00044 mg/L

Tylosin
7 test results were found in literature for tylosin. Crustacean, algae and higher plant EC(LC)50 values are available.
PNEC was derived using assessment factor (AF) method.
PNEC= 0,000034 mg/L

Annex 21. Risk assessments of APIs

Red colour indicates unacceptable risk, i.e. RQ values above 1. Green colour indicates no risk, i.e. RQ values below 1. In some cases, the limit of quantification (LOQ) for API determination was higher than the calculated PNEC values. In such situations, the analytical LOQ value was used as surrogate of the measured environmental concentration (MEC) resulting in RQs above 1, signaling that the risk cannot be excluded. In the tables below, these cases are marked with red text. Because doxycycline and tetracycline were not distinguishable in analytical measurements worst case scenario was applied and the lower PNEC for doxycycline was used in RQ calculations.

The colour codes used in table 9.6-9.10 are summarized below.

Colour codes:

RQ	No risk: risk quotient was below 1. The API was quantified (i.e. above LOQ) and the MEC is below PNEC.
<RQ	No risk: risk quotient was below 1, but the true RQ is even lower than presented in tables. The API was below LOQ and the LOQ was used as MEC. LOQ was below PNEC.
RQ	Risk: risk quotient above 1. The API was quantified (i.e. above LOQ) and the MEC is above PNEC.
<RQ	Risk cannot be excluded: risk quotient might be above 1. The API was below LOQ and the LOQ was used as MEC. The LOQ was above PNEC. The real RQ is lower than presented in tables.

MEC=measured environmental concentration
LOQ= limit of quantification

Risk assessment of APIs in inland surface waters

Sampling points at which risk was identified for at least one API measured in inland surface waters (i.e. RQ values above 1).

Sampling point	Country	Sampling time	Clarithromycin	Diclofenac	Emamectin	Estrone	Metformin	Mometasone	Norethisterone	Ofloxacin	Tetracycline/ Doxycycline
Pärnu river, Jändja, SJA6245000	Estonia	12/2017	0.89	0.62	0.42	<87	0.061	<0.090	**2.66**	<0.49	<0.15
Pärnu river after river Esna, before city of Paide	Estonia	12/2017	**1.27**	0.13	**1.0**	<87	0.017	0.75	<0.16	<0.49	<0.15
Pärnu river, Jändja, SJA6245000	Estonia	6/2018	<0.26	0.32	<0.090	<87	0.058	<0.090	0.78	<0.49	<0.15
Pärnu river after river Esna, before city of Paide	Estonia	6/2018	<0.26	0.13	<0.090	<87	<1.78E-04	**1.99**	<0.16	<0.49	<0.15
Vantaa 68,2	Finland	12/2017	0.81	0.19	0.14	<87	0.038	<0.090	<0.16	0.63	<0.15
Vantaa 68,2	Finland	6/2018	**6.9**	**1.57**	0.1	**834**	0.14	0.11	**2.78**	<0.49	<0.15
Vantaa 68,2	Finland	11/2018	**13**	**2.29**	0.45	**1033**	0.12	<0.090	**2.28**	<0.49	0.53
Vantaa 64,8	Finland	12/2017	**1.38**	0.39	0.12	<87	0.046	<0.090	<0.16	0.69	<0.15
Vantaa 64,8	Finland	6/2018	**26**	**7.52**	0.1	<87	0.21	<0.090	**1.66**	<0.49	<0.15
Vantaa 64,8	Finland	11/2018	**15**	**5.23**	0.4	**836**	0.47	<0.090	**1.31**	<0.49	0.54
Vantaa 44,1	Finland	12/2017	**1.41**	0.4	0.12	<87	0.046	<0.090	<0.16	<0.49	<0.15
Vantaa 44,1	Finland	6/2018	**17**	**4.49**	0.1	**861**	0.16	<0.090	**2.4**	<0.49	<0.15
Vantaa 44,1	Finland	11/2018	**24**	**4.61**	0.42	**1262**	0.98	<0.090	**1.76**	<0.49	<0.15
Luhtajoki (tributary)	Finland	11/2018	**9.3**	**5.55**	0.39	**750**	0.19	<0.090	**1.23**	<0.49	0.55
Vantaa 4,2	Finland	12/2017	0.49	0.2	0.12	<87	0.029	<0.090	<0.16	<0.49	<0.15
Vantaa 4,2	Finland	6/2018	**1.08**	0.63	<0.090	<87	0.26	<0.090	<0.16	<0.49	<0.15
Vantaa 4,2	Finland	11/2018	**4.21**	**1.5**	0.45	**734**	0.25	<0.090	**1.41**	<0.49	0.55
Tollense river, downstream WWTP Neubrandenburg	Germany	2/2018	**12**	**3.86**	0.19	<87	0.12	<0.090	0.46	0.61	<0.15
Tollense river, upstream WWTP Neubrandenburg	Germany	2/2018	<0.26	0.046	0.21	<87	0.008	0.13	**14**	<0.49	<0.15
Warnow river, upstream Rostock	Germany	2/2018	**12**	**5.78**	0.19	<87	0.15	<0.090	0.45	<0.49	<0.15
Tollense river, downstream WWTP Neubrandenburg	Germany	5/2018	**6.98**	**4.06**	<0.090	**340**	0.42	<0.090	<0.16	<0.49	<0.15
Tollense river, upstream WWTP Neubrandenburg	Germany	5/2018	<0.26	<0.013	<0.090	<87	0.02	<0.090	<0.16	<0.49	<0.15
Warnow river, upstream Rostock	Germany	5/2018	**0.4**	**0.25**	<0.090	<87	0.17	<0.090	**1.36**	<0.49	<0.15
Pupla river, downstream Olaine	Latvia	11/2017	**7.16**	**10**	0.14	<87	0.12	<0.090	<0.16	0.94	<0.15
Driksa river, downstream Jelgava	Latvia	11/2017	**1.32**	0.37	0.25	<87	0.039	<0.090	0.98	<0.49	<0.15
Pupla river, upstream Olaine	Latvia	12/2017	0.43	**5.7**	0.15	<87	0.001	<0.090	<0.16	<0.49	<0.15
Driksa river, upstream Jelgava	Latvia	11/2017	**1.38**	0.39	0.29	<87	0.041	<0.090	<0.16	<0.49	<0.15
Mūsa river, Latvia - Lithuania border	Latvia	11/2017	**3.01**	0.67	0.19	<87	0.036	<0.090	0.38	<0.49	<0.15

Sampling point	Country	Sampling time	Clarithromycin	Diclofenac	Emamectin	Estrone	Metformin	Mometasone	Norethisterone	Ofloxacin	Tetracycline/ Doxycycline
Mēmele, 0.5 km below Skaistkalne	Latvia	11/2017	0.53	0.11	0.21	<87	0.014	<0.090	**1.56**	<0.49	<0.15
Pupla river, downstream Olaine	Latvia	5/2018	**27**	**13**	0.37	<87	**1.67**	<0.090	<0.16	**3.63**	<0.15
Driksa river, downstream Jelgava	Latvia	5/2018	**1.51**	0.39	<0.090	**104**	0.32	<0.090	**1.06**	<0.49	<0.15
Pupla river, upstream Olaine	Latvia	5/2018	<0.26	**3.57**	<0.090	**146**	0.009	<0.090	<0.16	<0.49	<0.15
Driksa river, upstream Jelgava	Latvia	5/2018	0.86	0.1	<0.090	**256**	<1.78E-04	<0.090	<0.16	<0.49	<0.15
Mūsa river, Latvia - Lithuania border	Latvia	5/2018	<0.26	0.5	<0.090	<87	0.13	<0.090	<0.16	<0.49	<0.15
Mēmele, 0.5 km below Skaistkalne	Latvia	5/2018	<0.26	0.039	<0.090	**297**	<1.78E-04	<0.090	**1.14**	<0.49	<0.15
Lielupe, 0.5 km below Kalnciems	Latvia	11/2017	0.001	<0.006	<1.80	<114	<6.96E-04	<2.57E-04	0.12	<0.021	<0.001
Lielupe, 0.5 km below Kalnciems	Latvia	5/2018	0.15	0.087	<1.80	<114	<6.96E-04	<2.57E-04	0.08	<0.021	<0.001
Rokitnica river, downstream Błonie WWTP	Poland	11/2017	**151**	**26**	0.17	<87	0.22	<0.090	<0.16	**1.79**	<0.15
Rokitnica river, upstream Błonie WWTP	Poland	11/2017	**4.85**	0.73	0.54	<87	0.16	<0.090	**1.4**	**2.99**	<0.15
Rokitnica river, downstream Błonie WWTP	Poland	7/2018	**17**	**25**	<0.090	**228**	0.24	<0.090	<0.16	<0.49	<0.15
Rokitnica river, upstream Błonie WWTP	Poland	7/2018	**2.12**	**8.62**	<0.090	**352**	0.16	<0.090	<0.16	<0.49	<0.15
Vättern	Sweden	12/2017	<0.26	<0.013	0.33	<87	0.024	<0.090	0.68	**1.93**	<0.15
Boren	Sweden	12/2017	0.36	0.019	0.1	<87	0.024	<0.090	0.3	<0.49	<0.15
Svartån	Sweden	12/2017	0.52	0.023	**3.22**	<87	0.039	<0.090	**4.24**	**10**	<0.15
Stångån upstream	Sweden	12/2017	0.33	<0.013	0.31	<87	0.011	<0.090	**1.4**	**17**	**1.26**
Stångån-Roxen	Sweden	12/2017	0.82	0.32	0.17	<87	0.021	<0.090	**1.06**	**2.28**	<0.15
Dovern	Sweden	12/2017	0.31	0.061	0.15	<87	0.042	<0.090	0.52	**1.73**	<0.15
Glan	Sweden	12/2017	0.34	0.051	0.21	<87	0.015	<0.090	0.72	<0.49	<0.15
Vättern	Sweden	6/2018	<0.26	<0.013	0.43	<87	<1.78E-04	<0.090	**4.23**	0.72	<0.15
Boren	Sweden	6/2018	<0.26	<0.013	<0.090	<87	0.077	<0.090	**4.05**	<0.49	<0.15
Svartån	Sweden	6/2018	<0.26	0.017	0.38	<87	0.13	<0.090	**1.37**	<0.49	<0.15
Stångån upstream	Sweden	6/2018	<0.26	<0.013	0.45	<87	<1.78E-04	<0.090	**2.91**	<0.49	<0.15
Stångån-Roxen	Sweden	6/2018	<0.26	**1.85**	<0.090	<87	0.72	<0.090	<0.16	<0.49	<0.15
Dovern	Sweden	6/2018	<0.26	0.068	0.68	<87	0.93	<0.090	<0.16	<0.49	<0.15
Glan	Sweden	6/2018	<0.26	0.04	0.53	<87	0.3	<0.090	**2.44**	<0.49	<0.15

Risk assessment of APIs in coastal surface waters

Sampling points at which risk was identified for at least one API measured in coastal waters (i.e. RQ values above 1).

Sampling point	Country	Sampling	Ciprofloxacin	Clarithromycin	Emamectin	Estrone	Norethisterone
Pärnu river in Pärnu by Tallinn road bridge	Estonia	12/2017	< 6.8	NA	< 0.020	**100**	< 0.080
Pärnu bay	Estonia	6/2018	< 6.8	NA	**1.2**	**215**	< 0.080
Katajaluoto (coast, 1-m)	Finland	3/2018	< 6.8	NA	< 0.020	**75**	0.78
Katajaluoto (coast, 13-m)	Finland	3/2018	< 6.8	NA	< 0.020	**127**	0.42
Katajaluoto (coast, 25-m)	Finland	3/2018	< 6.8	NA	0.23	< 21	< 0.080
Katajaluoto (coast, 1-m)	Finland	6/2018	< 6.8	NA	0.4	**40**	< 0.080
Katajaluoto (coast, 15-m)	Finland	6/2018	< 6.8	NA	0.32	< 21	0.22
Katajaluoto (coast 23-m)	Finland	6/2018	< 6.8	NA	< 0.020	**54**	< 0.080
Helsinki coast (outlet pipe of Viikki WWTP; 9-m)	Finland	6/2018	< 6.8	NA	0.45	**64**	0.7
Matinsilta (river mouth)	Finland	3/2018	< 6.8	NA	< 0.020	**46**	0.38
Matinsilta (river mouth)	Finland	6/2018	< 6.8	NA	0.18	< 21	0.54
Matinsilta (river mouth)	Finland	11/2018	NA	**1.9**	**1.9**	**573**	0.90
Vanhankaupunginselkä (estuary)	Finland	3/2018	< 6.8	NA	< 0.020	36	< 0.080
Vanhankaupunginselkä (estuary, 1-m)	Finland	6/2018	< 6.8	NA	0.73	< 21	0.64
Peene, BSE Autumn	Germany	2/2018	< 6.8	NA	< 0.020	**86**	**1.7**
Warnow, BSE Autumn	Germany	2/2018	< 6.8	NA	< 0.020	< 21	< 0.080
Peene, BSE Summer	Germany	5/2018	< 6.8	NA	**7.2**	**325**	**1.3**
Warnow, BSE Summer	Germany	5/2018	< 6.8	NA	**4.6**	**674**	< 0.080
Riga coast (outlet pipe of WWTP)	Latvia	12/2017	< 6.8	NA	**2.1**	< 114	0.06
Riga coast (outlet pipe of WWTP)	Latvia	12/2017	< 6.8	NA	< 1.80	< 114	0.069
Riga coast (outlet pipe of WWTP)	Latvia	5/2018	< 6.8	NA	< 1.80	< 114	0.093
Riga coast (outlet pipe of WWTP)	Latvia	5/2018	< 6.8	NA	< 1.80	< 114	0.13
Vistula River, Kiezmark	Poland	11/2017	< 6.8	NA	< 0.020	**31**	< 0.080
Vistula River, Kiezmark	Poland	7/2018	< 6.8	NA	**1.6**	< 21	**2.4**
Bråviken	Sweden	12/2017	NA	NA	0.21	< 87	**1.1**
Bråviken	Sweden	6/2018	NA	NA	0.79	< 87	< 0.16

Risk assessment of APIs in sediments

Sampling points at which risk was identified for at least one API measured in sediments (i.e. RQ values above 1).

Sampling point	Roosna-Alliku fishfarm	Pärnu river in Pärnu by Tallinn road bridge	Pärnu bay	Fish farm	~620 m from the fish farm	~930 m from the fish farm	Riga coast (outlet pipe of WWTP)	Riga coast (outlet pipe of WWTP)	Bråviken	Bråviken
Country	Estonia	Estonia	Estonia	Finland	Finland	Finland	Latvia	Latvia	Sweden	Sweden
Sampling time	12/2017	12/2017	6/2018	9/2018	9/2018	9/2018	5/2018	12/2017	12/2017	6/2018
Ciprofloxacin	**1.18**	**5.06**	<0.29	0.72	<0.29	**1.12**	**2.07**	**1.75**	**1.07**	<0.29
Clarithromycin	<2.03	**42**	<2.03	<2.03	<2.03	<2.03	**6.56**	<2.03	**4.57**	<2.03
Diclofenac	<0.21	**2.6**	0.21	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21	<0.21
Emamectin	**1.12**	**1.52**	<0.78	<0.78	<0.78	<0.78	<0.78	**1,0**	<0.78	<0.78
Erythromycin	<14	<14	<14	<14	<14	<14	<14	<14	<14	<14
Estriol	<290	<290	<290	<290	<290	<290	<290	<290	<290	<290
Estrone	<2595	<2595	<2595	48828	<2595	6496	9368	19545	<2595	<2595
Ivermectin	<810	<810	<810	<810	<810	<810	<810	<810	<810	<810
Metformin	**23**	**37**	**3.61**	**1.85**	**1.86**	**7.03**	**5.3**	**5.23**	**4.19**	**15**
Mometasone	<15	<15	<15	<15	<15	<15	<15	<15	<15	<15
Norethisterone	<27	**162**	NA	NA	<27	<27	NA	<27	<27	**105**
Ofloxacin	<0.65	**18**	<0.65	**2.57**	<0.65	<0.65	<0.65	<0.65	0.79	<0.65
Paracetamol	**14**	**17**	<0.20	<0.20	**14**	**410**	**3.07**	<0.20	**48**	**67**
Sulfamethoxazole	<1.13	<1.13	<1.13	<1.13	<1.13	<1.13	<1.13	<1.13	<1.13	<1.13
Tetracycline/ Doxycycline	**72**	<43	**92**	<43	<43	**107**	**54**	<43	**135**	<43
Tylosin	<33	<33	<33	<33	<33	<33	<33	<33	<33	<33

Risk assessments of APIs in soil

Sampling points at which risk was identified for at least one API measured in soil (i.e. RQ values above 1).

Sampling point	EST 1	EST 2	GER 1	LAT 1	SWE 1	SWE 2
Country	Estonia	Estonia	Germany	Latvia	Sweden	Sweden
Sampling time	10/2018	10/2018	5/2018	6/2018	6/2018	6/2018
Ciprofloxacin	<0.53	<0.53	**1.3**	<0.53	<0.53	<0.53
Diclofenac	<0.46	**2**	<0.46	<0.46	<0.46	<0.46
Estrone	<4900	<4900	**160000**	<4900	<4900	<4900
Ivermectin	<1500	<1500	<1500	<1500	<1500	**2700**
Metformin	<0.013	**1.8**	**10**	**1.6**	**4.8**	**1.6**
Ofloxacin	<1.2	<1.2	**1.8**	<1.2	<1.2	<1.2
Paracetamol	**26**	**18**	**5.7**	**110**	**9.7**	**9**
Erythromycin	<26	<26	<26	<26	<26	<26
Estriol	<630	<630	<630	<630	<630	<630
Mometasone furoate	<35	<35	<35	<35	<35	<35
Norethisterone	NA	<56	NA	<56	<56	<56
Sulfamethoxazole	<3.1	<3.1	<3.1	<3.1	<3.1	<3.1
Tetracycline / Doxycycline	<360	<360	<360	<360	<360	<360
Tylosin	<84	<84	<84	<84	<84	<84

Risk assessment of APIs in fish farms, pig farms and poultry farms

Sampling points at which risk was identified for at least one API measured in fish farms (i.e. RQ values above 1).

Sampling point	Country	Sampling time	Ciprofloxacin	Estrone	Norethisterone
Roosna-Alliku fish farm, effluent	Estonia	12/2017	<6.81	**137**	**16**
Roosna-Alliku fish farm, effluent	Estonia	6/2018	<6.81	**1227**	<0.080
14b, surface	Finland	8/2018	<6.81	**186**	0.78
14c, surface	Finland	8/2018	<6.81	**135**	<0.080
14b, bottom	Finland	8/2018	<6.81	**259**	<0.080
14a, bottom	Finland	8/2018	<6.81	<21	0.67
14a, surface	Finland	8/2018	<6.81	<21	<0.080
14c, bottom	Finland	8/2018	<6.81	<21	<0.080
14c, surface	Finland	9/2018	<6.81	<21	<0.080
14a, surface	Finland	9/2018	<6.81	<21	<0.080
14b, surface	Finland	9/2018	<6.81	<21	<0.080
14a, bottom	Finland	9/2018	<6.81	<21	<0.080
14c, bottom	Finland	9/2018	<6.81	<21	<0.080
14b, bottom	Finland	9/2018	<6.81	<21	<0.080

Sampling points at which risk was identified for at least one API measured in watercourses near pig and poultry farms (i.e. RQ values above 1).

Sampling point	Country	Sampling time	Estrone
LV Pig farm	Latvia	11/2017	< 87
LV Poultry farm	Latvia	11/2017	< 87
LV Pig farm	Latvia	5/2018	< 87
LV Poultry farm	Latvia	5/2018	**160**

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På så sätt bidrar vi till Länsstyrelsens vision om ett livskraftigt Östergötland

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