Baltic Marine Environment Protection Commission

Heads of Delegation
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Background

PRESSURE 2-2015 agreed on the preparation of the Status report on pharmaceuticals in the Baltic Sea in coordination with the State and Conservation Working Group and in collaboration with the Coordinator of EUSBSR PA Hazards from Sweden.

The draft report is based on the data call issued in September 2015 on pharmaceuticals to the Pressure (sources and pathways) and State and Conservation Working Groups (concentrations and effects). The data related to concentrations and effects was compiled through a cooperation with EUSBSR PA Hazards, and the component related to sources and pathways was compiled separately in cooperation with UNESCO. The draft Status report is a compilation of the two components.

The draft Status report was reviewed intersessionally for a one-month period (23 February to 21 March 2016) by contacts for – PRESSURE and State and Conservation. The comments were provide by Denmark, Estonia, Finland, Germany, Poland and Sweden. The revised version of the Status report was discussed at PRESSURE 4-2016 and STATE & CONSERVATION 4-2016. Both groups agreed in principle on publication of the report taking into account outcomes of the discussions at the Meetings and comments by the national experts during and additional commenting round in May 2016.

The results of the Status report will be considered in the development of the two pre-core indicators on 'Diclofenac concentration' and 'Estrogenic-like chemicals and effects' and also for possible revision of the existing HELCOM Recommendation 31E/1 'Implementing HELCOM's objective for hazardous substances' with regard of the list of priority substances and substances of concern (Outcome PRESSURE 3-2915, para 3.3). The Status report contributes to implementation of one of 14 new HELCOM actions agreed by HELCOM 37-2016, namely, Micropollutants in effluents from wastewater treatment plants.

The document contains an updated draft of the Status report taking into account comments received from the national experts by 17 May 2016. Annexes contain information which is not to be included in the final publication but will be used in further work on the issue.

PRESSURE 4-2016 agreed that the report is the starting point for further development of the regional strategy and suggested to establish a task group to work further in order to suggest further actions on pharmaceuticals in the Baltic Sea region.

Action requested

The Meeting is invited to:

- approve the draft Status report on pharmaceuticals and its publishing as a Baltic Sea Environment Proceedings (BSEP).

United Nations Educational, Scientific and Cultural Organization

International Hydrological Programme

Draft Status report on pharmaceuticals in the Baltic Sea region

Case study report

Interreg Baltic Sea Region

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

UNESCO-IHP International Initiative on Water Quality (IIWQ)

UNESCO project:
Emerging Pollutants in Wastewater Reuse in Developing Countries
Case Studies on Emerging Pollutants in Water and Wastewater

Sida
SWEDISH INTERNATIONAL DEVELOPMENT COOPERATION AGENCY

HELCOM

EUSBSR
EU STRATEGY FOR THE BALTIC SEA REGION

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HELCOM Working Group on the State of the Environment and Nature Conservation

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List of acronyms and abbreviations

BSAP	Baltic Sea Action Plan of HELCOM
EQS	Environmental quality standards
EU	European Union
EUSBSR	European Union Strategy for the Baltic Sea Region
GES	Good Environmental Status
HELCOM Commission	Baltic Marine Environment Protection Commission - Helsinki
LOD	Limits of detection
MSFD European Union	Marine Strategy Framework Directive of the
WFD	Water Framework Directive of the European Union
MWWTPs	Municipal Wastewater treatment plants

Executive Summary

The occurrence of pharmaceutical substances in the environment is of global concern and the extent of their impacts on biota is largely unknown. This report presents the first comprehensive overview of the occurrence and environmental pressures of pharmaceuticals in the Baltic Sea region.

The presented results are based on data available which have been provided by Contracting Parties of the Baltic Marine Environment Protection Commission (Helsinki Commission, HELCOM). The report compiles regional information on the occurrence of pharmaceuticals in the Baltic Sea environment and, identifies sources and pathways of pharmaceuticals into the environment. The report also presents estimates of sales and consumption of drugs and handling of pharmaceutical waste in some of the Baltic Sea countries.

The data on contamination of the Baltic Sea environment by pharmaceutical substances was compiled including concentrations of pharmaceuticals in Baltic coastal and offshore areas, primarily in biota, sea water and sediment. The concentrations are compared to threshold values when available. Information about the environmental effects of pharmaceuticals in the Baltic Sea is also provided.

Data was received from Denmark, Estonia, Finland, Germany, Poland, Russia and Sweden. The data presented in the report covers the period 2003-2014 and includes 47,600 data points on sources and pathways of pharmaceuticals (i.e. measurements of wastewater influent and effluents, sludge and river water) and 4,600 individual data points on concentrations of pharmaceuticals in the coastal, open sea and transitional areas of the Baltic Sea marine environment. The report includes data on 167 pharmaceutical substances measured in the marine environment and 156 pharmaceutical substances and 2 metabolites sampled at MWWTPs situated in Denmark, Estonia, Finland, Germany, Russia (St. Petersburg) and Sweden.

The main sources of pharmaceuticals in the Baltic Sea region are likely the excretion of active substances consumed by human and animal through urine and feces as well as the incorrect disposal of unused medical products. The main pathway of pharmaceuticals into the aquatic environment, according to the collected data, is via municipal wastewater treatment plants (MWWTPs).

Main results

According to the collected data, in the Baltic Sea region, the main sources of pharmaceuticals are believed to be the excretion of active substances consumed by humans and animals through urine and faeces. The main pathway of pharmaceuticals into the aquatic environment, according to the collected data, is via MWWTPs, which according to a rough estimate, release into the environment about 1.8 thousand tons of pharmaceuticals per year. Only nine out of 118 assessed pharmaceuticals were efficiently (> 95%) removed from wastewater during the treatment process and nearly half of the compounds were removed by <50%.

According to the data collected on concentrations of pharmaceuticals in the Baltic Sea environment, the most frequently detected substances belong to the therapeutic groups of cardiovascular and central nervous system agents, anti-inflammatory and analgesics and a metabolic agent. The most frequently detected pharmaceutical substances (mainly in water samples) are primidone (51 of 51 samples), clofibric acid (83 of 128) and carbamazepine 135

of 220). In biota, the largest number of pharmaceuticals and the highest concentrations were found in blue mussels.

Data gaps

Although the reported data provide an overview of the magnitude of inputs of several pharmaceutical substances to the Baltic Sea as well as their concentrations in the marine environment, there are shortcomings in the data that need to be addressed to get a more complete picture of the extent of contamination by pharmaceuticals. More data from the whole region are needed on:

- Sales and consumption of pharmaceuticals
- concentrations of pharmaceuticals in MWWTPs influent and effluent as well as rivers
- emissions of pharmaceuticals to environment
- the occurrence and fate of metabolites
- concentrations of pharmaceuticals in sewage sludge and soil
- sales and consumption, sources, pathways and loads of veterinary pharmaceuticals to soils and the aquatic environment (including aquaculture)
- sensitivity of analytical methods used for measuring concentrations

The presented study might underestimate concentrations of pharmaceuticals in the environment since the analytical methods used by many laboratories were at times not sensitive enough to detect substances at the level of the environmental quality standards for good status. There is therefore a need to improve the analytical methods used for measuring concentrations of pharmaceuticals in the environment. There is also lack of information on monitoring of concentrations in biota, as well as on the biological effects of pharmaceuticals.

In order to reduce the inputs of pharmaceuticals to the environment, measures should be taken at all stages of the product lifecycle from manufacturing to consumption to waste management but more data are needed to address concrete sources and pathways and identify priority measures.

This report supports the UNESCO project on Emerging Pollutants in Wastewater Reuse in Developing Countries project by providing scientific information and knowledge.

1. Introduction

Pharmaceuticals are an important element of modern society and their beneficial effects on human and veterinary health are widely acknowledged. However, their undesired occurrence and potential effects in the environment are of global emerging concern. Residues of various types of pharmaceuticals (hormones, pain killers, antibiotics, etc.) have been detected in several environmental compartments in different regions of the world, including the Baltic Sea (Pharmaceuticals in the environment – the global perspective).

Many regional and global projects have been carried out with the purpose of gathering data on the occurrence of medical substances in the environment as well as on harmful effect of these substances on particular species. This report presents the first comprehensive overview of the status and pressures of pharmaceuticals in the environment in the Baltic Sea region. The results are based on data available through e.g. national screening campaigns, projects and reports. This report is the first attempt to compile regional information on sales and consumption of pharmaceuticals, to identify sources and pathways of pharmaceuticals into the environment and to make a Baltic Sea regional level assessment of the occurrence and effects of pharmaceuticals in the marine environment.

1.1. Policy setting

In the 2010 HELCOM Ministerial Declaration, the Contracting Parties of HELCOM agreed to *'further assess the environmentally negative impacts of pharmaceuticals and other substances that are not monitored regularly, with the aim as a first step to assess in a coordinated manner their occurrence in the Baltic Sea and evaluate their impacts on the Baltic biota'* (HELCOM 2010). The commitment was followed up by the 2013 Ministerial Declaration, in which the Contracting Parties agreed *'to collect more information and assess the state of contamination with pharmaceuticals and their degradation products of the aquatic environment'* (HELCOM 2013).

The EU directive 2013/39/EU considers the contamination of water with pharmaceutical residues as an emerging environmental concern (European Commission 2013). Diclofenac, 17-beta-estradiol (E2), 17-alpha-ethinylestradiol (EE2) and estrone (E1), a breakdown product of E2, and three macrolide antibiotics erythromycin, clarithromycin and azithromycin are included on the first 'watch list' under the EU directive 2013/39/EU, with the aim to gather monitoring data on aquatic environment from EU Member States for the purpose of facilitating the determination of appropriate measures to address the risk posed by these substances (European Commission 2015).

Policy Area Hazards of the EU Strategy for the Baltic Sea Region (EUSBSR) has decided to give increased attention to the topic of pharmaceuticals in the Baltic environment during the years 2015-2017. The decision was based on the general growing concern over potential environmental impacts of pharmaceutical substances and the current policy movements within the EU, HELCOM region and globally. Furthermore, a specific objective related to decreased discharges of hazardous substances (including pharmaceuticals) in the Interreg Baltic Sea Region Programme 2014-2020 opens up possibilities for financial support to new projects within this area.

In addition to contributing to the above mentioned regional objectives, this report also serves as a case study for the UNESCO project "Emerging Pollutants in Wastewater Reuse in Developing Countries (2014-2017)", which aims to support UNESCO Member States to strengthen their scientific, technical and policy capacities to manage human health and environmental risks caused by emerging pollutants in water resources and wastewater.

1.2. Pharmaceuticals in the environment

Pharmaceuticals enter the environment during various stages of the product lifecycle. In the Baltic Sea region emissions from manufacturing facilities are generally assumed to be very low compared to inputs occurring during the consumption phase (Pharmaceuticals in the environment Results of an EEA workshop). However, there might be exceptions to this rule, and in other regions emissions from production may be very high The main pathway of human consumed pharmaceuticals to the marine environment is via direct discharges of effluents from coastal municipal wastewater treatment plants (MWWTPs) as well as via rivers carrying effluents from inland MWWTPs. Minor sources include land application of sewage sludge, whereby pharmaceuticals may leach into surface waters. Pharmaceuticals also enter the environment via agriculture, aquaculture and veterinary practice.

Awareness is growing that pharmaceuticals may have harmful effects for wildlife. Two well-documented global examples of pharmaceuticals adversely affecting wildlife are the hormone 17α-ethinylestradiol and the anti-inflammatory drug diclofenac. 17α-ethinylestradiol has been reported to be responsible for the feminization of male fish at concentrations that can be found in surface waters downstream of sewage treatment plants and the use of diclofenac for veterinary purposes has nearly wiped-out vulture populations in Southeast Asia. Psychotherapeutic drugs such as oxazepam and citalopram have also been reported to alter the behavior of fish.

Having a low biodiversity, with low functional redundancy and many species experiencing an increased physiological stress due to the brackish water environment, the Baltic Sea ecosystem is particularly sensitive to pollutants. The water exchange rate in the Baltic Sea is slow, meaning that there is a long retention time for persistent substances. This makes the Baltic Sea ecosystem more susceptible to hazardous substances in comparison with other marine areas.

2. Scope of the report

The scope of this report is to provide an overview of the extent of inputs of pharmaceuticals to the environment in the Baltic Sea region as well as to estimate contamination of the marine environment. The evaluation is based on data and information compiled within the framework of HELCOM and the Policy Area Hazards of the EU Strategy for the Baltic Sea Region.

The report presents available information on the following pressures to the Baltic Sea environment:

- Human consumption and use of pharmaceuticals in the countries
- Pathways of pharmaceuticals to the environment
- Concentrations of pharmaceuticals in municipal wastewater treatment plant (MWWTP) influent and effluent as well as sewage sludge, and in river water
- Information about the handling of pharmaceutical waste in countries

The estimation of contamination of the Baltic Sea environment by pharmaceutical substances is based on measured concentrations of pharmaceutical substances in Baltic coastal and offshore areas, primarily in water, sediment and biota. The concentrations are compared to threshold values (or PNEC values) where such information is available.

3. Data collection methodology and data availability

The HELCOM Secretariat together with the Swedish Environmental Protection Agency in its capacity as coordinator for Policy Area Hazards of the EUSBSR, initiated the elaboration of this regional status report on pharmaceuticals. Two HELCOM working groups contributed to the report: (1) the

Working Group on the State of the Environment and Nature Conservation (State and Conservation) regarding concentration of pharmaceuticals in the environment and (2) the Working Group on Reduction of Pressures from the Baltic Sea Catchment Area (Pressure) regarding inputs and pathways of pharmaceuticals to the sea.

3.1. Data collection methodology

Data collection was carried out in two stages. In the first stage, the HELCOM groups State and Conservation, Pressure, and Agri (Group on Sustainable Agricultural Practices) were asked to report on the availability of data regarding occurrences of pharmaceutical substances in the marine environment as well as on their sources and pathways. Information on data availability was provided by Denmark, Finland, Germany, Poland, Russia and Sweden. All the reports, complemented by published data, were compiled into a summary of data availability.

In the second stage, a questionnaire was circulated to national contacts of the HELCOM groups State and Conservation and Pressure. The questionnaire (together with reporting guidelines) was elaborated based on the information collected during the first phase and sent out in late August 2015. Filled in templates were submitted to the HELCOM Secretariat by October 2015. In addition to the data on measured concentrations of pharmaceuticals, countries were asked to provide data on sales, prescriptions, consumption of drugs in recent years as well as information on national systems for managing (handling) pharmaceutical waste.

The data were evaluated by experts and compiled into two background reports of which one focused on concentrations of pharmaceuticals in the environment (Hallgren and Wallberg, 2015) and the other on information on sources and pathway of these substances into the environment (Vieno 2015). This summary report is a compilation of the two background reports.

3.2. Reported data

The reported data were divided into two groups. One group included all measurements related to sources and pathways of pharmaceuticals into the environment (sales, consumption, waste water, rivers, waste handling), and the other group included data on concentrations of pharmaceuticals observed in compartments of the marine and coastal environment such as water, sediments and biota.

The majority of reported data on sources and pathways was concentrations in influents and effluents of MWWTPs as well as observations in rivers. Some data on sales and consumption of drugs available through national statistics was also reported as well as information on collection and handling of unused medical substances was provided.

The measured pharmaceuticals belong to seven therapeutic groups: anti-inflammatory and analgesics; antimicrobial (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote; cardiovascular agents; central nervous system agents; chemotherapeutic agents and X-ray contrast media; hormones and hormone antagonists; metabolic agents and gastrointestinal agents.

An overview of the data and information reported by countries is presented in Table 1. All HELCOM Contracting Parties except Latvia and Lithuania reported at least some data.

The information received from countries included national monitoring data, screening data, and results of scientific and commissioned studies. Many data have been published in national reports (in national languages) and some are available in national databases.

Table 1: An overview of data provided in response to a HELCOM questionnaire on occurrence, sources and pathways of pharmaceuticals in the Baltic Sea region

Country	Production & waste		Sales, Consumption		Monitoring data					
	Production	Waste management	Human	Veterinary	WWTPs	Sludge	Rivers	Sea water	Sediments	Biota
Denmark					x	x	x	x		
Estonia		x	x		x		x	x	x	
Finland	x	x	x	x	x	x	x	x	x	
Germany		x	x	x	x		x	x		
Poland								x		
Russia			x		x			x		
Sweden		x	x		x	x	x	x	x	x

Source: Original data

In total 47,600 data points from the period 2003-2014 were included in the dataset (Figure 1) on sources and pathways of pharmaceuticals (i.e. monitoring of wastewater influent and effluents, sludge and river water).

- In wastewater influent and effluents, 156 different pharmaceuticals and 2 metabolites were analysed, of which 142 pharmaceuticals and 2 metabolites were detected.
- In sewage sludge, 60 different pharmaceuticals were monitored, of which 34 were detected.
- In rivers, 111 different pharmaceuticals were monitored, of which 48 were detected.

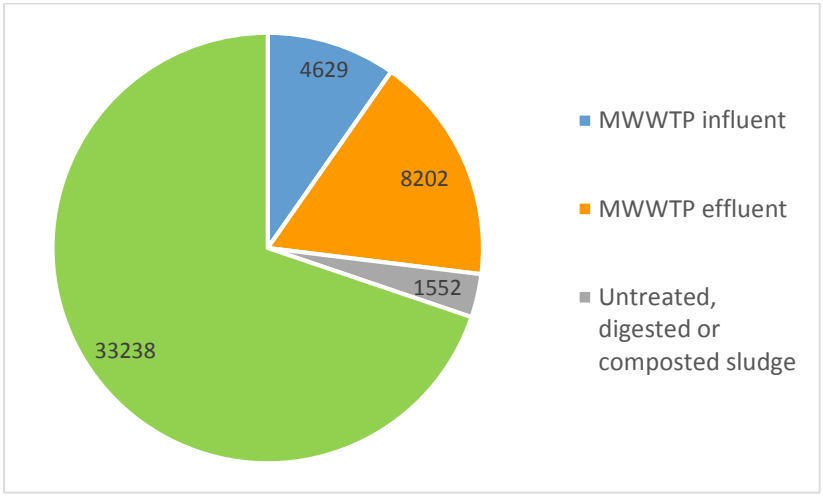

Figure 1: Number of data points for different sample matrices. *Source:* Original data

A more detailed overview of reported data from MWWTP influents, effluents, sludge and river water is presented in Annex 1.2. The compiled results are presented in Annex 3.

Data on concentrations of pharmaceuticals in the marine environment were reported for the time period 2003-2014 and included 4,600 individual data points from coastal, open sea and transitional areas.

- 167 different pharmaceuticals were measured, of which 74 were found in at least one of the matrices (water, sediment, biota)
- 51 different pharmaceuticals were detected in water (of 148 measured)
- 9 different pharmaceuticals were detected in sediment samples (of 25 measured)
- 35 different pharmaceuticals were detected in biota samples (of 116 measured).

A more detailed overview of reported data on concentrations of pharmaceuticals in the marine environment is presented in Annex 1.2. The compiled results are presented in Annex 4.

3.3. Major data gaps

Of the HELCOM Contracting Parties, Latvia and Lithuania were the only countries that did not provide any data.

No occurrence data were received from Poland, which makes it difficult to assess in detail the loads of pharmaceuticals into the Baltic Sea since Poland has the largest portion of the Baltic Sea catchment area, including half of the inhabitants of the catchment.

Sales and consumption data were only received from Estonia, Finland, Germany and Sweden. Thus the total sales and consumption of pharmaceuticals in Baltic Sea region cannot be reported. Statistical reports contain information on the amount of sold pharmaceuticals, which may not all be used.

No data were received on the occurrence of veterinary pharmaceuticals in manure or in the environment. Thus the assessment of the role of veterinary pharmaceuticals is incomplete.

No data were received on occurrence of pharmaceuticals in the sediments of inland water bodies or in the soil, thus the assessment of the role of these compartments as a source and pathway of pharmaceuticals into the Baltic Sea is incomplete.

No data were available for assessing inputs of pharmaceuticals via agriculture and aquaculture.

Information about medical waste handling was received only from Estonia, Finland, Germany, Sweden and partially from Russia. Therefore, the estimation of the threat to the environment via disposal of unused medical substances is incomplete.

No information was reported on biological effects.

4. Overview of recommendations for monitoring of pharmaceuticals

The HELCOM Baltic Sea Action Plan (BSAP) sets out assessment requirements for following progress towards reaching good environmental status (GES) by 2021, whereby the status is to be assessed for a set of ecological objectives. The HELCOM strategic goals and objectives are to a large extent comparable to the descriptors and criteria of the EU Marine Strategy Framework Directive (MSFD) (2008/56/EC), which stipulates that GES is to be achieved by 2020. HELCOM core indicators are used to follow up on the progress made to reach the goals of both policies within the Baltic Sea, by measuring the progress towards a BSAP objective and/or a MSFD criteria. Work has been initiated within HELCOM to develop core indicators for diclofenac and estrogenic-effects; these will be further developed using input from this assessment.

The EU directive 2013/39/EU requires that Member States monitor the ‘watch list’ substances across a wide range of water bodies in order to ascertain the extent of presence in the environment. This is a challenge as the proposed concentration levels at which these should be monitored are low (Table 2) and many laboratories cannot meet these requirements.

Table 2: 'Watch list' of pharmaceuticals for EU-wide monitoring.

Name of the substance	CAS number	EU number	Maximum acceptable detection limit (ng/l)
diclofenac	15307-86-5	239-348-5	10
17-alpha-ethinylestradiol (EE2)	57-63-6	200-342-2	0.035
17-Beta-estradiol (E2), Estrone (E1)	50-28-2 53-16-7	200-023-8	0.4
Macrolide antibiotics (erythromycin, clarithromycin, azithromycin)	114-07-8 81103-11-9 83905-01-5	204-040-1 617-500-5	90

Source: COMMISSION IMPLEMENTING DECISION (EU) 2015/495

Under the WFD each Member State can select substances of national or local concern (river basin specific pollutants) in addition to the substances of European Union (EU)-wide concern (the priority substances). In Sweden three pharmaceuticals are listed as specific pollutants (Table 3).

Table 3: Swedish assessment criteria for specific pollutants in coastal waters and transitional waters

Name of the substance	Good status Annual Average (ng/l)
diclofenac	10
17-alpha-ethinylestradiol (EE2)	0.007
17-beta-estradiol (E2)	0.08

Source: HVMFS 2013

In September 2015, a Swedish national working group, coordinated by the Swedish Medical Products Agency and consisting of a large number of national agencies within the health and medical sector and a representative from the industry, presented a list of substances that were suggested should be monitored in the environment on a regular basis (MPA 2015). In addition to the substances included on the WFD 'watch list', 17 pharmaceuticals were suggested (Table 4).

Table 4: Seventeen pharmaceuticals suggested for monitoring by a Swedish stakeholder working group in addition to the substances on the WFD 'watch list'

Name	Justification by Swedish MPA (2015)
Ciprofloxacin	Persistent and demonstrated resistance development in the environment
Citalopram	Has been detected in fish and drinking water. PBT- properties. Relatively large usage.
Fluconazol	Has been detected in drinking water, surface water and sludge.
Ibuprofen	Large usage and has been detected in surface water
Carbamazepin	Has been detected in drinking water and surface water.
Cetoconazol	Has been detected in sludge
Levonorgestrel	PBT- properties
Losartan	Large usage
Metoprolol	Large usage and has been detected in drinking water, surface water and sludge.
Metotrexat	Unknown environmental effects and presence. A chemotherapy that is used by the households.
Naproxen	Has been detected in drinking water and surface water. Increased usage as it is often used as a replacer for diclofenac.
Oxazepam	Has been detected in fish, surface water and drinking water. Toxic at environmental relevant concentration.
Sertralin	Has been detected in surface water, fish and sludge.
Sulfametoxazol	Has been detected in surface water, fish and sludge.
Tramadol	Has been detected in surface water and drinking water.
Trimetroprim	Large usage. Has been detected in drinking water, surface water and sludge
Zolpidem	Has been detected in drinking water, surface water and sludge

Source: MPA 2015

5. Production, sales, consumption and handling of pharmaceutical waste

5.1. Pharmaceutical production

Data about pharmaceutical production were only received from Finland. The Finnish Medicines Agency, Fimea, grants licenses for facilities producing medicinal products. Currently, pharmaceuticals are produced by at least eight companies in at least twelve manufacturing plants in Finland.

Although the contribution of manufacturing facilities to emissions of medicinal products and/or their residues is generally considered as negligible in the EU, there is no comprehensive information about pharmaceutical production facilities and their potential emission of pharmaceutical substances in the region. Information on pharmaceutical production in other countries in the region would be useful for mapping potential hot spots for releases of pharmaceuticals.

5.2. Consumption of pharmaceuticals

The consumption phase is considered to be the biggest contributor to the emissions of pharmaceuticals into the environment, mainly through excretions and incorrect disposal of unused medicines into sinks and toilets. Between 30 to 90% of the orally administered dose is generally excreted as active substance in the urine of humans and animals, with the nature and amount of medicinal residues mainly dependent on the volumes and nature of the administered substances, the mode of administration and metabolization rates (BIO Intelligence Service 2013).

Human consumption

Only four countries provided information on human consumption of pharmaceuticals mainly based on the data on sold amounts. The magnitude of consumption was calculated for the most frequently prescribed pharmaceuticals as well as for those that were often found in the environment (e.g. metoprolol, carbamazepine, diclofenac). Consumption data were available for 76 pharmaceuticals but data from all four countries were only available for 16 pharmaceuticals substances.

About 21 million people live in the area from where data were available (compared to the 85 million residing in the entire Baltic Sea catchment), therefore, the presented figures are not representative of the total consumption of pharmaceuticals in the Baltic Sea region.

Figure 2 shows the annual consumption of the top 20 most consumed pharmaceuticals. According to the available data, anti-inflammatory drug paracetamol was the most consumed pharmaceutical with a total annual consumption amount of more than 520,000 kg. The annual consumption of antidiabetic drug metformin, constipation drug macrogol and anti-inflammatory drug ibuprofen all exceeded 100,000 kg. In 2014, about 1,600 tonnes of the top 20 pharmaceuticals were consumed in the four countries from which data were available. Per inhabitant, this amount was about 80 g per person per year. If the consumption patterns are similar throughout the region, for the entire Baltic Sea catchment the consumption of the top 20 pharmaceuticals would be about 6,800 tonnes per year.

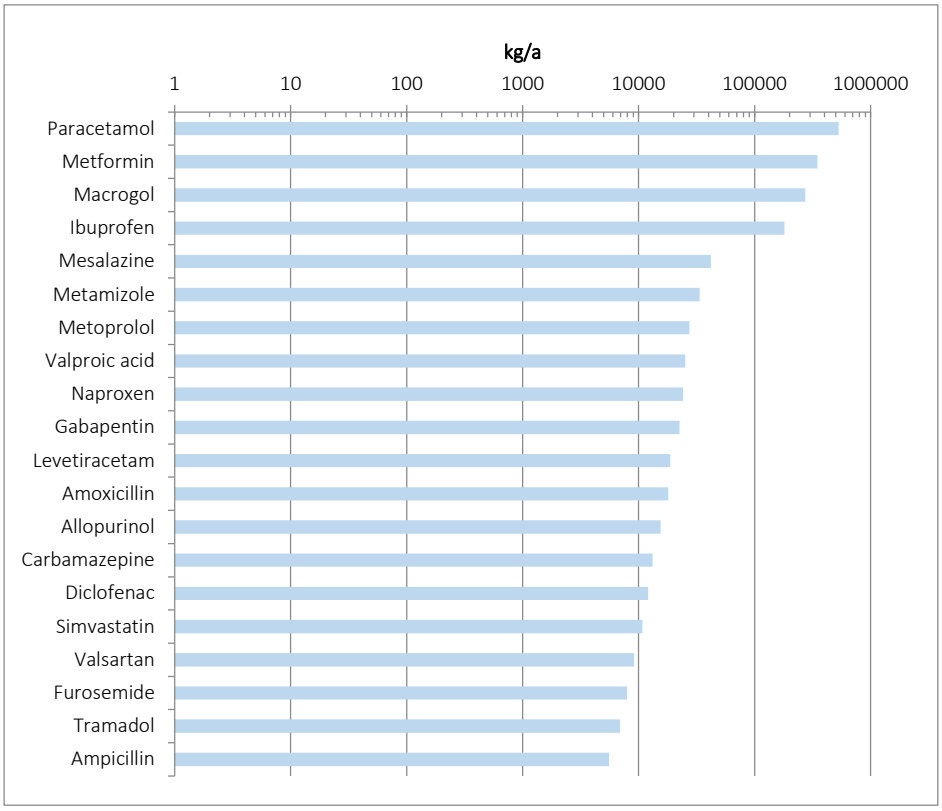

Figure 2: Top 20 most sold pharmaceuticals. Data were received from Estonia, Finland, Germany (only Mecklenburg Vorpommern and Schleswig Holstein – which are within the catchment area of the Baltic Sea) and Sweden. For diclofenac, also Russian (St. Petersburg) data are included. Metamizole was only prescribed in Germany. For ampicillin, furosemide, tramadol and naproxen data were available from Estonia, Finland and Sweden.

Source: Original data

More data on sales and consumption of pharmaceuticals are presented in Annex 2.

Veterinary sales and consumption

Due to very limited data reported on veterinary consumption of pharmaceuticals, it is difficult to estimate the total amount of veterinary pharmaceuticals used in the Baltic Sea catchment area. A very rough estimation, by extrapolating from the available Finnish and German data, would result in an annual sales and consumption of about 900 tonnes. This figure only includes antimicrobial drugs, since no data were reported on the sales and consumption of pharmaceuticals in other therapeutic groups. More data on sales and consumption of pharmaceuticals are presented in Annex 2.

5.3. Handling of pharmaceutical wastes

The improvement of take-back schemes for unused medical products represents one of the simplest ways for reducing inputs of pharmaceutical products into the environment. EU medicinal legislation has required take-back schemes for unused and expired human medicinal products since 2004 (Directive 2004/27/EC) to “ensure that appropriate collection systems are in place for human medicinal products that are unused or have expired”.

Only Estonia, Finland and Sweden provided information on the amounts of pharmaceutical waste collected (Table 5) and on procedures for handling pharmaceuticals waste.

Table 5: Amounts of pharmaceutical waste collected in Estonia, Finland and Sweden

Estonia (in 2014)	Finland (in 2006)	Sweden (in 2011)
89,190 kg All waste pharmaceuticals collected	185,000 kg Pharmaceuticals returned to the pharmacies	1,500,000 kg Estimate of the total amount involved in take-back schemes
	33,000 kg Incorrectly disposed via solid waste	800,000 kg Pharmaceuticals returned to the pharmacies
	28,000 kg Incorrectly disposed via sewers	250,000 kg Ending up in the mixed waste from households
		10,000 kg From the public to municipalities recycling centers
		50,000 kg Discarded by the internal operations of the pharmacies
		250,000 kg Discarded by the internal operations of the wholesale trades
		100,000 kg Discarded in hospital healthcare

Source: Original data

In Estonia, all pharmaceuticals are classified as hazardous waste and should therefore be collected.

In Finland, the local municipalities are responsible for the collection and processing of household hazardous wastes (incl. pharmaceuticals). The collection of pharmaceutical waste is most commonly arranged through cooperation with local pharmacies. Pharmacies accept medicines and mercury thermometers returned by customers at no cost. The municipality provides the pharmacy with collection containers and transports the waste to a toxic waste disposal plant for properly disposal.

According to the Finnish University Pharmacy's survey in 2009, the proportion of people returning medical waste properly has grown in recent years. About one in ten Finns admitted having thrown medicines into mixed waste or to have flushed them into the sewers. In a similar survey in 2006, the same figure was three in every ten Finns. The most common reported reason for improper disposal of medical waste was that people did not know how to treat them. Other reasons mentioned in the survey were indifference, hurry, long distances and that the amount of the medicine was small or that it was thought harmless.

In Sweden, producers are required to ensure free take-back collection systems for pharmaceutical waste from households. This is managed via the pharmacies. Pharmaceuticals classified as hazardous waste (cytostatic and cytotoxic pharmaceuticals) are, however, not formally covered by the producer responsibility, which means that municipalities are responsible for collection, transport and destruction of those wastes from household. In practice, however, many pharmacies have take-back of all types of pharmaceutical waste, since distinguishing different fractions of hazardous and non-hazardous pharmaceuticals is not always straightforward. Moreover, the amounts of cytostatic and cytotoxic pharmaceuticals handled by households are assessed to be very small since these types of drugs are mainly used within hospital healthcare. Medical waste from other activities, e.g. from hospitals or veterinary practices, are not covered by the producer responsibility and these practices are themselves responsible for correct waste handling.

Pharmaceutical waste is collected by the pharmacies, by the municipalities' collecting systems recycling centers and via other healthcare/hospital management. The County Councils' healthcare activities have also well-established routines for the handling of pharmaceutical waste. Currently there are some 20 facilities in Sweden licensed for the destruction of medical wastes.

Experts from the Russian Federation have indicated that there is a lack of a coherent system for handling medical wastes, especially outdated pharmaceuticals in households. Therefore, in most cases such pharmaceuticals end up at landfills or in municipal sewage systems. A number of federal legal acts identify dumping of medical wastes at the specific sites and incineration as the most preferable way for handing medical wastes.

In Germany there is no specific national regulation on waste management of pharmaceuticals. The management of pharmaceutical waste is regulated on local level. As a consequence different ways of disposal are established. A take back system for pharmaceuticals does not exist in Germany.

The most important disposal options are

- bins for residual waste (Hausmüll, Restmülltonne),
- local recycling center responsible for mobile services to collect hazardous waste (Recyclinghof resp. Schadstoffmobil),
- pharmacies (on a voluntary basis as pharmacies in Germany are not obliged to take back unused pharmaceuticals).

The Federal Ministry of Education and Research launched the project to establish a website informing consumers on environmentally sound dispose of unused pharmaceuticals in their hometown. The map-based web service is available via the link http://www.arzneimittelentsorgung.de.

6. Inputs of pharmaceutical substances into the Baltic Sea

6.1. Sources and pathways

Pharmaceuticals are released into the environment during various stages of the product lifecycle (manufacturing, consumption and waste disposal). In the Baltic Sea region, the main sources of pharmaceuticals are the excretion of active substances consumed by human and animal through urine and faeces as well as the incorrect disposal of unused medical products into toilets and sinks. Figure 3 illustrates the main sources and pathways of pharmaceuticals into the environment.

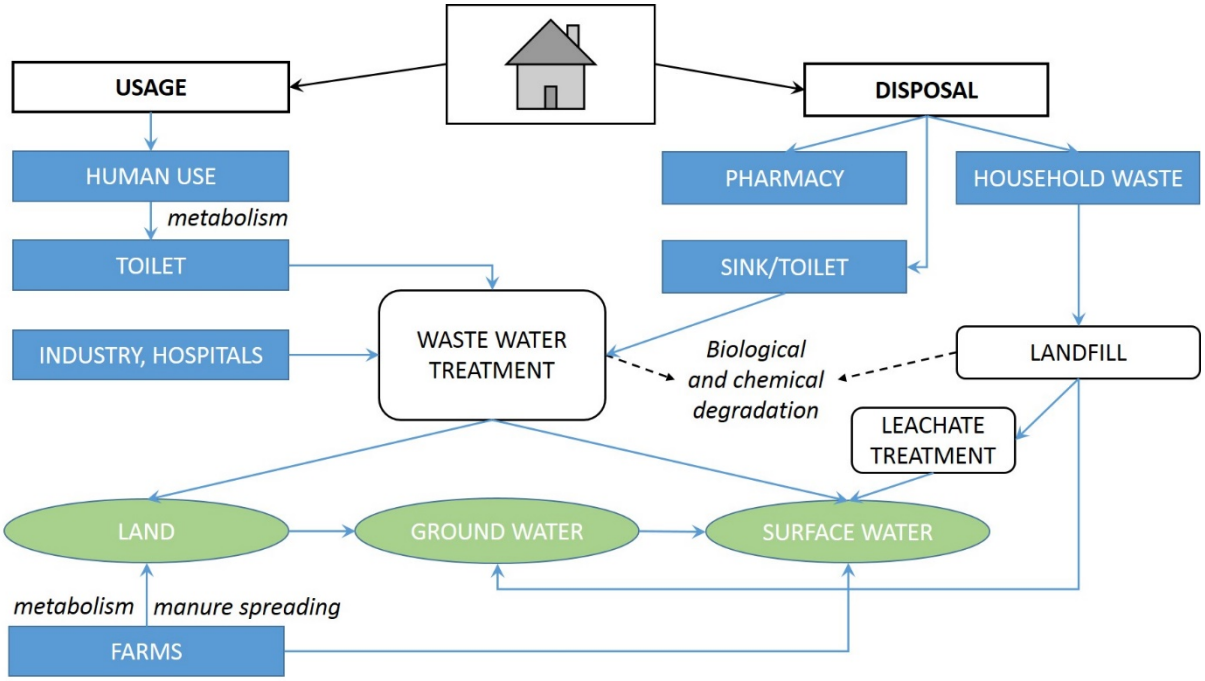

Figure 3: Sources and pathways of pharmaceuticals to the environment.

Since the majority of the population in the Baltic Sea region is connected to municipal wastewater treatment plants, MWWTPs are considered a major pathway of pharmaceuticals into the environment. Pharmaceuticals are directly released into the Baltic Sea via the effluents of coastal MWWTPs and indirectly by the rivers which carry effluents from inland MWWTPs. In some regions the pharmaceutical industry and hospitals may be important sources of pharmaceuticals that end up in the sewage system.

Other pathways of pharmaceuticals to the Baltic Sea include emissions from scattered dwellings not connected to centralized sewage systems, runoff/leaching from land where manure or sewage sludge has been applied and landfill leachate if medical waste is incorrectly disposed of via solid waste. The reported data do not allow to assess significance of these pathways at the moment.

6.2. Concentrations of pharmaceuticals in samples from MWWTP influents, effluents, sludge and river water

Analytical data were available for 143 pharmaceuticals and 2 metabolites sampled at WWTPs situated in Denmark, Estonia, Finland, Germany, Russia (St. Petersburg) and Sweden.

Figure 4 presents the top 20 pharmaceuticals present at the highest concentrations in MWWTP influents. The highest average concentration of 83 μg/l was measured for anti-inflammatory drug paracetamol. The highest concentration of 1,300 μg/l (in Denmark) was measured for diuretic drug furosemide.

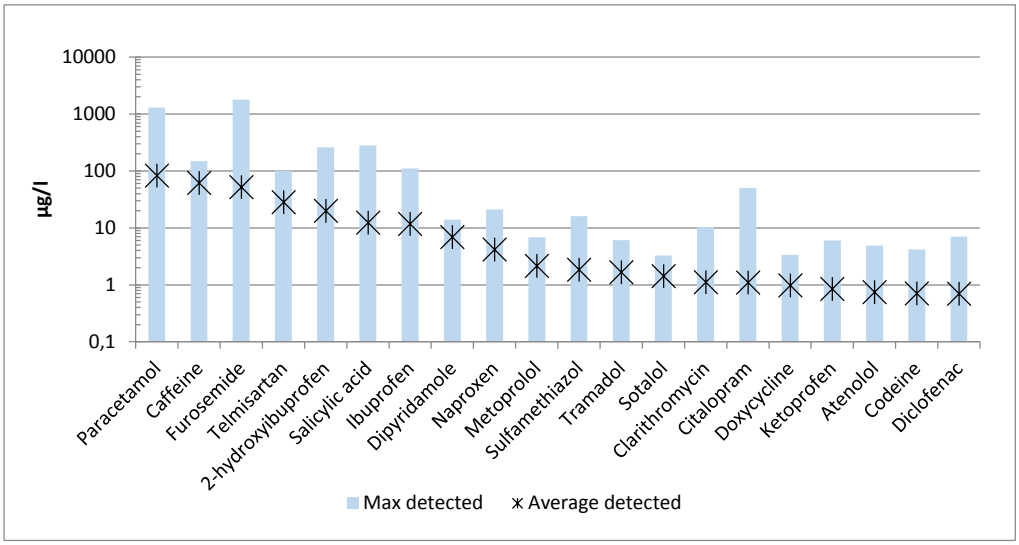

Figure 4: The top 20 pharmaceuticals measured in highest concentrations in MWWTP influents. X indicates the average concentration of the measurements and the bar indicates the maximum measured concentration.

Source: Original data

Figure 5 shows the top 20 pharmaceuticals with highest concentrations in MWWTP effluent (after treatment). The highest average concentration of 22.3 µg/l was measured for diuretic drug furosemide and the highest measured concentration of 360 µg/l was for anti-inflammatory drug paracetamol (in Denmark). In general, those compounds that were present in the influents at highest concentrations and which were the least removed during the treatment, were detected in the effluents at the highest concentrations.

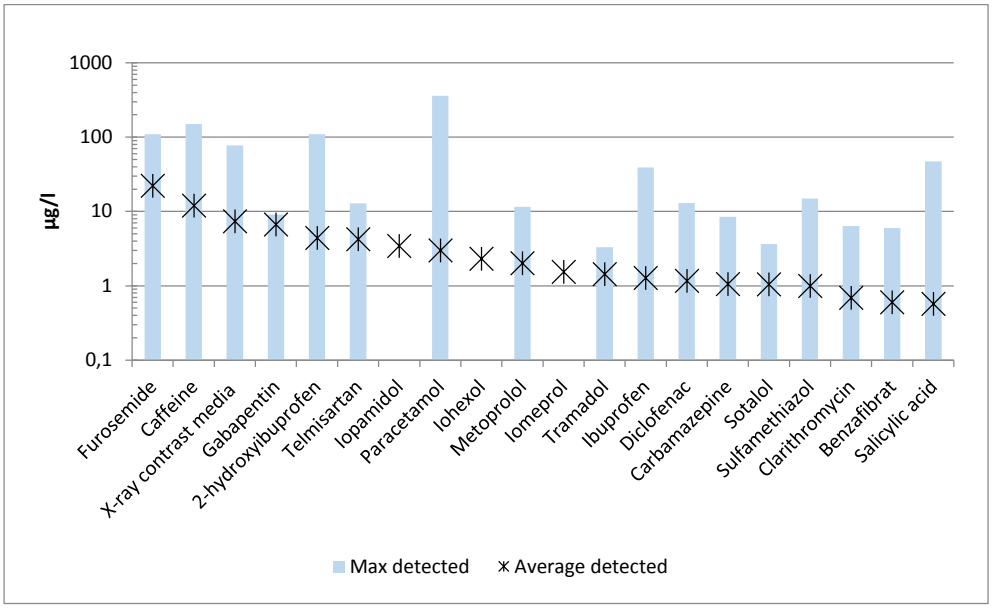

Figure 5: The top 20 pharmaceuticals measured in highest concentrations in MWWTP effluents. X indicates the average concentration of the measurements and the bar indicates the maximum

measured concentration. Maximum detected concentrations for iopamidol, iohexol and iomeprol are not included since only mean concentrations were reported.

Source: Original data

Removal rates were calculated for 118 pharmaceuticals by comparing the reported influent and effluent concentrations (Figure 6). It should be noted, that the removal rates consider only the removal of pharmaceuticals from the aqueous phase. Removal rates were not calculated for pharmaceuticals that were not detected in influent waters.

Only nine out of 118 pharmaceuticals were efficiently (> 95%) removed during the treatment process. Nearly half of the compounds were removed at a rate of <50%. For 16 pharmaceuticals, higher concentrations were reported in effluents than in influents, which may be due to analytical errors or the release of parent compounds from β-glucuronated pharmaceuticals that were excreted by the human body. Furthermore, in activated sludge, *E. Coli* secrete β-glucuronidase enzyme that is capable of deconjugating the glucuronated metabolites which could result in releasing the active pharmaceutical into the wastewater. Additionally, two of the compounds, identified in higher concentrations in the effluent than the influent, were metabolites of ibuprofen that are formed during the biological degradation of the parent compound.

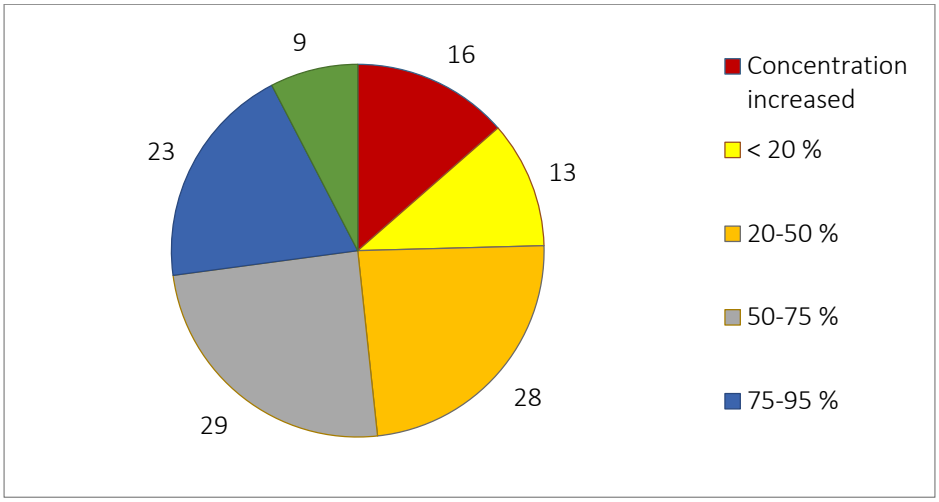

Figure 6: Number of pharmaceuticals removed in MWWTPs at different removal rates. Removal rates were estimated by comparing concentrations in influents and effluents

Source: Original data

Significantly fewer data were reported for sludge samples than for influent and effluent samples and only from Finland and Sweden. Data for composted sludge were only received from Finland. More data should be gathered on the presence of pharmaceuticals in sewage sludge as well as the fate of the compounds during sludge treatment. The top 20 pharmaceuticals (highest concentrations) in untreated sludge are presented in Figure 7. The highest average concentration of 3.3 mg/kg d.w. was measured for the antibiotic ciprofloxacin. Also the highest measured concentration was for ciprofloxacin (in Finland) at 8.8 mg/kg d.w.

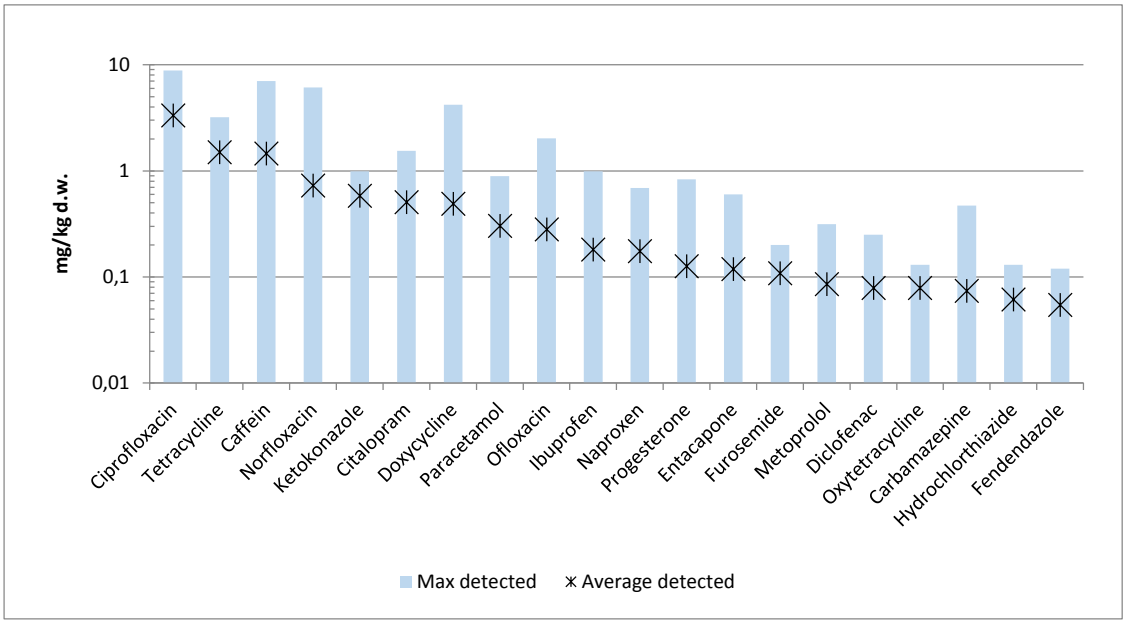

Figure 7: The top 20 pharmaceuticals measured in highest concentrations in untreated sewage sludge. X indicates the average concentration of the measurements and the bar indicates the maximum measured concentration.

Source: Original data

Average concentrations of pharmaceuticals in untreated, digested and composted sludge are presented in Figure 8. Concentrations of some pharmaceuticals are reduced through digestion and/or composting, however, certain compounds, such as antibiotics, seem to be fairly resistant to degradation during sludge treatment. More research is needed on the fate of pharmaceuticals in sludge treatment.

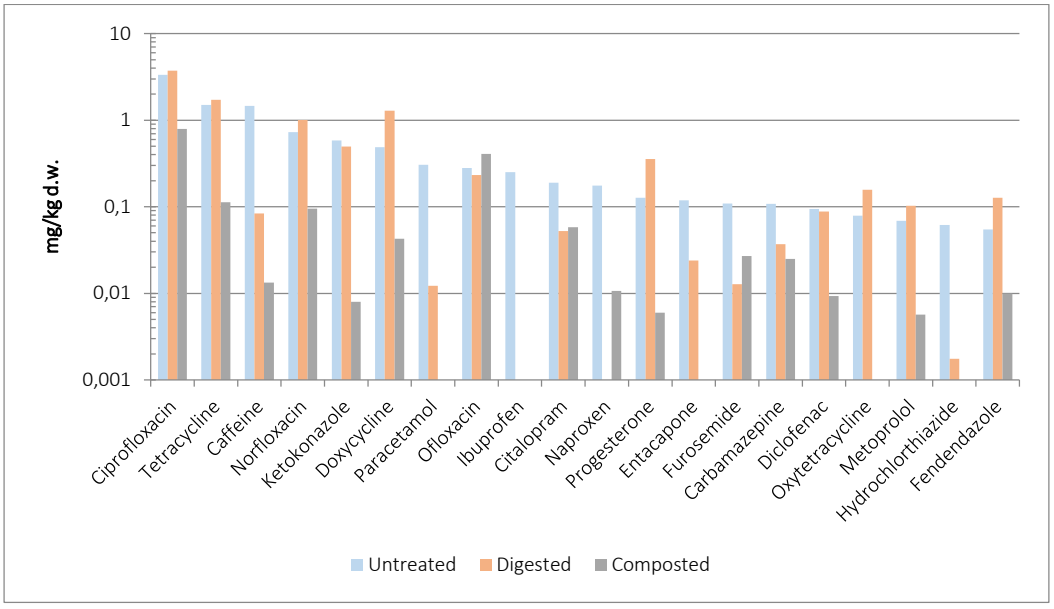

Figure 8: Average concentrations of pharmaceuticals in untreated, digested and composted sludge

Source: Original data

Data were reported for 100 pharmaceuticals in river water samples. Figure 9 presents the top 20 pharmaceuticals occurring at highest concentrations in sampled river water. The highest average concentration of 0.92 μg/l was measured for X-ray contrast media iopamidol. Iopamidol was also the pharmaceutical measured at the highest concentration of 20.8 μg/l (Pampower Graben, Germany). In general, the average concentrations were lower than 0.1 μg/l, however, for twelve compounds the highest concentrations exceeded 1 μg/l.

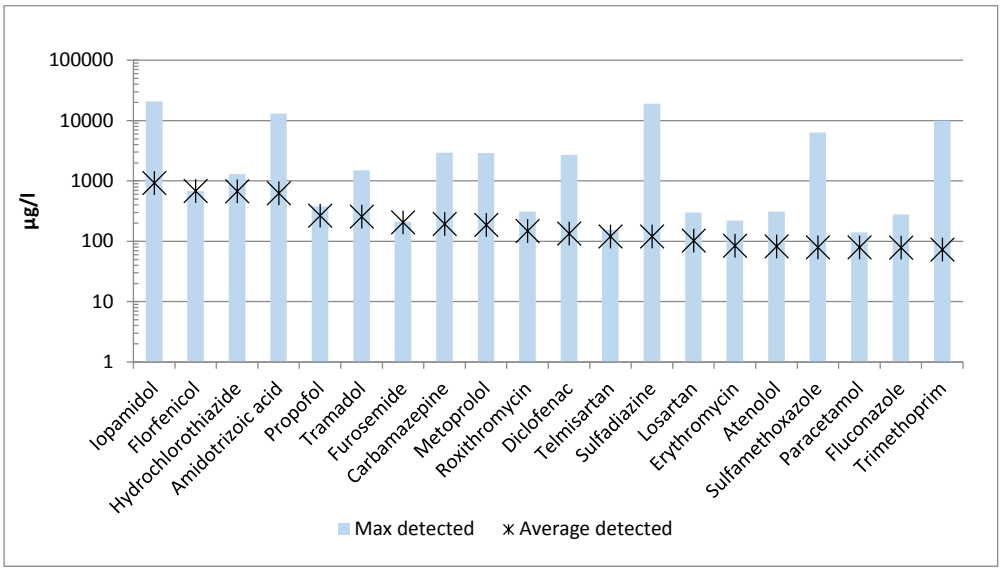

Figure 9: The top 20 pharmaceuticals measured in highest concentrations in river water samples. X indicates the average concentration of the measurements and the bar indicates the maximum measured concentration.

Source: Original data

7. Concentrations and effects of pharmaceuticals in the marine environment

Six Contracting Parties reported data on the concentrations of pharmaceuticals in the Baltic Sea environment for the period from 2003 to 2014. In total 4,600 observations in water, sediments and biota were reported. Presence of pharmaceuticals in the environment was detected in 640 samples. One hundred and sixty-seven different pharmaceuticals were measured and 74 of these were found in at least one of the matrices.

The overview of environmental concentrations only includes reported data from the Contracting Parties, i.e. it does not contain information on all the compounds detected in the Baltic Sea environment. No data on effects was received from the Contracting Parties, however data from scientific studies on effects of pharmaceuticals on Baltic biota was included. Additional information on methods, collected samples and concentrations of the individual pharmaceuticals are presented in Annex 4. An overview of all data submitted, including references, from the Contracting Parties is presented in Annex 1.2.

Maps and figures give an overview of sampling sites, sampling matrices and samples above the detection limit. The geographical distribution of all water, sediment and biota samples are presented in Figure 10 to Figure 12, respectively. For regional monitoring and assessment purposes within

HELCOM, the Baltic Sea is divided into sub-basins (referred to as Level 3 in the map legend) and coastal areas (see HELCOM monitoring and assessment strategy 2013).

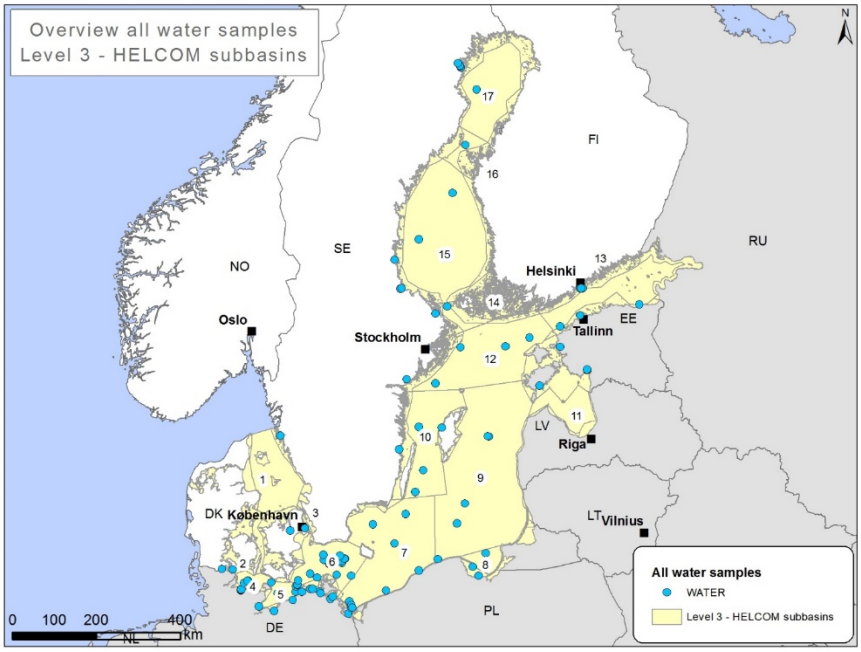

Figure 10: Overview of all 3,642 water samples in the compiled data set, including data submitted by Denmark, Estonia, Finland, Germany, Poland, and Sweden.

Source: Original data

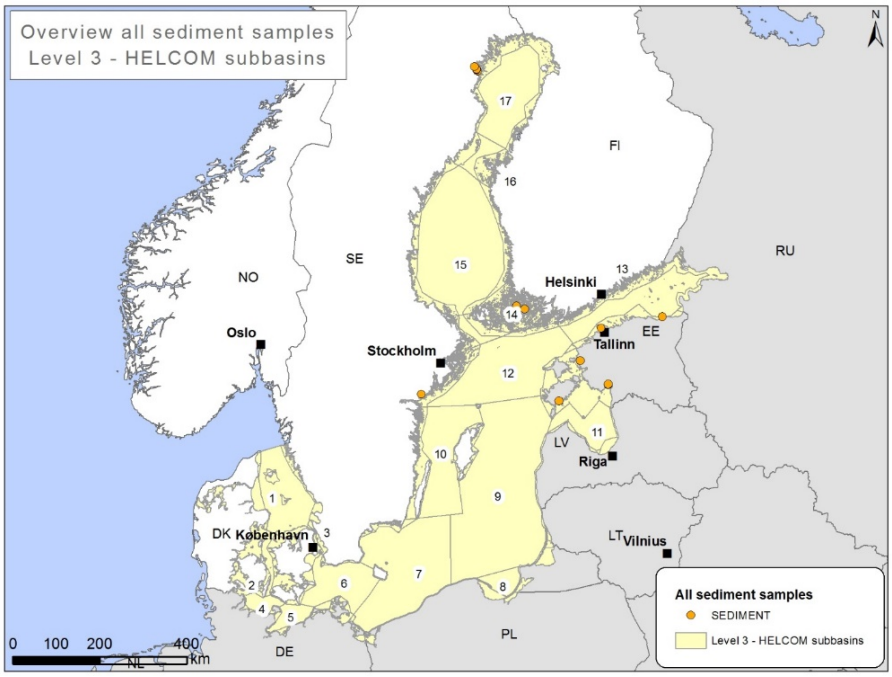

Figure 11: Overview of all 114 sediment samples in the compiled data set, including data submitted Estonia, Finland, and Sweden.

Source: Original data

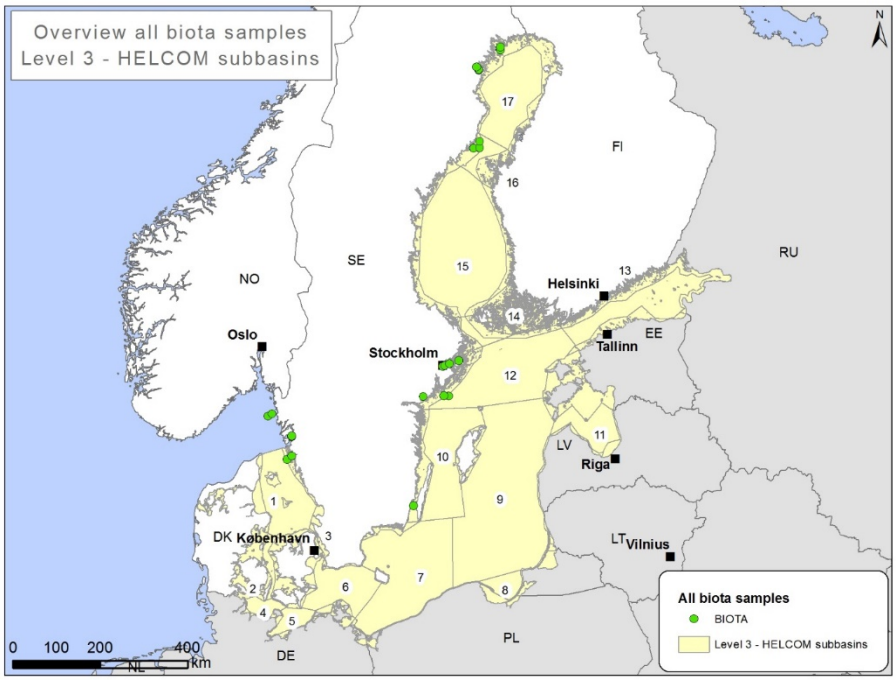

Figure 12: Overview of all 839 biota samples in the compiled data set, including data submitted by Sweden only.

Source: Original data

7.1. Concentrations of pharmaceuticals in the marine environment

Results are presented by grouping pharmaceuticals according to their general clinical use. Maps and figures present information about selected substances belonging to each group. More detailed information is presented in Annex 4.

The figures, presenting concentrations of individual pharmaceuticals, intend to visualize the variability in the sensitivity of the methods used, referred to as LOD (limit of detection) in the figures. The highest reported limit of detection (High-LOD) in the data set represents the least sensitive analytical method used, while the Low-LOD represents the most sensitive method used. However, LOD was not reported in all datasets. Therefore, in some cases the lowest reported measured concentration is presented as a proxy for the Low-LOD, representing a worst case scenario. The LOD indicator is missing when there were no sufficient data reported. The LOD indicated in the figures are thus indicative.

Anti-inflammatory and analgesics

Pharmaceuticals belonging to the anti-inflammatory and analgesics therapeutic group were detected in all matrices at different locations around the Baltic Sea. Most frequently detected were diclofenac (79 out of 322 samples; 25%) (Figure 13) and ibuprofen (38 out of 260 samples; 15%) (Figure 14). Paracetamol was detected in all eight reported samples of water and sediments in which the substance was analyzed. Phenazone was observed in only five out of 137 water samples (4%) (Figure 15). The maximum concentrations measured in water samples were 54 ng/l for diclofenac, 159 ng/l for ibuprofen, 360 ng/l for paracetamol and 504 ng/l for phenazone (Figure 16).

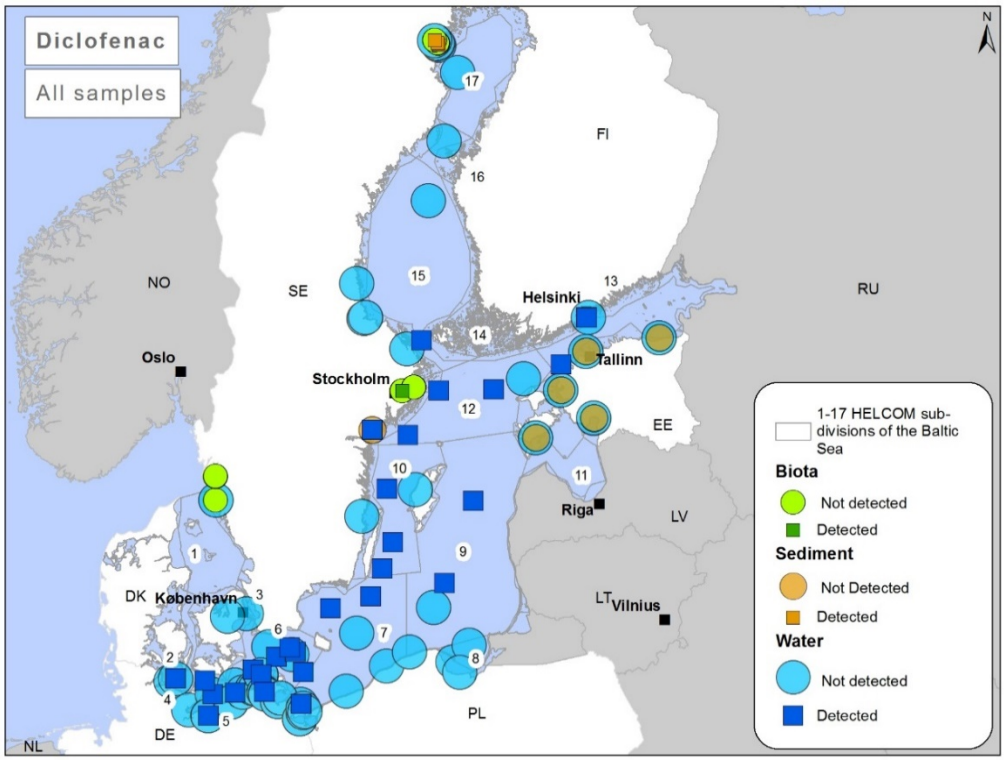

Figure 13: Sample locations for the compiled data of diclofenac. Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

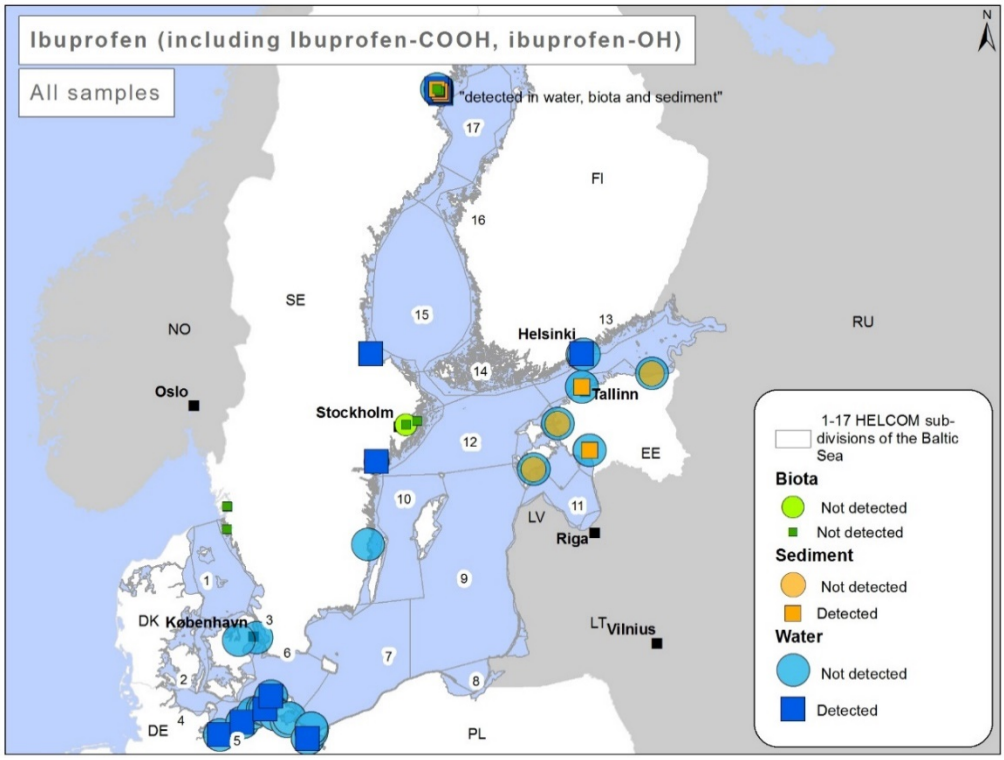

Figure 14: Sample locations for the compiled data of ibuprofen (including ibuprofen-OH and ibuprofen-COOH). Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

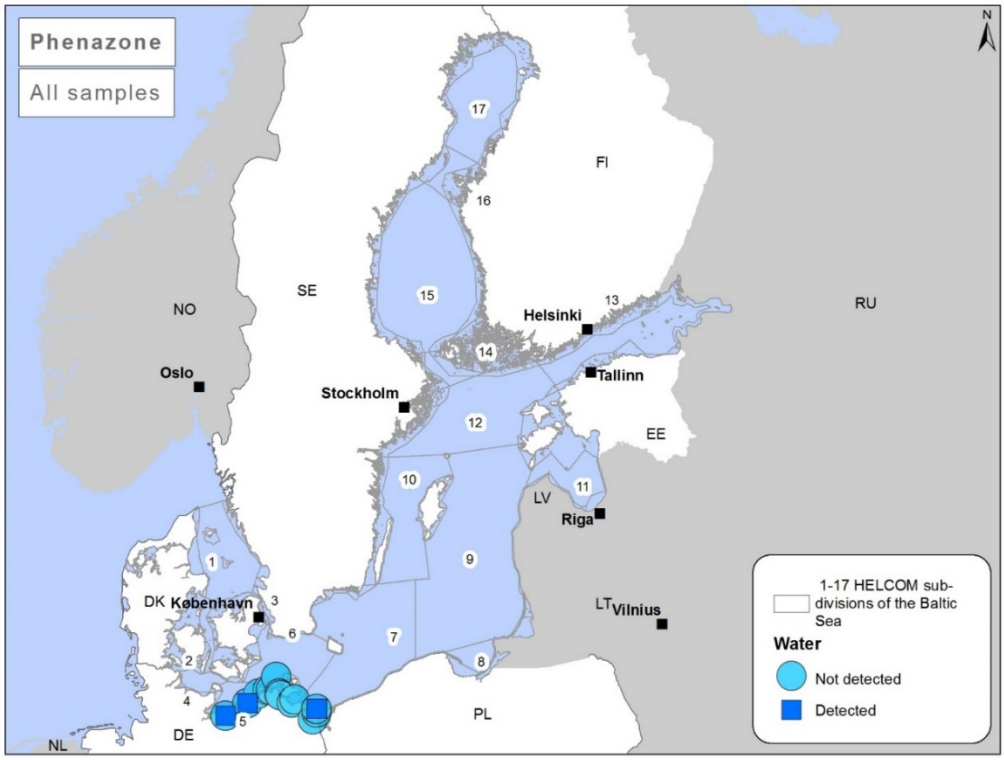

Figure 15: Sample locations for the compiled data of phenazone. Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

Diclofenac is on the directive 2013/39/EU 'watch list' of pharmaceuticals to be monitored EU-wide with a proposed annual average environmental quality standard (proposed AA-EQS) of 10 ng/l. This value was exceeded in six out of 257 (2.3%) samples.

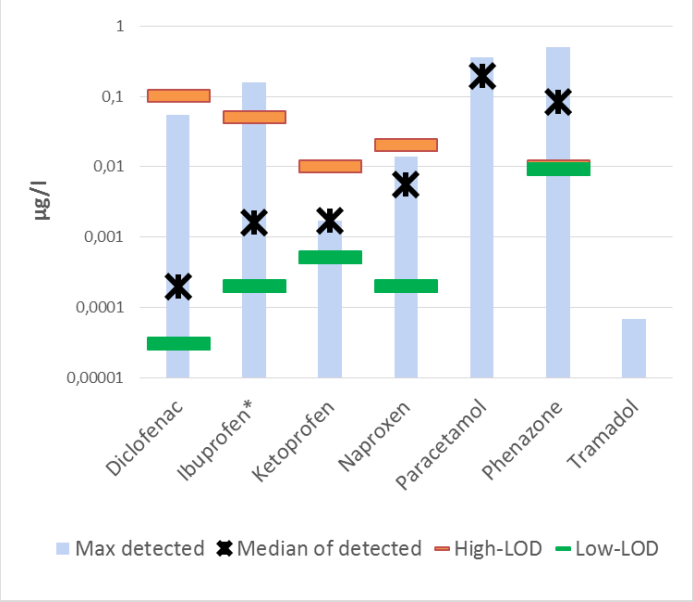

Figure 16: Anti-inflammatory and analgesics. Concentrations in Baltic Sea water. Ibuprofen* including ibuprofen-OH and ibuprofen-COOH. *Source:* Original data

Antimicrobials and antidotes

Of all monitored pharmaceuticals in the category of antimicrobial agents (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote, 11 out of 30 (37%) substances were detected in environmental samples (water, sediment or biota). Concentrations of antimicrobial agents in sea water are indicated in Figure 17. Claritromycin was detected in two water samples out of 126 and on one occasion in biota. However, in some studies, the reported analytical limit of detection (LOD) is above the highest reported value in other studies.

Sulfamethoxazole was detected in all matrices. In water this compound was detected in 12 out of 140 (9%) measurements; in sediments in 4 out of 8 (50%); and on one occasion this compound was detected in biota (Figure 18). The highest measured concentrations of this compound in water reached 33 ng/l with a median concentration of about 16 ng/l.

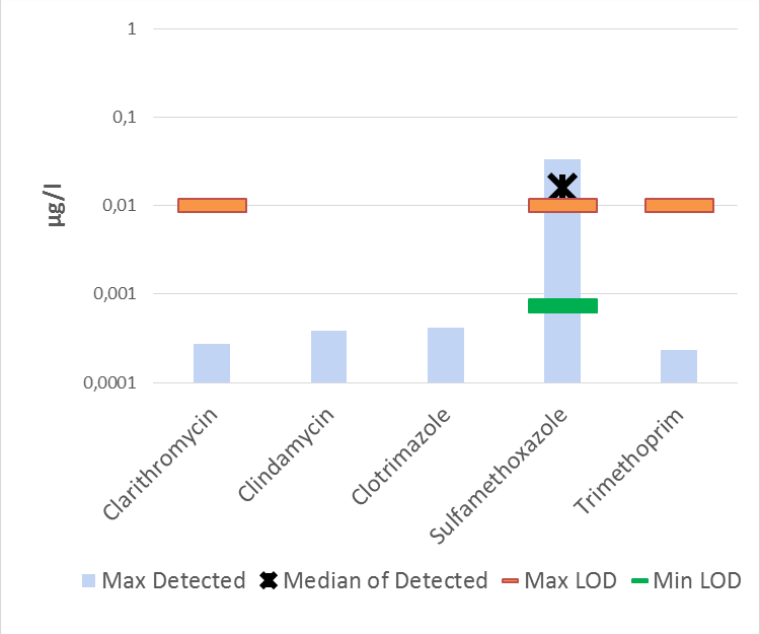

Figure 17: Antimicrobial (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote. Concentrations in Baltic Sea water. *Source:* Original data

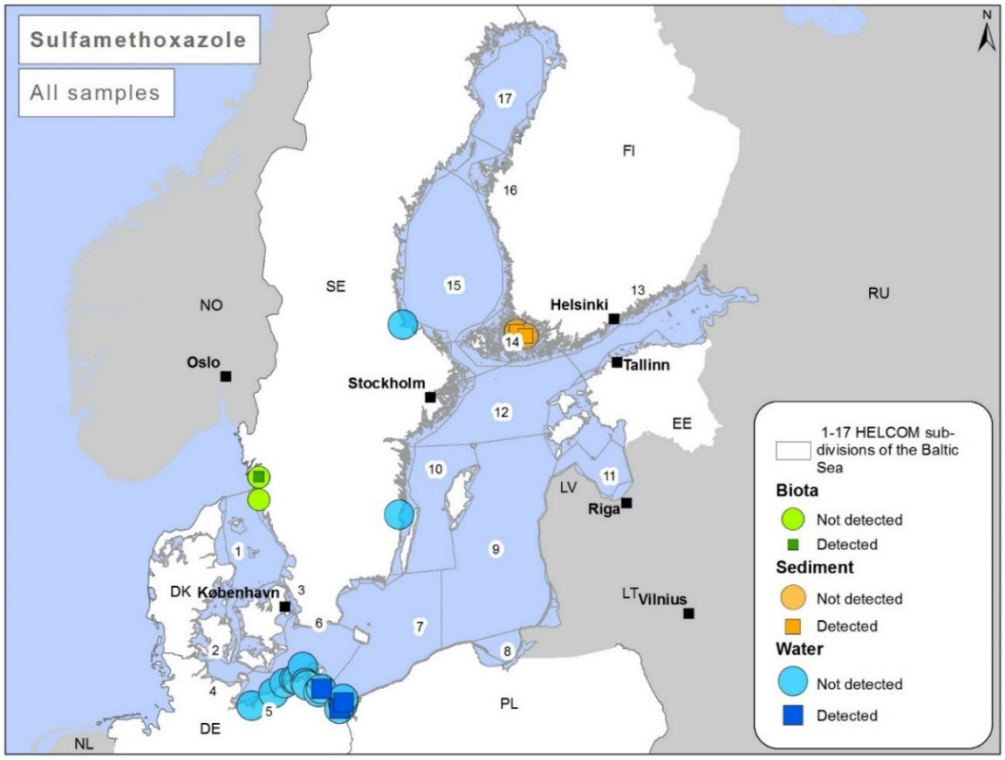

Figure 18: Sample locations for the compiled data of sulfamethoxazole. Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

Cardiovascular agents

Fourteen out of 25 (56%) cardiovascular agents were detected in water (concentrations in sea water are indicated in Figure 19). Only bisoprolol was also detected in a biota sample. Metaprolol was detected in 23 out of 144 (16%) water samples (Figure 20) with the highest measured concentration of 55 ng/l; bisoprolol was found in 33 out of 142 (23%) water samples (Figure 21) with the highest measured concentration of 128 ng/l; and sotanol was detected in 5 out of 139 (4%) water samples (Figure 22) with the highest measured concentration of 24 ng/l.

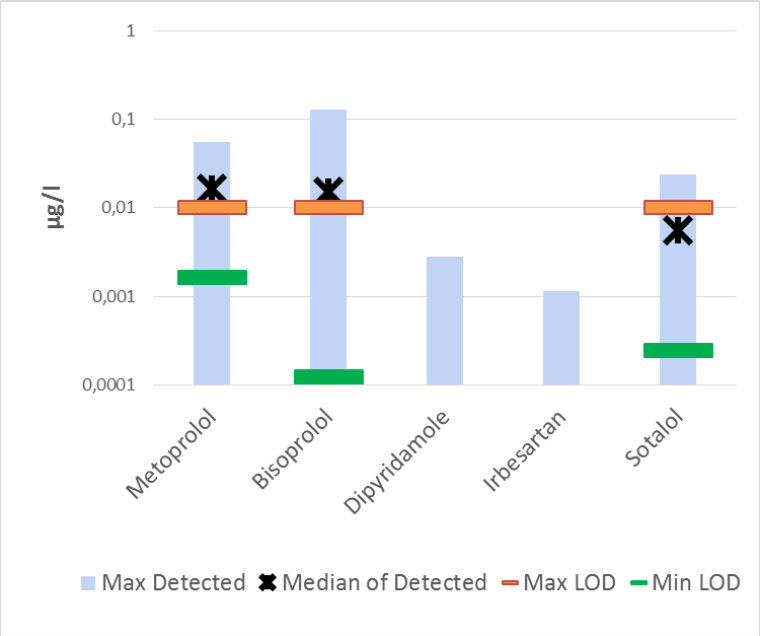

Figure 19: Cardiovascular agents (blood pressure, diuretics, anticoagulants, antihistamine). Concentrations in Baltic Sea water. *Source:* Original data

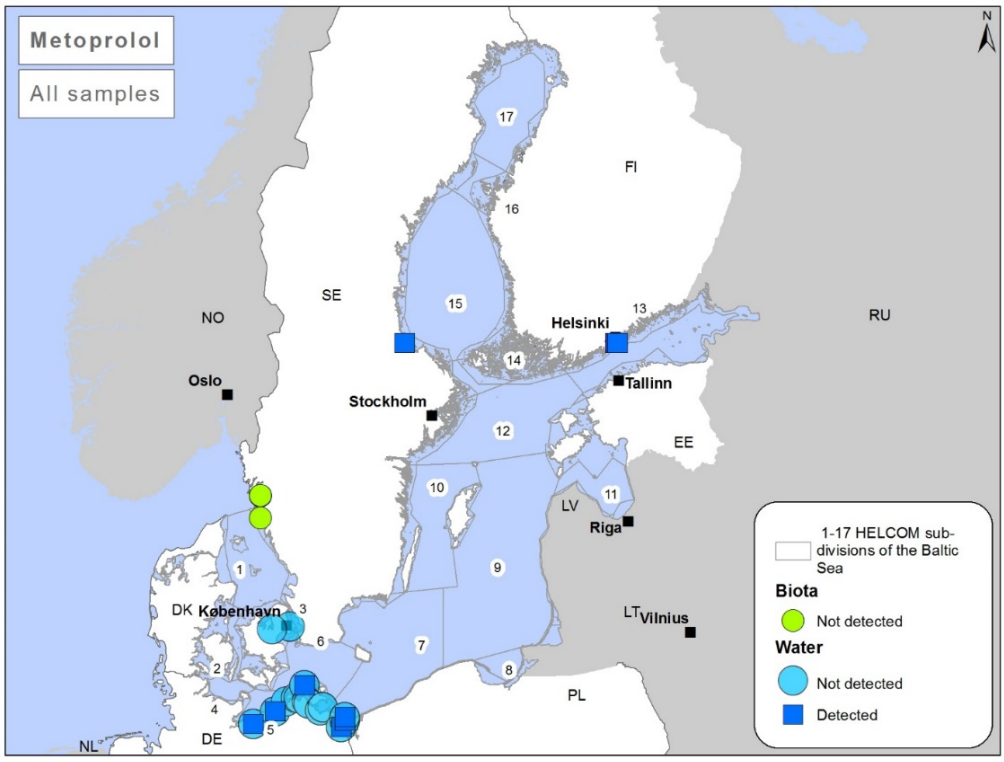

Figure 20: Sample locations for the compiled data of metoprolol. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

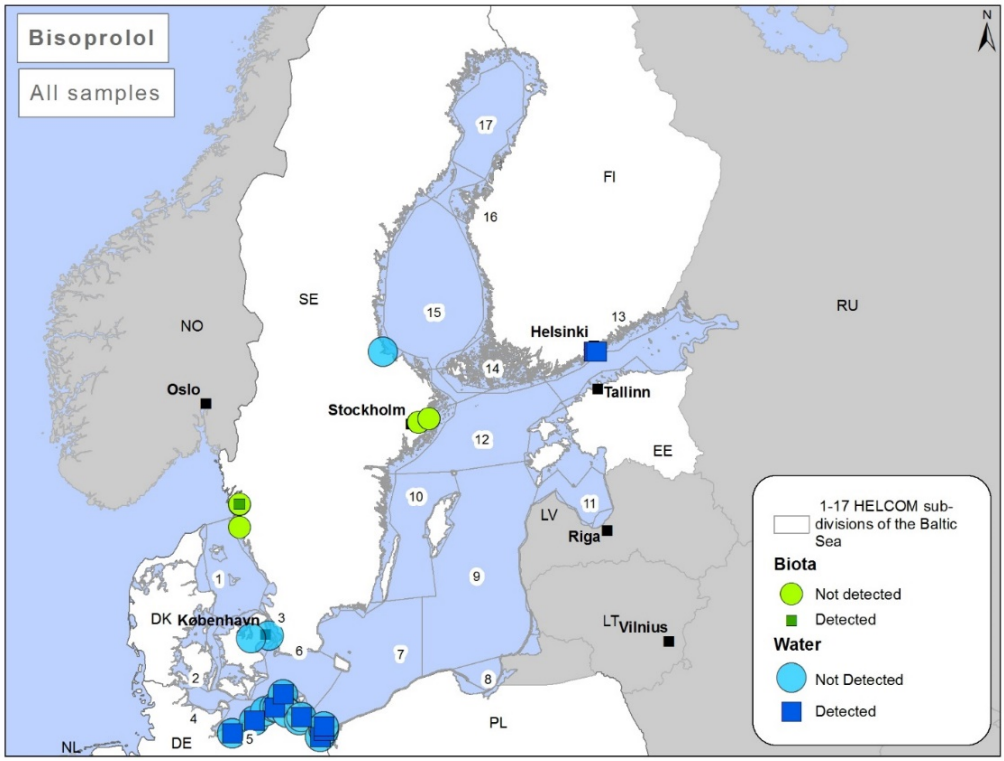

Figure 21: Sample locations for the compiled data of bisoprolol. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

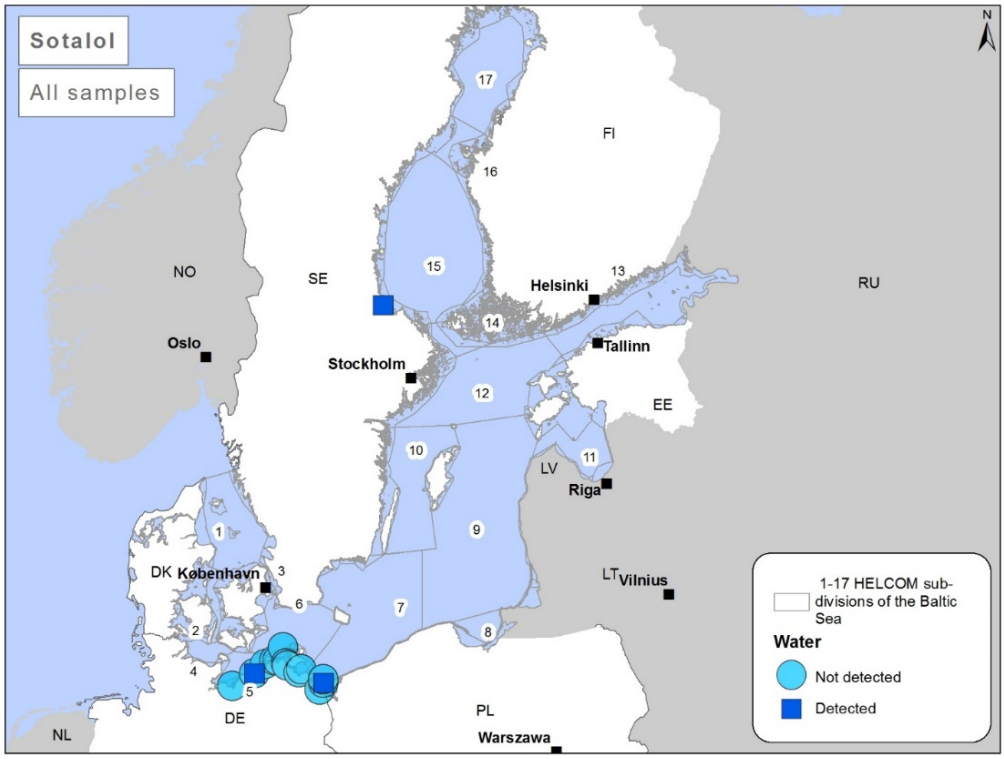

Figure 22: Sample locations for the compiled data of sotalol. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

Central nervous system agents

Twenty-one out of 44 (48%) monitored central nervous system agents were detected in water and biota (concentrations in sea water are indicated in Figure 23). The two compounds carbamazepine (Figure 24) and primidone (Figure 25) were detected on several occasions. Oxazepam (Figure 26) was detected in several cases but its median concentration only slightly exceeded the lowest LOD which indicates that the compound might be detected more frequently if more sensitive analytical methods were applied.

Carbamazepine was detected in more than 50% of reported water samples (135 out of 217) almost all around the Baltic Sea. On one occasion this compound was detected in biota. The highest measured concentration reached 73 ng/l. Since the median concentration of carbamazepine falls in the interval between the highest and lowest LOD it indicates that the compound possibly occurs more frequently. Primidone was detected in all 51 reported water sample taken in almost all sub-basins of the Baltic Sea. The highest measured concentration was 58 ng/l.

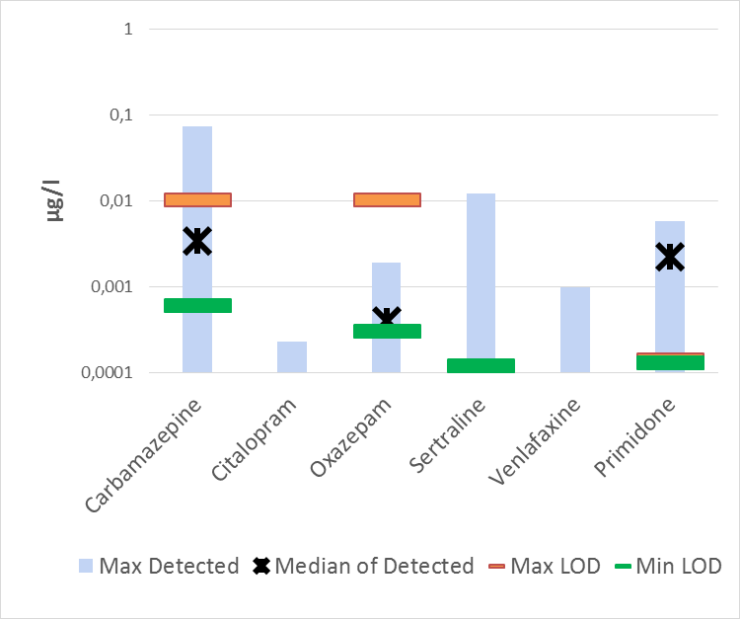

Figure 2133: Central nervous system agents (psychotherapeutic, antiepeleptic, antiparkinson, muscle relaxant). Concentrations in Baltic Sea water. *Source:* Original data

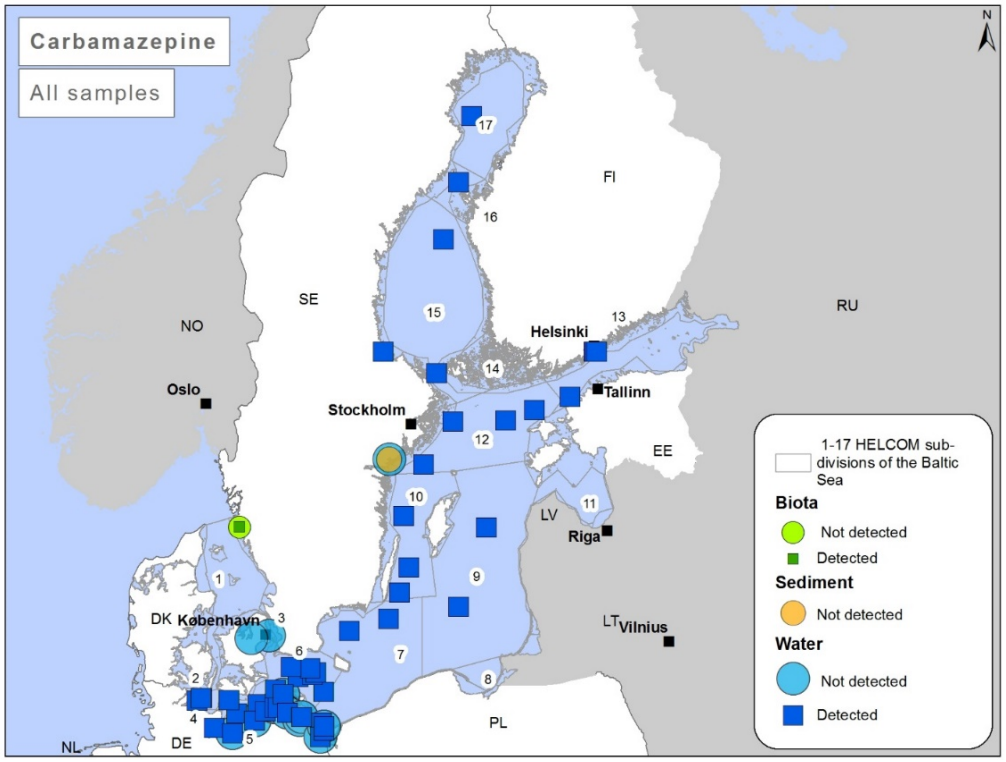

Figure 24: Sample locations for the compiled data of carbamazepine. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

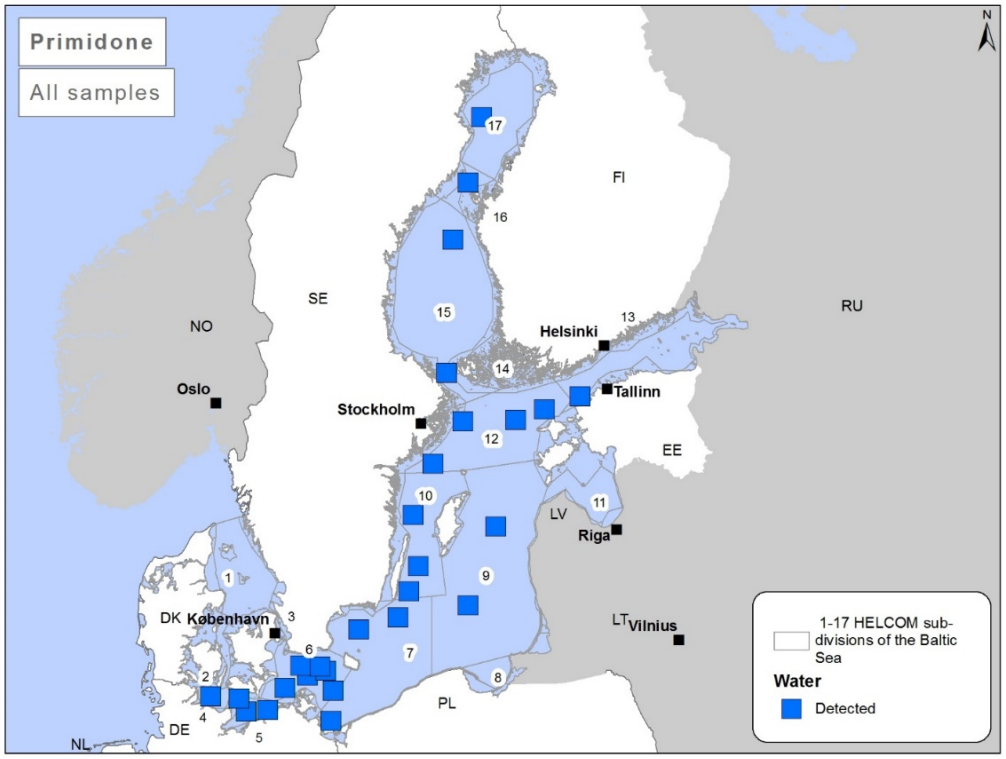

Figure 25: Sample locations for the compiled data of primidone. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

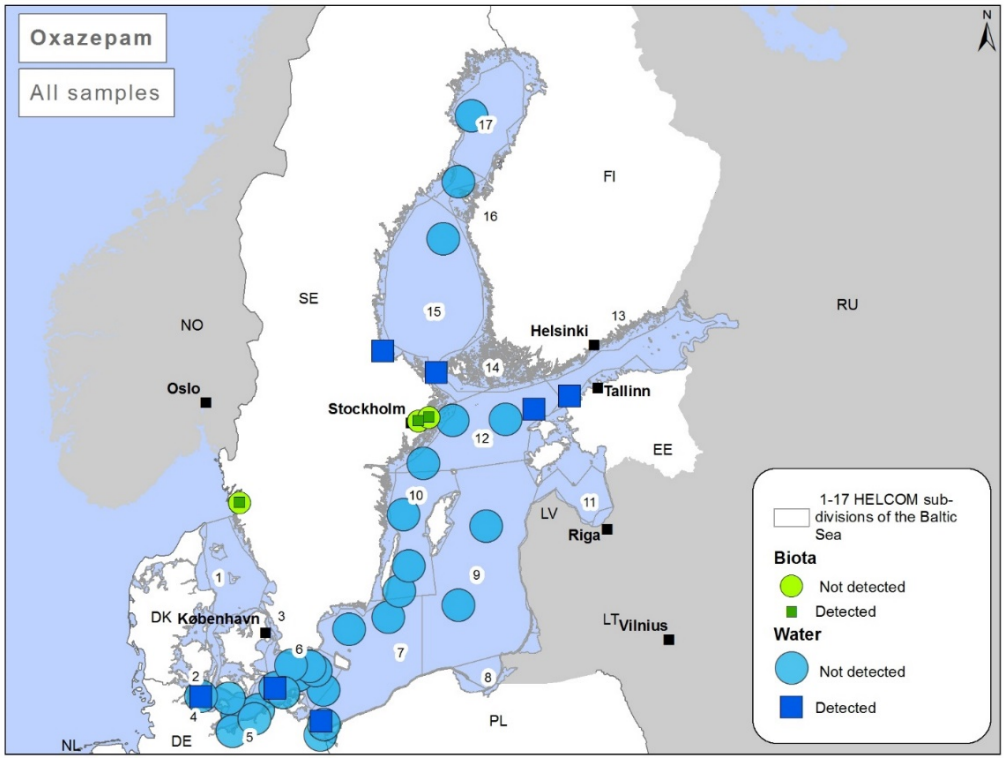

Figure 26: Sample locations for the compiled data of oxazepam. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

Chemotherapeutic agents and X-ray contrast media

Three different pharmaceuticals included in the drug class chemotherapeutic agents and X-ray contrast media were measured in water. Amidotrizoic acid was detected in 16 of 137 (12%) water samples from Germany. The highest recorded concentration of amidotrizoic acid was 0.125 µg/l and the median among the detected samples was 0.047 µg/l. Iopamidol was detected in 2 of 137 (2%) samples from Germany, the highest concentration being 0.09 µg/l. Capecitabine was measured but not detected in two water samples from Denmark.

Dermatological agents

Data on salicylic acid were available for water and sediment samples from Sweden where the substance was detected in 4 out of 8 (50%) water samples and in all four sediment samples. None of six biota samples indicated presence of this compound. The highest reported concentration was 14 ng/l with the median 12 ng/l.

Hormones and hormone antagonists

Of all monitored hormones and hormone antagonists, 5 out of 15 (33%) substances were detected in environmental samples (water, sediment or biota). Estradiol and 17α-ethinylestradiol were only detected in 3 water samples out of 228 reported samples taken from water, sediments and biota. The highest concentration detected for estradiol was 1.1 ng/l. For the synthetic estrogen 17α-ethinylestradiol, the minimum acceptable detection limit, as well as the proposed EQS, according to EU 'watch list' (Table 2) is 0.035 ng/l. For 105 out of 107 water samples the result was reported as being <LOD. In 90% of these cases (95 of 105) the reported LOD was 0.1 ng/l or higher, indicating

that monitoring of these substances is problematic since in general the analytical methods are not sensitive enough.

Metabolic and gastrointestinal agents

Of the metabolic agents and gastrointestinal agents only clofibric acid and rosuvastatin were detected in water. Clofibric acid concentrations were very low. Nonetheless, the compound was detected in 83 out of 128 (65%) open sea water samples all around the Baltic Sea. The maximum detected concentration was 0.4 ng/l. The fact that the median concentration is lower than the highest LOD means that the compound might be more frequently present in water bodies than it can be concluded from the number of detected samples.

7.2. Pharmaceuticals detected in biota

All reported biota samples were collected in Sweden and of totally 839 measurements, 77 (9%) had concentrations of pharmaceutical substances that were above the detection limit. All results on detected pharmaceuticals in biota (grouped by species) are presented in Figure 27 to Figure 31. It should be noted that information on type of tissue sampled (e.g. fish muscle or bile) was sometimes missing in the reported data.

The results indicate that the largest number of pharmaceuticals and the highest concentrations are found in blue mussels.

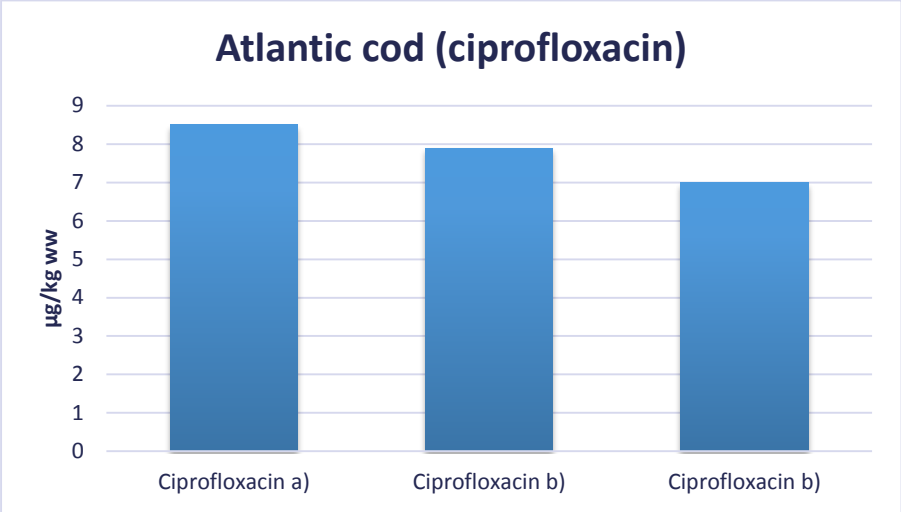

Figure 27: Ciprofloxacin in Atlantic cod (*Gadus morhua*). Location a) Kalmar, Western Gotland Basin (HELCOM sub-basin 10). Location b) Gothenburg, Kattegat (HELCOM sub-basin 1). *Source:* Original data

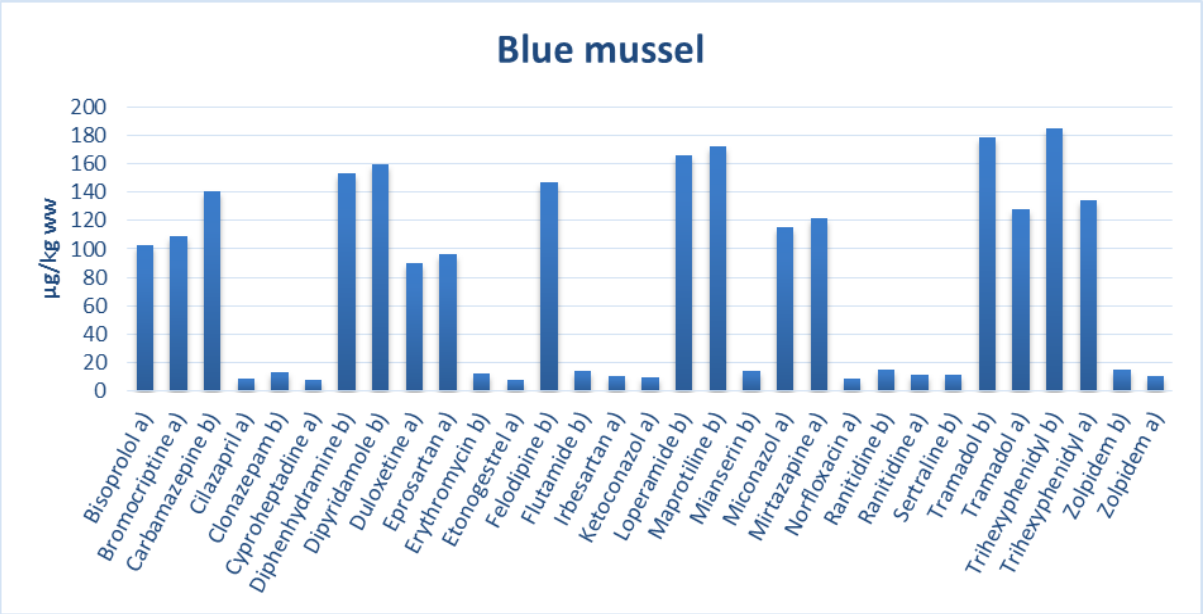

Figure 28: Detected pharmaceuticals in blue mussel (*Mytilus edulis trossulus*). Location a) Askeröfjorden, north of Gothenburg, Kattegat (north of HELCOM sub-basin 1). Location b) Älvsborgsfjorden, Gothenburg, Kattegat (HELCOM sub-basin 1). *Source:* Original data

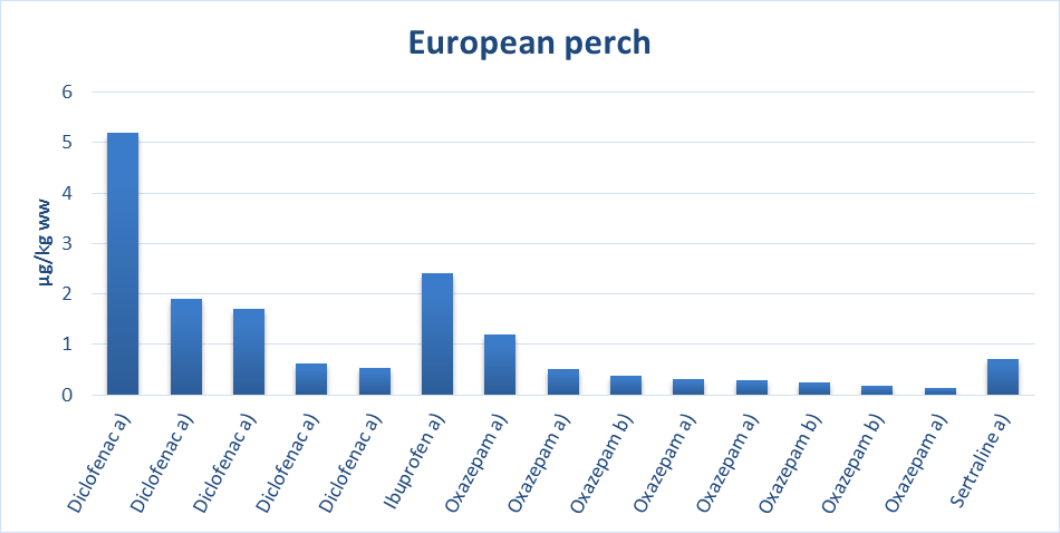

Figure 29: Detected pharmaceuticals in bile from European perch (*Perca fluviatilis*) (individual samples). Location a) Käppala (MWWTP), Stockholm, Northern Baltic Proper (HELCOM sub-basin 12). Location b) Gällnö (archipelago), Stockholm, Northern Baltic Proper (HELCOM sub-basin 12). *Source:* Original data

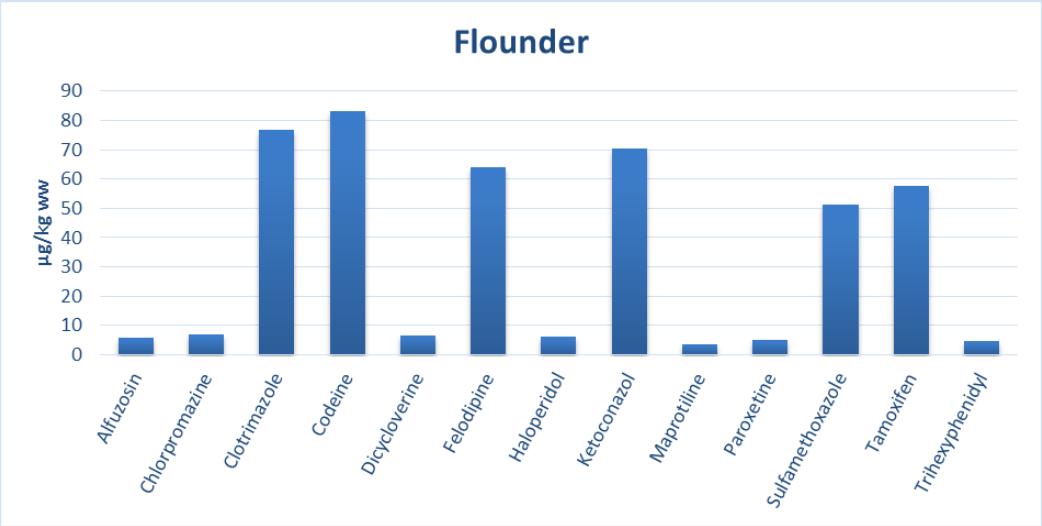

Figure 30: Detected pharmaceuticals in flounder (*Platichthys flesus*). All samples are from the location Askeröfjorden, north of Gothenburg, Kattegat (north of HELCOM sub-basin 1). *Source:* Original data

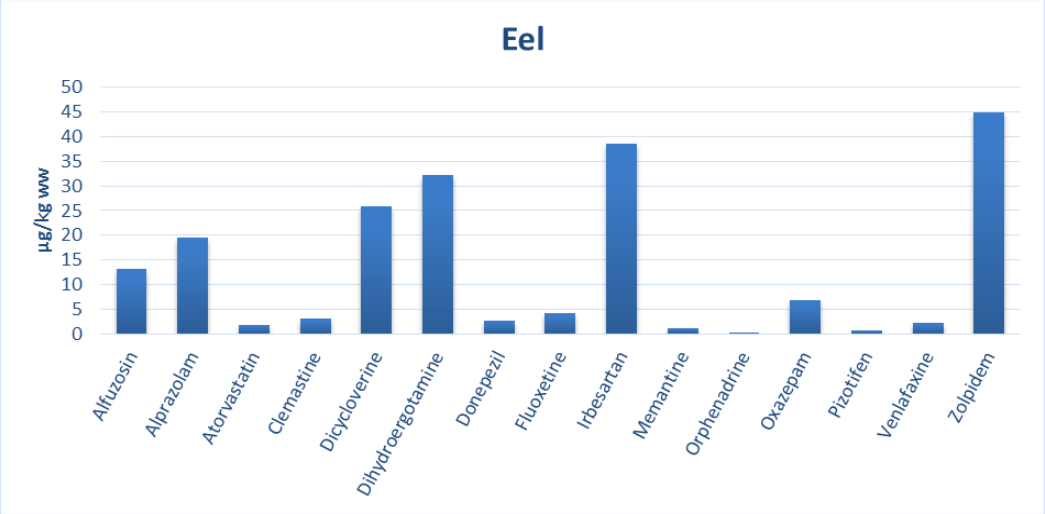

Figure 31: Detected pharmaceuticals in Eel (*Anguilla Anguilla*). All samples are from the location Askeröfjorden, north of Gothenburg, Kattegat (north of HELCOM sub-basin 1). *Source:* Original data

7.3. Effects of pharmaceuticals in the Baltic Sea marine environment

An overview of the results of different studies concerning the effects of pharmaceutical substances on Baltic Sea species is presented in Annex 5. Studies where combined effects of pharmaceuticals and other contaminants were studied have been excluded; e.g. Turja et al (2015). It was not within the scope of this report to assess the results of these studies.

In summary, several publications reported on effects of the β-blocker propranolol as well as the anti-inflammatory drugs diclofenac and ibuprofen on the littoral organisms blue mussel (*Mytilus edulis trossulus*), macroalgae (*Fucus vesiculosus* or *Ceramium tenuicorne*) and amphipod crustacean (*Gammarus spp)*. One study reported effects of the antidepressant drug citalopram on fish behavior (*Gasterosteus aculeatus*).

Propranolol showed effects on all the tested littoral organisms, of which the macroalgae *Fucus vesiculosus* was the most sensitive species. Ibuprofen and diclofenac only showed effects on blue mussels. In a microcosm study the blue mussel was the most sensitive species.

8. Conclusions and recommendations

8.1. Overview of results

Pharmaceuticals are released into the environment during various stages of the product lifecycle (manufacturing, consumption and waste disposal). In the Baltic Sea region, the main sources of pharmaceuticals are believed to be the excretion of active substances consumed by humans and animals through urine and faeces as well as the incorrect disposal of unused medical products. The main pathway of pharmaceuticals into the aquatic environment, according to the collected data, is via MWWTPs.

Chapter 6.2 presents the concentrations of the top 20 pharmaceuticals in MWWTP influent, effluent, sewage sludge and river water. The diuretic furosemide had the highest measured average concentration in MWWTP effluent at 22.3 μg/l and the highest single concentration measurement was for the anti-inflammatory drug paracetamol at 360 μg/l (measured in Denmark). Unfortunately, no measurements of furosemide in the BS environment were reported.

Only nine out of 118 assessed pharmaceuticals were efficiently (> 95%) removed from wastewater during the treatment process. Nearly half of the compounds were removed by <50% in MWWTPs.

The results of monitoring data on concentrations in the marine environment likely underestimate the actual concentrations since the analytical methods used in some cases are not sensitive enough to detect concentrations at the level where harmful biological effects take place (i.e. threshold level is exceeded) for the substance e.g. for estradiol. The data on concentrations in biota indicate that the largest number of pharmaceuticals and the highest concentrations are found in blue mussels.

According to the reported data on concentrations of pharmaceuticals in the Baltic Sea environment, the substances of greatest concern belong to the therapeutic groups of anti-inflammatory and analgesics, cardiovascular and central nervous system agents and antimicrobials. The most frequently detected anti-inflammatory pharmaceuticals were diclofenac, ibuprofen and paracetamol and they were detected in almost all compartments of the Baltic Sea environment. Sulfamethoxazole was the most frequently detected antimicrobial substance and it was detected in all matrices. Cardiovascular agents were detected mainly in water samples. The most confident data were obtained for metoprolol, bisoprolol and sotalol. But only bisoprolol was detected in a sample of biota. The central nervous system agents - carbamazepine and primidone - were frequently detected in water, where the latter was detected in all samples where it was measured. Carbamazepine was detected also in biota.

Pharmaceuticals which belong to the other therapeutic groups e.g. silicic and clofibric acids were also detected in many samples. Hormones were only found in a few samples, possibly explained by the use of analytical methods with high detection limits.

8.2. Recommendations for improving scientific knowledge and data

Although the reported data provide an overview of the magnitude of inputs of several pharmaceutical substances to the Baltic Sea as well as their concentrations in the marine environment, there are shortcomings in the data that need to be addressed to get a more complete picture of the extent of contamination by pharmaceuticals.

More data are needed on the sales, consumption, sources, pathways and loads of veterinary pharmaceuticals to soils and the aquatic environment. The very scarce data on sales and consumption of pharmaceutical substances in veterinary indicate that the annual turnover is comparable to the amount used in human medicine. Taking into account that manure is applied on the agricultural lands as fertilizer, agriculture could be a significant pathway of medical compounds to the environment.

More monitoring data are needed from WWTPs and especially rivers from every Baltic Sea country. Especially data from Poland are needed since it has the largest portion of the catchment area and population of the Baltic Sea region.

Monitoring data is missing for many highly consumed pharmaceuticals. Data is needed at least for the following substances:

- Allopurinol
- Gabapentin
- Levetiracetam
- Mesalazin
- Valsartan

Sales and consumption data are needed from all Baltic Sea countries. At present, data is missing from Latvia, Lithuania, Poland and Russia. Detailed sales and consumption data are needed in order to fully estimate the priority pharmaceuticals in the region as well as to target monitoring efforts.

More data are needed on the occurrence and fate of metabolites. It was noted in this study that the metabolites of ibuprofen often occurred at higher concentration than the parent compound. The role of metabolites should be considered in more detail, especially for easily biodegradable compounds.

More data are needed on concentrations of pharmaceuticals in sewage sludge and soil. Also the fate of sludge treatment should be better studied. In order to assess the risk of pharmaceuticals in soils and possible runoff of pharmaceuticals to surface water or infiltration to ground water, more information is needed about the fate of the compounds in sludge and soil.

The analytical methods of a higher resolution should be used for measuring concentrations of pharmaceuticals in the marine environment. As indicated by the results presented in Chapter 7 and Annex 4, the analytical methods used by many laboratories are at times not sensitive enough to detect substances at the level of the proposed environmental quality standards or the threshold values. More sensitive analytical methods should therefore be used.

More studies on the impacts of pharmaceuticals on the ecosystem should be carried out. There is limited knowledge of the effects of pharmaceuticals in the environment, especially when considering how many different pharmaceuticals substances there are and their potential cocktail effects. For many pharmaceutical substances, data concerning e.g. toxicity (i.e. base data to derive reliable threshold (or PNEC values), persistence and bioaccumulation is lacking, making it difficult to assess the impact and consequences of the spreading of these substances in the environment. A concept of using known human therapeutic doses to assess effect on biota could be applied.

Concentrations of pharmaceuticals in biota and their appearance in the food chain should be investigated. In a recent non-target screening conducted in Norway a relatively large number of pharmaceuticals were found in sea birds (Miljødirektoratet 2013). This suggests that

pharmaceuticals may be transferred in aquatic food chains up to seabirds. These results, together with the results presented on pharmaceuticals in blue mussels in the Baltic Sea, suggest that it should be of interest to include sea birds, such as Common eider, that primarily feed on blue mussels, in future monitoring studies for pharmaceuticals.

8.3. Potential measures for further consideration to reduce inputs

With pharmaceuticals being emerging pollutants that need to be addressed, it is necessary to take measures to reduce the inputs of these substances to the environment. Also, further information on the effects of pharmaceuticals in the environment is needed to support the prioritization of measures for reducing inputs of specific substances.

Measures to reduce the inputs of pharmaceuticals should address all stages of the product lifecycle from manufacturing to consumption to waste management. Measures can be taken via technical solutions or via low-tech solutions.

Technical solutions can be applied in WWTPs, mainly as tertiary treatment methods. At present, there are no WWTPs in the Baltic Sea catchment area that apply techniques to enhance the removal of pharmaceuticals from wastewater. However, there are two WWTPs in Sweden that are planning to apply ozonation to enhance the wastewater treatment. Other tertiary treatment methods that could be used to enhance the removal of pharmaceuticals are other oxidative processes (e.g. advanced oxidation, photocatalytic, Fenton based and pulsed corona discharge), adsorptive methods (e.g. activated carbon) and membrane filtration (e.g. nanofiltration and reverse osmosis). It should be remembered that oxidative treatment methods produce by-products, especially of those pharmaceuticals that are not easily oxidized, thus removal of these by-products may be necessary before discharging the water to the environment. Application of adsorptive methods transfers the pharmaceuticals from water to the solid phase, therefore the solid phase needs to be further treated or properly disposed. Also, in membrane filtration, pharmaceuticals remain in the retentate that needs to be further treated or properly disposed.

Oxidation, adsorption and filtration methods could also be used for the pre-treatment of hospital and manufacturing site wastewater prior to discharging to the sewer. However, the qualities of these waters are different from the secondary treated municipal wastewater, therefore pre-treatment of these waters is most probably needed before applying further treatment. Oxidative treatments may be attractive since the by-products that are formed during the process may be effectively removed at the later stage in the biological treatment process of municipal WWTPs.

Low-tech solutions for reducing inputs of pharmaceuticals to WWTPs and further to the environment include raising the awareness of doctors and consumers concerning possible harmful effects of pharmaceuticals in the environment. **Take-back of unused medicines by pharmacies should be applied or developed in countries where such systems are not yet in place or are inefficient, in order to reduce the disposal of unused medicines via solid waste or sewer**. Educational campaigns should be carried out to increase the awareness of the public on correct disposal of pharmaceutical waste.

Certification implying low environmental impact can help doctors, pharmacists and consumers to consider environmental perspectives when choosing medication. In Sweden, the FASS database (www.fass.se) includes also environmental data about pharmaceuticals and information booklets have been distributed to doctors so they may consider environmental

perspectives when prescribing medication. This system could be directly applied also in other Baltic Sea countries.

Promotion of sustainable consumption of pharmaceuticals naturally also reduces their loads to WWTPs. This can be done by educating people on proper use of medicines. Also, when doctors prescribe new medication, a small-sized trial package could be used so that if the medication is not suitable for the patient there would not be excess medical waste left. Also, overlapping medication should be avoided since it both poses a threat to the patient's health and results in unnecessary consumption of pharmaceuticals.

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Glossary

Adsorption	The adhesion of atoms, ions, or molecules from a gas, liquid, or dissolved solid to a solid or liquid surface
Analgesic	A drug that relieves pain
Anticoagulants	A substance that prevents blood from forming clots
Antidote	A substance that stops the harmful effects of a poison
Antihistamine	a drug that is used to treat allergic reactions and colds
Biodegradation	Chemical dissolution of materials by bacteria, fungi, or other biological means
Biota	The plant and animal life of a region
Diuretics	Drugs that increase the excretion of water from bodies
d.w.	Dry weight
Effluent	Water that has been treated by a wastewater treatment plant
HELCOM Contracting Parties	The Contracting Parties of HELCOM are Denmark, Estonia, the European Union, Finland, Germany, Latvia, Lithuania, Poland, Russia and Sweden.
HELCOM sub-basin	For HELCOM assessment purposes the Baltic Sea is divided into different sub-basins. These are defined in Attachment 4 of the HELCOM Monitoring and Assessment Strategy.
Hormone antagonists	Substances that inhibit the function of hormones upon their specific sites
Influent	Sewage entering the wastewater treatment plant
Limit of detection (LOD)	In analytical chemistry, the limit of detection is the lowest quantity of a substance that can be distinguished from the absence of that substance (a blank value) within a stated confidence limit (generally 1%)
Load	The amount of pollution entering the environment (i.e. input)
Nanofiltration	A membrane filtration-based method that uses nanometer sized cylindrical through-pores
Ozonation	Ozonation (also referred to as ozonization) is a chemical water treatment technique based on the infusion of ozone into water.
Photodegradation	The alteration of materials by light
Removal rates	The rate of removal of a substance through wastewater treatment
Retentate	That which is retained, for example by a filter or porous membrane
Sewage sludge	Sewage sludge refers to the residual, semi-solid material that is produced as a by-product during sewage treatment of industrial or municipal wastewater
Therapeutic group	Classification of pharmaceutical according to their therapeutic effects
w.w.	Wet weight

Annexes to the draft Status report on pharmaceuticals in the Baltic Sea environment.

Annex 1. Description of data collection and analytical methods

Annex 1.1. Data collection

Data collection was carried out using a step-wise approach and coordinated through relevant HELCOM working groups.

1st phase – A review of availability and sources of data (no data collection) was carried out. The aim was to also identify sources of relevant data with restricted access (e.g. commercial data, data which require anonymizing etc.). An overview of the following information was gathered via the HELCOM Group on the State of the Environment and Nature Conservation (State and Conservation) and the Working Group on Reduction of Pressures from the Baltic Sea Catchment Area (Pressure):

- National sources of data on concentrations of pharmaceutical substances in all the compartments of the environment (e.g. programme, project, reference to data source, etc.)
    - state and local environmental monitoring and screening programmes
    - regulated monitoring e.g. sewage treatment plants, industry
    - projects/screening studies
        - scientific studies
        - commissioned studies
- National sources of data on sales and consumption/use of pharmaceuticals per different of activity (e.g. human use, agriculture, veterinary)
    - authorities (environmental, health care, veterinary, agricultural etc.)
    - professional associations
    - projects/studies
- National sources of data on pathways of pharmaceuticals into the environment such as concentration of the compounds in wastewater, sludge, manure etc.
    - authorities
    - professional associations
    - projects/studies
- Information on accessibility to existing data e.g.:
    - open access - data base
    - reports
    - restricted
- Contact persons [likely a number of contact person in different authorities/institutions]

2nd phase – A template for data collection (questionnaire), together with reporting guidelines, was prepared based on the results from the 1st phase. Available data were collected according to the following categories:

1. concentrations of pharmaceuticals in the coastal and open water areas of the Baltic Sea environment (e.g. water, biota, sediment)
2. effects of pharmaceuticals on Baltic Sea biota

3. sources and pathways of pharmaceuticals to the environment (concentration of these substances in wastewater, sludge, manure etc.) as well as information on production, sales, consumption and waste management of pharmaceuticals

Further, appropriate metadata such as coordinates for concentration data, analytical methods, detection limits, data quality, etc., were collected.

Relevant experts compiled and analyzed the reported data.

Annex 1.2. Overview of reported data

Measurements in WWTP influent, effluent, sludge and river water

Table A1.1: Data overview. The total number of data posts on measurements of pharmaceuticals in Baltic Sea region submitted by each country. The number of data posts with detected values is presented together with the total number of data posts. Data approximately from 2003 to 2014. It should be noted that the detection frequencies between countries are not always comparable.

	Number of detections / number of reported samples					
	REFERENCES^	TOTAL	WWTP INFLUENT	WWTP EFFLUENT	SLUDGE*	RIVER
Denmark	[22] – [24]	2067/3571 (58 %)	949/1375	1118/2196		Data not included
Estonia	No info of the references, please add	173/540 (32 %)	58/135	52/135		63/270
Finland	[1] – [9]	1031/1587 (65 %)	275/301	247/306	377/778	132/202
Germany	[]	6898/32462 (21 %)		784/847		6114/31615
Russia	[10]	579/1199 (48 %)	374/603	205/596		
Sweden	[11] – [20]	2940/5656 (52 %)	882/1729	1705/3266	307/534	46/127
Total		**13688/45015 (30 %)**	**2538/4143**	**4111/7346**	**684/1312**	**6355/32214**

*raw, digested and composted sludge
^ References are listed below

Source: Original data

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Table A1.2: Data overview. Number of detections and samples in WWTP influents.

	Detections/Total no. samples						
Therapeutic group	Denmark	Estonia	Finland	Germany	Russia	Sweden	Total
Anti-inflammatory and analgesics	397/458	18/27	81/82	0/0	66/77	218/364	780/1008
Antimicrobial	229/345	20/39	53/63	0/0	167/309	136/233	605/989
Cardiovascular agents	113/115	17/30	84/84	0/0	57/62	126/169	397/460
Central nervous system agents		3/12	34/35	0/0	31/31	292/698	360/776
Chemotherapeutic agents and X-ray contrast media							
Hormones and hormone antagonists	180/342	0/27	10/24		28/31	54/176	272/600
Metabolic agents and gastrointestinal agent	30/115		13/13		25/93	56/89	124/310
Total	**949/1375**	**58/135**	**275/301**	**0/0**	**374/603**	**882/1729**	**2538/4143**

Source: Original data

Table A1.3: Data overview. Number of detections and samples in WWTP effluents.

	Detections/Total no. samples						
Therapeutic group	Denmark	Estonia	Finland	Germany	Russia	Sweden	Total
Anti-inflammatory and analgesics	360/732	14/27	72/84	155/155	48/77	667/962	1316/2037
Antimicrobial	367/549	19/39	43/63	73/77	93/309	156/364	751/1401
Cardiovascular agents	181/183	16/30	84/84	153/153	30/62	183/278	647/790
Central nervous system agents		3/12	35/36	154/154	6/31	459/1045	657/1278
Chemotherapeutic agents and X-ray contrast media				249/308			249/308
Hormones and hormone antagonists	152/549	0/27	1/26		3/24	158/469	314/1095
Metabolic agents and gastrointestinal agent	58/183		12/13		25/93	82/148	177/437
Total	**1118/2196**	**52/135**	**247/306**	**784/847**	**205/596**	**1705/3266**	**4111/7346**

Source: Original data

Table A1.4: Data overview. Number of detections and samples in untreated sludge.

	Detections/Total no. samples		
Therapeutic group	Finland	Sweden	Total
Anti-inflammatory and analgesics	29/30	43/44	72/74
Antimicrobial	132/210	95/212	227/422
Cardiovascular agents	46/78		46/78
Central nervous system agents	31/36		31/36
Chemotherapeutic agents and X-ray contrast media	0/30		0/30
Hormones and hormone antagonists	1/12	11/53	12/65
Other	0/6		0/6
Total	**239/372**	**149/309**	**388/681**

Source: Original data

Table A1.5: Data overview. Number of detections and samples in digested sludge

	Detections/Total no. samples		
Therapeutic group	Finland	Sweden	Total
Anti-inflammatory and analgesics	7/20		7/20
Antimicrobial	36/56	158/225	194/281
Cardiovascular agents	16/52		16/52
Central nervous system agents	19/24		19/24
Chemotherapeutic agents and X-ray contrast media	0/20		0/20
Hormones and hormone antagonists	6/40		6/40
Other	0/16		0/16
Total	**84/232**	**158/225**	**242/457**

Source: Original data

Table A1.6: Data overview. Number of detections and samples in composted sludge.

	Detections/Total no. samples
Therapeutic group	Finland/Total
Anti-inflammatory and analgesics	6/15
Antimicrobial	19/42
Cardiovascular agents	7/39
Central nervous system agents	14/18
Chemotherapeutic agents and X-ray contrast media	0/15
Hormones and hormone antagonists	8/30
Other	0/12
Total	**54/174**

Source: Original data

Table A1.7: Data overview. Number of detections and samples in rivers.

	Detections/Total no. samples				
Therapeutic group	Estonia	Finland	Germany	Sweden	Grand Total
Anti-inflammatory and analgesics	17/60	55/75	985/6767	9/19	1070/6927
Antimicrobial	26/78	7/41	413/7900	9/17	455/8036
Cardiovascular agents	16/66	57/67	2259/10244	11/29	2343/10406
Central nervous system agents	4/24	12/15	1301/2206	8/34	1321/2273
Chemotherapeutic agents and X-ray contrast media			1156/3290		1156/3290
Hormones and hormone antagonists	0/42	1/2	0/1208	7/15	8/1267
Metabolic agents and gastrointestinal agent				2/13	2/13
Other		0/2		0/0	0/2
Total	**63/270**	**132/202**	**6114/31615**	**46/127**	**6355/32214**

Source: Original data

Measurements in the marine environment

Table A1.8: Data overview. The total number of data posts on measurements of pharmaceuticals in the Baltic Sea region that were submitted by each Contracting Party. The number of data posts with detected values is presented together with the total number of data posts. Data from approximately 2003 to 2014.

		Number of detected / number of submitted data			
	REFERENCES	TOTAL	WATER	SEDIMENT	BIOTA
Denmark	[13][26][27]	0/54 (0 %)	0/54		
Estonia	[14]	2/75 (3 %)	0/40	2/35	
Finland	[11] [12]	30/51 (59 %)	19/27	11/24	
Germany	[9][28]	435/3148 (14 %)	435/3148		
Poland	[1] [2] [3] [4] [5] [6] [7] [8]	0/18 (0 %)	0/18		
Sweden	[10] [15] [16] [18] [19, [20] [21] [25]	173/1254 (14 %)	78/360	18/55	77/839
Total		**640/4600 (14 %)**	**532/3647**	**31/114**	**77/839**

Source: Original data

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Annex 1.3. Prioritization of pharmaceuticals for assessing inputs to the environment

An attempt has been made to prioritize pharmaceuticals based on sales and consumption, concentrations in WWTP influents, concentrations and detection rates in WWTP effluents and concentrations and detection rates in river waters. Out of the detected 143 pharmaceuticals, it was possible to evaluate 40 according to all above criteria. Of the 40 evaluated pharmaceuticals, those of highest priority and greatest concern for the Baltic Sea are indicated in Figure 16.

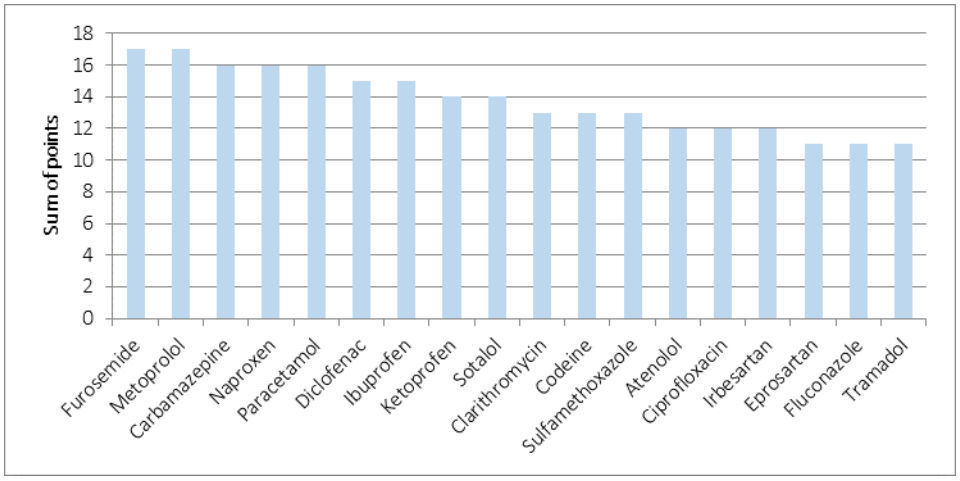

Figure 1: Priority pharmaceuticals (gained > 10 points out of 18 in the evaluation)

Source: Original data

Priority pharmaceuticals via sludge are listed in Table 6.

Table 1: Priority pharmaceuticals in sewage sludge

Antimicrobial	Central nervous system agents	Hormones and hormone antagonists
Ciprofloxacin	Caffeine	Progesterone
Tetracycline	Citalopram	
Norfloxacin		
Ketokonazole		
Doxycycline		
Ofloxacin		
Oxytetracycline		
Fenbendazole		

Source: Original data

It should be noted that several pharmaceuticals listed in e.g. the EU Water Framework Directive (WFD) (2013/39/EC) as 'watch list' substances[1] are not included among the priority substances. The estrogenic hormones are present in such low concentrations and they are fairly well removed in WWTPs and were therefore not included in these lists. However, their presence in the Baltic Sea should be monitored due to harmful effects to biota already at very low concentrations. Of the antibiotics, clarithromycin was present in wastewaters at the highest average concentration (1.5 μg/l) followed by erythromycin (0.16 μg/l) and azithromycin (0.05 μg/l). Therefore, clarithromycin was considered as higher priority than erythromycin or azithromycin. The prioritization criteria do not take properly into account substances occurring in emissions and environment and affecting environment at very low levels, even at levels below analytical LOD (e.g. hormones). Inherent properties of pharmaceuticals (e.g. PBT characteristics) should be considered somehow. Thus, prioritization criteria should be further developed.

Those pharmaceuticals that could not be assessed with all the criteria are listed as being of potential concern. For these substances, more information on their occurrence, fate and effects in wastewaters and environment should be gathered. The evaluation method and results are presented in Annex 1.3.

Methodology for prioritization of pharmaceuticals for assessment of inputs

To assess the priority pharmaceuticals entering the environment via aquatic pathways, the compounds were given a value from 0–3 for each criteria (Table A.1.9).

Table A1.9: Assessment of priority pharmaceuticals.

Criteria	Value 1	Value 2	Value 3
Sales/Consumption (mg/inh/a)	<100	100–1,000	>1,000
Detection rate in WWTP effluent (%)[1)]	<10 %	10–50 %	>50 %
Average WWTP influent concentration (μg/l)[2)]	<0.1	0.1 – 1	>1
Average WWTP effluent concentration (μg/l)[2)]	<0.1	0.1–0.5	>0.5
Detection rate in river water (%)[1)]	<10 %	10–50 %	>50 %
Average concentration in river water (ng/l)[2)]	<10	10–100	> 100

[1)] if 0% value given was 0

[2)] if <LOD value given was 0

Source: Original data

Those pharmaceuticals that had a total value of more than 10 were considered as being of highest priority and are presented in Table A1.10 in red. Additionally, those pharmaceuticals that could not be assessed with all the criteria were listed as being of 'potential concern'. For these substances more information on their occurrence, fate and effects in wastewaters and in the environment should be gathered. In Table A1.10, compounds presented in blue are of potential concern due to high sales and consumption, compounds presented in green are of

[1] The 'watch list' substances are 17α-ethinylestradiol, 17β-estradiol, estrone, azithromycin, erythromycin and clarithromycin.

potential concern due to high concentration and detection rate in WWTP effluents and compounds presented in purple are of potential concern due to high concentration and detection rate in river waters.

Table A1.10: Priority pharmaceuticals based on sales, consumption, concentrations and detection rates in WWTP influents, WWTP effluents and in river waters. For color coding, please refer to text above.

Anti-inflammatory	Antimicrobial	Cardiovascular agents	Central nervous system agents	Chemotherapeutic and X-ray contrast media	Hormones and hormone antagonists	Metabolites	Other
Naproxen	Clarithromycin	Furosemide	Carbamazepine	Amidotrizoic acid	Estriol	2-hydroxyi-buprofen	Allopurinol
Paracetamol	Sulfamethoxazole	Metoprolol	Gabapentin	Iopamidol		Ibuprofen-COOH	Macrogol
Diclofenac	Ciprofloxacin	Sotalol	Levetiracetam				Mesalazin
Ibuprofen	Fluconazole	Atenolol	Caffeine				
Ketoprofen	Sulfamethiazol	Irbesartan	Oxazepam				
Codeine		Eprosartan					
Tramadol		Valsartan					
Metamizole		Telmisartan					
		Hydrochlorothiazide					

Source: Original

Priority pharmaceuticals in sludge are presented in Table A1.11. The criteria for prioritization were high occurrence in untreated, digested or composted sludge, i.e. compounds that fulfilled at least one of the following criteria:

- average concentration in untreated sludge samples exceeded 0.5 mg/kg d.w., or
- average concentration in digested sludge exceeded 0.1 mg/kg d.w., or
- average concentration in composted sludge exceeded 0.05 mg/lg d.w.

Table A1.11: Priority pharmaceuticals in sludge.

Antimicrobial	Central nervous system agents	Hormones and hormone antagonists
Ciprofloxacin	Caffeine	Progesterone
Tetracycline	Citalopram	
Norfloxacin		
Ketokonazole		
Doxycycline		
Ofloxacin		
Oxytetracycline		
Fenbendazole		

Source: Original

Annex 1.4. Calculation methods

Consumption

The available national statistics report the sold amounts of pharmaceuticals as DDD/1000 inh/day where DDD (defined daily dose) is based on the ATC/DDD classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The reported figures indicate how many people per 1,000 inhabitants may in theory have received daily the standard dose of a pharmaceutical. From the reported values, the annual consumption of a pharmaceutical can be calculated using the following formula:

$$\text{Consumption (kg/a)} = \frac{\text{DDD (g)} \times \text{DDD/1000 inh/day} \times \text{Population} \times 365}{1\,000\,000}$$

Calculation of the consumption of all the pharmaceuticals reported in the statistics was beyond the scope of this report. Therefore, the consumption was calculated for the most often prescribed pharmaceuticals as well as for those that were most often found in the monitoring studies.

Load of pharmaceuticals from WWTPs

Only estimates of the load of human pharmaceuticals were made due to limited data on the sales and consumption and occurrence of veterinary pharmaceuticals reported by the Contracting Parties. The main source of human pharmaceuticals into the environment is via WWTPs. A rough estimation of the load of pharmaceuticals from WWTPs to environmental waters was done using the equation:

$$\frac{\text{Average concentration in WWTP effluent } (\mu\text{g/l}) \times \text{Population} \times 300 \text{ l/inh/d} \times 365 \text{ d/year}}{1\,000\,000\,000\ \mu\text{g/kg}}$$

where population = 85 million (inhabitants in the Baltic Sea catchment area). It was estimated that the annual wastewater production is 300 l/inhabitant. The load figures calculated in this way do not fully reflect actual loads since concentrations of some substances decrease during transportation in rivers. Further, inputs of pharmaceuticals via surface run-off (originating from manure or sludge) have not been considered in the calculations.

Amount of pharmaceuticals adsorbed to sludge

The amount of pharmaceuticals adsorbed to sludge was calculated according to the following equation:

$$\frac{\text{Concentration in the raw sludge (mg/kg d.w.)} \times \text{Population} \times 30 \text{ kg/inh/year}}{1\,000\,000 \text{ mg/kg}}$$

where population = 85 million (inhabitants in the Baltic Sea catchment area). It was estimated that the annual sludge production in WWTPs is 30 kg/inhabitant.

Annex 2. Data on sales and consumption of pharmaceuticals

Human consumption

Data on human sales and consumption of pharmaceuticals was received from Finland, Sweden, Estonia, Germany and Russia (only for diclofenac and St. Petersburg area). From Germany, data was received only about those pharmaceuticals that were prescribed at the highest amounts in Mecklenburg-Vorpommern and Schleswig-Holstein (the states within the Baltic Sea catchment area) in 2013 and 2014. German data were provided by GKV-Arzneimittelindex im Wissenschaftlichen Institut der AOK (WIdO). From Estonia, Finland and Sweden, data on pharmaceutical sales and consumption was received in the form of statistics on the most often prescribed pharmaceuticals from the following sources:

- Sweden: Swedish National Board of Health and Welfare, Statistikdatabas för läkemedel (2014) (www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel)
- Finland: Fimea, Finnish Statistics on Medicines 2014 (http://www.fimea.fi/web/en/about_us/publications)
- Estonia: State Agency of medicines, Statistical Yearbook of the State Agency of Medicines 2015.

Sales and consumption of pharmaceuticals by therapeutic group are given in Table A2.1 to Table A2.6. If a pharmaceutical was not consumed in the country, it is indicated in the tables as “0”. If no data were received or calculated for a pharmaceutical, it is indicated in tables as an empty cell.

Table A2.1: Sales and consumption of anti-inflammatory and analgesics in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig-Holstein)	Russia	Sweden
Acetylsalicylic acid			2110	2780		
Allopurinol	2770	700	3750	4080		4160
Buprenorphine	3,4	0,006				3
Codeine	1800	155				60
Diclofenac	1050	593		940	700	8800
Fentanyl	1,2	0,02				2,1
Ibuprofen	119000	15100	11900	20000		14400
Irbesartan	0	0	850	880		1095
Ketoprofen	470	100				1511
Naproxen	6200	210				17690
Paracetamol	173582	16950	618	778		338007
Tramadol	1756	321				4833

Source: Original data

Table A2.2: Sales and Consumption of antimicrobial pharmaceuticals in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig-Holstein)	Sweden
Amoxicillin	9300	2250	570	3270	2630
Ampicillin	80	225			5300
Azithromycin	300	80			95
Cefadroxil	0	245			840
Cefuroxime	615	290	560	775	0
Ciprofloxacin	1200	370			2300
Clarithromycin	240	445			
Clindamycin	16	4			110
Doxycycline	640	75			420
Erythromycin	120	0			390
Fluconazole	140	15			125
Metronidazol	1800	80			
Miconazol		40			
Norfloxacin	95	100			30
Ofloxacin	25	6			
Phenoxymethylpenicillin				970	
Roxithromycin	125				10
Sulfamethoxazole		470			1700
Sulfasalazine			730	990	
Tetracycline	1700	25			350
Trimethoprim	850	100			210

Source: Original data

Table A2.3: Sales and consumption of cardiovascular agents in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig-Holstein)	Sweden
Acebutolol	0	0			0
Alfuzosin	75	6			245
Amlodipine	485	80			810
Atenolol	445	35			2860
Atorvastatin	1330	135			2450
Bisoprolol	740	5			310
Cilazapril					
Colestyramine				1200	
Diltiazem	570	11			680
Dipyridamole			660*		
Enalapril	530	135			1830
Enalaprilat					
Eprosartan	600	6			105
Felodipine	90	13			470
Furosemide	3000	95			4880
Hydrochlorothiazide	330	475	955	1475	445
Metformin	125500	18800	30300	37400	135000
Metoprolol	4550	1670	2120	5340	13800
Nebivolol	13	45			0
Propranolol	645	38			890
Ramipril	345	74			245
Rosuvastatin	260	120			190
Simvastatin	3080	100	1280	1430	4870
Sotalol	200	130			520
Telmisartan	590	400			53
Torasemide	0	77			3,7
Trimetazidine	0	200			0
Valsartan	1760	215	3500	3000	665
Warfarin	235	30			300
Verapamil	370	410			870

*data from 2013 (no data from 2014)

Source: Original data

Table A2.4: Sales and consumption of central nervous system agents in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig-Holstein)	Sweden
Carbamazepine	3530	1090	1350	1331	5860
Clonazepam	14	3			6
Fluoxetine	170	29			370
Gabapentin	5860	575	2420	2690	11000
Levetiracetam	5600	185	2780	3840	6300
Levodopa			1060	1510	
Metamizole		0	11800	21850	0
Paroxetine	105	21			205
Piracetam			900		
Pregabalin			710	800	
Quetiapine				720	
Sertraline	690	68			4160
Tilidine			640		
Valproic acid	11200	1050	1880	2550	8600
Zopiclone	275	57			605

Source: Original data

Table A2.5: Sales and consumption of metabolic agents and gastrointestinal agents in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig-Holstein)	Sweden
Bezafibrate	95				335
Drotaverin		215			
Macrogol	154500	980	22300	41500	54400
Mesalazine	18000	685	2530	3840	17100
Omeprazole	565	240			3420
Pantoprazole			1440	1770	
Ranitidine	740	450			830
Sitagliptin			670*		

* data from 2013 (no data from 2014)

Source: Original data

Table A2.6: Sales and consumption of other pharmaceuticals in Baltic Sea countries

Compound	Finland	Estonia	Germany (Mecklenburg-Vorpommern)	Germany (Schleswig Holstein)	Russia	Sweden
Hormones and hormone antagonists						
Finasteride	66					120
Levothyroxine sodium	0	1.1				13
Tamoxifen	42	6				105
Respiratory system						
Acetylcysteine			540*	790*		
Terbutaline	6					
Xylomeazoline	6	864				0
Theophylline			780	780*		
Musculo-skeletal system						
Methocarbamol			650*	1020		

*year 2013 (no data from 2014)

Source: Original data

Veterinary sales and consumption

Data on the sales and consumption of veterinary pharmaceuticals were received from Finland and Germany. From Estonia, veterinary drug statistics are based on the reports of wholesalers and presented only as turnovers (Ravimiamet 2015).

From Finland, data were received on the sales of veterinary pharmaceuticals in years 2001–2013 (Figure A2.1). The total consumption of veterinary pharmaceuticals varied between 12,600 and 17,000 kg/year. In 2013 it was around 13,600 kg/year. The most used antimicrobial drug was a betalactam antibiotic penicillin G. Its consumption was 6,200 kg in 2013. In Finland, antimicrobials are the main pharmaceuticals used in the treatment of animals. No data was reported on the use of other type of pharmaceuticals.

Similar to Finland, Germany reported the sales of antimicrobial veterinary pharmaceuticals (BVL 2014; Agra-Europe 2014). No data are available for pharmaceuticals of other therapeutic groups. Consumption data for the years 2011–2013 are presented in Figure A2.2 Figure . Similar to Finland, tetracycline and penicillin were the most sold pharmaceuticals in animal medicine in Germany, however, the total sales of veterinary drugs in Germany was significantly higher than in Finland. In 2013, the total sales was 1,450,000 kg, however, there was a significant geographical variation in the consumption of veterinary pharmaceuticals. When only those areas relevant for the Baltic Sea (i.e. Mecklenburg-Vorpommern and Schleswig-Holstein) were considered, the total sales of veterinary pharmaceuticals was 86,000 kg in 2013.

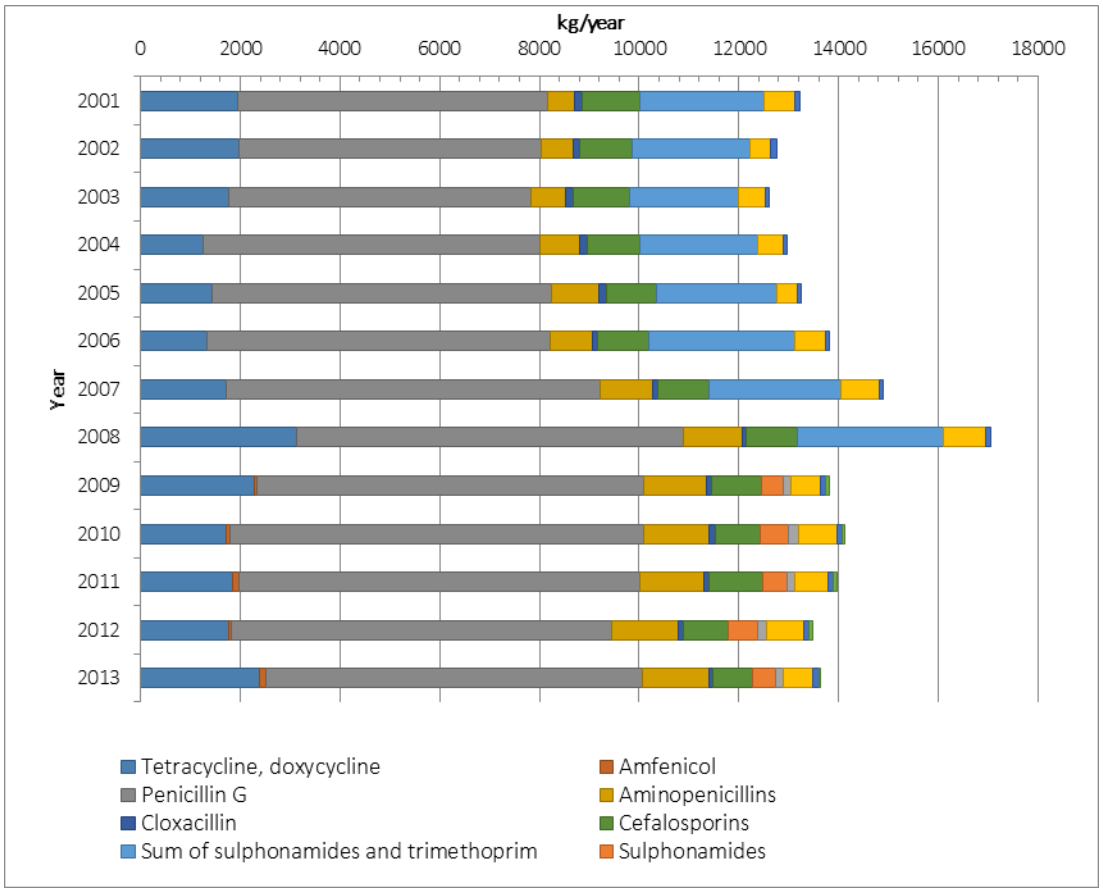

Figure A2.1. Sales of veterinary pharmaceuticals in Finland.

Source: Original data

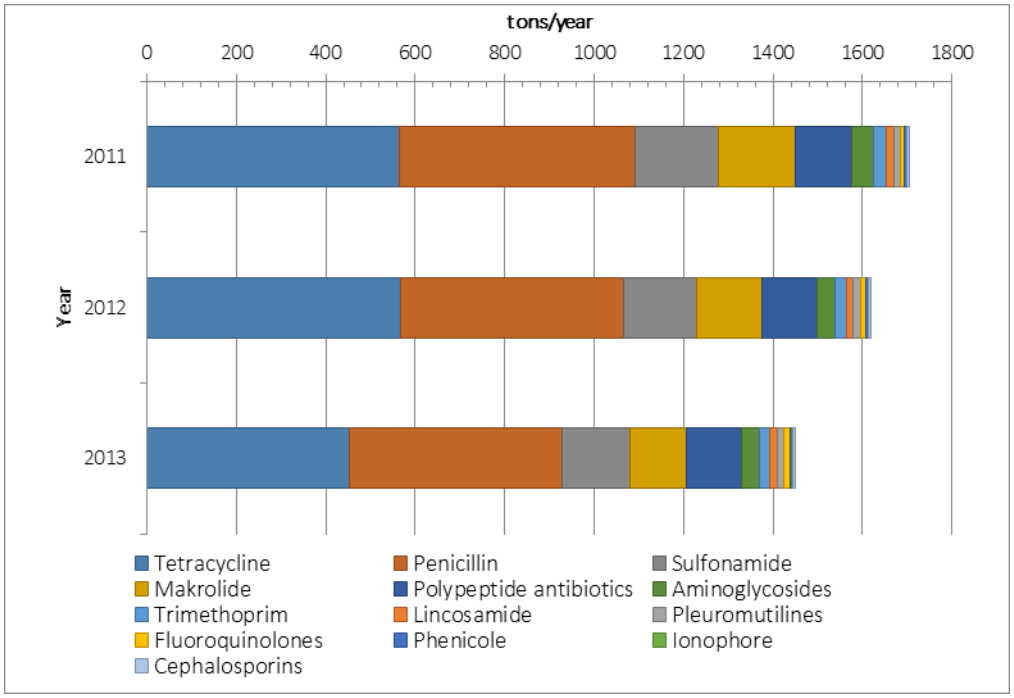

Figure A2.2. Sales of veterinary pharmaceuticals in Germany.

Source: Original data

Annex 3. Data on samples from WWTPs influent, effluent, sludge and river water by therapeutic group

When pharmaceuticals have been detected in influent, effluent, sludge or river, the average and maximum measured concentrations are presented in figures together with the sensitivity of the analytical methods. Removal rates are presented in tables. The results are presented by grouping pharmaceuticals according to their therapeutic group.

Contents

Anti-inflammatory and analgesics

An overview of reported data on pharmaceuticals belonging to the therapeutic groupanti-inflammatory and analgesics is presented in Table A3.1.

Table A3.1: Anti-inflammatory and analgesics. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
Azelastine	8/2	13/4		1/0	Beclomethasone	17	31		1
Buprenorphine	11/8	16/13		8/2	Budenoside				2
Codeine	42/32	47/19		7/6	Dextro-propoxyphene	23	32		
Diclofenac	78/77	349/330	17/16	1677/684	Irbesartan	3	3		
Dihydroergotamine	8/1	13/0		2/0	Norfentanyl	23	32		
Fentanyl	34/8	48/12		6/0	Norpropoxyphene	23	32		
Ibuprofen	175/175	359/253	17/7	1672/118	Orphenadrine				1
2-hydroxyibuprofen	119/119	194/182							
Ibuprofen-COOH	4/4	11/9							
Ketoprofen	81/78	196/174	17/16	26/11					
Naproxen	50/50	165/153	17/17	212/30					
Paracetamol	128/97	201/55	6/6	8/5					
Phenazone				1645/204					
Propyphenazone				1645/4					
Pizotifen	8/7	13/10		0/0					
Propofol	33/18	48/35							
Salicylic acid	121/86	205/38							
Tramadol	11/11	16/16		8/2					
Trihexyphenidyl	8/7	13/13		0/0					

Source: Original data

Of all the monitored pharmaceuticals in this category, 19 out of 26 (73%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum measured concentrations measured in WWTP influents and effluents are presented in Figures A3.1 and A3.2, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.2.

Sludge results are presented in Figures A3.3 and A3.4 and river water results in Figure A3.5. Data on the detection limits of the analytical methods are presented in the figures if the values were reported. For majority of pharmaceuticals, the reported analytical LOD in influent and effluent samples were low enough to detect these pharmaceuticals in wastewater samples. For salicylic acid, the highest reported LOD was higher than the values reported in other studies and thus more frequent detection could be anticipated for this pharmaceutical.

In WWTP influents the highest average (83 μg/l) and maximum (1,300 μg/l) concentrations were measured for paracetamol. Additionally, 2-hydroxyibuprofen (metabolite of ibuprofen), ibuprofen and salicylic acid were detected in influents at average concentrations of >10 μg/l. Similar to the influent, paracetamol was measured at the highest concentration of 360 μg/l. The highest average concentration (4.4 μg/l) was measured for metabolite 2-hydroxyibuprofen. Additionally, diclofenac, ibuprofen and tramadol were detected in effluents at average concentration of >1 μg/l.

Removal rates of >70% were calculated for eight out of 17 compounds (i.e. buprenorphine, codeine, dihydroergotamine, ibuprofen, ketoprofen, naproxen, paracetamol and salicylic acid). Removal rates of <20% (or even increase in concentrations during the treatment) were calculated for 7 compounds (i.e. azelastine, diclofenac, fentanyl, 2-hydroxyibuprofen, ibuprofen-COOH, propofol and tramadol). These compounds can be considered as being of highest concern from the environmental point of view due to low biodegradation potential in current WWTPs. Two of the compounds were metabolites of ibuprofen, which is a very biodegradable pharmaceutical. In the future, the occurrence and fate of not only the parent compounds but also the metabolites should be more thoroughly investigated.

In untreated sludge samples, highest concentrations were reported for ibuprofen and paracetamol. However, in digested sludge diclofenac was detected in highest average concentration and in composted sludge diclofenac and naproxen. Ibuprofen and paracetamol were not detected in composted sludge samples.

In river water samples the highest average and maximum concentrations were measured for diclofenac (164 ng/l and 2,710 ng/l, respectively). Additionally, ibuprofen and phenanzone were detected in rivers at average concentration of >50 ng/l.

It should be noted that no data on phenazone were reported from WWTP. This compound might be of interest to monitor in the future.

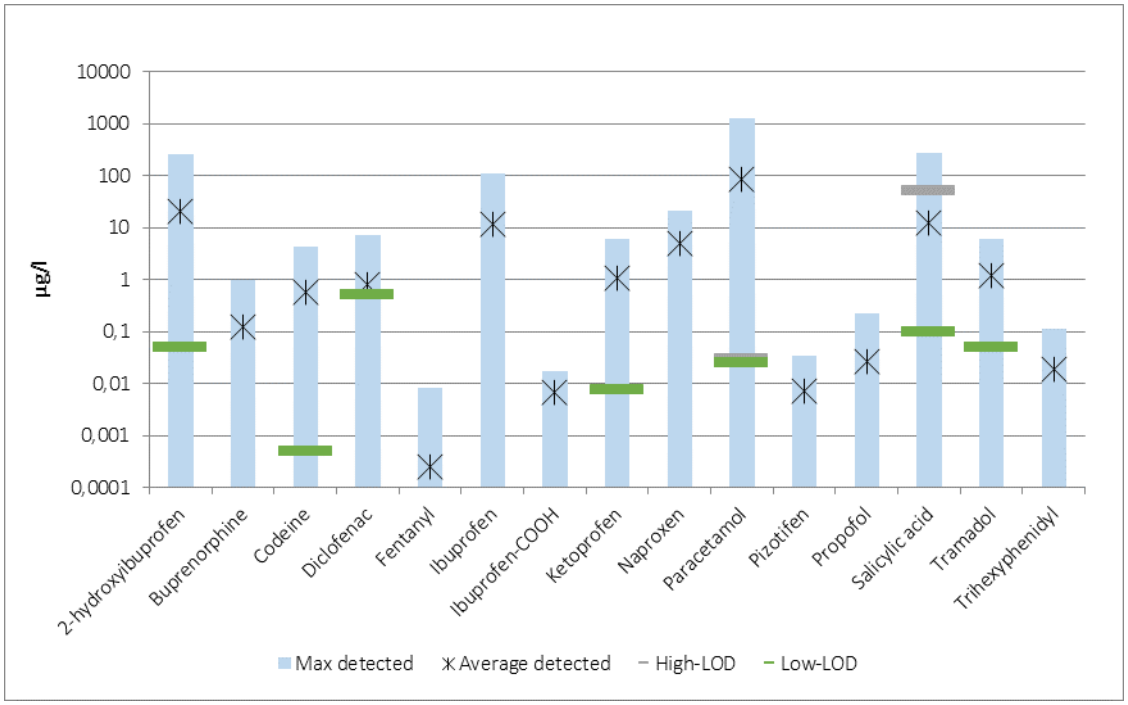

Figure A3.1: The average and maximum concentrations of anti-inflammatory and analgesics in WWTP influents.

Source: Original data

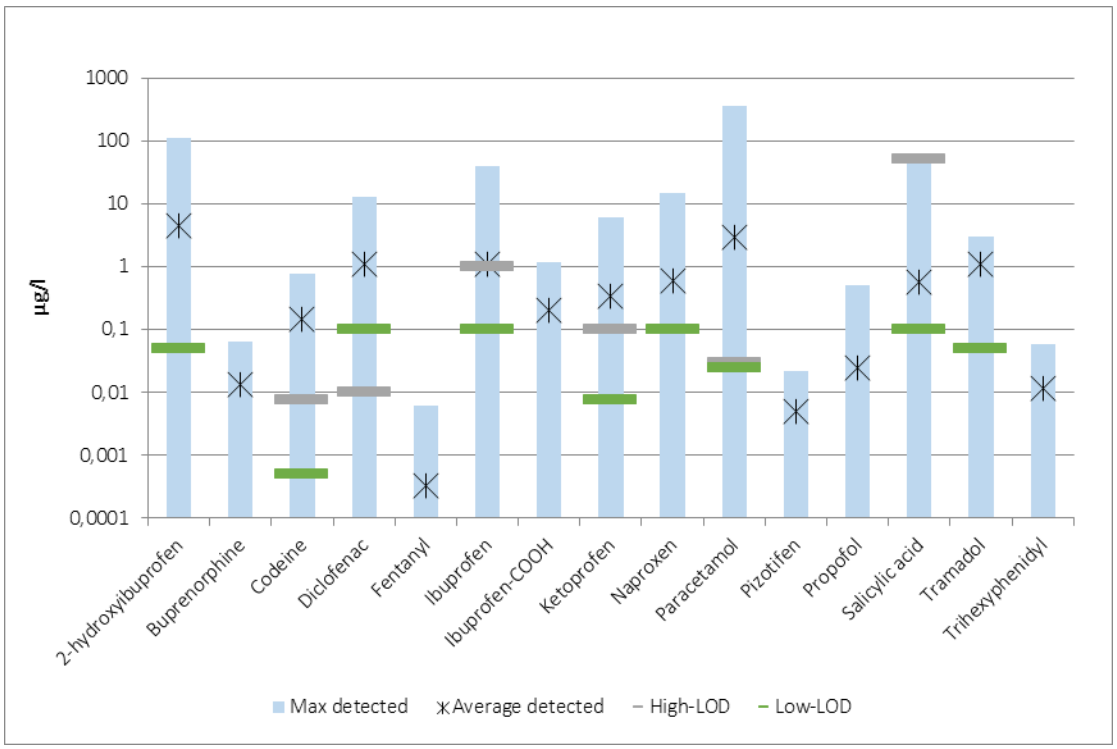

Figure A3.2: The average and maximum concentrations of anti-inflammatory and analgesics in WWTP influents.

Source: Original data

Table A3.2: Removal rates of anti-inflammatory and analgesics in WWTPs

Compound	Average removal (%)
Azelastine	14 %
Buprenorphine	89 %
Codeine	77 %
Diclofenac	-6%
Dihydroergotamine	>90 %[1)]
Fentanyl	-30 %
Ibuprofen	89 %
2-hydroxyibuprofen	-1,000 %*
Ibuprofen-COOH	-2,800 %*
Ketoprofen	72 %
Naproxen	87 %
Paracetamol	97 %
Pizotifen	32 %
Propofol	4 %
Salicylic acid	95 %
Tramadol	0 %
Trihexyphenidyl	41 %

[1)] average effluent concentration <LOD

* forms when ibuprofen biodegrades in the biological treatment process

Source: Original data

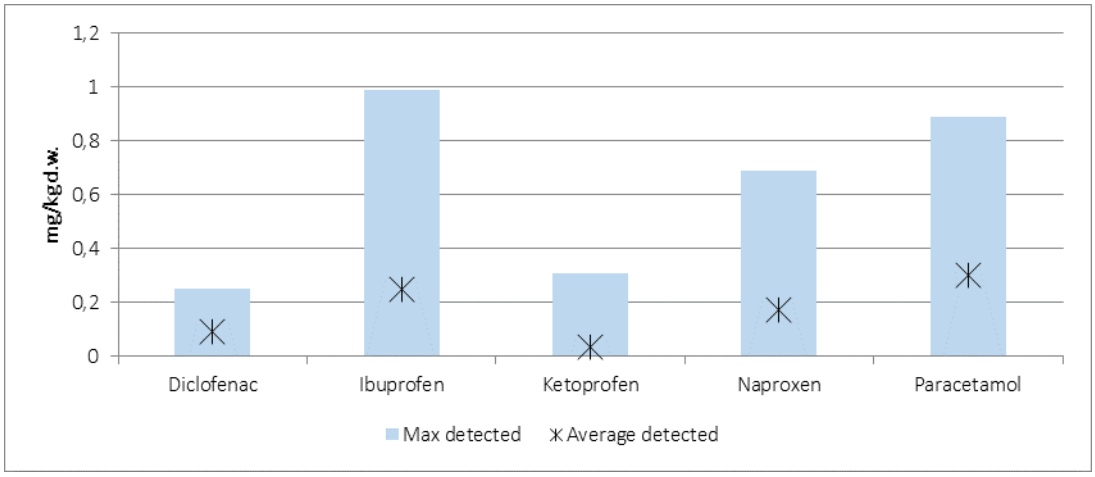

Figure A3.3: The average and maximum concentrations of anti-inflammatory and analgesics in untreated sludge

Source: Original data

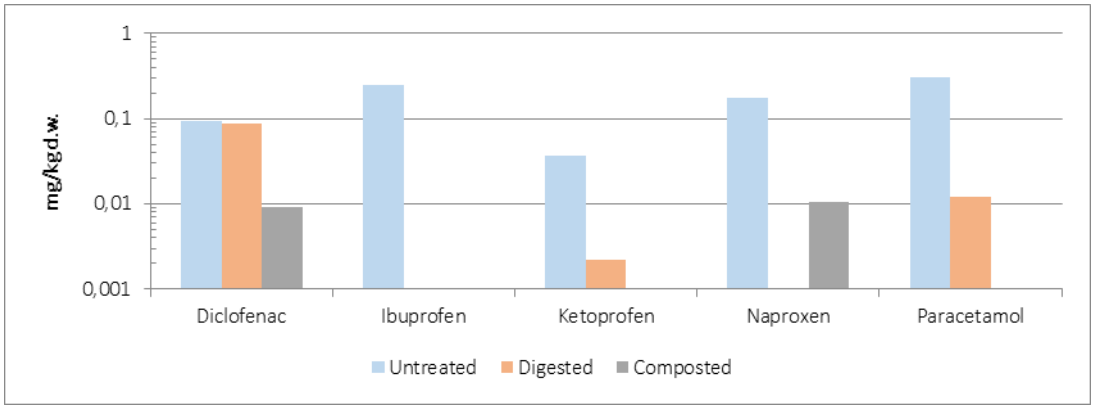

Figure A3.4: The average concentrations of anti-inflammatory and analgesics in untreated, digested and composted sludge

Source: Original data

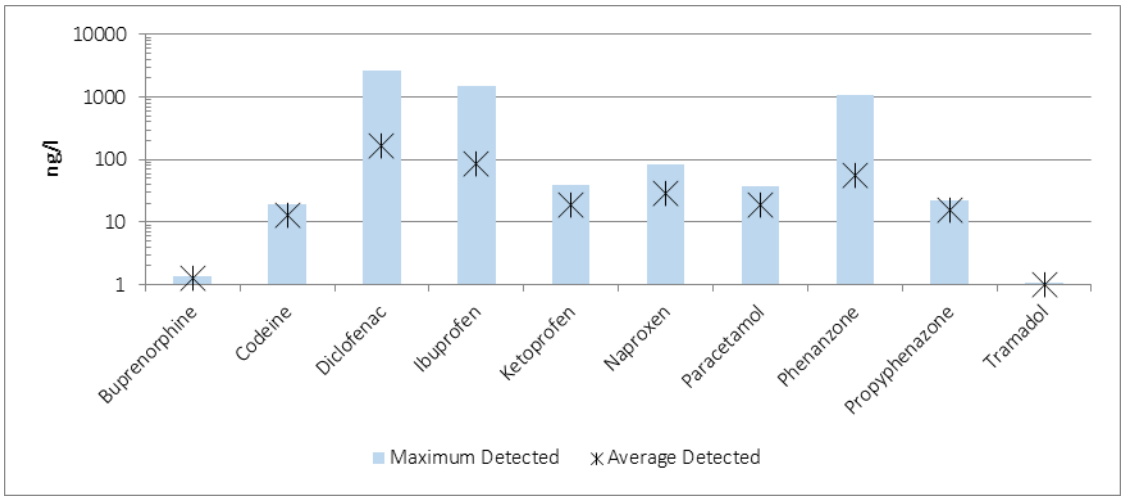

Figure A3.5: The average and maximum concentrations of anti-inflammatory and analgesics in river water samples

Source: Original data

Antimicrobial (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote

An overview of reported data on pharmaceuticals belonging to the therapeutic groupanti-inflammatory and analgesics is presented in Table A3.3.

Table A3.3: Antimicrobial and antidote. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
Amoxicillin	43/5	43/0	12/0		Penicillin V	12	12		
Ampicillin	43/4	43/2	12/0		Demeclocycline			11	
Azithromycin	39/37	44/29		1/1	Chlortetracycline				528
Cefadroxil	12/6	12/4	12/0						
Cefuroxime	12/4	12/0	12/0						
Ciprofloxacin	66/61	90/53	74/74	19/7					
Clarithromycin	8/8	13/12		935/41					
Clindamycin	11/9	16/16		8/3					
Clotrimazol	8/2	13/9							
Dibazol	31/2	31/3							
Doxycycline	12/12	12/7	29/17	528/0					
Erythromycin	51/39	56/27	12/0	187/4					
Fenbedazole			6/6						
Flubendazole			6/5						
Fluconazole	11/11	16/16		7/3					
Ketokonazole	20/8	34/3	6/6	8/0					
Meclozine	8/2	13/6							
Metronidazol	12/6	12/2	6/1						
Miconazole	11/5	16/5		6/0					
Norfloxacin	67/48	91/15	74/47	17/2					
Ofloxacin	36/22	60/28	74/46	19/4					
Oxytetracycline	3/0	3/0	6/6						
Roxithromycin	11/9	16/7		8/0					
Sulfadiazine				927/16					
Sulfadimidine				927/7					
Sulfamethiazol	115/102	183/173							
Sulfamethoxazole	118/57	293/175	6/1	1656/345					
Tetracycline	34/7	34/3	17/12	536/6					
Trimethoprim	161/109	229/124	18/5	196/11					

Source: Original data

Of all the monitored pharmaceuticals in this category, 29 out of 32 (91%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum concentrations measured in WWTP influents and effluents are presented in Figure A3.6 and Figure A3.7, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.4. Sludge results are presented in Figure A.8 and Figure A3.9 and river water results in Figure A3.10. Data on the detection limits of the analytical methods are indicated in the figures if the values were reported. For the majority of pharmaceuticals, the reported analytical LOD in influent and effluent samples were low enough to detect these pharmaceuticals in wastewater samples. In the influents, the highest reported LOD was higher than the values reported in other studies for tetracycline and in effluents, for erythromycin, ketoconazole, norfloxacin and sulfamethoxazole. Thus more frequent detection could be anticipated for these pharmaceuticals.

In WWTP influents the highest average concentration (1.85 μg/l) was measured for sulfamethiazol and the highest maximum concentration (29 μg/l) for sulfamethoxazole. Additionally, clarithromycin was detected in influents at average concentrations of >1 μg/l. Similar to the influent, sulfamethiazol was measured at the highest average concentration of 1 μg/l. The highest concentration (15 μg/l) was also measured for sulfamethiazol. Additionally, clarithromycin, clindamycin, doxycycline, fluconazole, roxithromycin, sulfamethoxazole and trimethoprim were detected in effluents at average concentration of >0.1 μg/l.

Removal rates of >70% were calculated for 12 out of 23 compounds. Increases in concentrations during the treatment were noted for three compounds (clindamycin, fluconazole and meclozine). These compounds can be considered as being of the highest concern from the point of view of the aquatic environment due to low removal potential in current WWTPs. For many antibiotics, adsorption to sludge seems to be an important fate in WWTPs. Thus, the concentrations in sludge samples were relatively high. In untreated sludge samples, 5 out of 10 compounds were detected at concentrations higher than 1 mg/kg d.w. The highest average concentration of 3.3 mg/kg d.w. was reported for ciprofloxacin. Also, the highest concentration of 8.8 mg/kg d.w. was reported for ciprofloxacin. Many antibiotics were present at similar concentrations in untreated and digested sludge. Only trimethoprim was not detected in digested sludge samples. In composted sludge samples, the concentrations were lower but still detectable for all other compounds except flubendazole, oxytetracycline and trimethoprim. In the future, the fate of antimicrobials and antidote should be more thoroughly studied especially in sludge treatment and land application of sludge.

In river water samples the highest average concentration (120 ng/l) was measured for sulfadiazine and the highest maximum concentrations (6,350 ng/l) for sulfamethoxazole. Additionally, sulfadiazine and trimethoprim were detected in rivers at average concentration of >50 ng/l. For clarithromycin, the maximum measured concentration exceeded 100 ng/l.

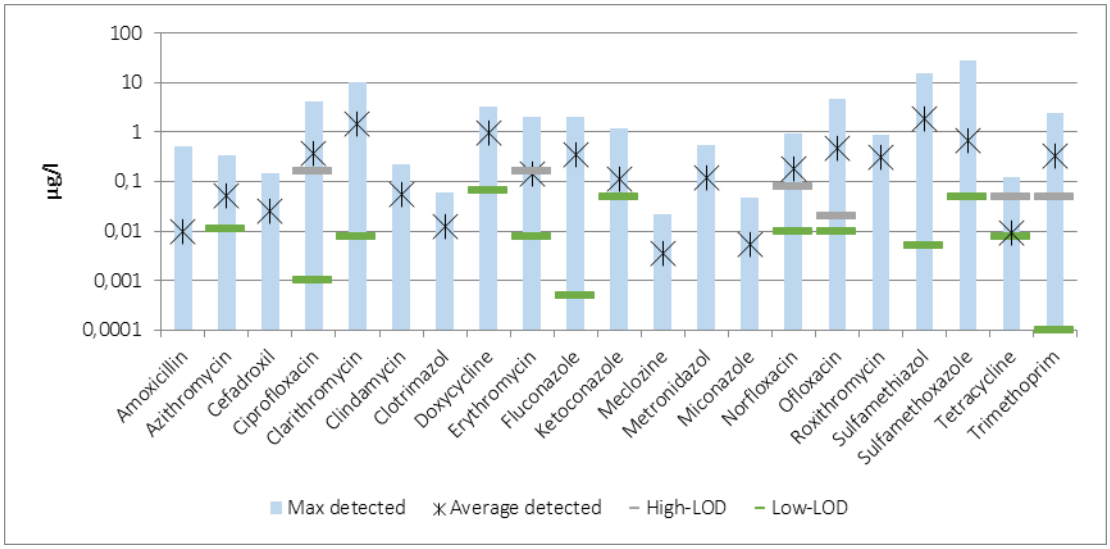

Figure A3.6: The average and maximum concentrations of antimicrobial and antidote in WWTP influents

Source: Original data

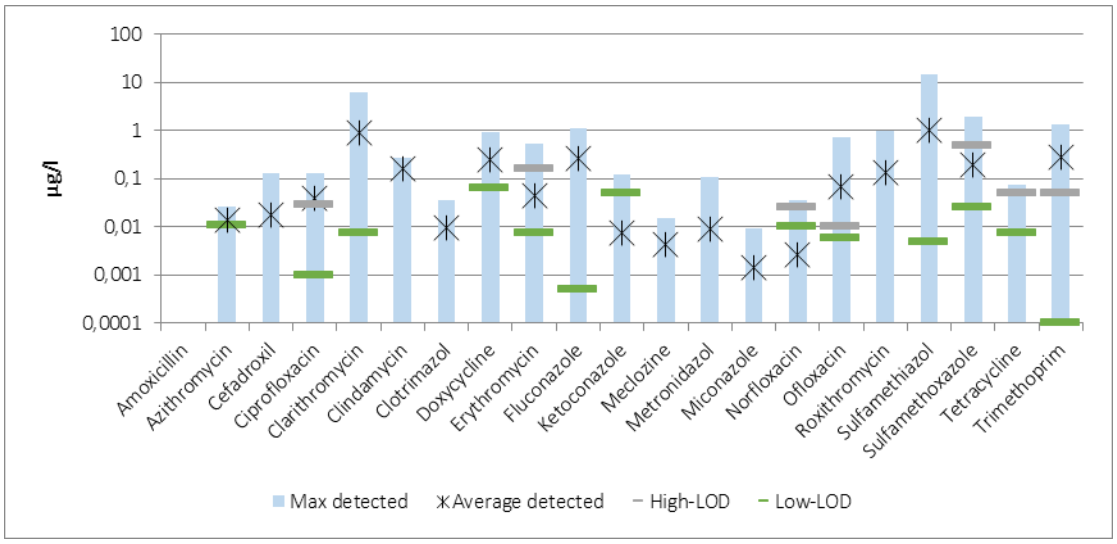

Figure A3.7: The average and maximum concentrations of antimicrobial and antidote in WWTP effluents

Source: Original data

Table A3.4: Removal rates of antimicrobial and antidote in WWTPs

Compound	Average removal (%)
Amoxicillin	>90 %[1)]
Ampicillin	62 %
Azithromycin	42 %
Cefadroxil	31 %
Cefuroxime	>90 %[1)]
Ciprofloxacin	90 %
Clarithromycin	41 %
Clindamycin	-470 %
Clotrimazol	19 %
Doxycycline	74 %
Erythromycin	74 %
Fluconazole	-34 %
Ketokonazole	93 %
Meclozine	-24 %
Metronidazol	93 %
Miconazole	72 %
Norfloxacin	99 %
Ofloxacin	87 %
Roxithromycin	55 %
Sulfamethiazol	46 %
Sulfamethoxazole	79 %
Tetracycline	>90 %[1)]
Trimethoprim	45 %

[1)] average effluent concentration <LOD

Source: Original data

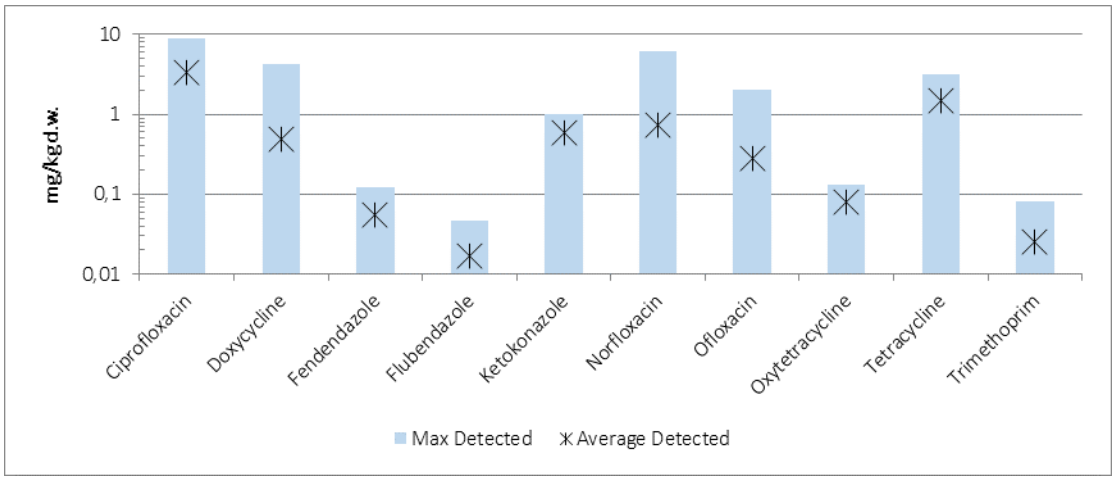

Figure A3.8: The average and maximum concentrations of antimicrobial and antidote in untreated sludge

Source: Original data

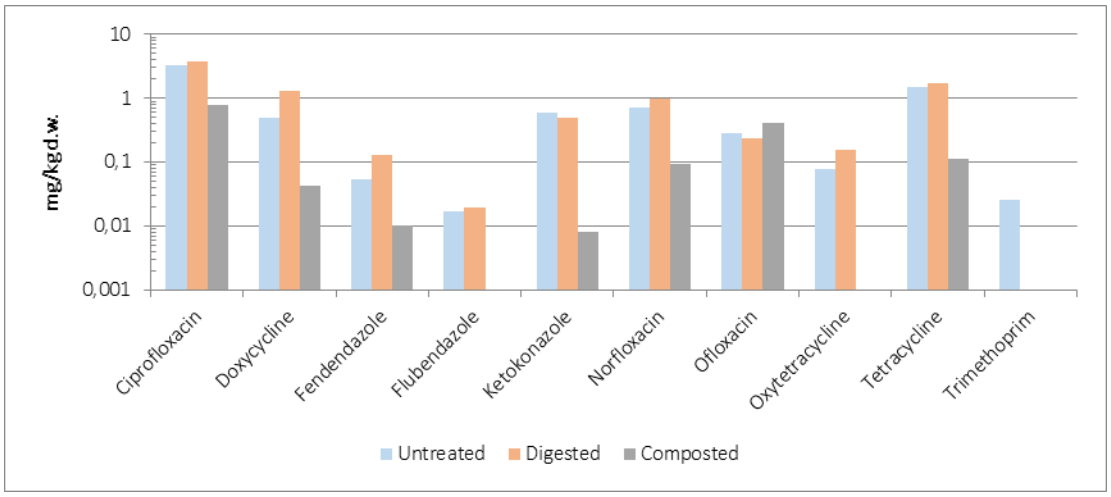

Figure A3.9: The average concentrations of antimicrobial and antidote in untreated, digested and composted sludge

Source: Original data

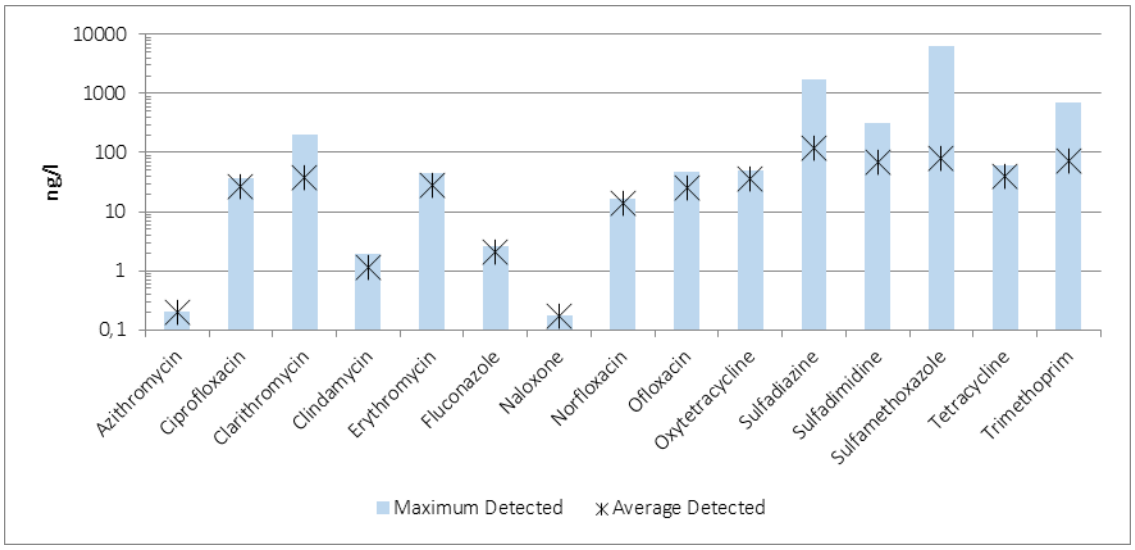

Figure A3.10: The average and maximum concentrations of antimicrobial and antidote in river water samples

Source: Original data

Cardiovascular agents (blood pressure, diuretics, anticoagulants, antihistamine)

An overview of reported data on pharmaceuticals belonging to the therapeutic group cardiovascular agents is presented in Table A3.5.

Table A3.5: Cardiovascular agents. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
Acebutelol	21/21	21/21		11/10	Amiodarone	8	13		
Alfuzosin	11/8	16/13		8/0	Felodipine	17	31		
Atenolol	32/32	37/37	6/2	1666/107	Gemfibrozil				187
Bisoprolol	8/8	13/13	6/5	1651/552					
Cilazapril	11/7	16/6		8/0					
Clemastine	8/2	13/6		2/0					
Cyproheptadine	8/2	13/6							
Desloratidin	8/8	13/13		2/0					
Diltiazem	11/8	16/13		8/0					
Diphenhydramine	8/8	13/13		2/0					
Dipyridamole	8/8	13/0		2/0					
Enalapril	31/30	31/10	6/5						
Enalaprilat	31/27	31/20							
Eprosartan	11/11	16/15		8/4					
Fexofenadine	8/8	13/13		2/2					
Flecainide	8/8	13/13							
Furosemide	115/113	183/181	6/6	2/2					
Hydrochlorthiazide			6/6	2/2					
Irbesartan	8/8	13/13		8/2					
Metoprolol	32/32	190/190	6/6	1665/956					
Promethazine	8/6	13/5							
Propranolol			6/6	1645/90					
Simvastatatin			6/1						
Sotalol	24/24	24/24	6/2	1664/477					
Telmisartan	11/8	16/12		7/4					
Verapamil	11/10	16/11		8/0					
Warfarin			6/1						

Of all the monitored pharmaceuticals in this category, 27 out of 30 (90%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum concentrations measured in WWTP influents and effluents are presented in Figures A3.11 and A3.12, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.6. Sludge results are presented in Figures A3.13 and A3.14 and river water results in Figure A3.15. Data on the analytical LOD are indicated in the figures if the values were reported. For all the pharmaceuticals, the reported analytical LOD in influent and effluent samples were low enough to detect these pharmaceuticals in wastewater samples.

In WWTP influents the highest average and maximum concentration (52 μg/l and 1,800 μg/l, respectively) was measured for furosemide. Additionally, telmisartan was detected in influents at average concentrations of >10 μg/l and dipyridamole, metoprolol and sotalol at >1 μg/l. Similar to the influent, furosemide was measured at the highest average and maximum concentrations of 22μg/l and 110 μg/l, respectively. Additionally, metoprolol, sotalol and telmisartan were detected in effluents at an average concentration of >1 μg/l and atenolol, eprosartan, flecainide and irbesartan at >0.1 μg/l.

Removal rates of >70% were calculated for only 3 out of 23 compounds. For two compounds (alfuzosin and atenolol) the removal rates were <20% and for one compound (clemastine) increase in concentrations during the treatment was noted. Generally, due to relatively poor removal in WWTPs, many compounds in this therapeutic group can be considered relevant from the point of view of the aquatic environment.

Sludge concentrations were submitted for only six compounds. Out of these six, the highest maximum concentration (0.27 mg/kg d.w.) was reported for felodipine. The highest average concentration (0.11 mg/kg d.w.) was reported for furosemide. Felodipine was not detected in digested sludge. Furosemide and propranolol were detected in the composted sludge samples at the highest concentrations.

In river water samples the highest average concentration (670 ng/l) was measured for hydrochlorotiazide and the highest maximum concentrations (3,810 ng/l) for bisoprolol. The maximum concentrations of metoprolol and sotalol exceeded 1,000 ng/l and furosemide and telmisartan were detected in rivers at average concentration of >100 ng/l.

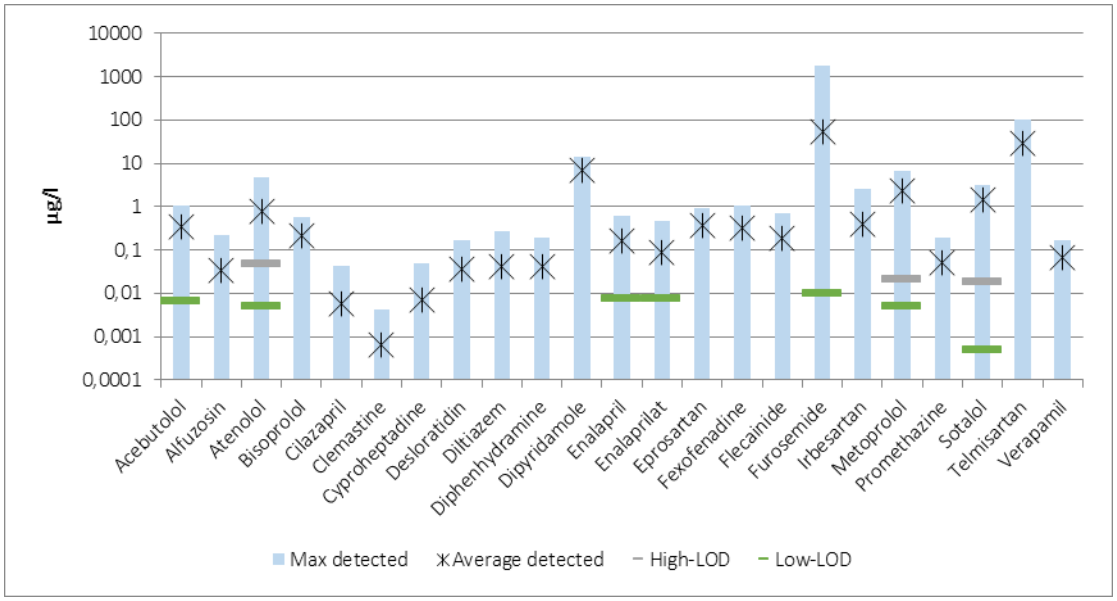

Figure A3.11: The average and maximum concentrations of cardiovascular agents in WWTP influents

Source: Original data

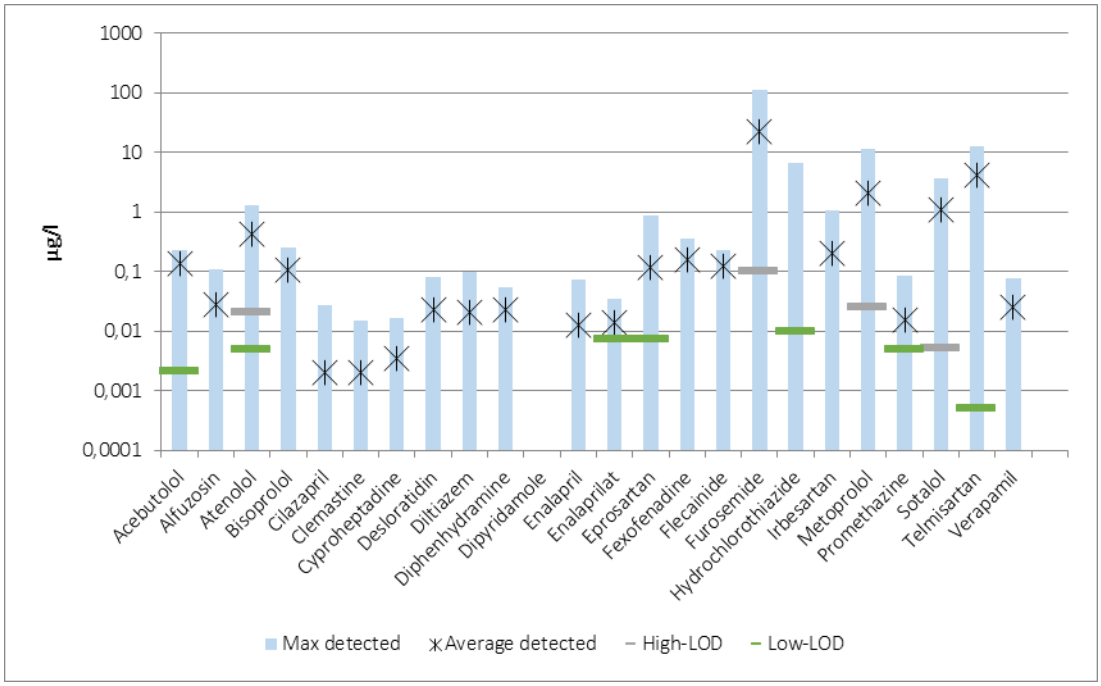

Figure A3.12: The average and maximum concentrations of cardiovascular agents in WWTP effluents

Source: Original data

Table A3.6: Removal rates of cardiovascular agents in WWTPs

Compound	Average removal (%)
Acebutolol	59 %
Alfuzosin	18 %
Atenolol	14 %
Bisoprolol	51 %
Cilazapril	66 %
Clemastine	-214 %
Cyproheptadine	50 %
Desloratidin	38 %
Diltiazem	50 %
Diphenhydramine	46 %
Dipyridamole	> 90 %
Enalapril	92 %
Enalaprilat	85 %
Eprosartan	65 %
Fexofenadine	49 %
Flecainide	32 %
Furosemide	57 %
Irbesartan	49 %
Metoprolol	28 %
Promethazine	68 %
Sotalol	36 %
Telmisartan	80 %
Verapamil	62 %

Source: Original data

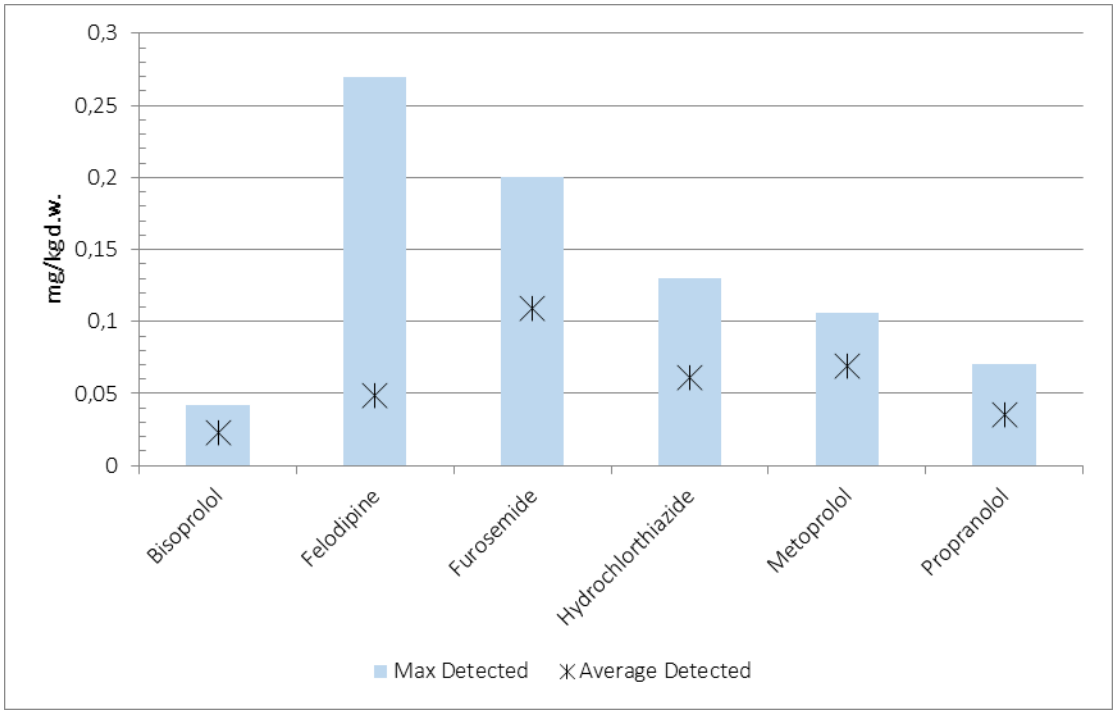

Figure A3.13: The average and maximum concentrations of cardiovascular agents in untreated sludge

Source: Original data

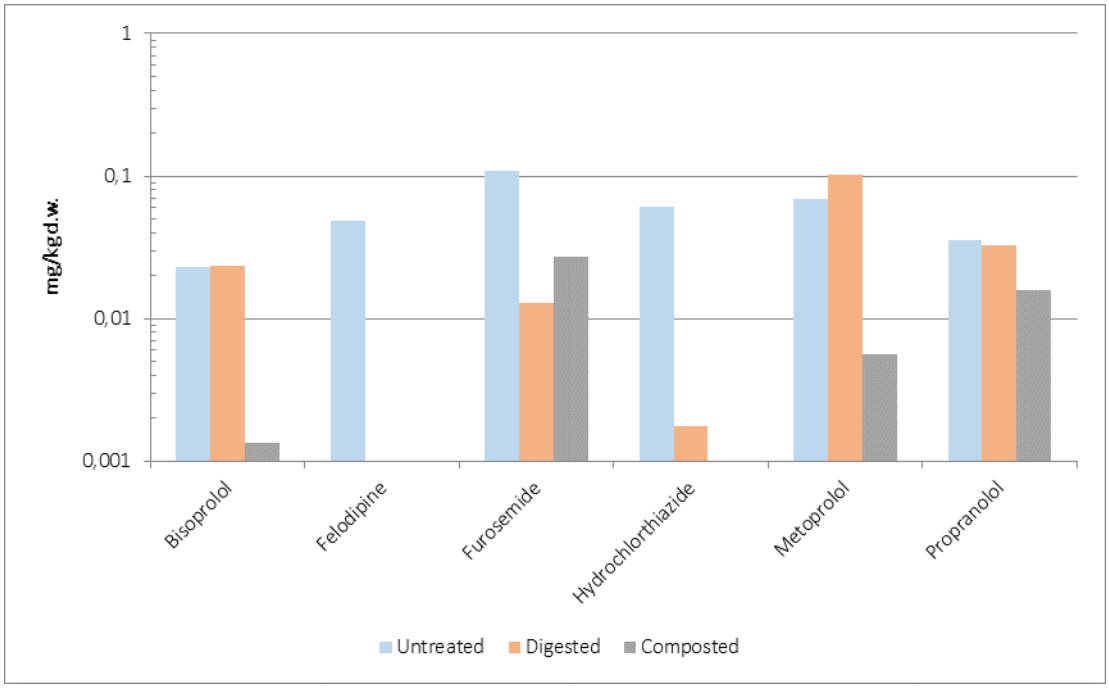

Figure A3.14: The average concentrations of cardiovascular agents in untreated, digested and composted sludge

Source: Original data

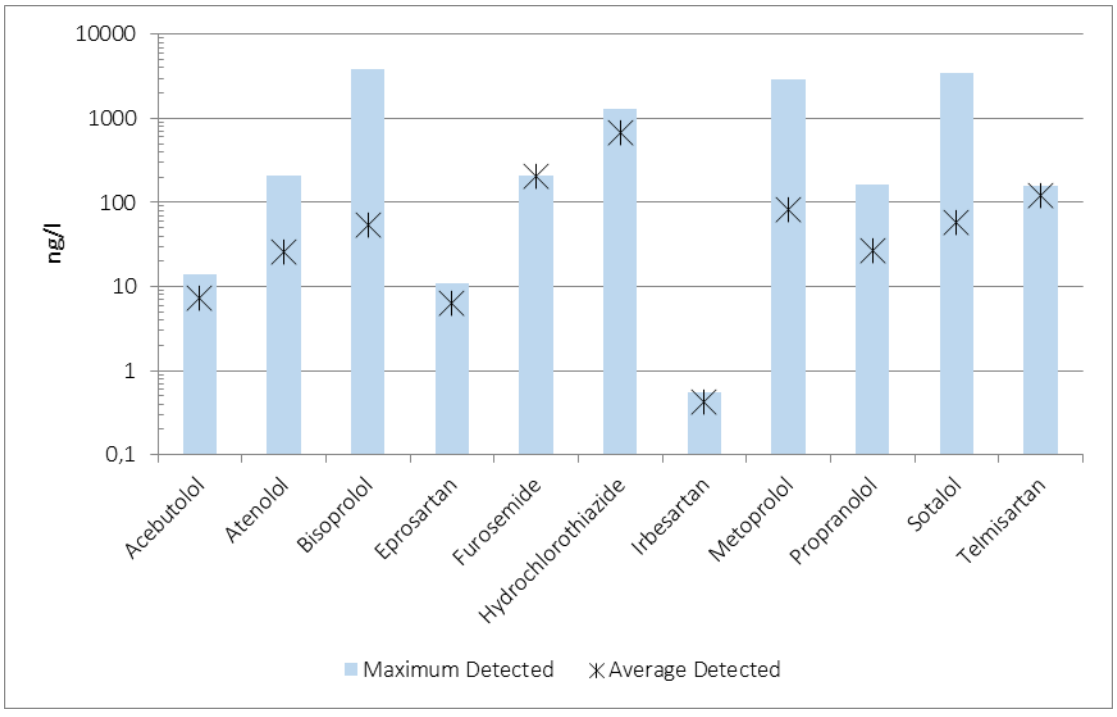

Figure A3.15: The average and maximum concentrations of cardiovascular agents in river water samples

Source: Original data

Central nervous system agents (psychotherapeutic, antiepileptic, antiparkinson, muscle relaxant)

An overview of reported data on pharmaceuticals belonging to the therapeutic group central nervous system agents is presented in Table A3.7.

Table A3.7: Central nervous systems agents. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
7-aminoflu-nitrazepam	22/1	32/1			Clozapine	23	32		
Alprazolam	8/7	13/6		2/0	Diazepam	23	32		187
Amitryptiline	8/6	13/6			Levopromazine	8	13		1
Atracurium	8/8	13/13			N-demethyl-flunitrazepam	23	32		
Biperiden	8/5	13/13		2/0	Thioridazine	23	32		
Bromocriptine	31/3	45/1		2/0	Zopiclone	23	32		
Bupropion	8/8	13/13							
Caffeine	23/21	32/26	6/6						
Carbamazepine	89/88	259/233	6/6	1666/1315					
Chlorpromazine	8/4	13/1		2/0					
Citalopram	31/28	45/44	6/6	2/2					
Clomipramine	8/8	13/13							
Clonazepam	11/0	16/1		7/0					
Donepezil	8/8	13/12		2/0					
Duloxetine	8/3	13/7		2/0					
Entacapone			6/1						
Flunitrazepam	31/1	45/0							
Fluoxetine	34/9	48/20	6/6	6/0					
Flupentixol	8/2	13/10							
Fluphenazine	8/2	13/2							
Haloperidol	8/8	13/13							
Hydroxyzine	8/8	13/13							
Maprotiline	8/5	13/6							
Memantine	8/8	13/13							
Mianserin	8/8	13/13		2/0					
Mirtazapin	8/8	13/13							
Nefazodone	8/6	13/11							
Nordiazepam	23/3	32/12							
Orphenadrine	8/8	13/13							
Oxazepam	31/29	45/45		189/3					
Paroxetine	31/10	45/14	6/6	2/1					
Perphenazine	8/1	13/3							
Risperidone	31/12	45/16		2/0					
Sertraline	43/14	66/17		8/0					
Temazepam				187/2					
Venlafaxine	8/8	13/13		2/2					
Zolpidem	31/11	45/19		2/0					
Zopiclone N-oxide	23/1	32/1							
Zuclopenthixol				2/0					

Source: Original data

Of all the monitored pharmaceuticals in this category, 27 out of 30 (90%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum concentrations measured in WWTP influents and effluents are presented in Figures A3.16 and A3.17, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.8. Sludge results are presented in Figures A3.18 and A3.19 and river water results in Figure A3.20.

In WWTP influents the highest average and maximum concentration (62 and 150 μg/l, respectively) was measured for caffeine. Additionally, citaloparam was detected in influents at average concentrations of >1 μg/l and carbamazepine, mirtazapine and oxazepam of >0.1 μg/l. Similar to the influent, caffeine was measured at the highest average and maximum concentrations of 12 and 150 μg/l, respectively. Additionally, carbamazepine was detected in effluents at average concentration of >1 μg/l and citalopram, mirtazapine and oxazepam >0.1 μg/l.

Removal rates of >70% were calculated for only 9 out of 35 compounds. For 11 compounds the removal rates were <20% or the concentrations were noted to increase during the treatment. Generally, due to relatively poor removal in WWTPs, many compounds in this therapeutic group can be considered relevant from the point of view of the aquatic environment.

Sludge concentrations were submitted for only six compounds. Out of these six, the highest average and maximum concentration (1.46 and 7 mg/kg d.w., respectively) was reported for caffeine. All the six compounds were also detected in digested sludge samples and all but entacapone in composted sludge samples.

River water concentrations were submitted only for six compounds. The highest average and maximum concentration (138 and 2,950 ng/l) was measured for carbamazepine. The average and maximum concentrations of other pharmaceuticals were <100 ng/l. More environmental monitoring data should be gathered for the pharmaceuticals that are present in the highest concentrations and are poorly removed in the WWTP influents, such as oxazepam and mirtazapine.

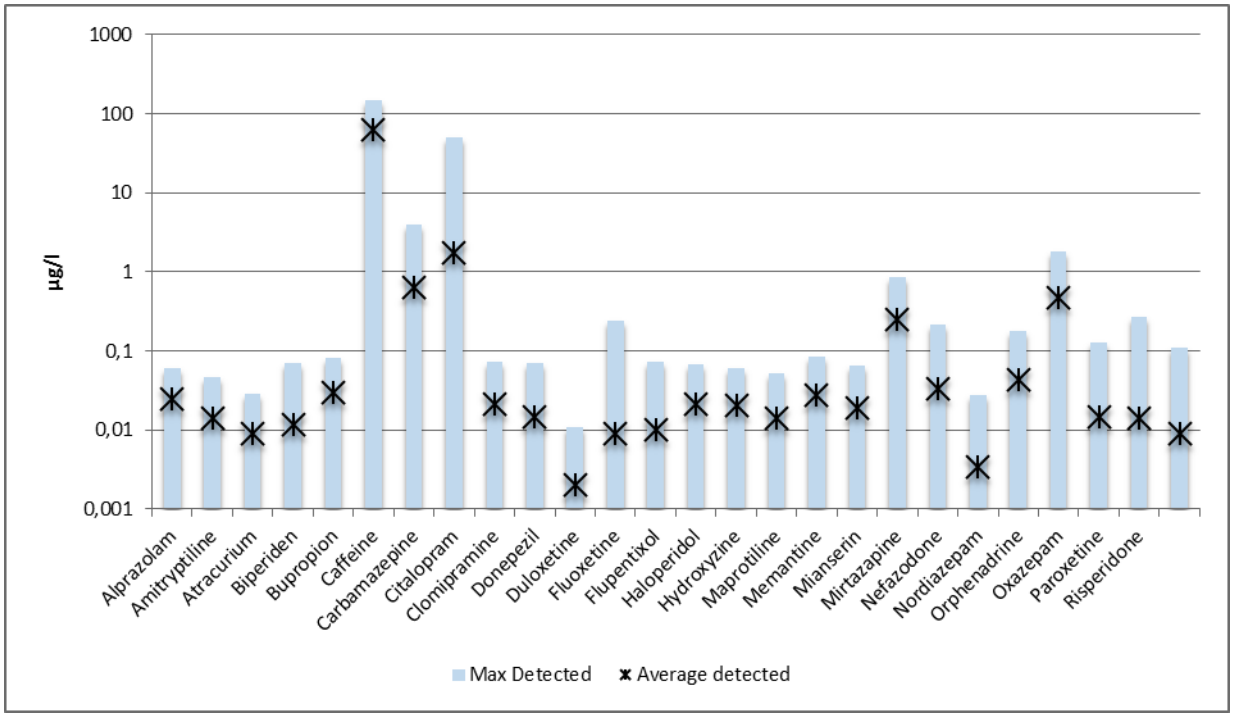

Figure A3.16: The average and maximum concentrations of central nervous system agents in WWTP influents

Source: Original data

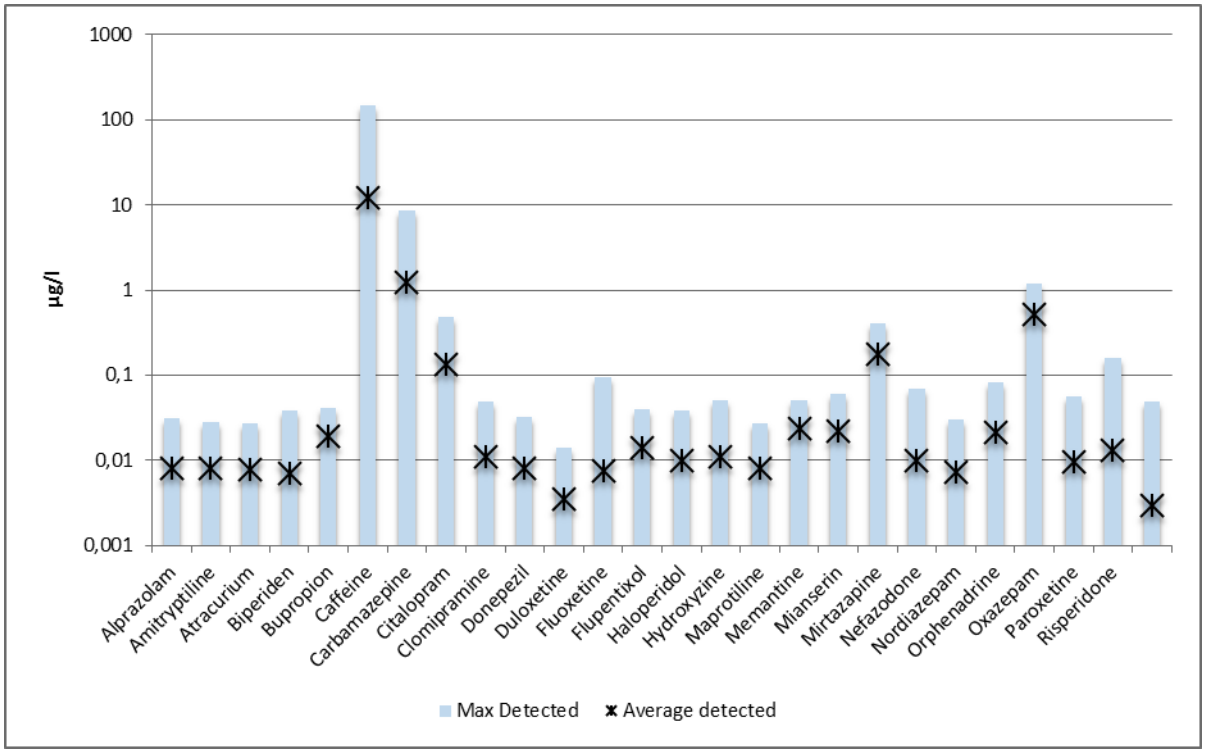

Figure A3.17: The average and maximum concentrations of central nervous system agents in WWTP effluents

Source: Original data

Table A3.8. Removal rates of central nervous system agents in WWTPs

Compound	Average removal (%)
7-aminoflunitrazepam	77%
Alprazolam	68%
Amitryptiline	44%
Atracurium	15%
Biperiden	40%
Bromocriptine	93%
Bupropion	37%
Caffeine	81%
Carbamazepine	13%
Chlorpromazine	81%
Citalopram	92%
Clomipramine	50%
Donepezil	43%
Duloxetine	-72%
Flunitrazepam	>90%[1)]
Fluoxetine	15%
Flupentixol	-39%
Fluphenazine	89%
Haloperidol	53%
Hydroxyzine	45%
Maprotiline	44%
Memantine	14%
Mianserin	-17%
Mirtazapine	31%
Nefazodone	70%
Nordiazepam	-111%
Orphenadrine	50%
Oxazepam	-9%
Paroxetine	35%
Perphenazine	71%
Risperidone	7%
Sertraline	67%
Venlafaxine	34%
Zolpidem	10%
Zopiclone N-oxide	72%

[1)] average effluent concentration <LOD

Source: Original data

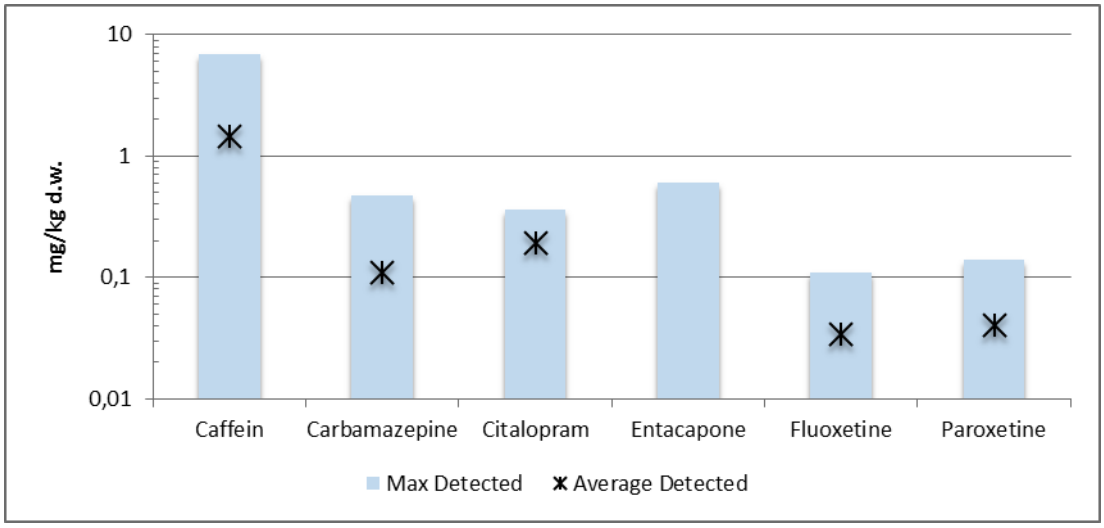

Figure A3.18: The average and maximum concentrations of central nervous systems agents in untreated sludge

Source: Original data

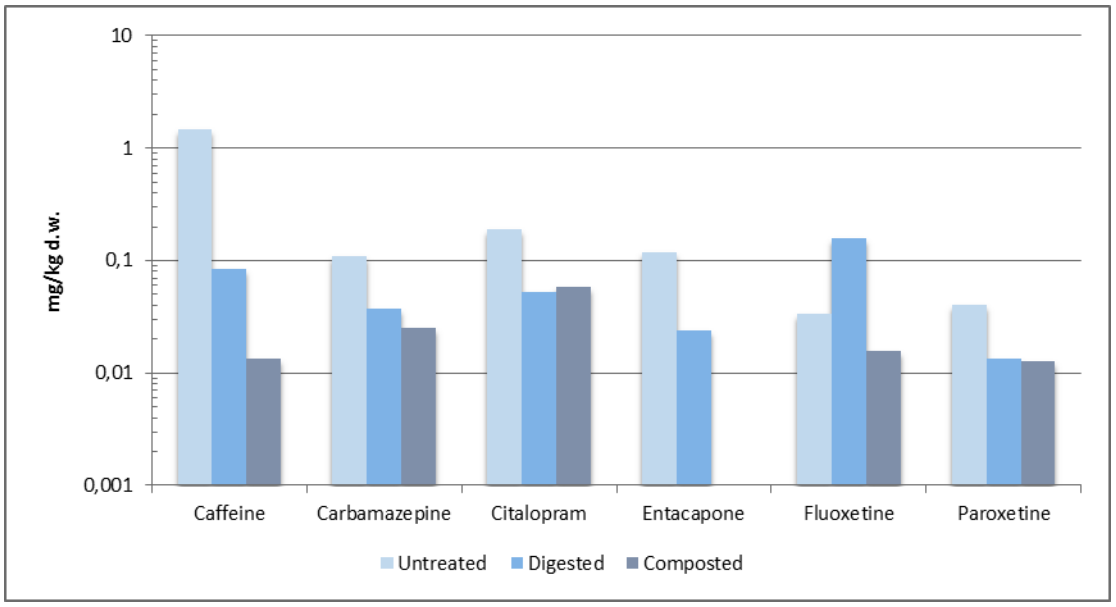

Figure A3.19: The average concentrations of central nervous system agents in untreated, digested and composted sludge

Source: Original data

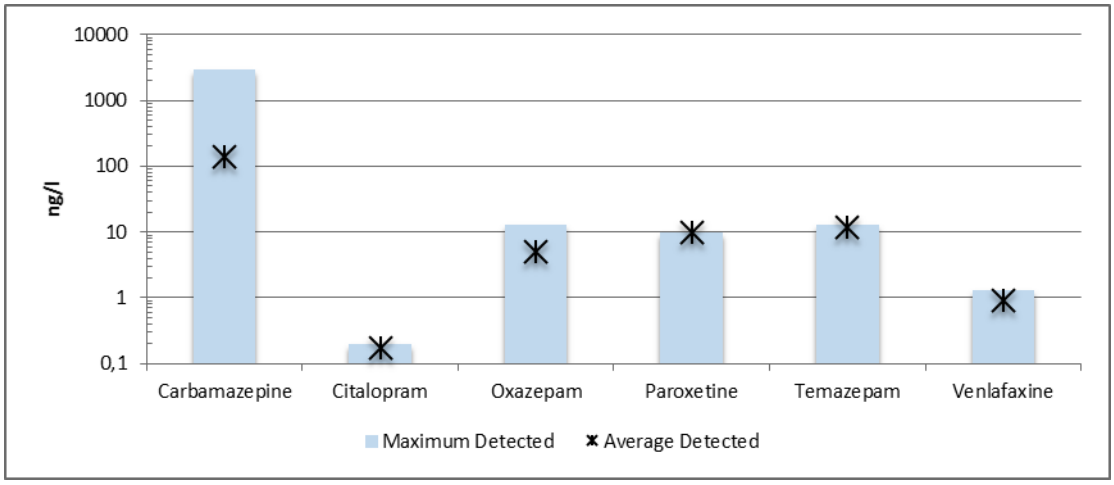

Figure A3.20: The average and maximum concentrations of central nervous system agents in river water samples

Source: Original data

Chemotherapeutic agents and X-ray contrast media

An overview of reported data on pharmaceuticals belonging to the therapeutic group chemotherapeutic agents and X-ray contrast media is presented in Table A3.9.

Table A3.9: Chemotherapeutic agents and X-ray contrast media. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
Amidotrizoic				1645/806	Cyclofosfamide			6	
Iopamidol			6/0	1645/350	Ifosfamide			6	
X-ray contrast media		308/249			Iopromide			6	
					Methotrexate			6	

Source: Original data

X-ray contrast media was only submitted by Germany. No individual compounds were identified but the therapeutic group was reported as total concentrations. In the WWTP effluents, X-ray contrast media was detected at the average concentration of 7.4 μg/l and at the highest concentration of 78 μg/l.

All the sludge concentration measured for X-ray contrast media or chemotherapeutic agents were under the detection limits. In the river water samples submitted by Germany, the X-ray contrast media agents amidotrizoic acid and iopamidol were detected at average concentration of 630 ng/l and 920 ng/l, respectively (Figure A3.21).

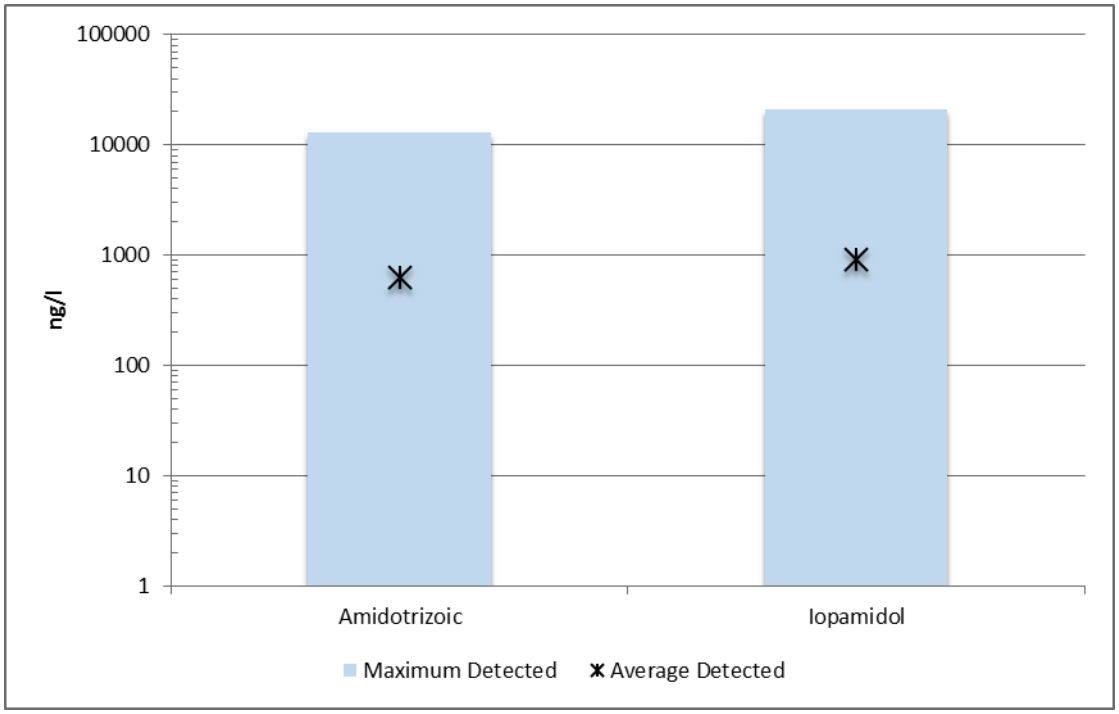

Figure A3.21: The average and maximum concentrations of X-ray contrast media agents in river water samples

Source: Original data

Hormones and hormone antagonists

An overview of reported data on pharmaceuticals belonging to the therapeutic group hormones and hormone antagonists is presented in Table A3.10.

Table A3.10: Hormones and hormone antagonists. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
17α-ethinylestradiol	160/4	273/5	1/11	612/1	Medroxyprogesterone		13		1
17β-estradiol	157/89	270/34	0/11	405/1	Hydrocortisone			6	
Estriol	26/4	64/10	1/11	1/1					
Estrone	148/133	210/127		3/1					
Etonogestrel	11/0	16/11		6/0					
Finasterinde	11/4	16/5		7/0					
Flutamide	11/4	16/2		7/0					
Levonorgestrel	20/0	53/19		8/2					
Megestrol		13/12		1/0					
Mestranol				201/0					
Methylprednisolone			6/1						
Norethindrone	22/15	58/17	2/11						
Progesterone	23/18	77/66	7/9	7/0					
Tamoxifen	11/3	16/6	6/0						
Testosterone			3/6						

Source: Original data

Of all the monitored pharmaceuticals in this category, 15 out of 17 (88%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum concentrations measured in WWTP influents and effluents are presented in Figures A3.22 and A3.23, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.11. Sludge results are presented in Figures A3.24 and A3.25 and river water results in Figure A3.26. Data on the detection limits of the analytical methods are indicated in the figures if the values were reported. At least for 17α-ethinylestradiol, 17β-estradiol and estrone the highest reported LOD were higher than the values reported in other studies and thus more frequent detection could be anticipated for these pharmaceuticals.

In WWTP influents the highest average concentration (0.06 μg/l) was measured for estrone and tamoxifen. The highest maximum concentration (1.2 μg/l) was measured for 17β-estradiol. Additionally, the highest maximum concentration of estrone exceeded 1 μg/l. In the effluents, estrone and etonogestrel were measured at the highest concentration (0.61 μg/l). The highest average concentration of 0.08 μg/l was measured for etonogestrel. The maximum concentrations of levonogestrel, progesterone and tamoxifen also exceeded 0.1 μg/l.

Removal rates of >70% were calculated for 3 out of 9 compounds. The concentration of progesterone was noted to increase during the treatment. It should be remember that 17β-estradiol can break down to estriol in aerobic conditions and thus removal rates of estriol may not be correctly estimated.

Similar to influent and effluent samples, for sludge samples, the LOD values are often so high that the concentrations of hormones and hormone antagonists fall below these values. The highest concentrations in sludge samples were measured for progesterone (0.83 mg/kg d.w.) and 17α-ethinylestradiol (0.69 mg/kg d.w.). It should be noted that for 17α-ethinylestradiol, only one data point exceeding LOD was reported. Generally, all except progesterone and testosterone were sporadically detected in sludge samples. Estrone and progesterone were detected also in digested and composted sludge samples.

In river water, hormones and hormone antagonists were only detected sporadically. This is most probably due to higher detection limits than the occurrence of the compounds in the environmental waters. Estrone was measured at the highest concentration of 20 ng/l.

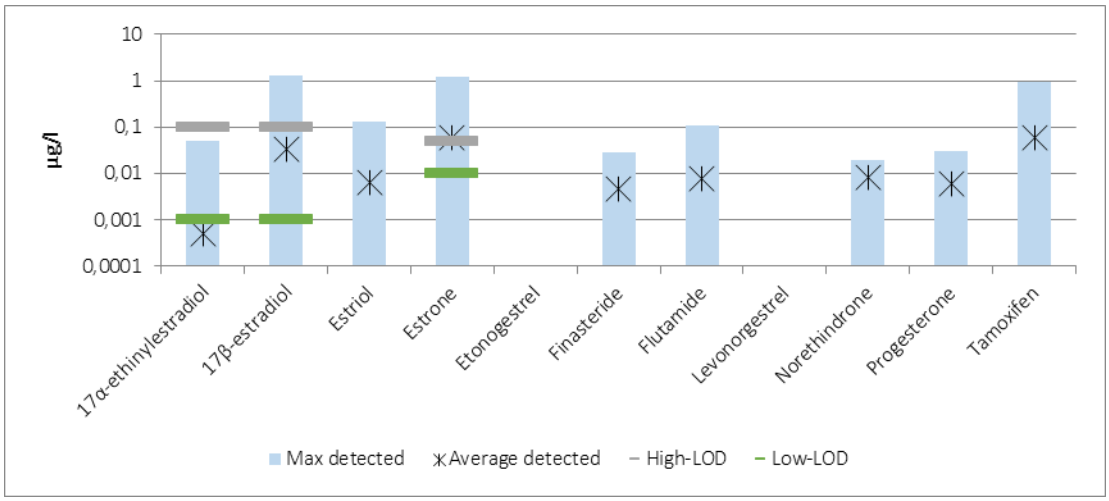

Figure A3.22: The average and maximum concentrations of hormones and hormone antagonists in WWTP influents

Source: Original data

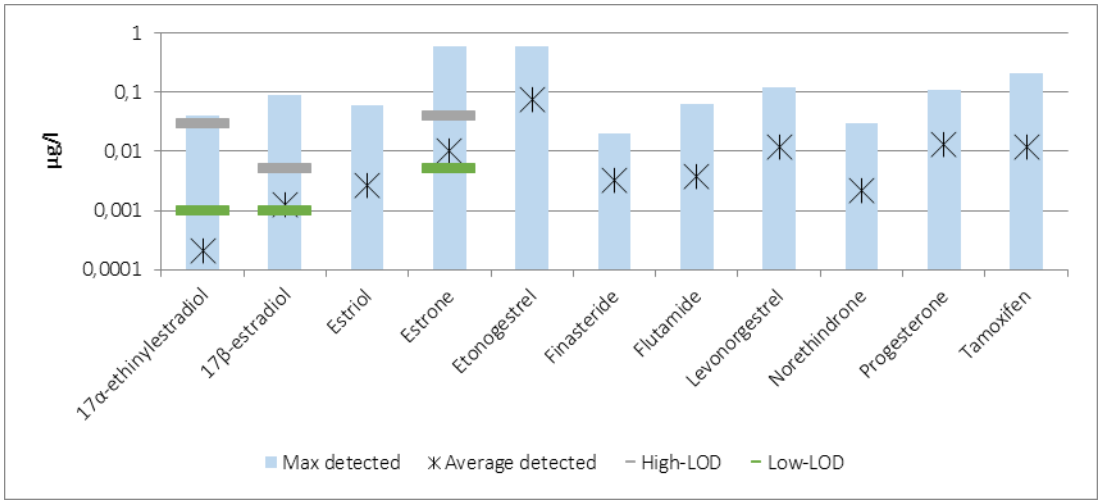

Figure A3.23: The average and maximum concentrations of hormones and hormone antagonists in WWTP effluents

Source: Original data

Table A 3.11. Removal rates of hormones and hormone antagonists in WWTPs

Compound	Average removal (%)
17α-ethinylestradiol	59%
17β-estradiol	62%
Estriol	58%
Estrone	88%
Finasteride	33%
Flutamide	51%
Norethindrone	73%
Progesterone	-60%
Tamoxifen	80%

Source: Original data

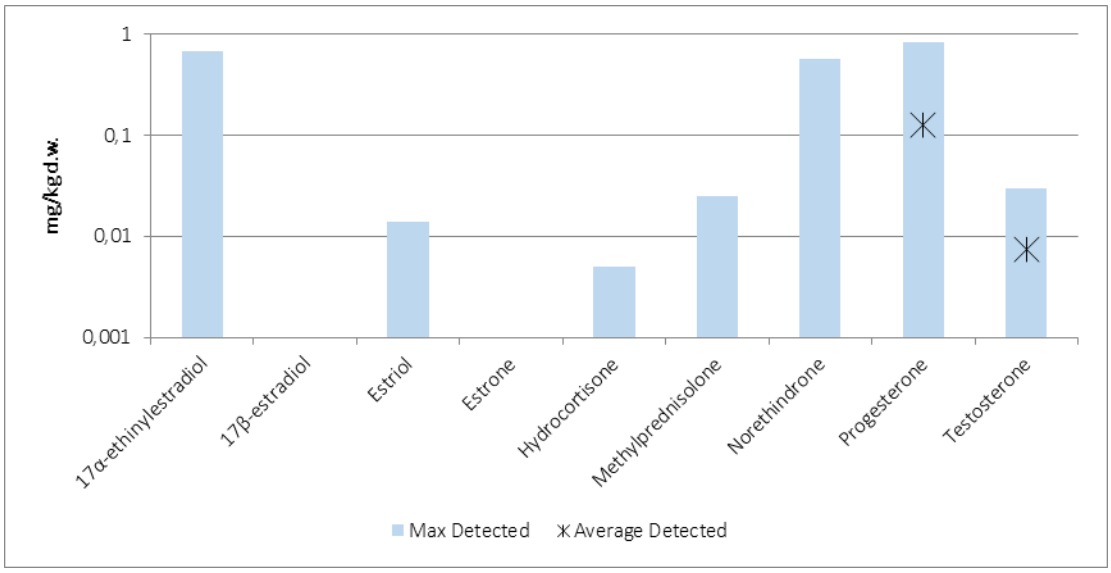

Figure A3.24: The average and maximum concentrations of hormones and hormone antagonists in untreated sludge

Source: Original data

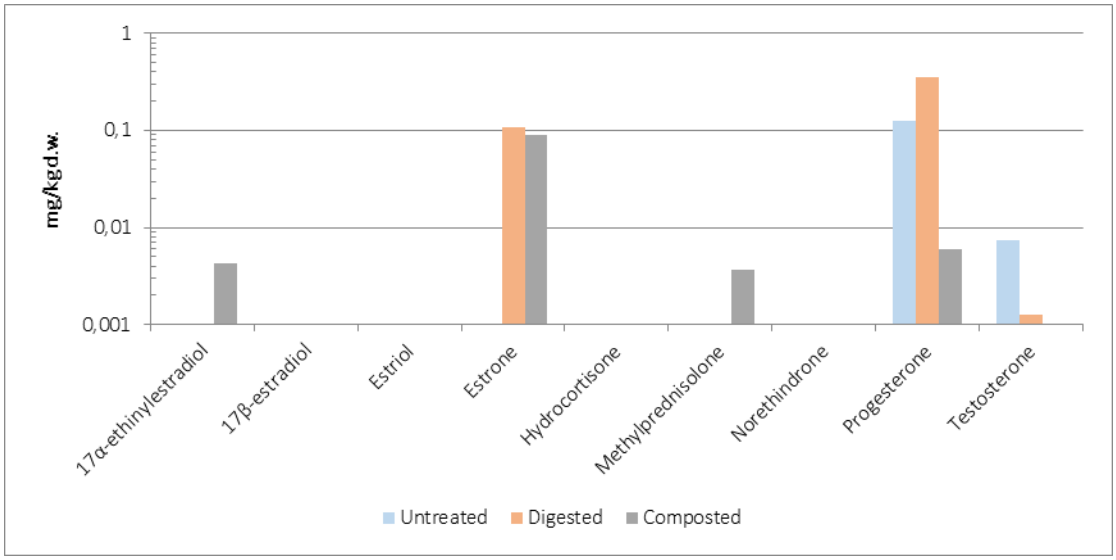

Figure A3.25: The average concentrations of hormones and hormone antagonists in untreated, digested and composted sludge

Source: Original data

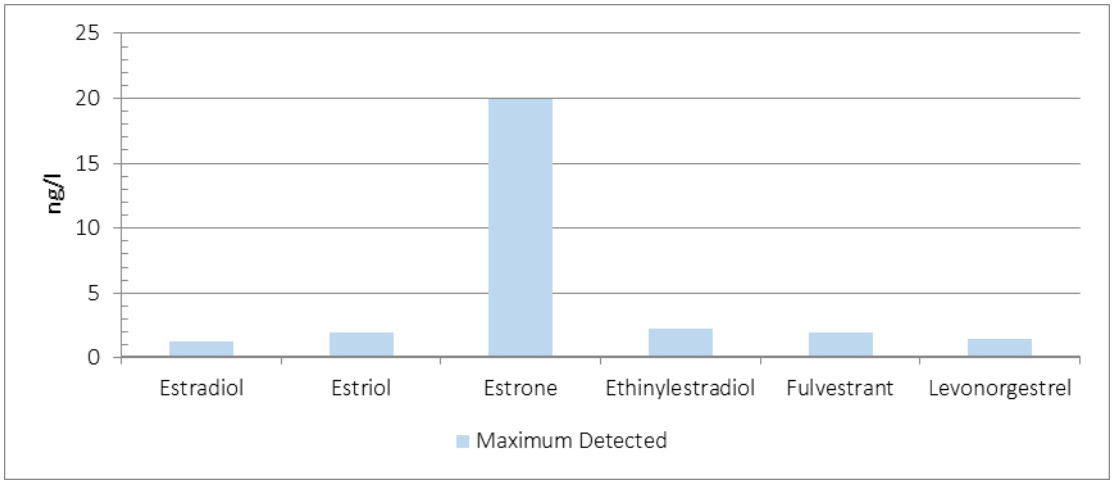

Figure A3.26: The average and maximum concentrations of hormones and hormone antagonists in river water samples

Source: Original data

Metabolic agents and gastrointestinal agents

An overview of data reported on pharmaceuticals belonging to the therapeutic group metabolic agents and gastrointestinal agents is presented in Table A3.12.

Table A3.12: Metabolic agents and gastrointestinal agents. Summary of pharmaceuticals monitored in influents, effluents, sludge and rivers in Baltic Sea countries.

Sampled/detected					Not detected, number of samples				
Pharmaceutical	INFLUENT	EFFLUENT	SLUDGE	RIVER	**Pharmaceutical**	INFLUENT	EFFLUENT	SLUDGE	RIVER
Atorvastatin	8/3	13/2							
Bezafibrate	44/14	44/13	6/0	135/1661					
Cimetidin	115/30	183/58							
Dicycloverin	8/1	13/2		2/0					
Drotaverin	31/20	31/23							
Ezetimibe	8/1	13/0		2/0					
Glimepiride	8/1	13/8		1/0					
Loperamide	8/8	13/13							
Metformin	17/11	31/15							
Ranitidine	39/12	44/12		2/0					
Repaglinide	8/8	13/13		2/0					
Rosuvastatin	8/8	13/8		2/2					

Source: Original data

Of all the monitored pharmaceuticals in this category, 12 out of 12 (100%) were detected in WWTP influent, WWTP effluent, sludge or river samples. The average and maximum concentrations measured in WWTP influents and effluents are presented in Figures A3.27 and A3.28, respectively. Removal rates of pharmaceuticals in WWTPs are presented in Table A3.13. River water results are presented in Figure A3.29. Sludge data was only submitted of bezafibrate and all the values were lower than method detection limits. Data on the detection limits of the analytical methods are indicated in the figures if the values were reported. For the majority of pharmaceuticals, the reported analytical LOD in influent and effluent samples were low enough to detect these pharmaceuticals in wastewater samples.

In WWTP influents the highest average and maximum concentration (0.5 µg/l and 3.2 µg/l, respectively) was measured for bezafibrate. Also the highest maximum concentration of metformin exceeded 1 µg/l. Additionally, the average concentrations of ranitidine and rosuvastatin exceeded 0.1 µg/l. In the effluents, the highest average and maximum concentration was measured for metformin (0.16 µg/l and 0.92 µg/l, respectively). Also the average concentration of bezafibrate exceeded 0.1 µg/l. Generally, the average concentrations of the compounds in effluents were < 0.02 µg/l.

Removal rates of >70% were calculated for five out of 13 compounds. For cimetidine, the removal rate was <20% and for dicycloverin, glibenclamide, glimepiride and loperamide, the concentrations were noted to increase during the treatment. In river waters, only data for bezafibrate was submitted. The maximum detected concentration of bezafibrate was 290 ng/l and average concentration was 53 ng/l.

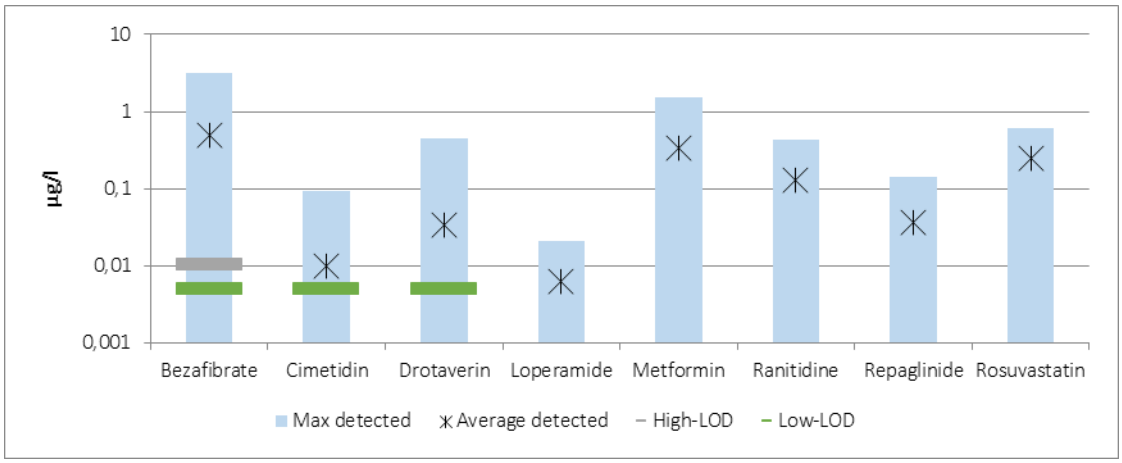

Figure A3.27: The average and maximum concentrations of metabolic agents and gastrointestinal agents in WWTP influents

Source: Original data

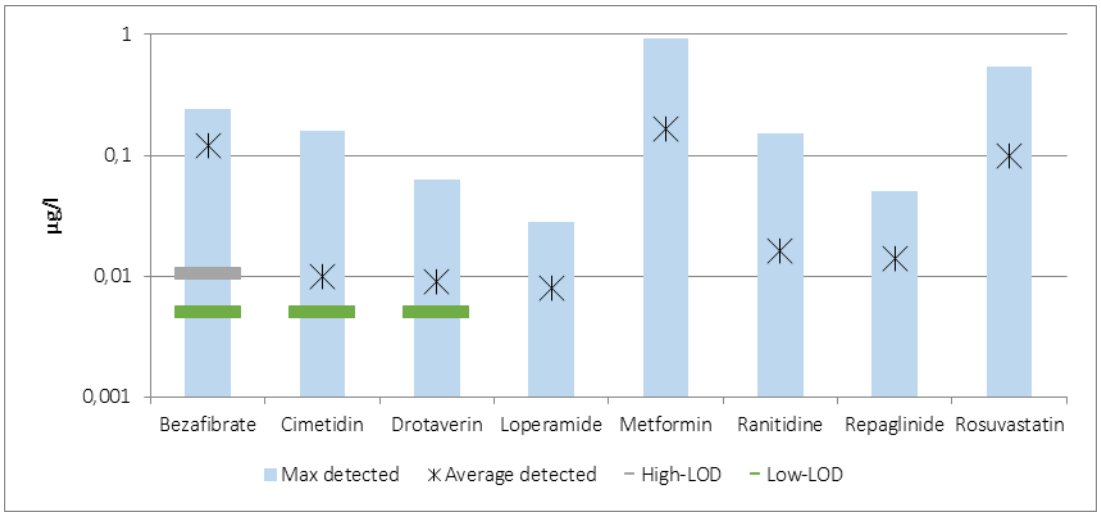

Figure A3.28: The average and maximum concentrations of metabolic agents and gastrointestinal agents antagonists in WWTP effluents

Source: Original data

Table A3.13: Removal rates of metabolic agents and gastrointestinal agents in WWTPs

Compound	Average removal (%)
Atorvastatin	77%
Bezafibrate	75%
Cimetidin	0%
Dicycloverin	-37%
Drotaverin	74%
Ezetimibe	> 90 %[1)]
Glibenclamide	-15%
Glimepiride	-678%
Loperamide	-24%
Metformin	51%
Ranitidine	93%
Repaglinide	62%
Rosuvastatin	60%

[1)] average effluent concentration <LOD

Source: Original data

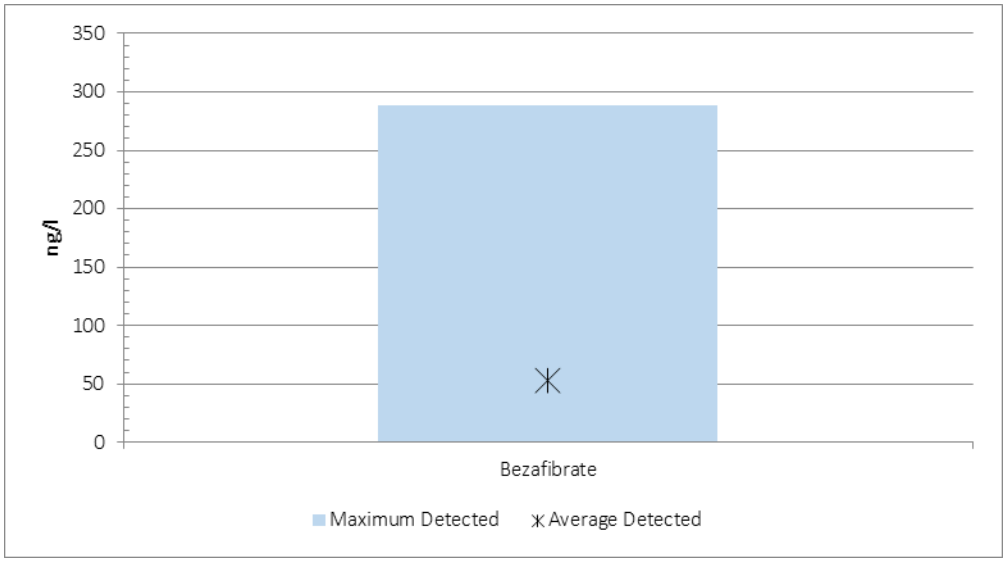

Figure A3.29: The average and maximum concentrations of metabolic agents and gastrointestinal agents in river water samples

Source: Original data

1.1. Estimated loads of pharmaceuticals to the Baltic Sea

With the presently available data it is possible to estimate the loads of pharmaceuticals to the Baltic Sea only for inputs via WWTPs, since there is insufficient data to estimate loads via rivers and surface water runoff. The load figures presented in this chapter have been calculated based on data reported by six out of nine countries in the Baltic Sea catchment. Inputs of pharmaceuticals via manure or sludge spreading to soil have not been estimated. Loads of pharmaceuticals to aquatic environment via surface run-off (originating from manure or sludge spreading) have not been considered in the calculations. A description of the calculation method is provided in Annex 1.4.

The load of 145 measured pharmaceuticals to WWTPs was estimated to be 2,800 tonnes per year. Of these, 650 tonnes per year were estimated to end up in the environment. Since there is no monitoring data available for the majority of pharmaceuticals on the market, it is difficult to estimate the total load of pharmaceutical to the environment from WWTPs. However, a rough estimation can be made that the presented annual load of 650 tonnes accounts for 30% of the total load of pharmaceuticals, meaning that the total load of pharmaceuticals to the environment from WWTPs would be about 2,200 tonnes per year.

By therapeutic groups, the highest load were estimated for cardiovascular agents, followed by central nervous system agents and anti-inflammatory and analgesic drugs (Figure 17).

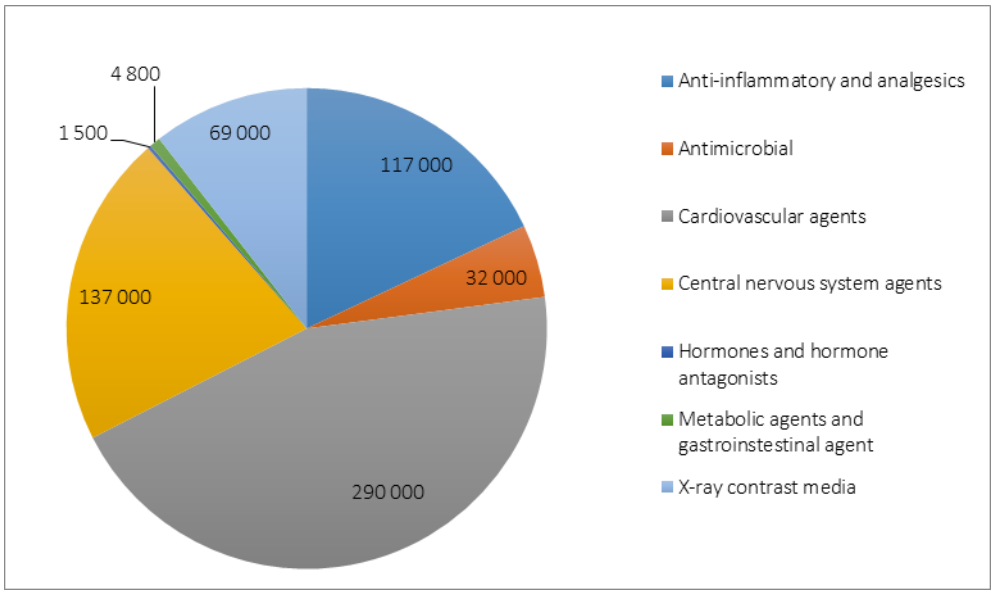

Figure 2: Estimated load (in kg per year) of pharmaceuticals by different therapeutic groups from WWTPs to the environment (based on the reported data).

Source: Original data

Out of the 145 measured pharmaceuticals, 40 were estimated to be discharged from WWTPs at loads of >1,000 kg/year and eight compounds at loads of >10,000 kg/year. Highest loads from WWTPs to the environment were estimated to be for the diuretic furosemide (210,000 kg/year), stimulant caffeine (110,000 kg/year) and for X-ray contrast media (69,000 kg/year) (Figure 18).

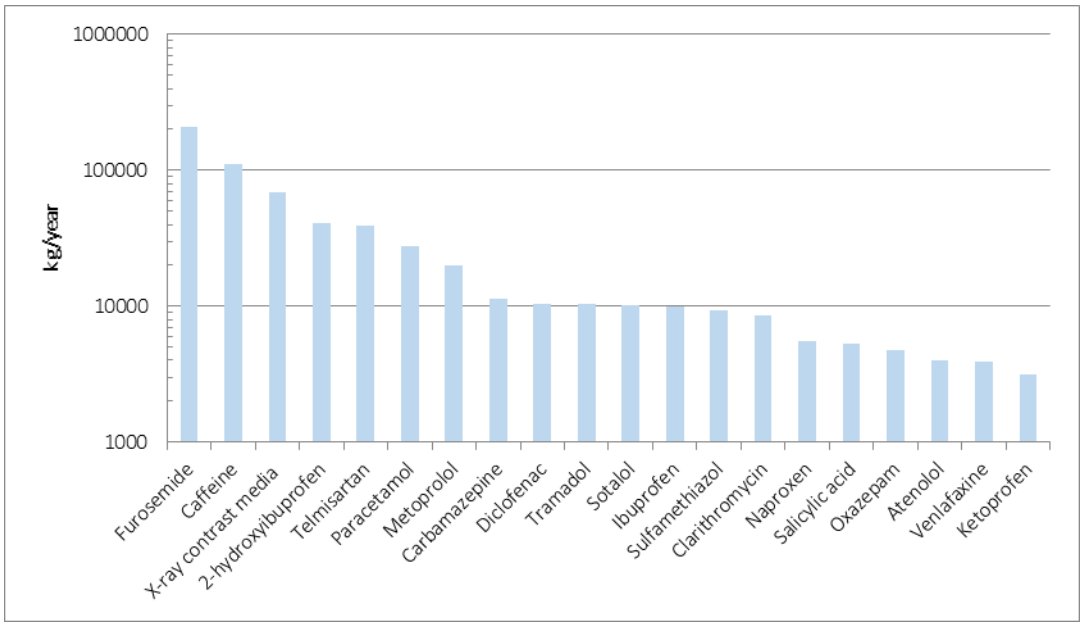

Figure 3: Top 20 pharmaceuticals with highest estimated loads from WWTPs (based on the reported data).

Source: Original data

The loads of prioritized pharmaceuticals from WWTPs to the aquatic environment in the Baltic Sea catchment area were estimated based on the reported data and are indicated in Figure 19. The total annual load of these compounds was estimated to be annually 545 tonnes, which is about 85% of the total estimated load of all the 145 pharmaceuticals assessed.

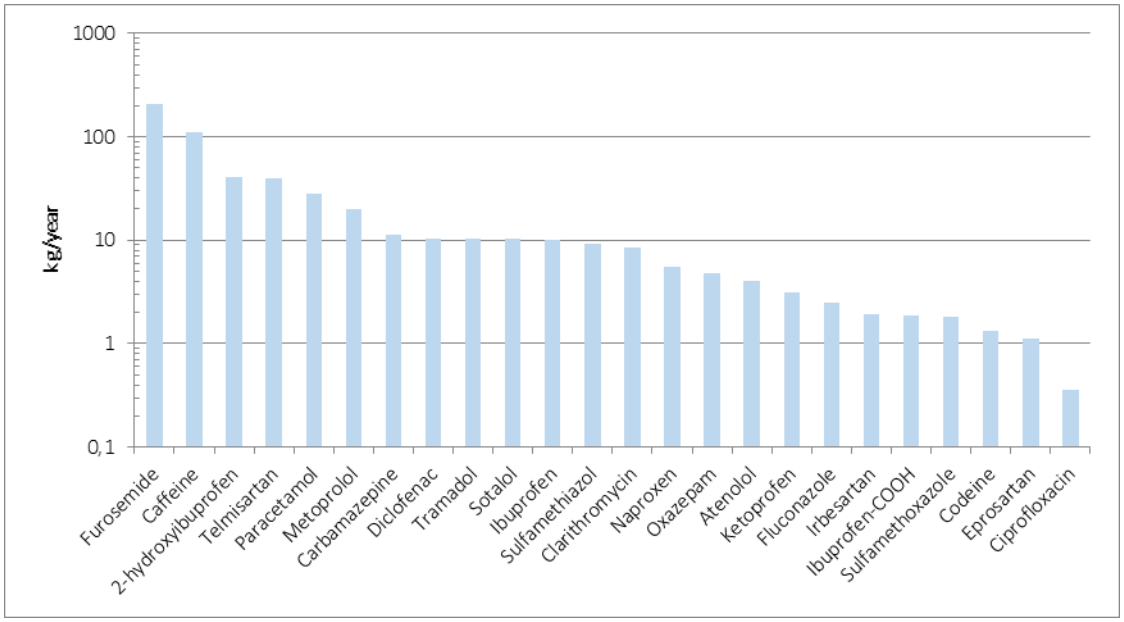

Figure 4: Estimated load of prioritized (or TOP24?) pharmaceuticals from WWTPs to the aquatic environment **in the Baltic Sea catchment area** (based on the reported data).

Source: Original data

Rivers carry pharmaceuticals from inland WWTPs to the Baltic Sea. Since the concentration of pharmaceuticals decreased through biodegradation, photodegradation and sedimentation processes in rivers, the presented load values do not directly represent the amounts of pharmaceuticals entering Baltic Sea. Pharmaceutical data from river water samples were only received from Finland and Germany, making it difficult to make an estimate of riverine loads of pharmaceuticals to the sea.

Annex 4. Data on samples from the marine environment

When pharmaceuticals have been detected in water, the median and maximum concentrations are presented in graphs together with the sensitivity of the analytical methods used. For pharmaceuticals with a WFD assessment criterion detected in water, the assessment criterion has been included in the graphic presentation. Concentration data from sediment and biota samples are not presented in graphs as these data are less suitable for comparison, few data points, highly influenced by choice of sampling method, analytical method, sampled species, age of species, sampled tissue etc.

Figures and maps have been elaborated for pharmaceuticals that are:

- on the EU WFD 'watch list' (Table 2) and have been detected
- of relevance for monitoring according to the Swedish Medical Products Agency (Table 4) and have been detected in >5 measurements
- none of the above but have been detected in >5 measurements.

An overview of all data submitted, including references, from the Contracting Parties is presented in Annex 1.2.

The figures which have no numbers are included into the Status report.

Contents

Methodology for statistical and visual presentation of data

Maps are presented to give an overview of sampling sites, sampling matrices and, samples above the detection limit.

When pharmaceuticals have been detected in water, the median and maximum concentrations are presented in graphs together with the sensitivity of the analytical methods used. For pharmaceuticals detected in water, with an assessment criterion according to the Water Framework Directive, the assessment criterion was included in the graphic presentation. Concentration data from sediment and biota samples are not presented in graphs. This data is less suitable for statistical comparison since sediment and biota data are not as abundant and are highly influenced by choice of sampling method, analytical method, sampled species of biota, age of species, sampled tissue etc.

Maps and graphs are presented for pharmaceuticals that:

- are on the WFD watch list (table 2) and have been detected
- are of relevance for monitoring according to the Swedish Medical Products Agency (table 4) and have been detected
- are none of the above but have been detected in >5 measurements

For more information, see background report Background report on pharmaceutical concentrations and effects in the Baltic Sea (Hallgren and Wallberg, 2016).

Anti-inflammatory and analgesics

An overview of data reported and compiled on pharmaceuticals belonging to the therapeutic group anti-inflammatory and analgesics is presented in Table A4.1below. Of all monitored pharmaceuticals in this category, 11 out of 26 (42%) were detected in environmental samples (water, sediment or biota).

Table A4.1: Summary of anti-inflammatory and analgesic pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not detected in any media are listed to the right along with further information on number of samples analyzed for each media.

Detected, details in tables and figures below				**Not detected, number of samples**			
Pharmaceutical	***Detected, map***	***Concentration, graph***	***Detected, statistics***	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
Codein			Table A4.6	Acetylsalicylic	8	4	6
Diclofenac	Figure	Figure	Table A4.2	Azelastine	2		4
Dihydroergotamine			Table A4.6	Beclomethaso	3	1	5
Ibuprofen	Figure	Figure	Table A4.3	Biperiden	2		
Ketoprofen		Figure	Table A4.6	Bromocriptine	2		
Naproxen	Figure A4.1	Figure	Table A4.4	Budenoside	1		
Paracetamol		Figure	Table A4.6	Buprenorphine	2		4
Phenazone	Figure	Figure	Table A4.5	Dextropropoxy			2
Pizotifen			Table A4.7	Fenoprofen	1		
Tramadol		Figure	Table A4.7	Fentanyl	4		6
Trihexyphenidyl			Table A4.7	Indomethacin	1		
				Norpropoxyph			2
				Propofol	2		2
				Propyphenazo	137		
				Tolfenamic acid	1		

Source: Original data

Table A4.2: Overview of submitted and compiled data on measurements of **diclofenac** in different marine matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected. The WFD assessment criteria for diclofenac in coastal waters and transitional waters is 0.01 µg/l.

Diclofenac	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected/sampled	70/257	0/2	0/10	2/3	67/212	0/9	1/21
Max (µg/l)	**0.054**			*	**0.054**		**0.002**
MD (µg/l)	0.002						
SEDIMENT							
Detected/sampled	4/15		0/10				4/5
Max (µg/kg d.w.)	**3.5**						**3.5**
BIOTA							
Detected/sampled	5/50						5/50
***Max* (µg/kg w.w.)**							**5.2**

* 33 ng/passive sampler (POCIS), not translatable to a concentration per litre

Source: Original data

Table A4.3: Overview of submitted and compiled data on measurements of ibuprofen in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Ibuprofen**	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected/ sampled	31/180	0/2	0/10	1/3	6/137		24/28
Max (µg/l)				*	**0.158**		**0.011**
MD (µg/l)	0.0016						
SEDIMENT							
Detected / sampled	6/18		2/5				4/13
***Max* (µg/kg d.w.)**			**45**				**6**
BIOTA							
Detected / sampled	1/62						1/62
***Max* (µg/kg w.w.)**							**2.4**
*12 ng/passive sampler (POCIS), not translatable to a concentration per litre **including Ibuprofen-OH and Ibuprofen-COOH							

Source: Original data

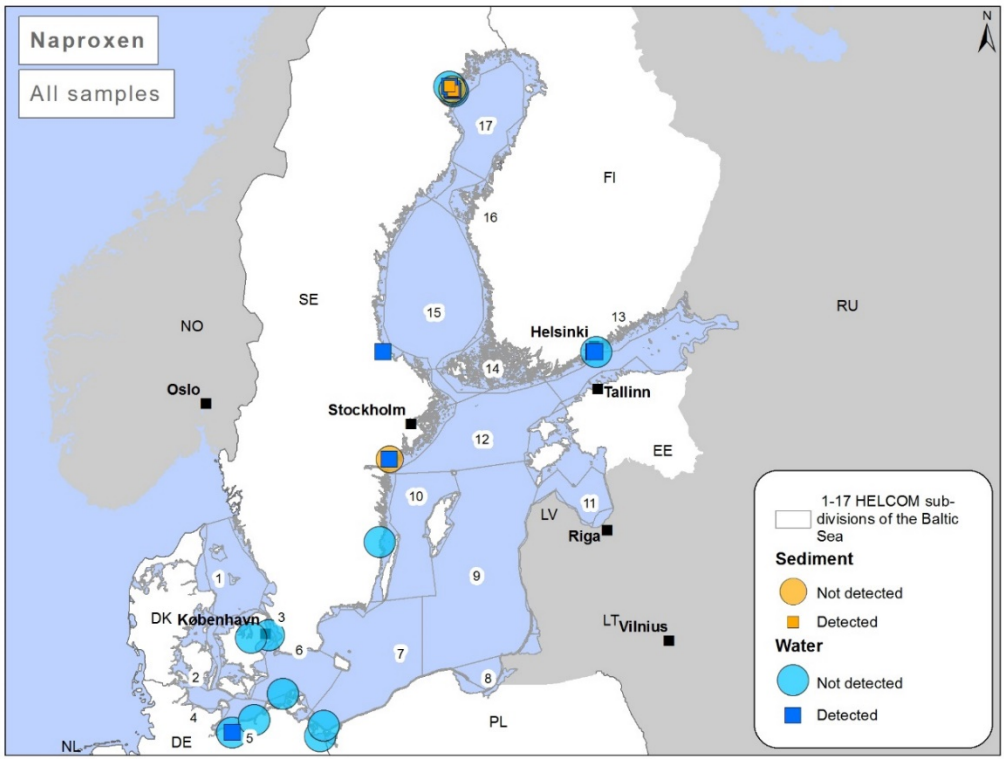

Figure A4.1: Sample locations for the compiled data of naproxen. Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

Table A4.4: Overview of submitted and compiled data on measurements of **naproxen** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Naproxen	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	10/33	0/2		2/3	1/16		7/12
Max (µg/l)				*	**0.014**		
MD (µg/l)	0.0056						
SEDIMENT							
Detected / sampled	2/5						2/3
***Max* (µg/kg d.w.)**							**0.31**
BIOTA							
Detected / sampled	0/10						0/10
***Max* (µg/kg w.w.)**							
*39 ng/passive sampler (POCIS), not translatable to a concentration per litre							

Source: Original data

Table A4.5: Overview of submitted and compiled data on measurements of **phenazone** in water. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Phenazone	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	5/137				5/137		
Max (µg/l)					**0.504**		
MD (µg/l)	0.034						

Source: Original data

Table A4.6: Overview of submitted and compiled data on measurements of **codein**, **dihydroergotamine**, **ketoprofen** and **paracetamol** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Codein	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	0/4	0/2					0/2
Max (µg/l)							
MD (µg/l)							
BIOTA							
Detected / sampled	1/4						1/4
***Max* (µg/kg w.w.)**	**83**						**83**
Dihydro-ergotamine	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected/sampled	0/2						0/2
Max (µg/l)							
MD (µg/l)							
BIOTA							
Detected/sampled	1/4						1/4
***Max* (µg/kg w.w.)**	**32**						**32**
Ketoprofen	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	6/17	0/2		1/3			
Max (µg/l)				*			
MD (µg/l)	0.0017						
SEDIMENT	0/15						
Detected / sampled							
***Max* (µg/kg d.w.)**							
BIOTA							
Detected / sampled	0/10						0/10
***Max* (µg/kg w.w.)**							
Paracetamol	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	4/4						4/4
Max (µg/l)							**0.36**
MD (µg/l)	0.195						
SEDIMENT							
Detected / sampled	4/4						4/4
***Max* (µg/kg d.w.)**							**69**
BIOTA							
Detected / sampled	0/10						0/10
***Max* (µg/kg w.w.)**							
*20 ng/passive sampler (POCIS), not translatable to a concentration per litre							

Source: Original data

Table A4.7: Overview of submitted and compiled data on measurements of **pizotifen**, **tramadol** and **trehexyphenidyl** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Pizotifen	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	0/2						0/2
Max (µg/l)							
MD (µg/l)							
BIOTA							
Detected / sampled	1/4						1/4
***Max* (µg/kg w.w.)**							**0.7**
Tramadol	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	3/4	1/2					2/2
Max (µg/l)		**0.0016**					**0.00069**
MD (µg/l)							
BIOTA							
Detected / sampled	2/4						2/4
***Max* (µg/kg w.w.)**							**179**
Trihexy-phenidyl	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	0/2						0/2
Max (µg/l)							
MD (µg/l)							
BIOTA							
Detected / sampled	3/4						3/4
***Max* (µg/kg w.w.)**							**185**

Source: Original data

Antimicrobial (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote

An overview of data reported on pharmaceuticals belonging to the therapeutic group antimicrobial (antibiotic, antifungal, antiviral, antiparasitic, disinfectant, antiseptic) and antidote is presented in Table A4.8 below.

Table A4.8: Summary of antimicrobial and antidote pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not detected in any media are listed to the right along with further information on number of samples analysed for each media.

Detected, details in tables and figures below				Not detected, number of samples			
Pharmaceutical	***Detected, map***	***Concentration, graph***	***Detected, statistics***	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
Ciprofloxacin				9,10-Anthraquinone	9		
Clarithromycin	Figure A4.2		Table A4.9	Amoxicillin	2		
Clindamycin		Figure		Azithromycin	4		4
Clotrimazole				Chloramphenicol	1		
Erythromycin	Figure A4.2		Table A4.9	Chlortetracyline	51	1	
Ketoconazol				Cloxacilline	1		
Miconazol				Demeclocycline	1	1	1
Norfloxacin				Dicloxacilline	1		
Sulfadiazine				Doxycycline	51	1	
Sulfamethoxazole	Figure	Figure	Table A4.10	Fluconazole	4	3	4
Trimethoprim		Figure		Lufenuron	9		
				Nafcilline	1		
				Naloxone	2		
				Ofloxacin	2		4
				Oxacillin	1		
				Oxytetracycline	51	1	
				Phoxim	101		
				Roxithromycin	4		4
				Tetracycline	51	1	4

Source: Original data

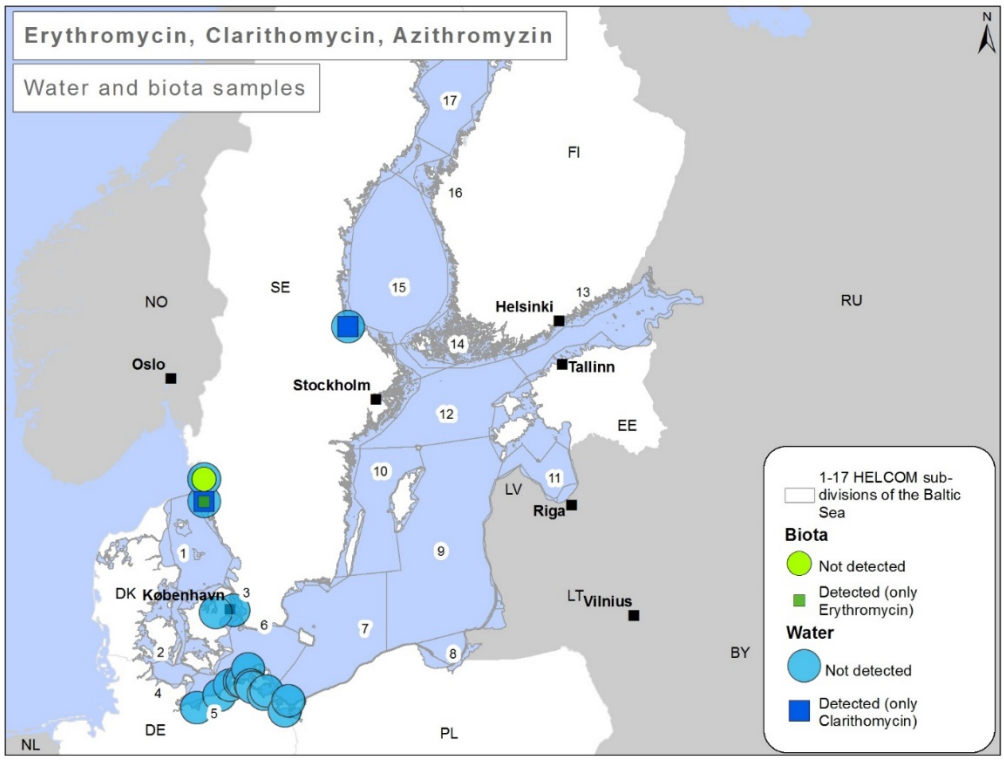

Figure A4.2: Sample locations for the compiled data of erythromycin, clarithromycin and azithromycin. Each presented data point might conceal several measurements conducted on the exact same location. *Source:* Original data

Table A4.9: Overview of submitted and compiled data on measurements of **erythromycin**, **clarithromycin** and **azithromycin** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Erythromycin, Clarithomycin, Azithromycin	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	2/126	0/6			0/116		2/4
Max (µg/l)	**0.00027**						**0.00027**
MD (µg/l)							
BIOTA							
Detected / sampled							1/8
***Max* (µg/kg w.w.)**							**12.7**
MD (µg/kg w.w.)							

Source: Original data

Table A4.10: Overview of submitted data on measurements of **sulfamethoxazole** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Sulfamethoxazole	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	12/140				12/137		0/3
Max (µg/l)	**0.033**				**0.033**		
MD (µg/l)	0.016						
SEDIMENT							
Detected / sampled				4/8			
***Max* (µg/kg d.w.)**				**101**			
BIOTA							
Detected / sampled							1/4
***Max* (µg/kg w.w.)**							**51**

Source: Original data

Cardiovascular agents (blood pressure, diuretics, anticoagulants, antihistamine)

An overview of data reported on pharmaceuticals belonging to the therapeutic group cardiovascular agents (blood pressure, diuretics, anticoagulants, antihistamine) is presented in Table A4.11 below.

Table A4.11: Summary of cardiovascular agent pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not detected in any media are listed to the right along with further information on number of samples analyzed for each media.

Detected, details in tables and figures below				**Not detected, number of samples**			
Pharmaceutical	***Detected, map***	***Concentration, graph***	***Detected, statistics***	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
Acebutolol				Amiloride	2		
Alfuzosin				Amiodarone	2		2
Atenolol				Desloratadine	2		4
Bisoprolol	Figure	Figure	Table A4.13	Diltiazem	2		4
Cilazapril				Fexofenadine	2		4
Clemastine				Flecainide			4
Cyproheptadine				Isradipine	1		
Diphenhydramine		Figure		Losartan	2		
Dipyridamole				Meclozine	2		4
Eprosartan				Promethazine	2		4
Felodipine				Propranolol	139		40
Irbesartan		Figure					
Metoprolol	Figure	Figure	Table A4.12				
Sotalol	Figure	Figure	Table A4.14				

Source: Original data

Table A4.12: Overview of submitted data on measurements of **metoprolol** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Metoprolol	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled		0/2		3/3	18/137		2/2
Max (µg/l)				*	**0,055**		**0,0016**
MD (µg/l)							
BIOTA							
Detected / sampled							0/4
***Max* (µg/kg ww)**							
MD (µg/kg ww)							
*40 ng/passive sampler (POCIS), not translatable to a concentration per liter							

Source: Original data

Table A4.13: Overview of submitted data on measurements of **bisoprolol** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Bisoprolol	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled				3/3	30/137		0/2
Max (µg/l)				*	**0,128**		
MD (µg/l)							
BIOTA							
Detected / sampled							1/44
***Max* (µg/kg ww)**							**102**
MD (µg/kg ww)							
*39 ng/passive sampler (POCIS), not translatable to a concentration per liter							

Source: Original data

Table A4.14: Overview of submitted data on measurements of **sotalol** in water. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Sotalol	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled					3/137		2/2
Max (µg/l)					**0,024**		**0,00024**
MD (µg/l)							

Source: Original data

Central nervous system agents (psychotherapeutic, antiepeleptic, antiparkinson, muscle relaxant)

Table A4.15: Summary of central nervous system agent pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not been detected in any media are listed to the right along with further information on number of samples analyzed for each media.

Detected, details in tables and figures below				Not detected, number of samples			
Pharmaceutical	***Detected, map***	***Concentration, graph***	***Detected, statistics***	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
Alprazolam				7-aminoflunitrazepam			2
Bromocriptine				Amitryptiline	2		4
Carbamazepine	Figure	Figure	Table A4.16	Atracurium besylate	2		4
Chlorpromazine				Biperiden			4
Citalopram		Figure		Bupropion	2		4
Clonazepam				Caffeine			2
Donepezil				Clomipramine	2		4
Duloxetine				Clozapine			2
Fluoxetine				Diazepam	16		4
Haloperidol				Flunitrazepam			6
Maprotiline				Flupentixol	2		4
Memantine				Fluphenazine	2		4
Mianserin				Hydroxyzine	2		4
Mirtazapine				Levomepromazine	2		4
Orphenadrine				N-demethylflunitrazepam			2
Oxazepam	Figure	Figure	Table A4.17	Nefazodone	2		4
Paroxetine				Perphenazine	2		4
Primidone	Figure	Figure	Table A4.18	Risperidone	2		6
Sertraline		Figure		Temazepam	16		
Venlafaxine		Figure		Thioridazine			2
Zolpidem				Zopiclone			2
				Zopiclone N-oxide			2
				Zuclopenthixol	1		

Source: Original data

Table A4.16: Overview of submitted data on measurements of **carbamazepine** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Carbamazepine	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled		0/2		3/3	130/212		2/3
Max (µg/l)				*	**0,073**		**0,0031**
MD (µg/l)							
SEDIMENT							
Detected / sampled							0/1
Max (µg/kg d.w.)							
BIOTA							
Detected / sampled							1/45
***Max* (µg/kg w.w.)**							**141**
*232 ng/passive sampler (POCIS), not directly translatable to a concentration per liter							

Source: Original data

Table A4.17: Overview of submitted data on measurements of **oxazepam** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Oxazepam	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled					9/67		2/2
Max (µg/l)					**0,0019**		**0,00085**
MD (µg/l)							
BIOTA							
Detected / sampled							9/46
***Max* (µg/kg ww)**							**6,7**

Source: Original data

Table A4.18: Overview of submitted data on measurements of **primidone** in water. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Primidone	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled					51/51		
Max (µg/l)					**0,0058**		
MD (µg/l)							

Source: Original data

Chemotherapeutic agents and X-ray contrast media

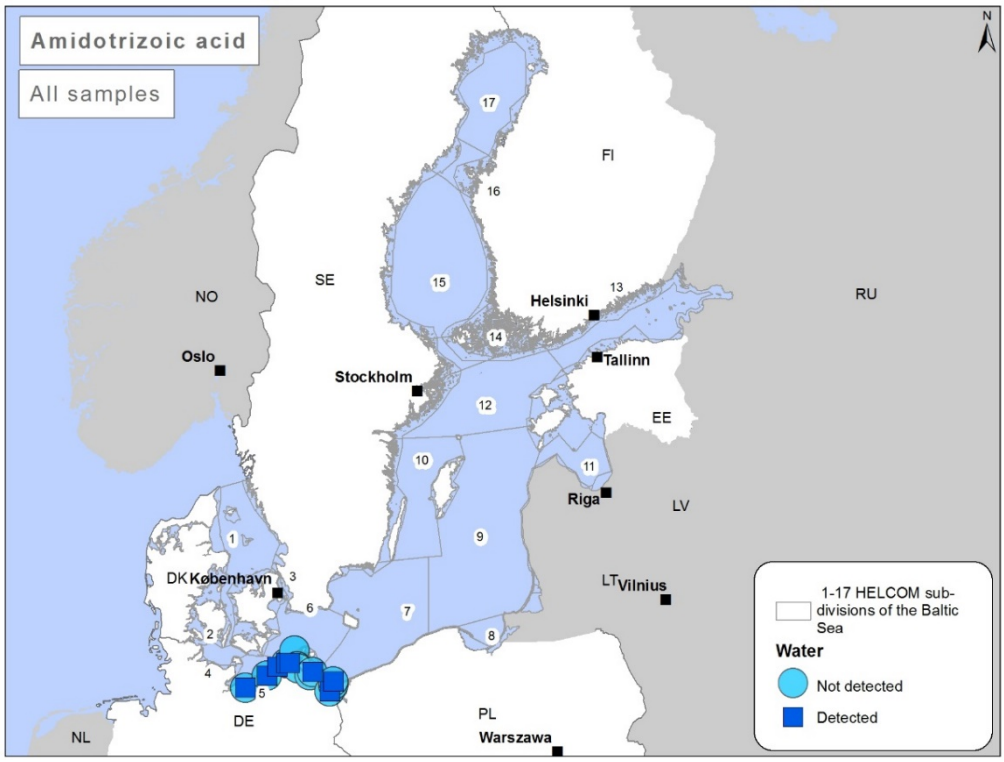

Figure A4.3: Sample locations for the compiled data of amidotrizoic acid. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

Dermatological agents

Table A4.19: Overview of submitted data on measurements of **salicylic acid** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Salicylic acid	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	4/8						4/8
Max (µg/l)	**0.014**						**0.014**
MD (µg/l)	0.012						0.012
SEDIMENT							
Detected / sampled	4/4						4/4
***Max* (µg/kg d.w.)**	**3.9**						**3.9**
BIOTA							
Detected / sampled	0/6						0/6
***Max* (µg/kg w.w.)**							

Source: Original data

Hormones and hormone antagonists

Table A4.20:. Summary of hormones and hormone antagonist pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not detected in any media are listed to the right along with further information on number of samples analyzed for each media.

Detected, details in tables and figures below	Not detected, number of samples			
Pharmaceutical	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
17β-estradiol	Estriol	3	1	
17α-ethinylestradiol	Estrone	1		
Etonogestrel	Finasteride	2		4
Flutamide	Fulvestrant	1		
Tamoxifen	Levonorgestrel	3	1	5
	Medroxyprogesterone	2		
	Mestranol	43		
	Norethindrone		1	
	Norethisteron	2		
	Progesterone	2		

Source: Original data

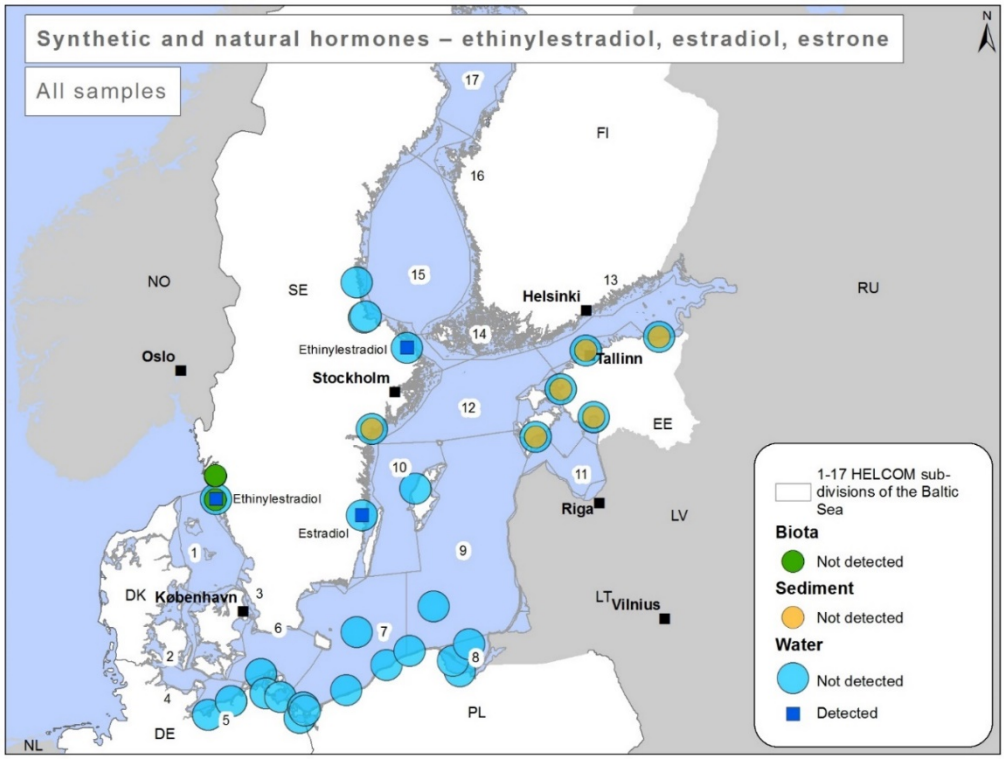

Figure A4.4: Sample locations for the compiled data of 17α-ethinylestradiol, 17β-estradiol and estrone. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

Table A4.21: Overview of submitted data on measurements of **17α-ethinylestradiol, 17β-estradiol** and **estrone** in different matrices. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

17α-ethinylestradiol, 17β-estradiol, Estrone	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled			0/20		0/154		3/24
Max (µg/l)							**0,0011***
MD (µg/l)							
SEDIMENT							
Detected / sampled			0/20				0/2
***Max* (µg/kg d.w.)**							
BIOTA							
Detected / sampled							0/8
***Max* (µg/kg w.w.)**							
*maximum detected concentration is for 17β-estradiol							

Source: Original data

Metabolic agents and gastrointestinal agents

Table A4.22: Summary of metabolic and gastrointestinal agent pharmaceuticals monitored in the Baltic Sea. Pharmaceuticals detected in any sample of water, sediment or biota, are listed in the left column. Pharmaceuticals not detected in any media are listed to the right along with further information on number of samples analyzed for each media.

Detected, details in tables and figures	**Not detected, number of samples**			
Pharmaceutical	**Pharmaceutical**	WATER	SEDIMENT	BIOTA
Atorvastatin	Bezafibrate	139		
Clofibric acid (metabolite of Clofibrate)	Ezetimibe	2		4
Dicycloverine	Fenofibrate	1		
Loperamide	Gemfibrozil	17		
Ranitidine	Glibenclamide			4
Rosuvastatin	Glimepiride	2		4
	Metformin	1		5
	Repaglinide	2		4

Source: Original data

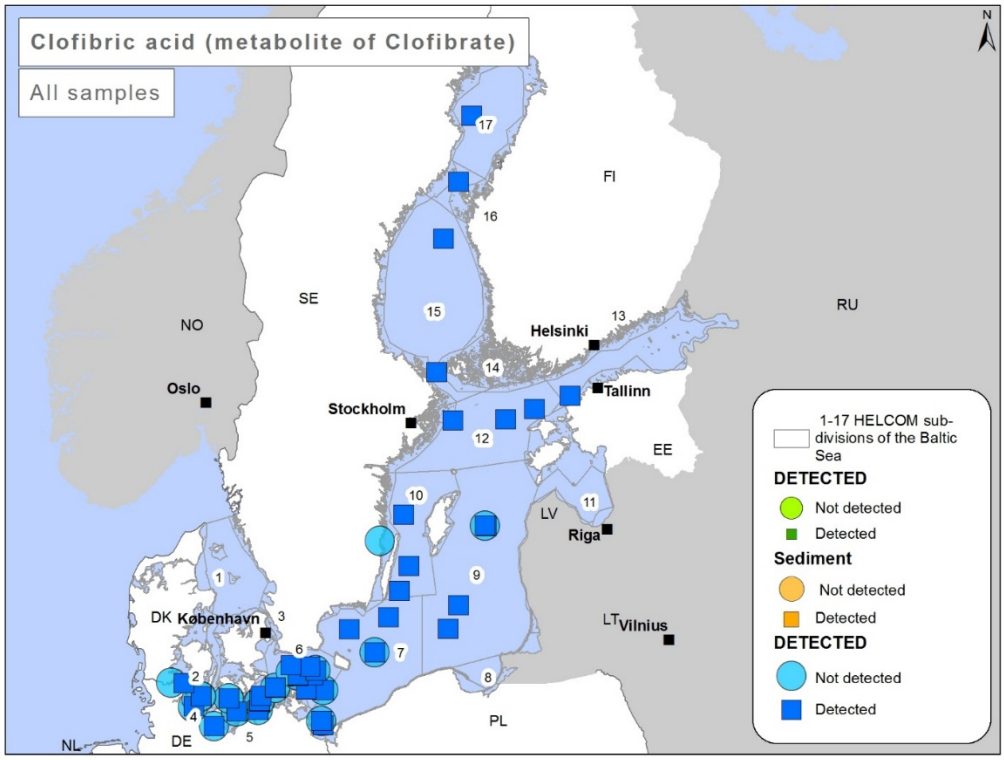

Figure A4.5: Sample locations for the compiled data of clofibric acid. Each presented data point might conceal several measurements conducted on the exact same location. *Source*: Original data

Table A4.23: Overview of submitted data on measurements of **clofibric acid** in water. Number of detected values is presented together with the total number of measurements. Max= maximum value, MD= median among detected.

Clofibric acid	Total	Denmark	Estonia	Finland	Germany	Poland	Sweden
WATER							
Detected / sampled	83/128				83/127		0/1
Max (µg/l)	**0,0004**				**0,0004**		
MD (µg/l)	0.0001						

Source: Original data

Annex 5. Overview of studies carried out on effects of pharmaceuticals in Baltic biota

The tables below provides an overview of the results of different studies concerning the effects of pharmaceutical substances on Baltic Sea species. The results are summarized according to species, test conditions (concentration and duration) and the essential outcome of the studies.

Table A5.1: Effects of **propranolol** on Baltic Sea species. LOEC= lowest observable effect concentration.

Species	Test conditions	LOEC (µg/l)	Endpoints	Ref
Mytilus edulis trossulus	1, 100, 1,000, 5,000 and 10 000 µg/l (1-3 weeks)	1,000	Physiology: Lower byssus strength and lower byssus thread abundance at 10,000 µg/l. Lower SFG* after 2 weeks at 1,000 µg/l. Mortality 16% > 1,000 µg/l (2% in control treatments)	Ericson (2010)
Gammarus spp	100, 1,000 and 5,000 µg/l (1 week)	100	Behavioral: Swimming activity decreased and time to find habitat increased with increased concentration. Feeding rates were more than 2 times higher than the control.	Eriksson (2011)
Fucus vesiculosus	100, 1,000 and 5,000 µg/l (1 week)	5,000	Physiology: Significant dose-/response relationship and the significantly lower GP/R**	Eriksson (2011)
Fucus vesiculosus	10 – 1,000 µg/l (8 weeks)	10	Physiology: Lower GP/R** at 10 µg/l after 4 weeks. Effects increased with increasing concentration and with exposure time. Lower chlorophyll fluorescence after 4 weeks at 1000 µg/l Negative effect on the photosynthesis.	Oskarsson (2012)
Gammarus spp	10 -1,000 µg/l (8 weeks)	100	Physiology: Reduced respiration (4 weeks). Inconsistent results at different concentrations over time.	Oskarsson (2012)
Microcosm study *Ceramium tenuicorne, Mytilus edulis trossulus, Gammarus spp., water and sediment*	1,000 µg/l 100 µg/l (6 weeks)	1,000 µg/l	Algae: Higher carbon content at 1,000 µg/l. At 1,000 µg/l: Mussels: increased mortality Amphipods: Increased reproduction. Algae: Higher carbon content Ecosystem structural change: The effect on the mussel led to a feeding shift from alga to mussel by the amphipods. Better food quality increased reproduction. Less amphipod grazing, and increased nutrient levels in the water was favorable for the alga.	Oskarsson (2012)

**(SFG) Scope for growth: the energy available for normal metabolism*
***(GP/R): primary production (GP) to respiration (R) ratio*

Source: Original

Table A5.2: Effects of **diclofenac** on Baltic Sea species. LOEC= lowest observable effect concentration.

Species	Test conditions	LOEC (µg/l)	Endpoints	Ref
Mytilus edulis trossulus	1, 100, 1,000, 5,000 and 10,000 µg/l (1-3 weeks)	100	Physiology: Lower byssus strength and lower byssus thread abundance at 10,000 µg/l. Lower SFG* after 2 weeks at 100 µg/l Mortality: 14% >1,000 µg/l (2% in control treatments)	Ericson (2010)
Fucus vesiculosus	10, 100, 1,000 µg/l (4 weeks)	>1,000	No significant effects	Oskarsson (2012)
Gammarus spp	10, 100, 1,000 µg/l (4 weeks)	>1,000	No significant effects	Oskarsson (2012)

**(SFG) Scope for growth: the energy available for normal metabolism*

Source: Original

Table A5.3: Effects of a mixture of **diclofenac** (D) and **propanolol** (P) on blue mussels in the Baltic Sea. LOEC= lowest observable effect concentration.

Species	Test conditions	LOEC (µg/l)	Endpoints	Ref
Mytilus edulis trossulus	Mixture exposure 2 weeks	P: 250 D: 750 Total:1,000	Physiology: lower SFG*	Ericson (2010)
Mytilus edulis trossulus	50/50 mixture of diclofenac and propranolol. Total exposure concentration: 20, 200 and 2,000 µg/l. Sampled with increasing distance to a WTP outlet, exposed to the mixture for 3 weeks, and then tested for their physiological response and subsequent recovery from the exposure.	P: 100 D: 100 Total: 200	Physiology: increased effect on SFG (and its components) Mussels collected further from outlet were more affected by the exposure and did not recover to the same extent as mussels closer to the outlet. The authors suggests that the mussels sampled closer to the WTP, have a higher food availability (= improved health status) and/or pre-exposure to natural disturbances, and the test substances, via the WTP effluent.	Kumblad (2015)

**(SFG) Scope for growth: the energy available for normal metabolism*

Source: Original

Table A5.4: Effects of **ibuprofen** on Baltic Sea species. LOEC= lowest observable effect concentration.

Species	Test conditions	LOEC (µg/l)	Endpoints	Ref
Mytilus edulis trossulus	1, 100, 1,000, 5,000 and 10,000 µg/l (1-3 weeks)	1000	Physiology: lower SFG* after 2 weeks at 1000 µg/l Byssus strength = Control treatment Mortality = Control treatments	Ericson (2010)
Gammarus spp	1, 1,000 and 10,000 µg/l (1 week)	> 10 000	No significant effects	Eriksson (2011)
Fucus vesiculosus	1, 1,000 and 10,000 µg/l (1 week)	> 10 000	No significant effects	Eriksson (2011)
Fucus vesiculosus	10, 100, 1,000 µg/l (4 weeks)	> 1000	No significant effects	Oskarsson (2012)
Gammarus spp	10, 100, 1,000 µg/l (4 weeks)	> 1000	No significant effects	Oskarsson (2012)

**(SFG) Scope for growth: the energy available for normal metabolism*

Source: Original

Table A5.5: Effects of **citalopram** on three-spined stickleback in the Baltic Sea. LOEC= lowest observable effect concentration.

Species	Test conditions	LOEC (µg/l)	Endpoint	Ref
Gasterosteus aculeatus	0.15 and 1.5 µg/l (3 weeks)	< 0.15 µg/l (based on mode of action)	Behavioral: Decreased food intake within less than 1 week.	Kellner (2015)

Source: Original