Pharmaceutical consumption patterns in four coastal regions of the South Baltic Sea

Germany, Sweden, Poland and Lithuania

Project MORPHEUS 2017 - 2019
Deliverable 3.1

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Cover photo

Various pharmaceuticals. Photo: Franziska Stoll

Key facts of the MORPHEUS project

MORPHEUS (Model Areas for Removal of Pharmaceutical Substances in the South Baltic) is a project financed by the European Union Interreg South Baltic Programme. The project duration is January 2017 – December 2019, with a total budget of EUR 1.6 million with a contribution from the European Regional Development Fund of EUR 1.3 million. The project has a total of 7 partners from four countries; Sweden, Germany, Poland and Lithuania: Kristianstad University (Lead Partner) – Sweden, EUCC – The Coastal Union Germany – Germany, University of Rostock – Germany, Gdansk Water Foundation – Poland, Gdansk University of Technology – Poland, Environmental Protection Agency – Lithuania and Klaipeda University – Lithuania. The project also has a total of 11 associated partners from these countries. For additional information on the project and activities please visit the MORPHEUS homepage at: www.morpheus-project.eu

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Summary

This report of MORPHEUS Project Partners documents the outcome of WP3 – consumption patterns. Herein, the project aims to identify and quantify the emission of selected pharmaceuticals especially discharged via wastewater of WWTP. A comprehensive data research was performed and prioritized pharmaceutical consumption loads have been calculated for the model areas in Lithuania, Poland, Sweden and Germany. The outcome of this report can be summarized in the following key facts:

1. Consumption data is based on either sales data of wholesalers/pharmacies or data from health care institutions. The unit of consumption is number of reimbursed packages and DDD, respectively.
2. The resolution and data coverage (only partly including OTC, hospital etc.) is country-specific: The best time-resolution was found in Poland (monthly), the best spatial resolution in Lithuania (population group <3000).
3. Country-specific consumption was comparable by a developed value intake load per inhabitant per year.
4. For Swedish and German data, a comparison of different distributing sites of pharmaceuticals was possible (over the counter sales, application in hospitals, prescriptions/pharmacies).
5. For Lithuanian data, the high spatial resolution enabled a potential correlation with the local demographic data in regard of consumption of beta blocking pharmaceuticals.
6. For Polish data, a seasonal variation can be clearly shown for antibiotics.
7. For German data, an accumulation within the river catchment shows that a complete picture of the whole system is essential to understand the actual burden of pharmaceuticals in the environment.
8. Comparing the model areas, all results have been in the same order of magnitude more or less depending on consumption and doses. Metformin and diverse analgesics revealed high intake loads. In general, mostly German intake loads exceed the others which may lies in the fact that the selection of pharmaceuticals is mostly based on German literature and statistics due to availability/accessibility. An adjustment to each country-specific list may lead to other results.
9. Some substances remain unclear: Contrast media and hormones are still a matter of burden to the environment but caused some difficulties during data collection and research.

1 Introduction

"Emerging pollutants present a new global water quality challenge with potentially-serious threats to human health and ecosystems. Pharmaceuticals represent a major group of emerging pollutants found in freshwater and coastal waters. Pharmaceuticals are an important element of modern society and their beneficial effects on human and animal health are widely acknowledged. However, their undesired occurrence and potential effects in the environment are a global emerging concern." (UNESCO and HELCOM 2017) This motivation is the driving force for several international projects, also in the South Baltic Sea area. One of the project is MORPHEUS – Model Areas for Removal of Pharmaceutical Substances. The project aims initially to combine information on upstream pharmaceuticals consumption patterns with estimates of the downstream discharge of pharmaceuticals from a few selected WWTPs located in the coastal regions of Sweden. Germany, Lithuania and Poland (Figure 1). By a top-down approach, the consumption patterns are investigated within WP3. The main objective is to obtain an overview on spatial and temporal patterns of pharmaceutical substances in coastal waters of the different model areas. Following this approach, this report documents the processes and results of Activity 3.1 and 3.2 (Mapping and analyzing the consumption). Firstly, the general parameters are described to achieve a basis for common understanding and how the list of investigated pharmaceuticals was developed. Afterwards, each national analysis regarding the model area is described in detail and finally compared and evaluated regarding uncertainties.

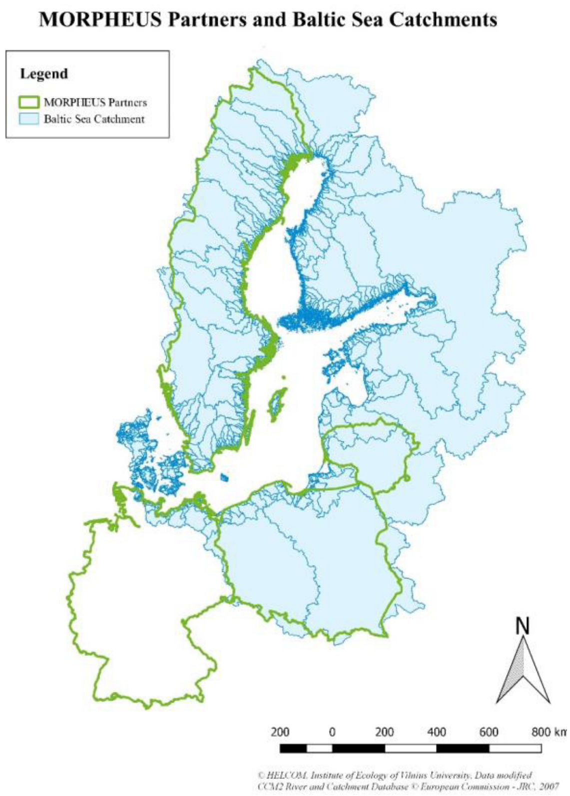


Figure 1 Map of Baltic Sea Catchment and Project Partners of MORPHEUS

2 Sources and Discharge of pharmaceuticals into the environment

The occurrence of pharmaceuticals and their potentially serious threats they pose towards human health and the environment are already widely investigated, but the development of efficient mitigation measures still require further research. Identifying the source and pathways of these emerging pollutants is one of the main concerns. So quantification and localization of input pathway of both veterinary and human pharmaceuticals need to be considered. Figure 2 shows an overview of potential pharmaceutical discharge pathways into the environmental media soil, surface water and groundwater.

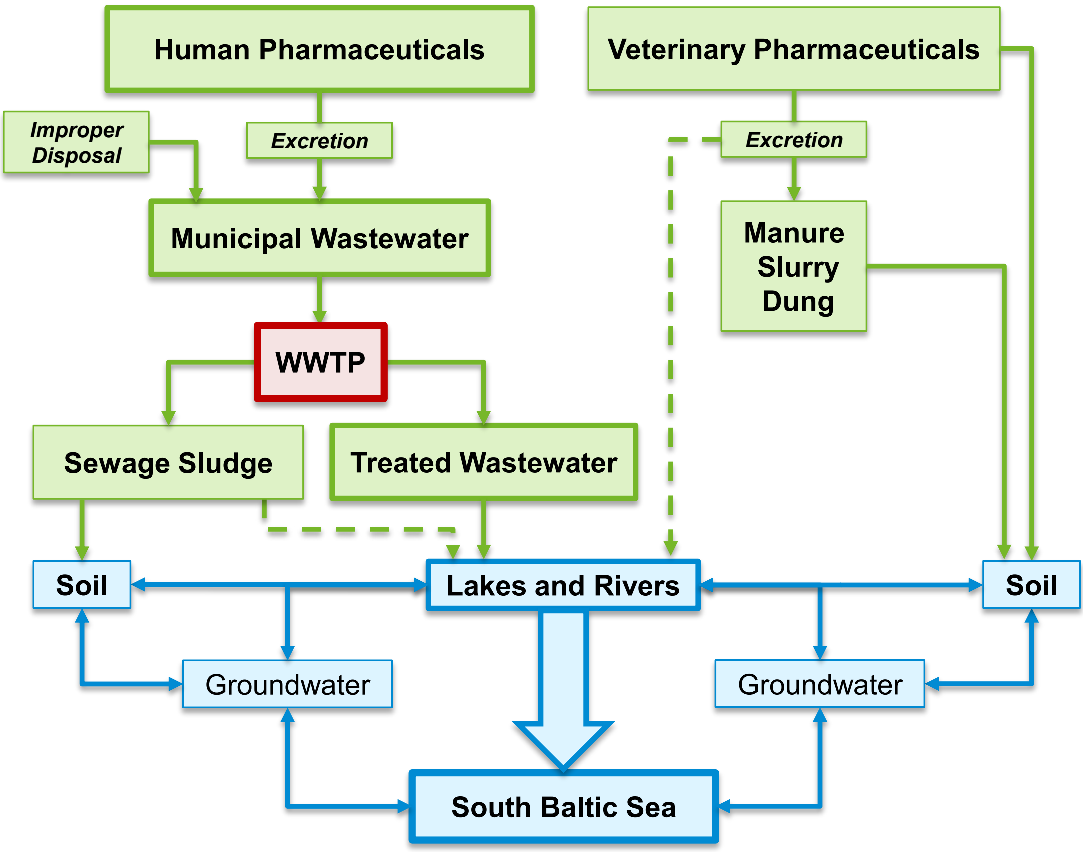


Figure 2 Discharge pathways of pharmaceuticals into the environment, according to Ebert et al. 2014)

According to the focus of MORPHEUS project, only pharmaceuticals applied for human use are investigated in this project. When concentrating on human pharmaceuticals, it is known that the main load is discharged by treated and untreated wastewater into surface water and further accumulating in the Baltic Sea. Since only a few industrial productions of pharmaceuticals are located in the model areas and the connection rate to sewer systems is comparatively high, MORPHEUS focused on the main sources: wastewater treatment plants (WWTP). On the contrary, pharmaceuticals applied in the veterinary area cannot be located that easily since the excretion of animals is usually collected as manure and distributed on agricultural lands, meaning a diffusive source of pharmaceuticals. An additional assessment of veterinary pharmaceutical emissions remains however mandatory.

Previous studies showed that the consumption pattern of human pharmaceuticals cannot be explained by single hot spots such as hospitals, nursing homes etc., but can be matched with the population (number of inhabitants) and data on overall consumption of specific pharmaceuticals. The importance of hospitals as driving factor of pharmaceutical occurrence in the wastewater is varying with the substance (shown in Swedish and German analysis). The specific regional consumption requires a thorough data research which can be combined then with WWTP characteristics, such as real-connected inhabitants and treatment techniques showing different efficacies of pharmaceutical removal. As starting point, this preliminary analysis of consumption pattern allows a good understanding on several aspects: The highly deviating application of pharmaceuticals in each of the countries, the uncertainties in obtaining different data sources as well as different considered group of persons, so that a final comparison of model areas can be elaborated thoughtfully.

3 Selection of representative pharmaceuticals – the MORPHEUS list

3.1 General Parameters applied for Pharmaceutical Characterization

There is a large number of drug classes, active substances and related mechanisms. Well-known classes are for example antibiotics, beta-blocker, antidepressants or painkillers (analgesics). In 1969 the need of a classification system for pharmaceuticals was emphasized. In Europe, a system was established by the European Market Research Association (EPhMRA). In order to adapt this European system at an international level, the World Health Organization (WHO) – Collaborating Centre for Drug Statistics Methodology (WHOCC) modified and extended the EPhMRA-classification. By this, the current anatomical-therapeutic-chemical classification (ATC) was developed. Herein, the drugs are classified in several levels according their characteristics and application areas:

- Level 1: Main Anatomic group (LETTER)
- Level 2: therapeutic/pharmacologic sub-group (TWO DIGITS)
- Level 3: therapeutic/pharmacologic sub-group (LETTER)
- Level 4: chemical/therapeutic/pharmacologic sub-group (LETTER)
- Level 5: Sub-group of chemical substance (TWO DIGITS)

The classification in Level 2,3 and 4 is often adjusted to logical reasons if pharmacological sub-groups seem more useful according to WHOCC (2018). As a result of this classification, each active substance can be coded by numerous ATCs if it is applied for different purposes in human medicine.

In combination with the ATC-codes, a so-called DDD (daily defined dosis) value is defined. "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults." (WHOCC 2018) which is commonly used for pharmaceutical consumption statistics. The DDD is a theoretical value and not necessarily the same as recommended daily dose or prescribed dose. The relation of DDD-consumption numbers and resulting loads can be calculated by the use of the ATC/DDD-Index which provides the conversion factor from DDD to an actual load in grams. Since the ATC/DDD classification system is slightly modified according to different national markets, slight deviations in the numbers may occur (DIMDI 2017).

3.2 Prioritization of pharmaceuticals to be investigated within the project

Within this project, the occurrence of pharmaceuticals in the environment, more precisely in the South Baltic Sea will be investigated. The total number of pharmaceutical substances cannot be analyzed within a single project, so a representative subset of substances was selected. Therefore, several criteria were chosen to form a comprehensive list to be used in MORPHEUS for further consumption pattern analysis.

The first criteria is the legal framework specified in European water policy. A pre-selection of environmentally relevant pharmaceuticals is done by the EU within the watchlist for Union-wide monitoring in the field of water policy (EU decision 2015/495). Whereas including initially four pharmaceuticals, the list was actualized in 2018 up to six mandatory substances which should be monitored (see JRC Technical Report). Moreover, the status report on Pharmaceuticals in the aquatic environment of the Baltic Sea Region published by UNESCO and HELCOM (2017) revealed substances of special interest in the region also covering the South Baltic investigated in this project.

In order to cover the pharmaceutical consumption as well as different characteristics of pharmaceutical substances, a cross-selection concerning active ingredients (ATC-coding) was combined with consumption data from Germany (ranking list of prescription frequency according to active ingredients in 2015, Germany) as well as Sweden, Lithuania (consumption statistics of Baltic States 2015/2016) and Poland if available. A review performed by the German Environment Agency (UBA) in 2011, listed the pharmaceuticals found in the environment by research projects and published case studies. Especially those occurring in the WWTP outflow and surface waters are highly relevant for investigation of human consumption pattern. Additionally, prioritized compounds for environmental concentrations were considered so that the ecologically toxic potentials are included. Another main literature basis was the prioritization of pharmaceuticals of the Swedish Medical Products Agency (SMPA). By comparison with previous projects related to pharmaceuticals discharged into surface waters, such as PILLS and noPILLS, the relevance in other European countries can be underlined. The broad pre-selection was then finally compared with the substances which could be analyzed in the associated laboratory of Kristianstad University, performed in WP4.

As a result, 23 pharmaceuticals were selected initially as shown in Figure 3. During ongoing research in the deviating model areas, the list was adjusted to each country's specific needs and data availabilities.

J – Antiinfectives for systemic use

Amoxicillin
Azithromycin
Ciprofloxacin
Clarithromycin
Erythromycin
Sulfamethoxazole

M – Muscolo-skeleton system

Diclofenac
Ibuprofen
Naproxen

N – Nervous system

Paracetamol
Carbamazepine
Oxazepam
Risperidone
Fluoxetine

G – Genito urinary system and sex hormones

Estradiol
Estrone
Ethinylestradiol

C – Cardiovascular system

Atenolol
Metoprolol
Propranolol
Bezafibrate

A – Drugs used in diabetes

Metformin

V – Various

Iopromid

Figure 3 Pharmaceuticals investigated in the scope of MORPHEUS' consumption patterns

4 Consumption Patterns in the Model Areas

The actual analysis of consumption patterns differs among the countries relating to their given and available datasets of pharmaceutical consumption and the chosen model areas with specific characteristics. To understand the difficulties and uncertainties in the national analysis, the data sources and model areas are described in detail. After presenting the overall outcome of consumption pattern calculations, each national Chapter contains a so-called special issue where the advantages/higher resolutions of the specific data set are applied for potential further investigation and resulting in a better understanding of variations in terms of pharmaceutical consumption data.

In general, there are tax-financed healthcare systems in Northern Europe and Latvia – healthcare systems financed by social security contributions in Germany, Poland and Estonia. The social charter of the European Union emphasizes the entitlement of every citizen to free access to comprehensive and high caliber healthcare, irrespective of income and state of health. As a general rule, healthcare is financed by the public sector in Europe (taxes, social security contributions). In 2009, it covered healthcare expenditure across the spectrum of 72% in Poland to 84% in Denmark, with Latvia as the only exception. Here, the public sector finance accounted for just 60%, with the private sector covering almost 40% (status quo in 2008).

In the period 2003-2009, the Baltic Sea Region did not reflect a general trend towards a rise in private-sector healthcare provision. Since the economic and financial crisis of 2008/2009, private health insurances and top-up insurances are becoming increasingly important, in particular in Poland and the Baltic States. This may lead to changes in pharmaceutical consumption, which are difficult to forecast.

4.1 Germany

In general, Germany is known for a high level of health care but at the same time, reveals the highest amount of invested costs in this sector (more than 10% of BIP). In order to apply the data of pharmaceutical intake for analyzing consumption patterns, it is essential to understand the health care system in Germany. (ScanBalt Report 2016)

In principle, each inhabitant is ensured legally within the statutory insurances. 15.5% of the income goes to the health insurances, whereby one part is also covered by the employer. By this amount, the health care is also covered for children, unemployed people or elderly ones after the so-called solidarity principle. All contributions are going into the health fund which then distributes the financial means over the statutory insurances corresponding to their compilation of insurance members. The so-called Association of Statutory Health Insurance Physicians is responsible for the interaction of medical staff and health insurances which is then supervised by the regional health administrations/ministries. Another opportunity besides the statutory insurance is the private one. Here, the contribution is determined according to age, health status and the spectrum of services which is demanded. The insurance is in principle free of choice, as well as which doctor is consulted or in which hospital the treatment is favorited.

4.1.1 Data sources and availability

Based on the health care structure, one of the main important yearly publication of consumption data within legal insurances since 1985 is the so-called “Arzneimittelverordnungsreport” (Schwabe & Paffrath, 1985ff). This market-research focused report is supported by a scientific institute of a health insurance (WIdO-Wissenschaftliches Institut der AOK) with prescription data. Additionally, the WIdO develops the ATC/DDD-Index for the German pharmaceutical market based on the publication of WHO Collaborating Centre for Drug Statistics Methodology („ATC Index with DDDs and Guidelines for ATC Classification and DDD Assignment“). This adaption is yearly reported under “Amtlicher ATC-Index” and published by the German Institute of Medical Documentation and Information (DIMDI). Thanks to very helpful support of WIdO, a pre-calculated data set was provided for the set of pharmaceuticals investigated in MORPHEUS within the federal-state Mecklenburg-Western Pomerania for the years 2015 and 2016. Hence, each available number of DDD was considered within a sum of each pharmaceutical in the unit kg/year. In detail, each application case (ATC-Code) with noticeable amounts is included which means that also combined pharmaceuticals were pulled out in these calculations. These loads represent the total consumption of insured persons within the federal state in the related year.

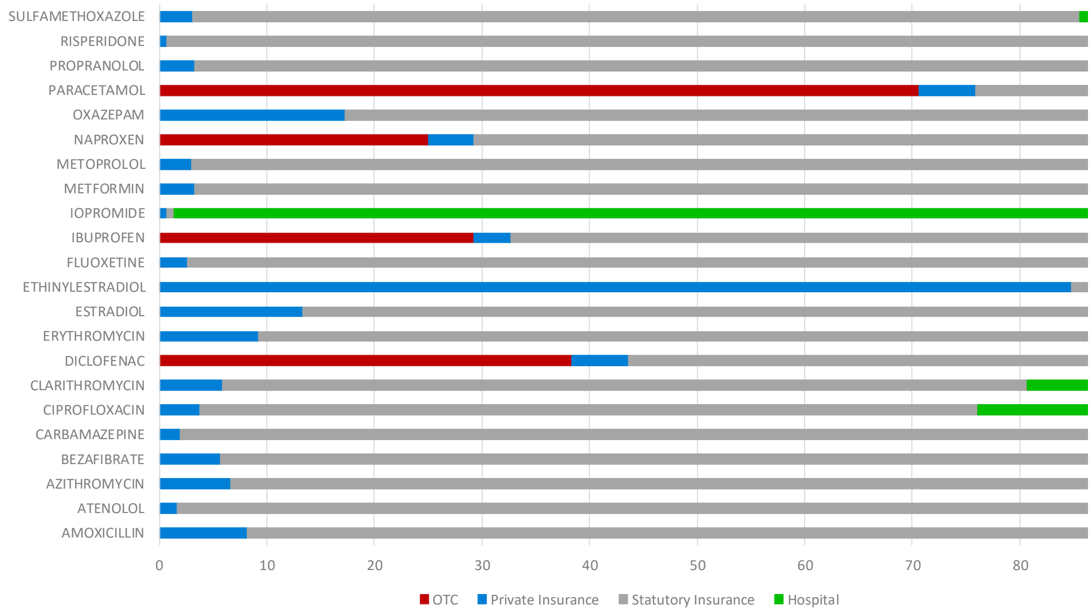


Figure 4 Relation of consumption [%] according to sale sites Over the counter (OTC), private and statutory insurances via pharmacies and hospital of investigated pharmaceuticals in the Federal State Mecklenburg-Western-Pomerania

The data provided by WiDO do not comprise the total consumption of a pharmaceutical but only the amount prescribed for the people within the social insurance system. These data needs to be extrapolated taking other ways of consumption into account. For this, a second database provided by the health data company IQVIA GmbH & Co OHG was used. It includes private prescriptions, over-the-counter-sales as well as data from hospital-pharmacies within the Federal State level. It has to be noted that hospital data was only available at a national scale for data security reasons. Here, a simple downscaling was applied to adjust the proportions to the model area. The unit applied here is slightly different: either counting unit (abbreviated as ZE) or days of treatment

(DOT), similar used as daily defined doses (DDD). Both national and regional data sets from IQVIA were given of the years 2015, 2016 and 2017. Figure 4 shows the exemplary relations of pharmaceutical consumption according to sale sites, prescribed in pharmacies (divided into private and statutory insurances), and hospital and over the counter (OTC) for 22 investigated pharmaceuticals.

In the schematic overview in Figure 5, the general steps to calculate the consumption pattern are shown. In the first level, the two relevant datasets are combined according to their coverage related to sale sites and expected precision regarding pre-calculations, so that a total intake of each pharmaceutical in the unit DDD/a is given. In order to convert the numbers into a real mass load (kg, g or mg), the so-called ATC/DDD-Index [g/DDD] is applied for a simple multiplication. As a result, the total yearly intake of the inhabitants in the Federal State Mecklenburg-Western Pomerania is known. For adjustment to the actual model area and comparisons between model areas, a yearly pharmaceutical intake load per inhabitant is calculated by dividing through the number of inhabitants. Then again multiplied with the number of inhabitants in the model area, a total consumption of each pharmaceutical per year can be produced.

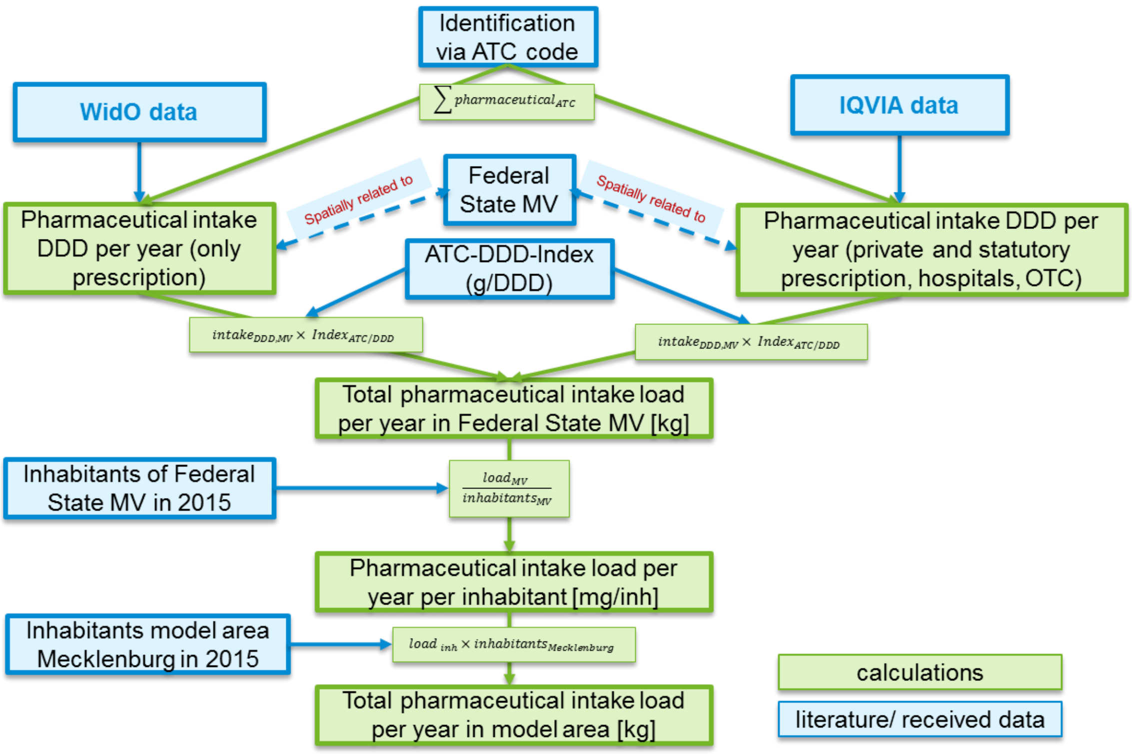


Figure 5 Consumption pattern of German Model Area

4.1.2 Model Area Description

Most of the German Baltic Sea Catchment Area is located within Mecklenburg-Western Pomerania (German: Mecklenburg-Vorpommern) which is one out of 16 Federal States. The model area is defined by both administrative boundaries of the Federal State and the North Sea/Baltic Sea watershed (see Figure 6). Due to the very low population density (only app. 2%

of the total German population) the model area is characterized by a high number of smaller WWTP (app. 450), larger WWTP can be found in coastal towns (such as Rostock).

Hospitals are mainly located in larger cities, while nursing homes can mostly be found in touristic areas, often on the coast. Depending on number of beds, stations and therapeutically focus the applied pharmaceuticals will differ significantly. But these data are publically not available and various efforts to get more precise information were not successful. So, in this study, pharmaceutical hot spots could not be quantified separately. Accordingly, the calculated total consumption is directly related to number of inhabitants and their discharged WWTP inflow. This may lead to an overestimation for WWTP without those infrastructures in the catchment and an underestimation, where large hospitals and other medical infrastructures exist. However, this refers only to the allocation but not to the total consumption in the model area.

It has to be considered that any fluctuations into and out of the considered region are not implemented in the data, for example by tourism. For the German model area, it can be stated that for most areas the tourism has not a large influence. Comparing overnight-stays with permanently staying inhabitants, they represent less than 4% in the Federal State. Nevertheless, the fact that tourism is mostly linked with water (e.g. the coastal area), cities and villages in those areas are influenced by a higher degree than the average within the state.

The number of inhabitants within the model area is estimated to app. 1.2 million by alignment with municipal territories and their corresponding inhabitants according to [source BKG].

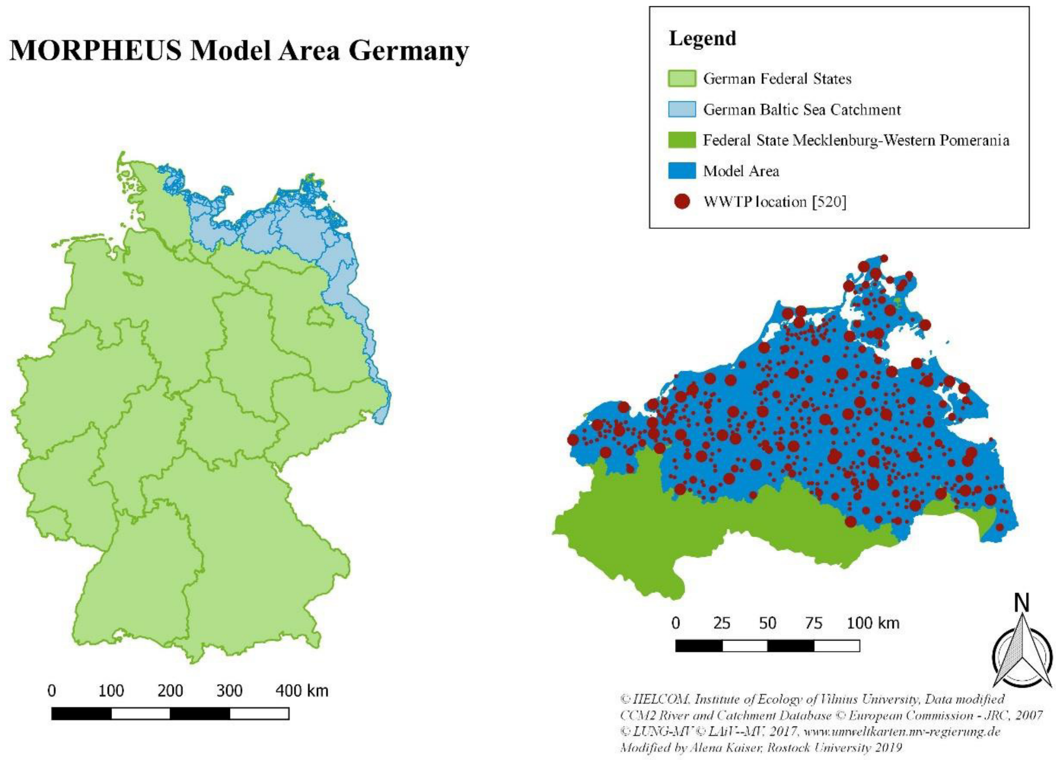


Figure 6 The German model area Mecklenburg within the administrative borders of Federal States as well as the WWTP locations

4.1.3 Consumption Analysis

The evaluation of the two combined data sets enabled to compile a comprehensive list of consumption loads for 22 pharmaceuticals of the suggested list (see Chapter 2). Data for Estrone were not available, neither in the WidO nor in the IQVIA data. With the exception, a mostly complete analysis of pharmaceutical intake in the Federal State Mecklenburg-Western Pomerania is possible. Due to spatial uncertainty, the data related to the Federal State level is the best geographical resolution available when investigating single pharmaceuticals instead of application groups. Table 1 shows the results of consumption analysis for both the total intake of the model area and the intake load per inhabitant in the year 2015.

*Table 1 Results of consumption load calculations of the German model area Mecklenburg [kg] and intake per inhabitant [mg] in 2015 of investigated pharmaceuticals, implementation of IQVIA data marked by **

Pharmaceutical	total intake in 2015 [kg/a]	Intake per inhabitant [mg/a]
Amoxicillin	1,046.06	840.9
Atenolol	64.44	51.8
Azithromycin	101.97	82.0
Bezafibrate	203.25	163.4
Carbamazepine	1,110.49	892.7
Ciprofloxacin*	454.18	365.1
Clarithromycin*	256.02	205.8
Diclofenac*	766.49	616.2
Erythromycin	435.80	350.3
Estradiol	4.11	3.3
Ethinylestradiol*	6.72	5.4
Fluoxetine	14.14	11.4
Ibuprofen*	15,686.53	12,610.4
Iopromide*	24,321.05	19,551.7
Metformin	36,847.20	29,621.5
Metoprolol	2,234.18	1,796.1
Naproxen*	325.18	261.4
Oxazepam*	1.22	1.0
Paracetamol*	1,098.24	882.9
Propranolol	109.08	87.7
Risperidone	3.77	3.0
Sulfamethoxazole*	324.60	260.9

In Figure 7, the consumption loads per inhabitant of the investigated antibiotics are shown. Amoxicillin is a representative antibiotic of the widely applied and prescribed broad-band active penicillin group. In the German model area, it represents with more than one ton per year quantitatively the most relevant antibiotic. Among the remaining substances, Ciprofloxacin and Erythromycin show intake loads above 400 kg in 2015, Clarithromycin and Sulfamethoxazole only slightly less than that. An outstanding low consumption is revealed for Azithromycin (102 kg). In Figure 8, the differences of pharmaceutical intake loads for the cardiovascular system (heart system, beta blocker) are more obvious to see. The mostly applied beta blocker is – by far – metoprolol with about 2100 kg in 2015 within this model area. Intake loads of Propranolol, Atenolol and Bezafibrate range between 64 and 203 kg per year.

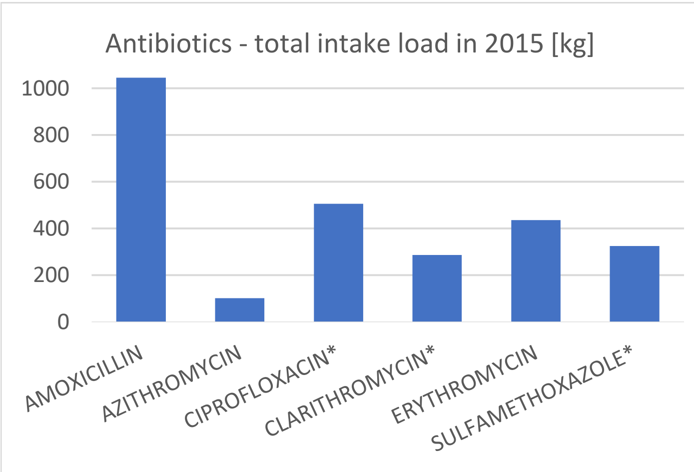


Figure 7 Antibiotics - total intake load within model area Germany in 2015

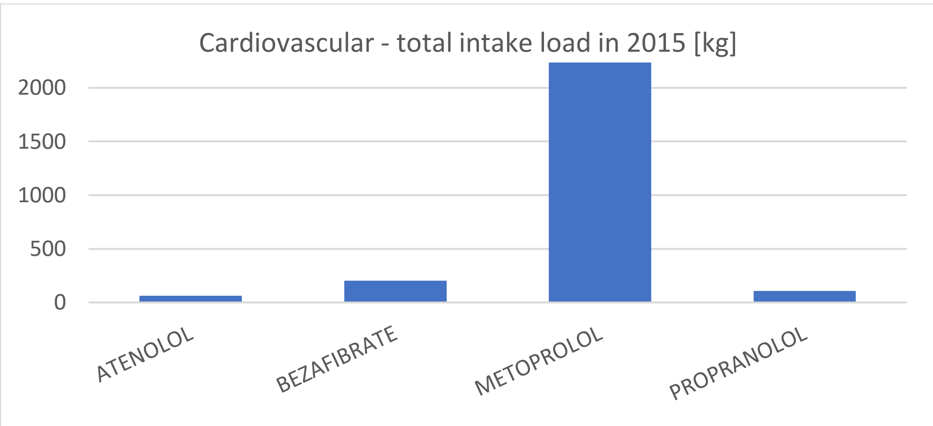
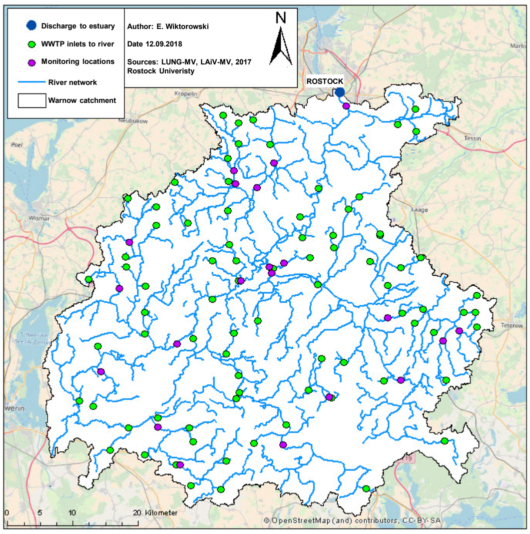


Figure 8 Cardiovascular - total intake load within model area Germany in 2015

4.1.4 Special issue: Accumulation in river catchments

In many situations, a pollution is not only caused by a single point source, especially in a large river catchment. Each of the point sources located within the catchment area poses a risk to the water body, most likely discharging the pollution further downstream, in our case to the South Baltic Sea. The pharmaceutical pollution loads discharged by each WWTP treating domestic wastewaters are accumulating alongside the river flow direction and may cause an increased pharmaceutical burden to the water body and receiving Baltic Sea. In order to evaluate the risk of accumulated pollution loads, the potential WWTP outflow concentrations need to be considered in combination with dilution by river flow. The resulting concentration can be compared then to preliminary limitation values such as the PNEC to identify potential hotspots.

Within the frame of MORPHEUS, such an accumulation model was tested initially in the Warnow catchment which is in the central part of the German Model Area Mecklenburg. Here, the calculated intake loads of pharmaceuticals was proven to be crucial in order to estimate the total burden in the catchment which accumulates downstream. So MORPHEUS consumption data was combined with further river characteristics. However, this analysis requires a large and complete data set both, of the river catchment and the WWTP discharge locations (Figure 9). The Warnow catchment covers 82 mostly small WWTP with known characteristics. 3 pharmaceuticals out of the MORPHEUS consumption patterns have been selected, the result for estimated Carbamazepine concentrations is shown here exemplarily (Figure 10). To verify the calculated concentrations, single monitoring spots in the catchment were identified (see Figure 9, purple dots) where the selected pharmaceuticals have already been measured multiple times.



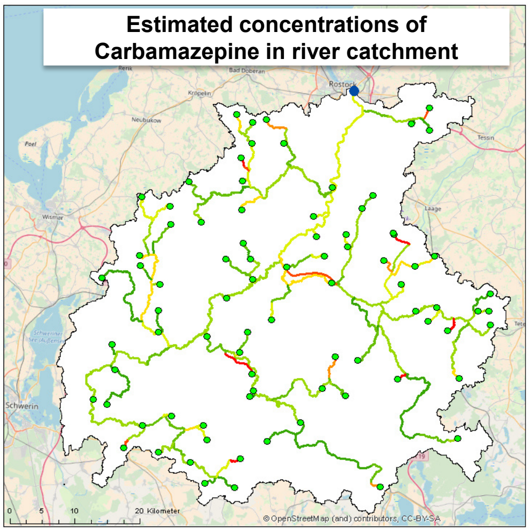


Figure 9 (left) River network of Warnow catchment including WWTP discharge and monitoring locations

Figure 10 (right) Carbamazepine concentration hot-spots in river sections according to yearly mean flow Q, modelled by E.Wiktorowski (2018), masterthesis integrated in project MORPHEUS

The combination of river specific data such as mean flow and number/sizes of discharging WWTP with the consumption (intake load per inhabitant) of Carbamazepine revealed that not only the final outlet of the river towards the Baltic Sea shows high concentrations but also small streams upstream (high concentrations yellow/red, low concentrations green). Especially the dilution factor, meaning the relation of discharged wastewater to natural river water seems to be a driving factor for the pharmaceutical burden – the smaller the stream, the lower the dilution – the higher the pharmaceutical concentrations in these sections. When looking into the Warnow catchment, some upstream sections present higher concentrations but when flowing downstream it gets further diluted. It is also indicated in Figure 10 that the last third of the main river shows medium concentrations (light green/yellow). Here, the discharges are accumulated in the comparable large river. So it can be concluded that for further investigation of consumption pattern and discharges into the environment the background concentration is highly relevant. For a complete investigation of the current status, the whole river network and catchment needs to be considered, especially also in respect to small and medium WWTP discharging here, too. For several pharmaceuticals like some antibiotics, this requires also an expansion of the analysis to veterinary sources and pathways.

4.2 Lithuania

The Lithuanian health care system represents a combination of two different ones, since it is both financed by tax revenues (as in Sweden) and social security contributions (as in Poland and Germany) (ScanBalt Report 2016). The health system is mainly funded through the National Health Insurance Fund (NHIF), which virtually covers the entire resident population (OECD/European Observatory on Health Systems and Policies 2017). The NHIF provides the possibility to insured persons to receive individual health care services and is also responsible for the purchase of specific pharmaceuticals, which are included in the state's approved lists of reimbursable medicines and medical aids: list A, covering pharmaceuticals for specific diseases; list B - active substances or combinations reimbursed for certain social groups, including children under 18 years old, the disabled and pensioners (Latvian State Agency of Medicines 2016). Although most of the public spending on health comes from the NHIF, a substantial share (30% in 2015) of NHIF revenue comes from the state's budget (NHIF 2017) which funds the insurance coverage for the nonworking part of the population.

4.2.1 Data sources and availability

When investigating pharmaceutical consumption in Lithuania, there are two main sources for data. On the national level of Lithuania, the State Medicines Control Agency (SMCA) is collecting and analyzing the drug utilization data comprehensively. Here, monthly reports on pharmaceutical sales from the wholesalers of medical products are collected according to the Pharmaceutical Law and Order of the Head of State Medicines Control Agency (Latvian State Agency of Medicines 2016). These reports include package ID-numbers related to the total number of sold packages to health care institutions such as general and hospital pharmacies or private health care providers. On a regional level, the National Health Insurance Fund collects pharmaceutical consumption data according to the list of reimbursed medicines directly from pharmacies. The regional consumption data is not published in the reports, but can be provided on a case by case basis upon official request. The data specifying the numbers of sold packages in Lithuanian coastal municipalities in the years 2015 and 2016 were officially requested by Klaipėda University (2017-10-10 Nr. JTAPC-17-108) and provided then by the National Health Insurance Fund on 20th of October 2017. Hence, county-wise reports list the reimbursed pharmaceuticals, their ATC-Codes, name of substance, name of brand including the package content (e.g. mg/tablet) as well as the annual number of sold packages. Hereby it is important to mention that especially for smaller population groups and regions, the consumption of pharmaceuticals is allocated to the sale site which does not necessarily mean that it is consumed in the same area/region.

In this project, the regional data provided by NHIF was applied to calculate a total consumption load of the investigated pharmaceuticals within the Lithuanian model area, as shown in Figure 11.

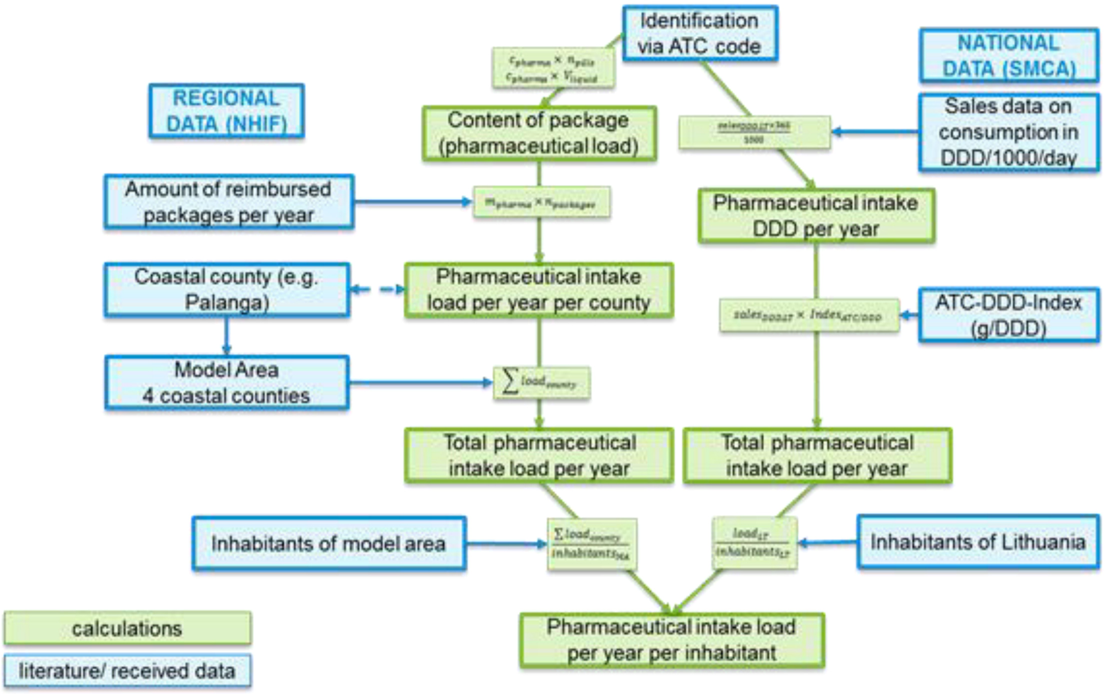


Figure 11 Consumption pattern of Lithuanian Model Area

According to the left path in the calculation scheme, the content of a single package can be determined by the package information related to the pharmaceutical identified via ATC-Codes in the unit of mass (kg or g). This means that the substance concentration is multiplied with the number of doses/pills in each package. Since identical pharmaceuticals are sold by different pharma industries with varying package contents, this multiplication has to be performed individually for each EAN-specific code/product. When the content is determined, the number of reimbursed packages of the NHIF-statistics are applied for a multiplication so that the total pharmaceutical intake load (mass in kg or g) of the related region is the result. The sum of all four total intakes in the selected counties define the total intake load of the model area. Dividing this total load by the sum of inhabitants, a comparable mean value as intake of each pharmaceutical per inhabitant can be estimated.

The year of investigation was 2015 and 2016. In order to implement also sales data on national scale, a comparable pharmaceutical intake load per inhabitant was calculated by SMCA-data. Therefore, the consumption in [DDD/a] is multiplied with the so-called ATC/DDD-Index, and in the following step this intake load is devided by the number of inhabitants in Lithuania. In case, national data reveal higher values than regional, SMCA is seen as the more comprehensive data base in terms of consumption patterns (includes pharmacies, hospital and OTC) and used to extrapolate data of the more precisely spatial resolution of county-wise datasets of NHIF. Therefore, intake per inhabitant results from SMCA can be seen as national average consumption.

4.2.2 Model Area Description

In Lithuania, the project's focus is on the coastal area. Therefore, 5 coastal municipalities were chosen for the model area: Klaipėda city and district area, Kretinga, Neringa and Palanga (Figure 12). In the following, the data of Klaipėda city and district area are merged due to the common NHIF-report on reimbursed pharmaceuticals.

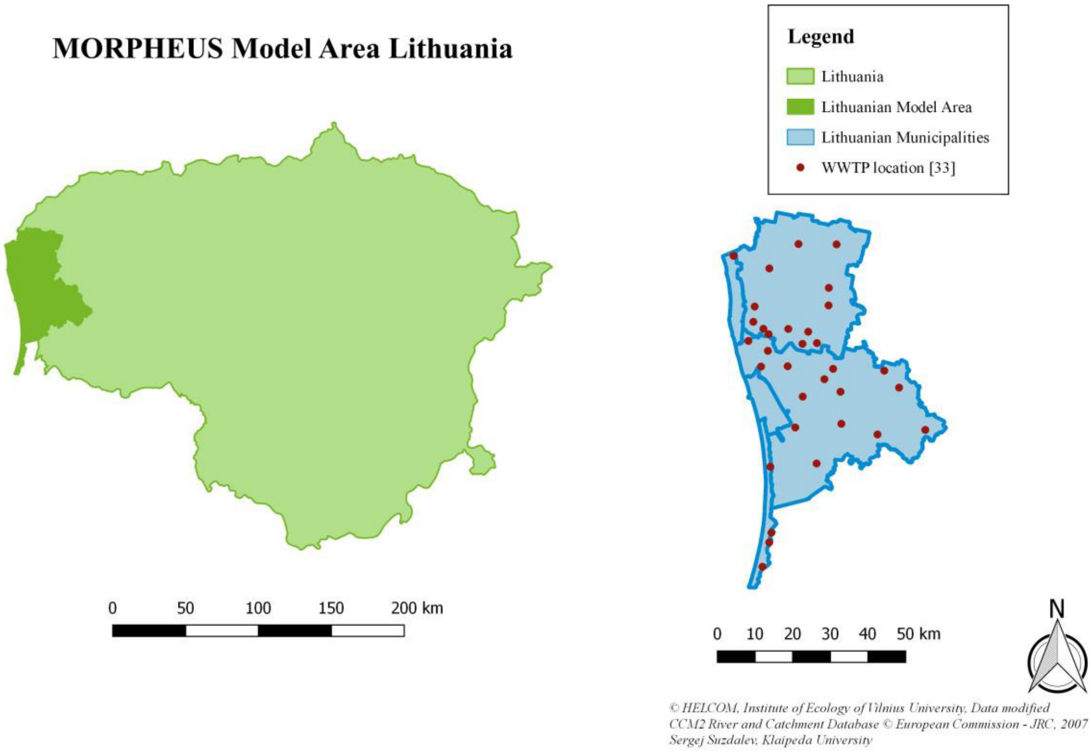


Figure 12 The Lithuanian model area defined by the administrative borders of Municipalities as well as WWTP locations

Table 2 Population of Lithuanian municipalities in the years 2015-2017

Administrative unit (municipality)	**Number of inhabitants**		
	2015	*2016*	*2017*
Klaipėda city	156,141	154,326	151,309
Klaipėda region	52,831	53,459	54,635
Kretinga	39,758	39,121	38,558
Palanga	15,379	15,542	15,449
Neringa	2,879	3,020	3,097
Lithuania (total)	**2,921,262**	**2,888,558**	**2,847,904**

The official number of inhabitants within the coastal municipalities is provided by the Lithuanian Department of Statistics (Statistics Lithuania - a public authority coordinating official statistics in the country) and reported in Table 2. It can be seen that less than 10% of Lithuanian citizens live in the coastal area, while more than half of them directly in the city of Klaipėda. During the last years, the population is decreasing in Klaipėda city and Kretinga, fluctuating in Palanga and increasing in Klaipėda district as well as in Neringa. In the summer season, the coastal area (especially Palanga and Neringa) is highly influenced by tourism so that the actual number of people residing in the municipalities within this time is probably much higher than the registered number of inhabitants.

The wastewater of all inhabitants residing in the investigated municipalities is treated in the 33 municipal WWTPs, which are shown in Figure 12. The largest WWTP is Dumpiai WWTP with a design capacity of > 300,000 PE and treating wastewater of more than half of the coastal population whereby the biggest part comprises inhabitants from Klaipėda city and district. Out of the 33 WWTPs, only Palanga WWTP discharges treated wastewater directly into the Baltic Sea, the remaining into rivers, smaller streams and Curonian lagoon.

4.2.3 Consumption analysis

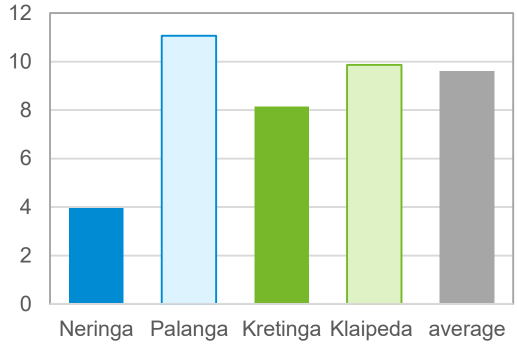
By application of the calculation scheme shown in Figure 12, the total consumption within the Lithuanian model area as well as the intake per inhabitant was calculated for 19 pharmaceuticals in the year 2015. Results are shown in Table 3 below. Extrapolated data from SMCA is marked by *. All of the other results are calculated by application of NHIF data. The counting of EAN-codes indicates how many different packages (not necessarily but often from different companies) have been included in this investigation. This number N varies from 1 up to 23 products. The higher the number the higher the potential spreading in the pharmaceutical market which is normally linked to the demand of health care and its patients. The notation “ATC” indicates that the number of EAN-codes was not included in the dataset but all products listed which have the pharmaceutical substance characterized by ATC-codes as ingredient.

*Table 3 Number of investigated EAN-Codes, results of consumption load calculations of the Lithuanian model area [kg] and intake per inhabitant [mg] in 2015 of the investigated pharmaceuticals, extrapolated data from SMCA is marked by **

Pharmaceutical	N (EAN-codes)	total intake in 2015 [kg/a]	Intake per inhabitant [mg/a]
Amoxicillin*	**20**	259.45	977.3
Atenolol	**5**	1.12	4.2
Azithromycin	**12**	2.03	7.6
Carbamazepine	**8**	54.17	204.1
Ciprofloxacin*	**4**	22.42	84.5
Clarithromycin	**23**	17.63	66.4
Diclofenac*	**14**	68.41	257.7
Erythromycin	**1**	0.24	0.9
Estradiol	**4**	0.00518	0.02
Fluoxetine	**3**	0.62	2.3
Ibuprofen*	**10**	531.37	2,001.6
Metformin	**12**	2,550.14	9,606.2
Metoprolol	**20**	164.26	618.7
Naproxen*	**ATC: 1**	35.94	135.4
Oxazepam*	**ATC: 1**	0.38	1.4
Paracetamol*	**ATC: 1**	257.13	968.6
Propranolol	**1**	1.13	4.3
Risperidone	**18**	0.31	1.2
Sulfamethoxazole	**3**	12.56	47.3

The intake of Metformin as diabetic-related pharmaceutical represents an outstanding high load of more than 2.5 t in 2015. However, also the consumption of Amoxicillin, Ibuprofen, Metoprolol and Paracetamol is calculated with more than 100 kg of intake loads. Regarding Metoprolol, other similar pharmaceuticals in terms of application (cardiovascular system) such as Propranolol or Atenolol are rarely consumed in the Lithuanian model area. Pharmaceuticals of anti-infective use/antibiotics vary from below 1 kg up to nearly 260 kg (Amoxicillin, Azithromycin, Ciprofloxacin, Clarithromycin, Erythromycin, and Sulfamethoxazole). Furthermore, pharmaceuticals applied for nervous system/muscular-skeleton system (including analgesics) show high intake loads for Diclofenac, Carbamazepine and Paracetamol on the one hand (68.41 kg, 54.17 kg, and 257.13 kg respectively) while on the other hand Risperidone, Oxazepam and Fluoxetine are represented by values below 1 kg. Even though the investigated hormone Estradiol reveals a total intake of about 5 g in 2015 it has to be considered that its effective area is in the lower nanogram-range. Therefore, comparison to other pharmaceuticals in this case is difficult.

4.2.4 Special issue: Spatial variation within four investigated counties



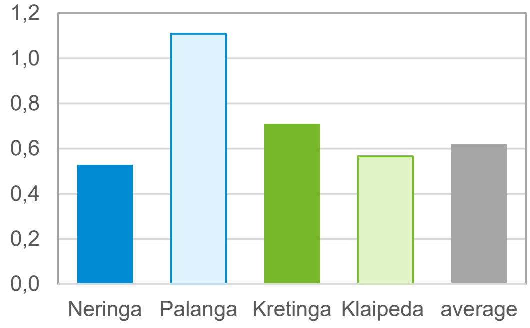


Figure 13 Metformin consumption in g/inhabitant in 2015 related to Lithuanian counties

Figure 14 Metoprolol consumption in g/inhabitant in 2015 related to Lithuanian counties

As shown in Figure 13 and Figure 14, both for Metformin and Metoprolol the consumption per inhabitant is the highest in Palanga. Beta-blocking substances are mostly consumed by elderly people. This correlates with the demographic structure of Palanga which is characterized by a relatively higher number of elderly people in comparison to other municipalities (Table 4).

Table 4 Population and distribution by age of Lithuanian Counties in 2015

Administrative unit of Lithuanian coastal area	Number of inhabitants in 2015	Number of inhabitants by age, %			
		> 30	> 60	> 70	> 85
Neringa municipality	2,879	67	19	9	1
Palanga municipality	15,379	70	29	16	3
Kretinga region municipality	39,758	65	24	14	2
Klaipėda district municipality	52,831	64	20	11	2
Klaipėda city municipality	156,141	66	24	13	2

The low consumption loads in Neringa may be explained both by the relatively lower amount of inhabitants (also the number of elder persons) and low number of pharmacies where pharmaceuticals can be sold. The pharmaceuticals offer and amount of medical services is much higher in the city of Klaipėda, this can also be the reason why inhabitants from Neringa buy more medical products in Klaipėda city.

4.3 Poland

In central Europe Poland is the largest country considering both population (38.1 million) and area (312,685 km²). Since 1989 Poland is a democracy with constant economic growth. At the same time the transition period of the 1990s shows a substantial improvement in the health status of the population. Average life expectancy at birth reached 80.2 years for women and 71.6 years for men in 2009. (Panteli and Sagan 2011)

Based on the Constitution of 1997 requirements all citizens have the right to equal access to health services financed from public sources (from health insurance contributions and from state and territorial self-government budgets). The system of compulsory health insurance is covering approximately 98% of the population (Panteli and Sagan 2011). In general, the Polish statutory health care provision is funded from social contributions of insured inhabitants and employers, similar to the German system. The National Health Fund (NHF) (pl: Narodowy Fundusz Zdrowia, NFZ) is responsible to manage this statutory health care provision by concluding agreements with service providers (Panteli and Sagan 2011, Nieszporska 2017). On authority level, the National Ministry of Health decides on the extent of the health care services, e.g. a detailed list of financed pharmaceuticals which is valid for all 16 voivodeships in Poland. The local governments are responsible for identifying health needs of their citizens and planning the supply of health services. All employed are insured and obliged to contribute a pay-rate of 8.5%. However, nearly 24% of the health care costs are covered by self-paying private households (ScanBalt Report 2016).

According to Central Statistical Office data, pharmaceuticals were used by 54% of the population in 2004 and 71% in 2009 (GUS 2010). Excess prescribing of pharmaceutical was observed inter alia in 2009 and it contributes to the increasing trend in pharmaceutical consumption. Thus Poland was placed among the countries with the highest level of pharmaceutical consumption per capita in Europe. (Panteli and Sagan 2011)

4.3.1 Data sources and availability

Pharmaceutical consumption data in Poland was obtained in the National Health Fund (NHF) which collects and monthly publishes information on the amount of refunds and the amount of reimbursed drug packages, foodstuffs for particular nutritional uses and unit medical devices, along with the EAN code or another code corresponding to the EAN code. In this project data for the Pomerania Voivodeship was received from NHF for the special request.

Data was accessed in excel format where the name of the pharmaceutical products, corresponding EAN-code, information on content (amount of active substance, number of pills/volume in ml) and number of sold packages related to each month was listed. With this information, it was possible to calculate a total load of the investigated pharmaceutical per related package (meaning mass in kg or g pharmaceutical per package multiplied with number of sold packages) which is then summed up, either to monthly or yearly values. Divided by the number of considered inhabitants in the model area, the consumption per inhabitant per month/year is calculated and applied for any kind of breaking down to sub-regions such as the defined model area within the Pomeranian Voivodeship. Figure 15 shows the calculation path proceeded to determine a total pharmaceutical intake load within the model area as well as a pharmaceutical intake load per inhabitant.

Both values are related to the year of investigation 2015. Data on population has been obtained from Central Statistical Office (GUS 2017).

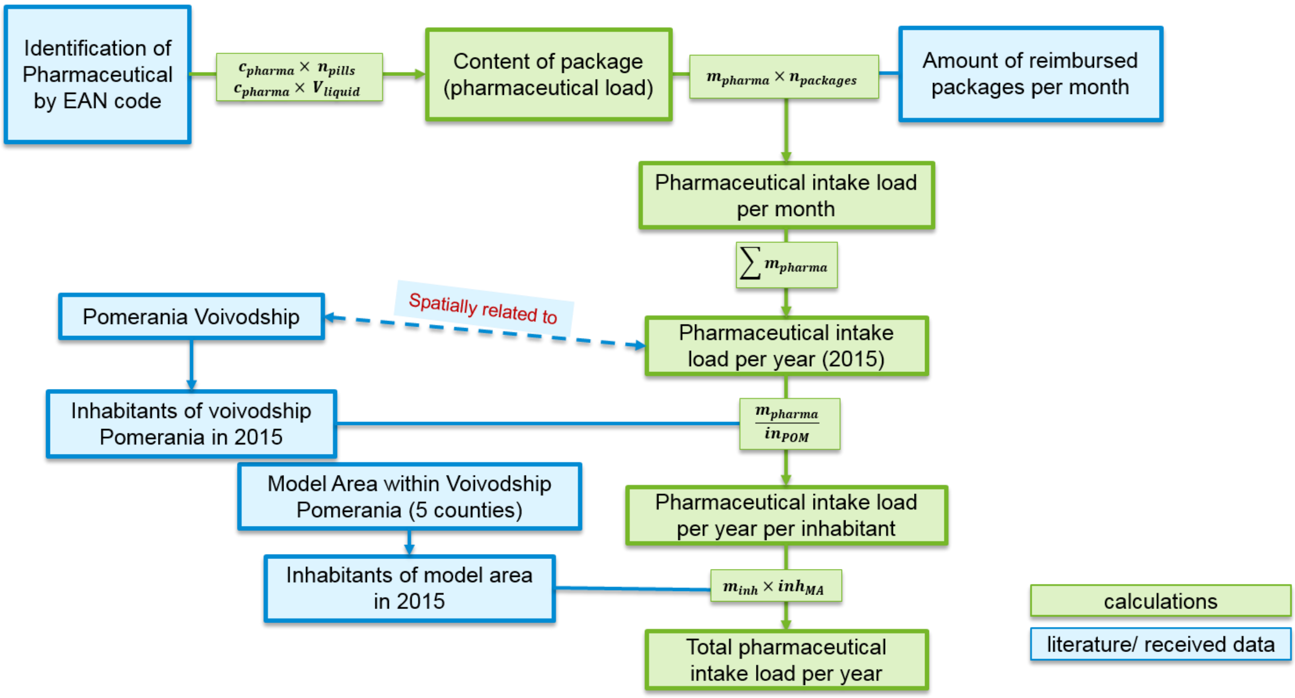


Figure 15 Consumption pattern of Polish Model Area

4.3.2 Model Area Description

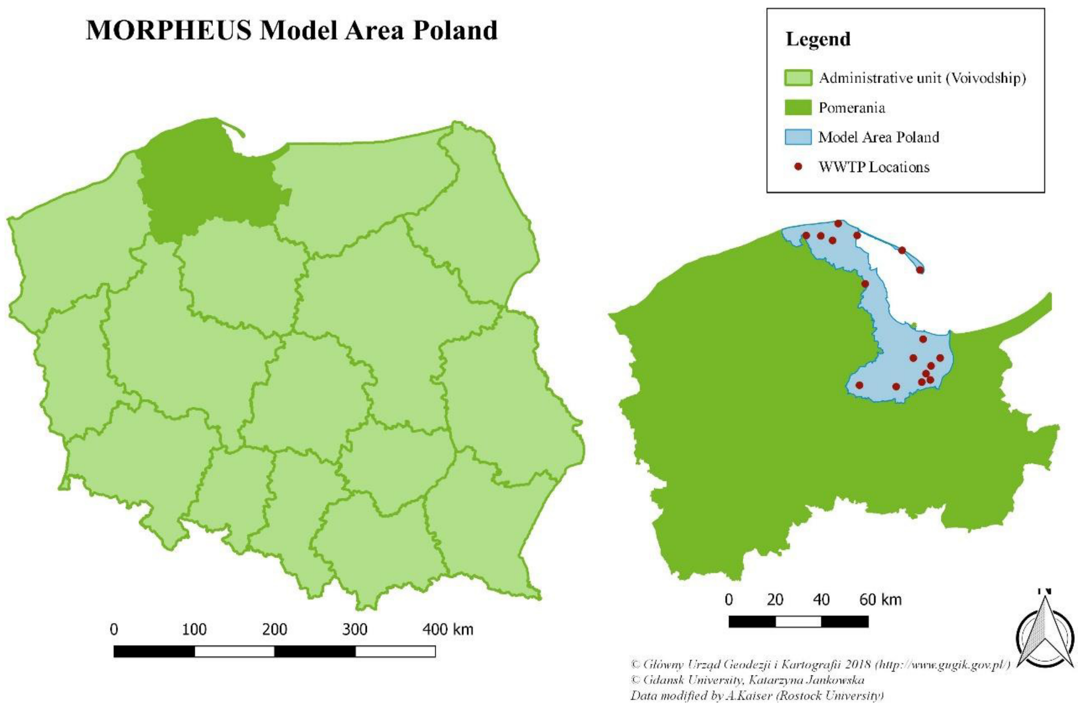


Figure 16 The Polish model area defined by the administrative borders of Municipalities within the Voivodeship Pomerania as well as WWTP locations

As MORPHEUS model area within the Pomeranian Voivodeship, five coastal counties were selected: Gdansk land county together with Gdansk city county and Sopot city county as well as Puck land county together with Gdynia city county (see Figure 16). In Table 5, the number of inhabitants are listed for the different relevant scales in Poland.

Table 5 Populations in Poland and its regions in the year 2015

Name	Administrative level	Inhabitants (2015)
Poland	**National, country**	38,100,000
Pomerania	**Regional, voivodeship**	2,307,710
Model area	**Local, five counties**	844,514

By combining the information from the table and Figure, it can be seen that the Polish model area covers both densely populated areas as well as rural areas alongside the Baltic Sea coast. Consumption sites are strongly connected with population density and therefore also with the corresponding location of WWTP which are finally seen as the main point pollution sources of human pharmaceuticals. Figure 16 shows the location of WWTPs within the model area of Poland. These discharge points represent the collection points of consumption sites within the whole region whereby the resulting impact on the aquatic environment can be located. In total, 20 WWTPs are located in this area, out of which 3 will be shut down within the next years. Additionally, the coastal region is highly influenced by tourism during the summer season. At this time, not only wastewater from inhabitants is discharged but also from tourists and needs to be treated in the local WWTP. Hence, the fluctuating inflow volume and corresponding load of pharmaceuticals (compare Deliverable 4.1) is potentially a challenging task for plant operators. A majority of the WWTPs are discharging into rivers and streams, while 6 WWTPs directly into the Baltic Sea or Gdansk Bay. However, the pharmaceutical burden both in surface water bodies and the final recipient, the Baltic Sea, needs to be considered to evaluate the environmental impact.

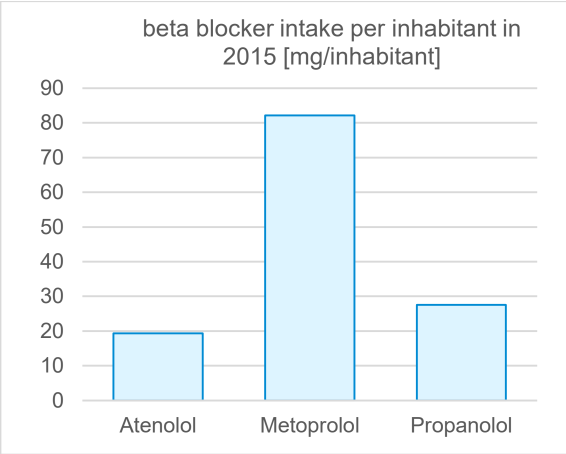
4.3.3 Consumption analysis

According to the population in the counties considered as model area (see Table 5), the total consumption of investigated pharmaceuticals as well as the intake per inhabitant are calculated by application of the scheme in Figure 15 and results are shown in Table 6**.** The number of EAN-codes (N) indicates how many different products were considered for each pharmaceutical. N differs both among the substances and the monthly datasets from 1 up to 63 (Amoxicillin) products.

Table 6 Number of investigated EAN-codes, results of consumption load calculations of the Polish model area [kg] and intake per inhabitant [mg] in 2015 of the investigated pharmaceuticals

Pharmaceutical	N (EAN-codes)	total intake in 2015 [kg/a]	Intake per inhabitant [mg/a]
Amoxicillin	**63**	2,493.73	2,952.9
Atenolol	**2**	16.31	19.3
Azithromycin	**34**	61.66	73.0
Carbamazepin	**11**	604.55	715.9
Ciprofloxacin	**9**	211.93	251.0
Clarithromycin	**32**	191.46	226.7
Diclofenac	**22**	177.47	210.1
Erythromycin	**6**	0.03	0.03
Estradiol	**28**	0.64	0.760
Ethinylestradiol	**8**	0.02	0.025
Fluoxetine	**10**	16.93	20.0
Ibuprofen	**4**	188.80	223.6
Metformin	**22**	14,865.76	17,602.7
Metoprolol	**3**	69.38	82.2
Naproxen	**24**	659.07	780.4
Oxazepam	**2**	0.03	0.0
Propranolol	**2**	23.27	27.6
Risperidone	**53**	1.04	1.2
Sulfamethoxazole	**5**	126.32	149.6

At first sight it can be noticed that the total consumption varies between several grams (Oxazepam) up to nearly 15 tons (Metformin). This strengthens the point that each pharmaceutical needs to be investigated according to its application area as well as in context with similar affecting substances. Figure 17 and Figure 18 show the intake loads per inhabitant for pharmaceuticals applied for cardiovascular use (beta-blockers etc.) and anti-infective use (antibiotics), respectively.



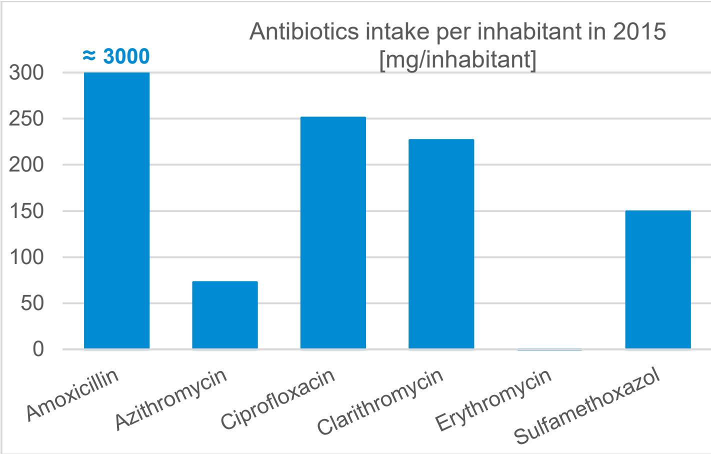


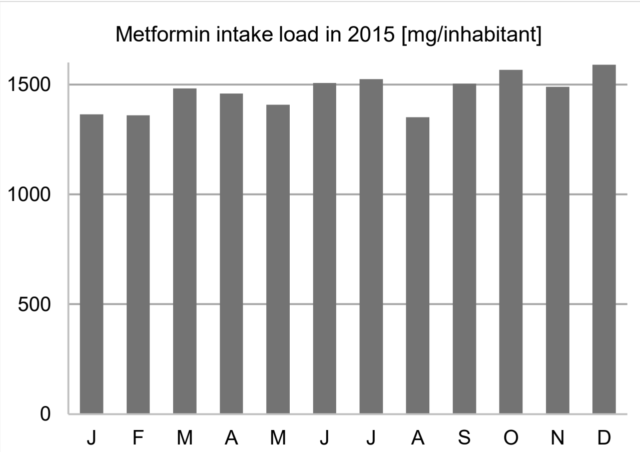
Figure 17 Beta-blocking pharmaceutical's consumption in mg/inhabitant in 2015 in the Polish model area

Figure 18 Antiinfective pharmaceutical's consumption in mg/inhabitant in 2015 in the Polish model area

The pharmaceutical intake load of Metoprolol is nearly three times higher than for other beta-blocking pharmaceuticals. However, the intake of the investigated beta-blockers is still comparable but Metoprolol appears to be favorited or applicable in a broader spectrum of symptoms. The intake of Amoxicillin is nearly 3000 mg per inhabitant whereas Erythromycin intake was calculated to 0.03 mg. This large variation could be explained by different applications or frequencies in the medical routine: Within the investigated pharmaceuticals, only Amoxicillin belongs to the intensively prescribed group of penicillin. This is also underlined by the high number of EAN-codes which leads to the assumption that a high demand of penicillin generated a broad spectrum of products offered by the market. Pharmaceuticals such as Azithromycin, Ciprofloxacin as well as Clarithromycin (intake 73 mg, 251 mg and 227 mg per inhabitant, respectively) are chemically developed out of the preliminary generated Erythromycin which could have been resulting in a replacement. The intake of pharmaceuticals typically applied as analgesics such as Diclofenac and Ibuprofen is only partly covered by the present data set of refunded substances since they are also available without prescriptions, so-called OTC (over the counter). Therefore, the intake loads about 210.1 mg and 223.6 mg respectively are most likely underestimated. If studies reveal a specific relation of refunded to OTC pharmaceutical loads, these numbers can be applied for an extrapolation to achieve more realistic values for the Polish model area.

4.3.4 Special issue: Temporal variation within monthly datasets

Due to the availability of very good temporal resolution of the pharmaceutical data, the monthly variation can be depicted for the year 2015 in the Pomeranian Voivodeship. Hereby, seasonal variations in consumption may reveal high fluctuations in corresponding loads of discharged pharmaceuticals into the environment via WWTPs.



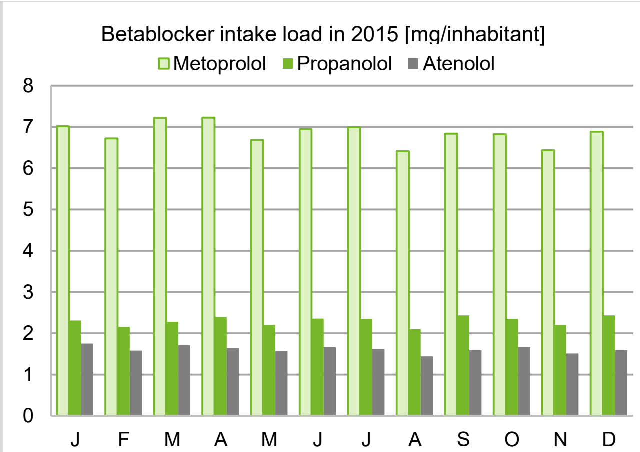
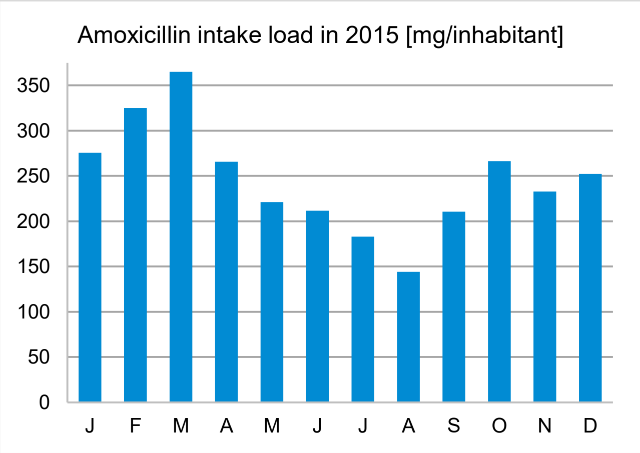


Figure 19 Monthly Metformin consumption in mg/inhabitant in 2015

Figure 20 Monthly beta-blocking pharmaceutical's consumption in mg/inhabitant in 2015

As shown in Figure 19, the intake load of Metformin is nearly steady with a variation of about 5.5% between the monthly intake loads (corresponds to ± 80 mg/inhabitant). A slight increase over the year is visible which would correlate with the overall trend in Europe that the number of diabetic patients increases, too. However, this first impression needs to be proven/supported by further data (previous/following years). When looking into the monthly consumption data of cardiovascular pharmaceuticals (beta-blockers) it can be stated that the intake loads are rarely varying over the year (see Figure 20). Even though the level of intake loads differs between Metoprolol, Propranolol and Atenolol, the deviation of all three pharmaceutical intake loads is maximal about 5% (3.8%, 4.8% and 5.2%, respectively).

In contrast to the previously mentioned monthly pharmaceutical intake loads, the data of antibiotics reveal similar characteristic variations alongside the seasons (see Figure 21 and Figure 22). With deviations from 16% up to 42% for Sulfamethoxazole and Clarithromycin, respectively, the intake loads of antibiotics is much higher in the winter season than in the summer season, whereby Clarithromycin appears to be the most season-dependent pharmaceutical compared to the other investigated antibiotics. As a result, the most applied antibiotic from January until March is Clarithromycin, during the other months Ciprofloxacin loads per inhabitant show higher amounts. When analyzing the overall variation of antibiotic intake loads the results seem to be reasonable: During winter season, the risk of bacterial infections, colds etc. is much higher than during summer season. This correlates probably directly with the monthly intake loads. For further investigation, this initial data set may give a direction but needs to be supported with more reliable prevalence data (counting of infections in a specific area in a time period) by experts in pharmacology and/or medicine.



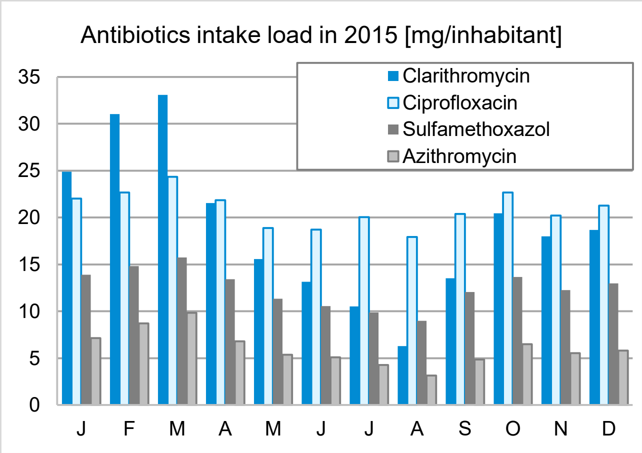


Figure 21 Monthly Amoxicillin consumption in mg/inhabitant in 2015 in the Polish model area

Figure 22 Monthly antibiotics consumption in mg/inhabitant in 2015 in the Polish model area

4.4 Sweden

The Swedish health care system is completely state financed by taxes like other Nordic countries as Norway, Denmark and Finland. Both employed and unemployed inhabitants have free access to health care services, which are organized autonomously by provincial authorities. Hospital care is financed in the same way and therefore also free. In total, 80% of the health care expenditures are paid by state whereas less than 17% of the costs are paid by private households. (ScanBalt Report 2016)

The statutory health care service is provided by a single insurance, called Försäkringskassan, but it is possible to extend the insurance by private supplementary packages. Even though each doctoral consultation demands a personal financial contribution, the maximum amount each patient has to afford is capped to 900 SEK (ca.100 €) per year. The access to health care information is centralized by Vårdguiden mainly online (see www.1177.se) and specific for each region. Here, Swedish inhabitants have the opportunity to inform themselves on several topics, especially also on environmental-friendly pharmaceuticals listed in the so-called Kloka Listan (The Wise List) which is available for both patients and medical staff in different versions (Stockholms läns läkemedelskommitté 2018, Gerster 2018).

4.4.1 Data sources and availability

Pharmaceutical statistics of Sweden were available from two different sources with varying extents. It was investigated that the best spatial resolution of statistical data is related to the administrative units managing the health care, accordingly Region Skåne in the south of Sweden. On the one hand, an open-source database is provided by the Swedish National Board of Health and Welfare (Socialstyrelsen 2015) describing drug consumption on an annual basis. It has to be considered that here only pharmaceuticals obtained from prescriptions in pharmacies are covered by these statistics. However, these information is available for free and accessible for each interested person for the year 2006-2017. On the other hand, personnel from Region Skåne is able to extract more detailed and comprehensive consumption statistics using their internally accessible data bases. Here, the total consumption included prescription, closed care at hospitals and OTC sales. During the process of data acquisition, it turned out that only four of the compounds can be acquired as OTC drugs: paracetamol, ibuprofen, diclofenac and naproxen. In order to minimize the effort of administrative personnel, the obtained data here was reduced to 14 pharmaceuticals.

Nevertheless, both datasets from different sources are given in the same units, namely DDD. The schematic overview for calculating the consumption patterns in the Swedish model area is shown in Figure 23. The similar datasets with different extents have been combined in this project. Whenever data from Region Skåne was available, it was favourized due to the larger coverage of data including OTC and hospital. Before starting the calculation of both, the corresponding ATC-Codes of each investigated pharmaceutical has to be identified. By searching for these specific ATC-Codes in the databases, the regional consumption of each specification can be obtained in the unit DDD/a. The first step of calculation is to convert the number of consumed DDDs into a mass load (unit is kg, g, mg etc.) by applying the so-called ATC/DDD-Index in g/DDD (see chapter 3.1). Once the consumption data as absolute mass per year was calculated for the entire Region Skåne, a comparable mean value of consumption per inhabitant per year was calculated by relating to the actual number of population in the Region. With this value, the total consumption in Kristianstad municipality was estimated by considering its inhabitants.

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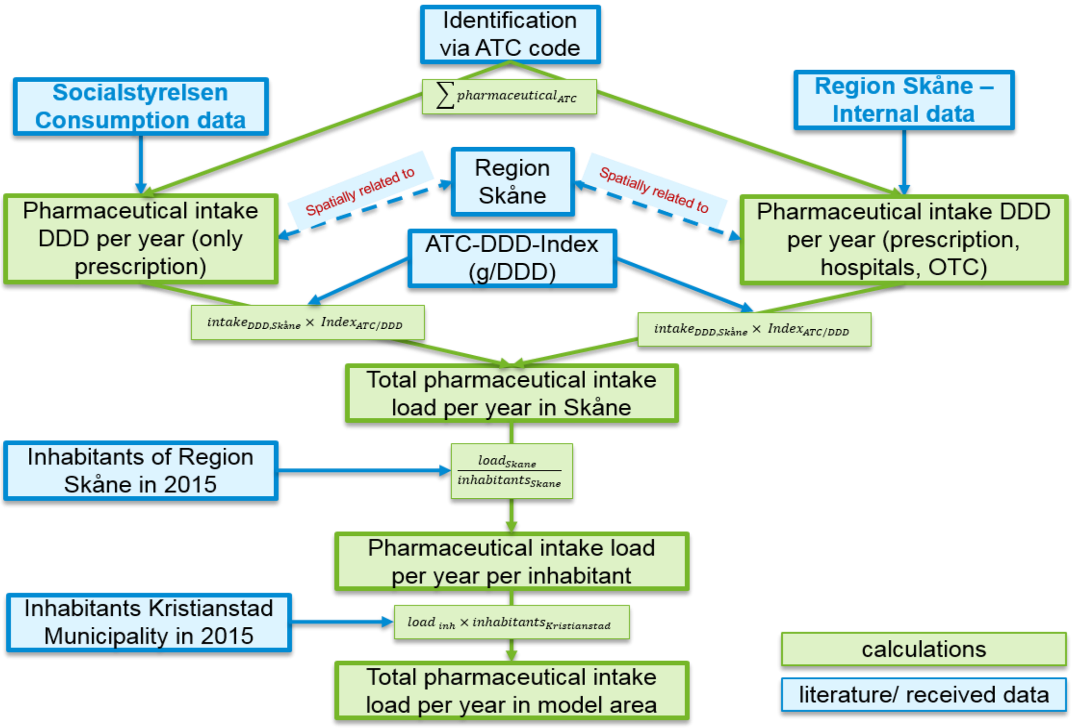

Figure 23 Consumption pattern of Swedish Model Area

The year of investigation was 2015, further data for 2016 and 2017 is available, too. In this way, a large set of open access data based on prescriptions is combined with exemplary internal data providing additional information on pharmaceutical intake in hospitals and sales over the counter, mainly relevant for analgesics such as Ibuprofen or Paracetamol.

4.4.2 Model Area Description

Since Region Skåne was identified to represent the smallest geographical unit of available statistics for pharmaceutical consumption, population data was obtained. However, as already shown in the schematic overview, the model area in Sweden is set to the Kristianstad Municipality within Region Skåne (Figure 24). It is located in the north-east of the Region directly on the coast. Consumption data is based on the level of Region Skåne with round about 1.3 Million inhabitants which corresponds to 13% of the total Swedish population. Table 7 lists the number of inhabitants of Region Skåne and Kristianstad Municipality, data obtained from Sociastyrelsen and Statistiska Centralbyrån, respectively (https://www.scb.se/en/).

Table 7 Population of Region Skane and Kristianstad municipality in the years 2015-2017

Year	Inhabitants of Skåne	Inhabitants of Kristianstad
2015	1,288,908	82,510
2016	1,303,627	83,191
2017	1,324,565	84,151

The population of Skåne and Kristianstad municipality is 13.1% and 0.8% of the entire population of Sweden, respectively. Kristianstad Municipality in turn, represent 6.4% of the population in Skåne. The total area of Sweden, Skåne and Kristianstad Municipality are 447,419 km^2, 11,301 km^2 and 1,346 km^2, respectively. This means that Skåne and Kristianstad Municipality represent 2.5% and 0.3% of the Swedish area, respectively. Skåne as a whole is therefore relatively densely populated. However, the eastern part of Skåne including Kristianstad Municipality belongs to the least populated parts of Skåne, since the major cities of Skåne are situated on the west coast, including Malmö municipality (338,000), Helsingborg municipality (145,000) Lund Municipality (122,000) and Landskrona municipality (45,000). Within the model area Kristianstad municipality, three WWTPs have been investigated deeply in WP4 and WP5 (compare: Deliverable 4.1 and 5.1). These are Kristianstad Central WWTP and the WWTPs of the villages of Tollarp and Degeberga. In total Region Skåne has little more than 90 WWTPs, some of which are indicated with red spots in Figure 24.

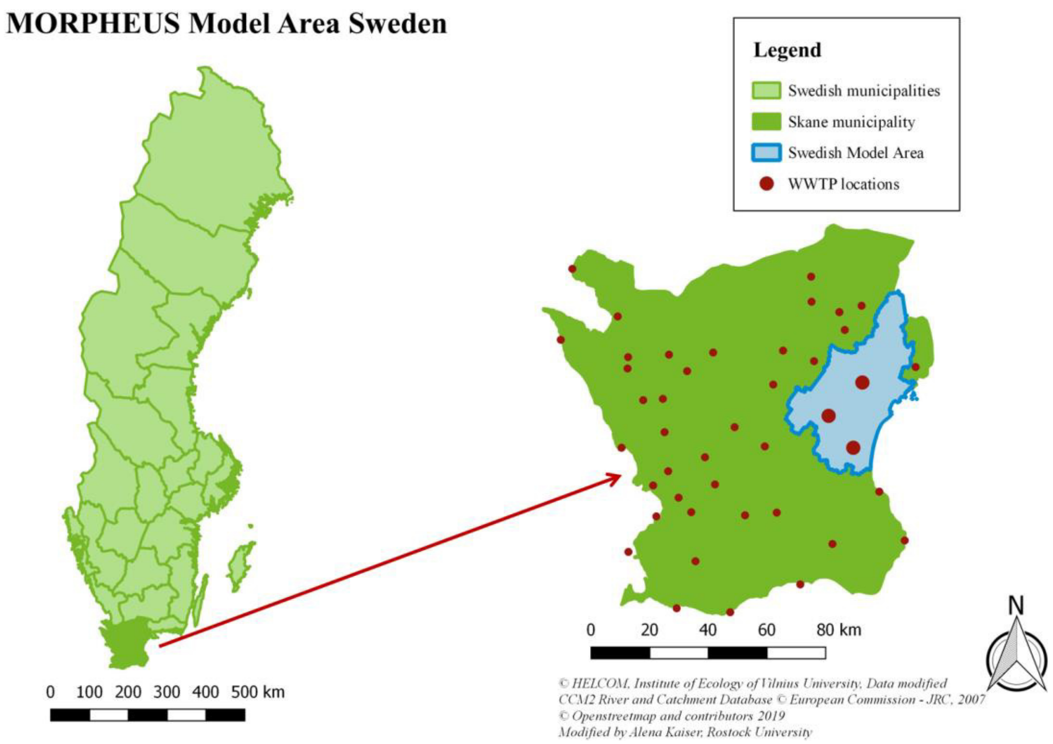

Figure 24 The Swedish model area Kristianstad within the administrative border of Region Skåne as well as WWTP locations

4.4.3 Consumption analysis

According to the population in Region Skåne and Kristianstad Municipality considered as model area, the total consumptions of investigated pharmaceuticals as well as the intake per inhabitant are shown in Table 8**.** For selected pharmaceuticals available without prescription, OTC-sales are included, namely Diclofenac, Ibuprofen, Naproxen as well as Paracetamol.

Table 8 Results of consumption load calculations of the Swedish model area Kristianstad [kg] and intake per inhabitant [mg] in 2015 of the investigated pharmaceuticals

Pharmaceutical	total intake Kristianstad in 2015 [kg/a]	Intake per inhabitant in 2015 [mg/a]
Amoxicillin	34.2	414.7
Atenolol	21.7	262.8
Azithromycin	0.8	9.8
Bezafibrate	2.6	31.4
Carbamazepine	43.5	526.6
Ciprofloxacin	24.6	298.6
Clarithromycin	1.1	13.4
Diclofenac	27.6	334.4
Erythromycin	4.1	50.1
Ethinylestradiol	0.021	0.2
Fluoxetine	3.8	46.0
Ibuprofen	873.4	10,585.6
Metformin	1,275.5	15,459.0
Metoprolol	118.9	1,441.2
Naproxen	91.5	1,108.6
Oxazepam	5.7	69.6
Paracetamol	4,819.9	58,416.1
Propranolol	6.3	76.7
Risperidone	0.1	1.4
Sulfamethoxazole	19.7	238.2

Besides Metformin, the OTC-pharmaceuticals accounted for the largest loads of pharmaceutical consumption within the investigated substances, especially Paracetamol revealed a consumption with >58 g/inhabitant which means that more than 4.8 tons are consumed only in Kristianstad municipality in average in 2015. Metformin, as the most commonly applied pharmaceutical in diabetic therapy also showed more than one ton as total load consumed in the model area.

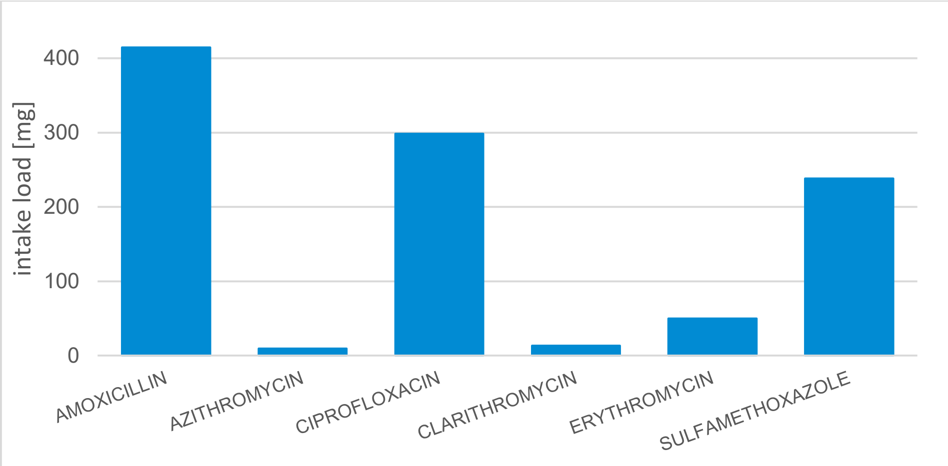

Figure 25 intake loads for six pharmaceuticals per inhabitant in the region Skåne in 2015 [mg].

A comparison of all 7 investigated antiinfectives (antibiotics, antimycotics, and antivirals) reveals huge differences of yearly average intake per inhabitants from 9.8 up to 414.7 mg (Figure 25). It can be clearly seen that Amoxicillin, Ciprofloxacin and Sulfamethoxazole are more consumed than others. It is very interesting that this result matches exactly with the EU-watchlist compounds: Azithromycin, Clarithromycin as well as Erythromycin are compounds listed in the EU-watchlist version before 2018, while the updated list now also includes Amoxicillin and Ciprofloxacin, too.

4.4.4 Special issue: Relation of OTC, Hospital and Prescription of pharmaceuticals

The internal data improved the data comprehension significantly. Therefore, the special issue of the Swedish model area focusses on the relation of prescription data and OTC-sales as well as pharmaceuticals applied in health care institutions. In Table 9 the shares of each consumption pattern for 14 pharmaceuticals based on internal data provided by Region Skåne are presented.

Pharmaceuticals available as OTC show that up to 82 % (Ibuprofen) are represented by this consumption pattern and underline that the additional dataset is essential to get closer to reality in terms of total pharmaceutical intake. However, the OTC-shares are varying widely, e.g. Naproxen is still mostly prescribed (88.6 %) while approximately 20 to 30 % of Paracetamol and Diclofenac are sold OTC.

In general, the pharmaceutical intake in hospital/health care institutions is much lower compared to prescribed amounts and vary between 0.5 and 17.3 % of the yearly consumption. The most important of the investigated pharmaceuticals for application within this pattern seem to be Ciprofloxacin, Erythromycin and Sulfamethoxazole (15.0 %, 10.4 % and 17.3 % respectively). It has to be mentioned that Erythromycin is the least applied pharmaceutical of these three, the intake load is only about 50.1 mg/inhabitant while Sulfamethoxazole and Ciprofloxacin exceed 238 and 298 mg/inhabitant, respectively. Conversely, this means that these pharmaceuticals may indicate a hospital wastewater inflow when measuring higher concentrations than expected/ extrapolated by inhabitant numbers of the catchments, both for WWTP inflow and water bodies.

Table 9 Relation of pharmaceutical consumption paths according to sale sites, prescribed in pharmacies, hospital and health care, over the counter (OTC) for 14 selected pharmaceuticals

Pharmaceutical	Prescribed [%]	hospital [%]	OTC [%]
Atenolol	99.5	0.5	
Azithromycin	94.8	5.2	
Cabamazepine	98.2	1.8	
Ciprofloxacin	85.0	15.0	
Clarithromycin	95.3	4.7	
Diclofenac	69.2	2.4	28.4
Erythromycin	89.6	10.4	
Ibuprofen	17.7	0.5	81.8
Metoprolol	99.0	1.0	
Naproxen	88.6	0.6	10.8
Oxazepam	97.0	3.0	
Paracetamol	75.1	3.0	21.9
Propranolol	99.3	0.7	
Sulfamethoxazole	82.7	17.3	

5 Comparison

As shown before, the analysis of regional consumption patterns of pharmaceuticals is based on different data sets and preconditions. On the one hand, the level of administrative authorities and/or insurances can deliver relevant data which are sometimes restricted in their extent of considered consumer groups, such as based on prescriptions but no OTC in pharmacies or drugstores are covered. On the other hand, wholesalers are obliged to deliver data to national institutions which then are able to provide information on the amount of sold packages. However, despite the differences in databases, general uncertainties are equal in all model areas which can be summarized in the following questions:

- Is the pharmaceutical sold at the same place as consumed?
- Is the package/prescribed amount of pharmaceutical completely consumed?
- How are non-consumed pharmaceuticals disposed?
- Was the given dataset complete?

All these preconditions have been set equal for all model regions. More detailed information could improve the analysis of consumption pattern considerably but are difficult to obtain. Beside the preconditions, the data sets reveal deviating levels of both spatial and temporal resolution as shown in the special cases of Lithuania and Poland. The special case of the Swedish model area focusses on the previously mentioned circle of considered consumer groups and their shares to total consumption. In the German model area (with an existing topological river network), the whole catchment can be investigated with regard to accumulation of pharmaceutical loads downstream. It was shown that the results and reliability strongly variates with the provided data which needs to be looked at individually.

The consumption pattern model is also strongly related to the definition of model areas. Within this project, the chosen extents vary with respect to the given environmental circumstances as well as availability of data for WWTPs and receiving waters related data. While the German model area is restricted to the Baltic Sea Catchment within the administrative boundaries of the Federal State, the remaining model areas were depicted according to their relevance in coastal areas and consequently restrcited by only administrative boundaries. This is also a result of the fact that in Lithuania, Poland and Sweden large proportions up to the total of their national territories discharge into the Baltic Sea. A consideration of these catchment areas would exceed the project's extent and mismatch with the aim to concentrate on the local model area level. However, the country specific calculation schemes can now be easily expanded to other areas of interest.

In Table 10, the total intake loads are related to the area in km² of each investigated Model Area. By this relation, a need for action may be localized when higher intake loads in specific model areas occur than in the others. Here, the potential burden to the environment is consequently higher. This comparison shows again the large variation according to the selected pharmaceutical whereby some are of great relevance in all of the model areas. Similar intake loads can be found for Carbamazepine, Metformin and Diclofenac. For several compounds, the intake load per km² is much higher in Sweden, namely Atenolol, Naproxen Oxazepam and Paracetamol. The by far highest intake loads related to the area of Amoxicillin, Azithromycin and Clarithromycin.

Bezafibrate, Diclofenac and Erythromycin pose the highest burden related to considered spatial extent in the German Model Area. Nevertheless, despite clear differences it can also be stated that each of the intake loads is a potential risk to the environment dependent on their removability at WWTPs, dilution by receiving rivers and their corresponding limitation values (PNEC), which will be investigated in detail in Del. 4.1/4.2.

Table 10 Comparison of intake loads in 2015 related to the spatial extent of the model area in g/km². Highest values for each pharmaceutical load among the model areas are marked in red

Pharmaceutical	SE [g/km²]	PL [g/km²]	LT [g/km²]	GER [g/km²]
Amoxicillin	47.8	371.8	99.9	62.3
Atenolol	30.3	2.4	0.4	3.8
Azithromycin	1.1	9.2	0.8	6.1
Bezafibrate	3.6			12.1
Carbamazepine	60.7	90.1	20.9	66.1
Ciprofloxacin	34.4	31.6	8.6	27.0
Clarithromycin	1.6	28.5	6.8	15.2
Diclofenac	38.6	26.5	26.4	45.6
Erythromycin	5.8		0.1	25.9
Estradiol		0.1		0.2
Ethinylestradiol				0.4
Fluoxetine	5.3	2.5	0.2	0.8
Ibuprofen	1220.6	28.1	204.7	933.9
Iopromide				1448.0
Metformin	1782.5	2216.5	982.3	2193.8
Metoprolol	166.2	10.3	63.3	133.0
Naproxen	127.8	98.3	13.8	19.4
Oxazepam	8.0		0.1	0.1
Paracetamol	6735.6		99.0	65.4
Propranolol	8.8	3.5	0.4	6.5
Risperidone	0.2	0.2	0.1	0.2
Sulfamethoxazole	27.5	18.8	4.8	19.3
Population Density [inh./km²]	**115**	**125**	**102**	**74**

For the purpose of international comparison of pharmaceutical consumption the results can be normalized to yearly consumption loads intake per inhabitant (see Table 11). However, the previously described uncertainties and deviations in the way of calculations allow an initial idea of the main differences. Hereby, Sweden and Germany as well as Lithuania and Poland are more comparable with one another due to the fundamental difference of data source (insurances and wholesalers, respectively). It has to be kept in mind that this analysis shows the consumption of selected pharmaceuticals and does not cover the total pharmaceutical range by far. Nonetheless, these pharmaceuticals can serve as guide substances when investigating the pharmaceutical burden in the South Baltic Sea caused by selected areas and substances in a yearly average value for 2015.

Table 11 Comparison of regional consumption per inhabitants in 2015 of the model areas. Highest values for each pharmaceutical load among the model areas are marked in red

Pharmaceutical	SE	PL	LT	GER
	[mg/inh.]	[mg/inh.]	[mg/inh.]	[mg/inh.]
Amoxicillin	414.7	2,952.9	977.3	840.9
Atenolol	262.8	19.3	4.2	51.8
Azithromycin	9.8	73.0	7.6	82.0
Bezafibrate	31.4			163.4
Carbamazepine	526.6	715.9	204.1	892.7
Ciprofloxacin	298.6	251.0	84.5	365.1
Clarithromycin	13.4	226.7	66.4	205.8
Diclofenac	334.4	210.1	257.7	616.2
Erythromycin	50.1		0.9	350.3
Estradiol		0.8		3.3
Ethinylestradiol				5.4
Fluoxetine	46.0	20.0	2.3	11.4
Ibuprofen	10,585.6	223.6	2,001.6	12,610.4
Iopromide				19,551.7
Metformin	15,459.0	17,602.7	9,606.2	29,621.5
Metoprolol	1,441.2	82.2	618.7	1,796.1
Naproxen	1,108.6	780.4	135.4	261.4
Oxazepam	69.6		1.4	1.0
Paracetamol	58,416.1		968.6	882.9
Propranolol	76.7	27.6	4.3	87.7
Risperidone	1.4	1.2	1.2	3.0
Sulfamethoxazole	238.2	149.6	47.3	260.9

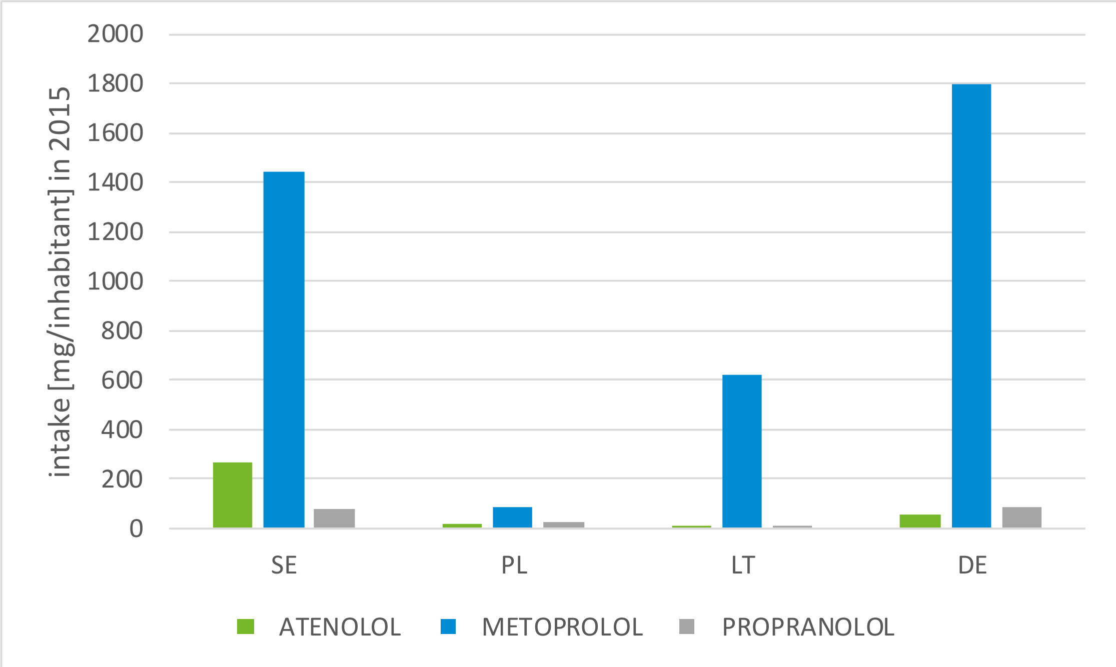

Figure 26 Comparison of beta blocking pharmaceuticals intake in 2015 [mg/inhabitant] of the four model areas Sweden Poland, Lithuania and Germany

In Figure 26 the intake of beta-blocking pharmaceuticals in each model area is presented. It can be seen that for all of the considered regions and investigated pharmaceuticals that Metoprolol is the mostly highly consumed. However, the intake in Sweden and Germany is on distinctly higher level above 1400 mg/inhabitant in 2015 while Poland and Lithuania do not exceed 100 and 620 mg/inhabitant, respectively. It needs to be established whether the differences may occur due to the selection of pharmaceuticals, other beta-blocking substances could potentially be preferred which are not analyzed within this project. Even though the intake levels show a clear range from most consumption to least consumption.

Another group of pharmaceuticals are the analgesics or colloquially named painkillers. In Figure 27, the intake loads per inhabitant in 2015 are shown. The numbers are varying up to 58 g/inhabitant in Sweden for Paracetamol. Also high intake loads are shown for Ibuprofen but predominantly by Swedish and German consumption data. This is reasonable due to the incomplete data availability. In Poland it is known that these pharmaceuticals are not reimbursed and therefore not included in the statistics where the consumption pattern calculation is based on. Nevertheless, the applied data source still serves as reliabable orientation which could be extended by further data. For Lithuania it was possible to include national data on painkiller consumptions but are most likely not covering the whole extent of consumption. However, the comparison of intake loads per inhabitant shows that a thorough understanding of the data sources is essential to understand and interprete the results when doing further calculations based on the statistics of pharmaceutical consumptions.

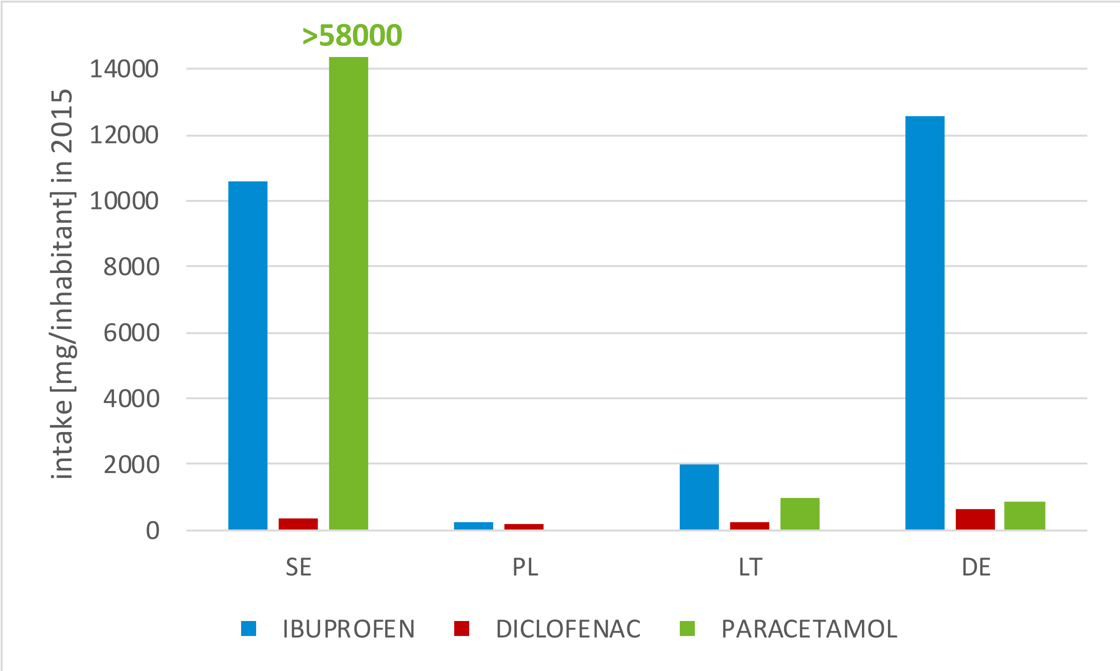

Figure 27 Comparison of analgesics (painkillers) intake in 2015 [mg/inhabitant] of the four model areas Sweden, Poland, Lithuania and Germany

6 Outcome of this report

By the start of the project MORPHEUS it turned out that most of the model areas within the South Baltic Sea catchment cannot cover the required extent of basic data concerning regional specific consumption as well as the pharmaceutical burden in the environment without obstacles. Therefore, the thorough investigation of data availability, re-allocation to the model areas and local measurements became the core of the project. Consumption data analysis represents here one of the main knowledge gaps in order to estimate the emission of pharmaceuticals into the wastewater system and consequently – without sufficient removal at WWTP – the environment.

For the model areas in Germany, Lithuania, Poland and Sweden, the top-down approach was successfully applied even though different data bases and availabilities were given. At the same time, uncertainties and differences of the data sets were carved out to draw attention to the high variability of provided information by different sources. Nevertheless, the output created here is a data set quantifying the consumption of specific pharmaceutical substances both, in the highest spatial and temporal resolution which was provided. On the one hand, the total consumption per year of a defined area allows specific load estimations in kg of how much of a defined pharmaceutical could be emitted via WWTP into the receiving waters and finally reach the South Baltic Sea, theoretically. On the other hand, a comparable but region-specific consumption per inhabitant per year was calculated for the investigated pharmaceuticals (see Table 11, Chapter 5 Comparison). Combined with the number of real-connected inhabitants instead of the usually applied personal equivalents (PE) a WWTP-related inflow can now easily be determined. Hence, the consumption per inhabitant constitutes a useful tool to allocate regional data to local levels, such as WWTPs and their inflow loads.

In the upcoming steps, the consumption data can be related now to direct measurements implemented within WP4 "Estimating regional pharmaceutical burden in WWTP and water bodies". In Del. 4.1, the extensive monitoring campaign is represented. The pharmaceutical concentrations measured in the inflow of model WWTPs related to the annual wastewater flow will be compared to consumption data when considering human excretion rates of the investigated pharmaceutical. Additionally, the relation of inflow and outflow concentrations show an experimental removal rate which is both WWTP and substance specific. By implementing this rate and consumption loads reaching the WWTP inflow, a potential outflow load can be determined which completes the WWTP-related mass flow analysis (Activity 3.3).

Finally, the knowledge we created in this working package WP3 and presented in this report is fundamental to understand the pharmaceutical burden to the environment from the emission perspective and to build up a reasonable mass flow from the source (intake of individual humans) down to the receiving water bodies accumulating in the South Baltic Sea. Furthermore, Deliverable 4.2 will carry out the mass flow analysis by actually merging consumption data analysis with monitoring data and therefore be based on the common output of WP3 and WP4.

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