KAUNAS UNIVERSITY OF TECHNOLOGY
VYTAUTAS MAGNUS UNIVERSITY
LITHUANIAN ENERGY INSTITUTE

INGA BARANAUSKAITĖ-FEDOROVA

RISK ASSESSMENT OF SELECTED PHARMACEUTICAL SUBSTANCES USED FOR HUMAN TREATMENT TO THE WATER ENVIRONMENT IN LITHUANIA

Summary of Doctoral Dissertation
Technological Sciences, Environmental Engineering (T 004)

Kaunas, 2023

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Scientific Supervisor:
Prof. Dr. Jolanta DVARIONIENĖ (Kaunas University of Technology, Technological Sciences, Environmental Engineering, T 004).

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Dissertation Defense Board of Environmental Engineering Science Field:
Prof. Dr. Žaneta STASIŠKIENĖ (Kaunas University of Technology, Technological Sciences, Environmental Engineering, T 004) – **chairperson**;
Assoc. Prof. Dr. Morten Lykkegaard CHRISTENSEN (Aalborg University, Denmark, Technological sciences, Environmental Engineering, T 004);
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Prof. Dr. Arvydas POVILAITIS (Vytautas Magnus University, Technological Sciences, Environmental Engineering, T 004).

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Address: K. Donelaičio 73-402, Kaunas, LT-44249, Lithuania
Phone: (+370) 608 28 527; e-mail doktorantura@ktu.lt

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Mokslinis vadovas:
prof. dr. Jolanta DVARIONIENĖ (Kauno technologijos universitetas, technologijos mokslai, aplinkos inžinerija, T004).

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doc. dr. Morten Lykkegaard CHRISTENSEN (Olborgo universitetas, Danija, technologijos mokslai, aplinkos inžinerija,T 004);
dr. Jūratė KRIAUČIŪNIENĖ (Lietuvos energetikos institutas, technologijos mokslai, aplinkos inžinerija, T 004);
prof. dr. Jolita KRUOPIENĖ (Kauno technologijos universitetas, technologijos mokslai, aplinkos inžinerija, T 004);
prof. dr. Arvydas POVILAITIS (Vytauto Didžiojo universitetas, technologijos mokslai, aplinkos inžinerija, T 004).

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Adresas: K. Donelaičio g. 73-402, Kaunas, LT-44249, Lietuva.
Tel. (+370) 608 28 527; el. paštas doktorantura@ktu.lt

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INTRODUCTION

Relevance of the subject. Chemical pollution of surface water bodies poses a threat to the aquatic environment. Its impact manifests itself in both acute and long-term toxicity to aquatic organisms, accumulation of pollutants in ecosystems and loss of biodiversity as well as human health hazards. Pharmaceutical substances diclofenac, 17-β-estradiol and 17-α-ethinylestradiol were first mentioned as priority substances in the water policy area in Directive 2013/39/EC of 12 August 2013 in order to gather monitoring data for facilitating the determination of appropriate measures that address the risk posed by those substances. In 2015, macrolide antibiotics – erythromycin, clarithromycin, and azithromycin were added to the list of substances for the European Union (EU) wide monitoring [1]. According to the World Health Organisation, macrolides are among the most important antibiotics in human medicine. Antibiotics are widely known as medicines for the treatment of human and animal infectious diseases, or as animal growth promoters used in agriculture and aquaculture [2]. Excessive and increasing consumption and abuse of these medicines has become a matter of public concern [3]. It is a major concern that this can accelerate the spread of resistance to antibiotics in the natural environment [4,5], which affects humans, too. As much as 90% of pharmaceutical substances are discharged into the environment in their initial form [6]. Antibiotics, however, are released as metabolites or primary compounds that do not fully disintegrate in the bowels under incomplete metabolism and, after passing wastewater collection and treatment systems, enter the aquatic environment and ecosystems [7]. Their residues get into water and soil in various ways; dispersal through municipal wastewater treatment facilities is the most common pathway [8].

It is very important to point out that it has been known for decades that usual wastewater treatment methods are not adapted to proper removal of residues of antibiotics and other pharmaceutical substances, which remains a major issue [9]. As already mentioned, antibiotic residues in water bodies are studied due to their constant presence, pseudo-resistance, and ecotoxic impact on human health and the natural environment. From the holistic point of view, it is paramount to identify, monitor, and manage the release of medicinal preparations into the environment. However, very few investigations into the pharmaceutical substances on the list of substances for the Union-wide monitoring have been carried out in Lithuania so far.

According to results of the literature review, the substance flow analysis (SFA) approach provides a sound basis for sustainable environmental management enabling researchers to quantify the flows of substances through social and economic systems (e. g. on a level of a business, industry, city, or state), therefore, management of substances on these levels would help tackle issues of resource consumption and environmental pollution control [10,11]. The SFA has

been chosen for the investigation as the most suitable management tool to determine the main sources of pharmaceutical substances and the pathways of their distribution.

Hypotheses:

1. The integration of the pharmaceutical substance flow analysis into the environmental risk assessment methodology makes it possible to systematically identify potential sources of environmental pollution with pharmaceutical substances at a state level and, at the same time, the environmental medium or specific object suitable for investigating the impact.
2. Wastewater treatment facilities are very important in managing the release of pharmaceutical substances into the aquatic environment and make a large contribution to the development of tools for managing pharmaceutical pollutants in the environment.

The object of the thesis: Pharmaceutical substances included in the watch list under Commission Implementing Decision (EU) 2022/1307 of 22 July 2022 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council: diclofenac (DCF), 17-β-estradiol (E2), 17-α-17-α-ethinylestradiol (EE2), estrone (E1), erythromycin (ERY), azithromycin (AZI) and clarithromycin (CLA).

The boundaries of the study: the state of Lithuania.

The purpose of the thesis: to perform studies of the risk of 7 pharmaceutical substances, i.e. DCF, E2, EE2, E1, ERY, AZI, CLA on the aquatic environment on the basis of substance flow analysis.

The objectives of the thesis:

1. To analyze the application of substance flow analysis for studies of pharmaceutical substances in the environment;
2. To analyze the consumption of the studied pharmaceutical substances in Lithuania;
3. To perform the analysis of the selected substance flows, and draw up balance flow charts of these substances at a national level for Lithuania;
4. To perform the risk assessment of the impact of the substances on the aquatic environment of surface water bodies;
5. To propose a system for managing the concentrations of the substances in wastewater, with integrated recommendations for the prevention of aquatic environmental pollution with pharmaceutical substances.

Scientific novelty of the work

While environmental hazards posed by active substances of medicinal preparations are widely investigated, and the permissible concentration limits of such substances in surface water bodies have been set and approved in the EU, too few studies were carried out in Lithuania to provide data on prevalence and concentrations of pharmaceutical substances in surface water bodies and to make recommendations for pollution prevention and control. This work is the first study in Lithuania that analyses the flows of diclofenac and macrolide antibiotics on a national level and provides balance models – from the import of substances into Lithuania to their release to the natural environment. The analysis of literature did not result in finding studies that apply the full substance flow analysis on a national level. The SFA was most frequently applied at the UBR level or in analyses of theoretical load of pharmaceutical substances on wastewater treatment facilities, by individual treatment processes. The methodology formulated in this work, and the proposed system for the management of these substances in the environment together with recommendations could be applied also in other countries similar to Lithuania.

Practical value of the thesis

The analysis made in this study and the system proposed for the management and reduction of the release of pharmaceutical substances to the environment would contribute to the improvement of the national water policies in Lithuania and would be useful for environmental education purposes. The proposed investigation methodology can be used to estimate the residue concentrations of pharmaceutical substances in surface water bodies and assess the relevant environmental hazard. The methodology can be applied in countries similar to Lithuania in terms of socio-cultural situation, level of development and wastewater treatment systems. The SFA approach enables the identification of the main source of pollution with pharmaceutical substances and the main object through which they are dispersed in the environment.

Approval of the thesis

There are three scientific publications on the subject of the thesis including two in Clarivate Analytics Web of Science database with a citation index, and one in a peer reviewed journal that is referred to in other databases.
Data from the studies on the subject of the thesis were reported at four international scientific conferences: *Computational Science and Its Applications* in 2021; *Ecotechnologies for Wastewater Treatment* – the 3rd IWA ecoSTP 2016 specialized conference in Cambridge (UK) in 2016; *Micropol & Ecohazard Conference* in 2015; *9th IWA Specialist Conference on Assessment and Control of Micropollutants and Hazardous Substances in Water*, Singapore 2014; and

Littoral 2014. Facing Present and Future Coast Challenges, Klaipėda, Lithuania, 2014.

Scope and structure of the thesis

The thesis consists of an introduction and three main sections, the conclusions, and a list of literature (151 sources including 127 scientific ones). The thesis also includes a summary, a list of abbreviations, and lists of figures and tables, comprising 24 figures and 19 tables. The thesis consists of 105 pages.

SECTION 1. ANALYSIS OF LITERATURE

The pathways of pharmaceutical substance dispersal in the environment, their persistence, toxic impact on the environment and other studies have been conducted for several decades, however, there are still no reliable answers or modes of operation applicable to all the pharmaceutical substances or their groups. The analysis of literature has shown that the pharmaceutical substances under investigation undoubtedly pose a threat to the natural environment and, through the food chain or water cycle, to human health as well.

It has been established that humans are the main source of release of the pharmaceutical substances to the environment. The majority of these substances get into wastewater by excretion, together with feces and urine, then into surface bodies and further into the entire water cycle.

Highest concentrations of the pharmaceutical substances are found in densely populated urban areas, particularly, in domestic wastewater. Therefore, wastewater treatment facilities should play the central role in managing pharmaceutical substance releases and have the potential of a significant contribution to the development of measures to control and reduce pharmaceutical pollutants in the environment.

An analysis of legal regulation has shown that today pharmaceutical substances are included in various important initiatives. Measures have been designed for preventing antimicrobial resistance (AMR) such as urging people to reduce taking antibiotics and to return medicinal waste to the primary manufacturer. Directive 2000/60/EC establishing a framework for Community action in the field of water policy sets out the relevant actions and a strategy for the control of water pollution. Article 16 of this Directive requires that the Commission submits a proposal setting out a list of priority substances selected amongst those which present a significant risk to or via the aquatic environment, and proposals for European environmental quality standards (EQSs) applicable to the concentrations of the priority substances in surface water, sediments, or biota. In 2013, the first watch list identifying priority substances appeared; along with the list, first pharmaceutical substances were included in political strategies aimed at reducing the impact of potentially hazardous substances on humans and the environment. The watch list is reviewed and updated every two years. Since 2013, a few pharmaceutical substances are on the list at the time of each update. On 15 July 2022, the Commission's Health Emergency Preparedness and Response Authority (HERA) presented a priority list of three greatest health hazards requiring coordination of medical response measures on the EU level, one of them being antimicrobial resistance. Globally, over 1.2 million people die every year due to AMR [12].

The literature review confirms that exceeding the therapeutical doses of the substances under investigation has a toxic impact on the environment. Due to very

low concentrations (ng/l, µg/l) of the investigated pharmaceutical substances in the water cycle, the probability of a threat to human health may be low because the dose that has been adopted as an active therapeutic dose of the substances can be larger up to one million and more times. This remains a subject of researchers' discussions until now. However, many studies have proved that fish and amphibians affected for a long time by even low concentrations of pharmaceutical substances in water (<1 ng/l), change gender; the impact is strongest on biota.

Global concern over the impact of pharmaceutical substance residues on the environment necessitates carrying out investigations locally, more so that such studies in Lithuania have been scarce. The literature review has shown that very few studies dealt with the pharmaceutical substance residues in the environment, and none examined the environmental impact by the risk assessment method or the substance flow analysis covering the entire cycle of substances, from manufacture to release to the environment due to anthropogenic activities. Furthermore, only a few studies that applied a full SFA on a national level were found in literature. Most often the SFA approach was applied on a level of river basin districts or with the aim to analyze the theoretical load of pharmaceutical substances on wastewater treatment facilities or to WTP in determining the quantities of pharmaceutical substance residues eliminated at each wastewater treatment process.

To sum up, a literature review has shown that the importance of the selected pharmaceutical substances, ongoing studies into their presence in the environment, and their management have been recognized on both national and EU level. Relying on this conclusion, the main purpose of the doctoral thesis is to investigate the threat posed by these substances to the environment in Lithuania. On revealing the main benefits of the SFA, this approach was selected as the key methodology for a quantitative assessment of potential pathways of the pollution to the environment. In this way, the object of investigations into pollutant concentrations was identified and substantiated. The methodological part below describes how the investigation sequence was defined.

A review of the literature showed, as early as in 2013, that there is a lack of studies into the prevalence of pharmaceutical substances in the environment, and without data on actual concentrations it is difficult to assess potential risk for the environment. Therefore, after reviewing the literature, the first pharmaceutical substances were selected for investigation – DCF and substances of estradiol group, and the objective was set to determine the concentration of these substances in the wastewater treated at Lithuania's wastewater treatment facilities. Investigations have shown that concentrations of pharmaceutical substances are comparable with other countries and have a significant impact on the environment. Therefore, environmental investigations were expanded and continued, and the object of investigations was supplemented by three relevant pharmaceutical substances, i. e. three macrolide antibiotics.

SECTION 2. RESEARCH METHODOLOGY

This section defines the structure of the investigations carried out for the purposes of the thesis. A schematic representation of the methodology applied throughout the investigations is provided below.

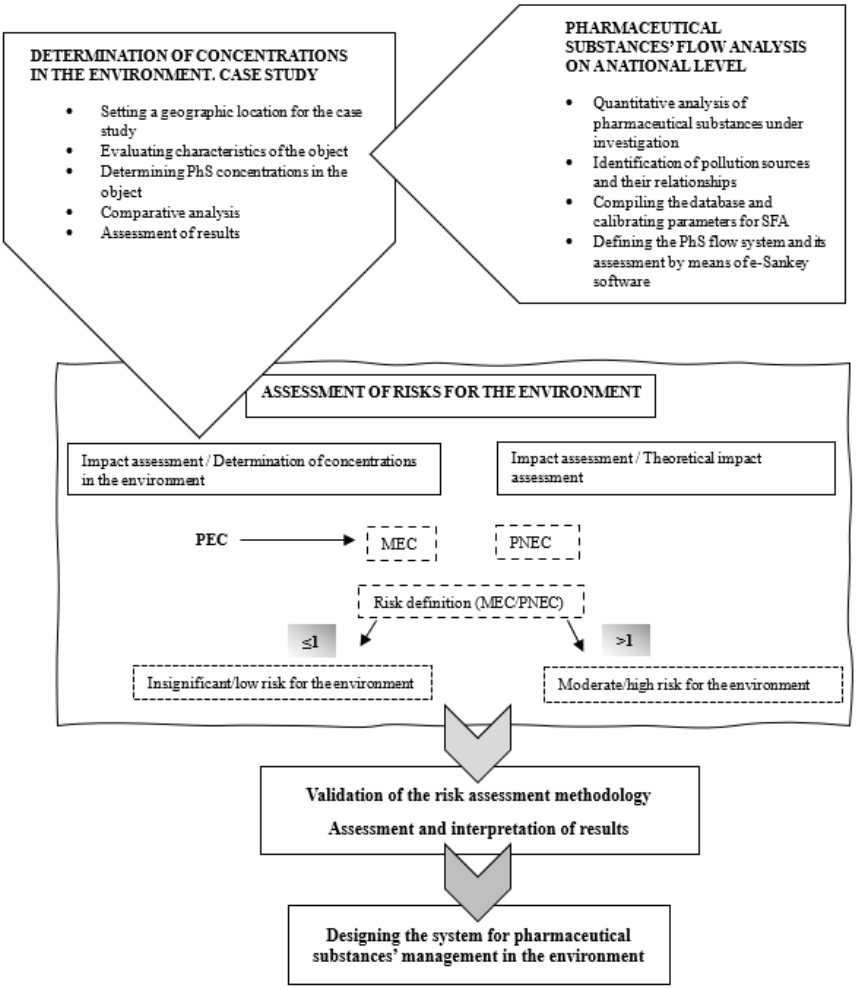


Figure 1. Integration of the pharmaceutical substances flow analysis in the environmental risk assessment methodology

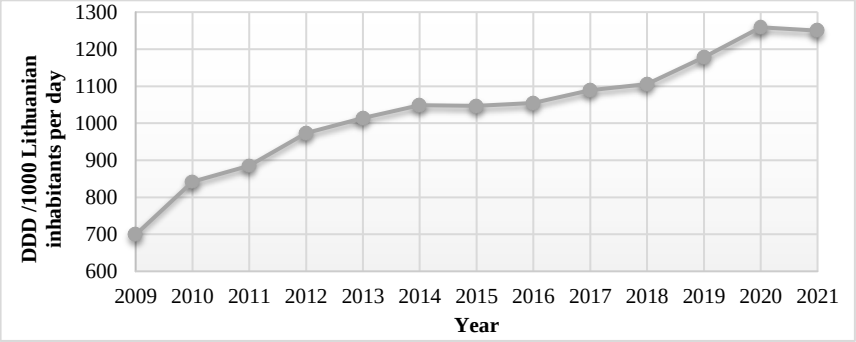
As shown in the flow chart, the methodological section consists of four main parts: description of the methodology of the pharmaceutical substances' flow

analysis; description of the methodology for the wastewater sample collection and wastewater analysis; detailing of the assessment of the environmental impact risk; and formulation of the environmental management system methodology. From the theoretical point of view, the environmental management system was based on the mathematical theory of an environmental system. Theoretically, the main task of the management system is to determine an environmental management effect U ($_t$) and the relevant factors that would enable setting the objectives (X_{in} (t)) for the environmental system. The main purpose of the management system is to reduce the negative impact on the environment by most cost-effective pollution prevention measures.

SECTION 3. RESULTS OF THE INVESTIGATION AND DISCUSSION

Trends of consumption of the pharmaceutical substances under investigation

In the period 2009–2021, a strong growth in the demand for medicines was recorded in Lithuania, reaching a peak in 2021, the overall change was 56% (see Figure 2). It is probable that after the end of the COVID-19 pandemic in 2021, consumption of medicines remained on a level similar to that of 2020, with a slight decrease (1%).



Note: The data on drug sales are expressed as DDD per 1,000 inhabitants per day and are an estimation of the share of the population treated with the relevant drugs in a certain locality.

Figure 2. Data on consumption of medicinal preparations in Lithuania in 2009–2021

According to anatomic group, the pharmaceutical substances under investigation are classified as medicines having effects on the musculoskeletal system (DCF) and medicines affecting the urogenital system and sex hormones (E2 and EE2). In 2021, these groups ranked 5th and 7th, respectively, according to medicines consumption. In 2009–2021, the demand for medicines affecting the musculoskeletal system increased by 33.66%, and the demand for medicines

affecting the urogenital system and sex hormones increased by 73.11%. While the sales of the first group were growing continuously, the demand for diclofenac remained on the same level (see Table 1). Sales of non-steroidal anti-inflammatory and anti-rheumatic drugs (NSAIDs) ranked 5th in Lithuania in 2021.

Table 1. Diclofenac and estradiol sales volumes in Lithuania in 2009–2021

Group of medicinal preparations	**Active substance**	**DDD/1000 of Lithuanian inhabitants per day**					**Max impact, %**
		2009	**2013**	**2017**	**2019**	**2021**	
Medicines affecting the musculoskeletal system		**56.77**	**72.40**	**74.07**	**80.35**	**85.57**	+33.66
	DCF	20.52	20.91	22.68	19.30	19.09	-15.83
Medicines affecting the urogenital system and sex hormones		**9.65**	**29.59**	**30.27**	**35.09**	**35.89**	**+73.11**
	Estradiol	0.54	1.62	1.20	1.75	2.36	+337.04
	Ethinylestradiol	0	13.98	11.38	11.82	10.77	-22.96*

* Year 2013 when ethinylestradiol was put into use and year 2021 are compared.

Sales of diclofenac remained stable over the period concerned; on recalculation into mass units, the average annual consumption was approx. 2,060 kg.

Based on the latest ESAC-Net data on systematic consumption of anti-bacterial substances, the same or slightly higher consumption is seen in 2019 compared with 2018, and a clear decrease in 2020 in all countries except Bulgaria, which can be explained by a number of reasons.

More frequent and improper consumption of antimicrobial substances that could result in a significant increase in antimicrobial-resistance in the future has been the main cause of concern [13, 14]. While there were indications of an increased demand for antibiotics, still the situation in the EU Member States in terms of their consumption was much better than expected. It is important to note that, even though a decreasing general trend is seen, consumption of certain antibiotics decreased but sales of others were growing. While no marked changes were recorded at the EU level, there was a strong growth in the consumption of macrolides that include azithromycin in the hospital sector [15].

According to the data collected by the Lithuanian State Medicines Control Agency (LSMCA), the consumption of antibiotics concerned in Lithuania in 2017–2021 reveals a different picture. As shown by Figure 3 below, a drop in consumption of the three target antibiotics is seen only in 2020 (by 20%), with the

consumption peak recorded in 2019. According to statistical data on consumption of antibiotics, macrolides account for 13% of total consumption [16].

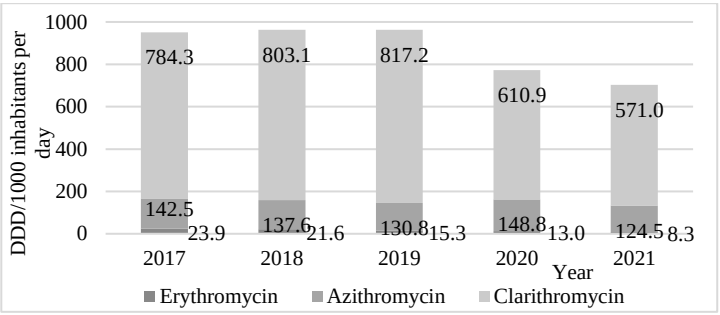


Figure 3. Consumption of macrolide antibiotics in Lithuania in the reporting years 2017–2021

Consumption of antibiotics in Lithuania is very similar to the EU average. One may assume that the level of consumption – and of release – is very high.

An overview of consumption of all the selected pharmaceutical substances over many years shows a rather stable demand for these substances and trends of changes in their consumption that lead to a conclusion that the issue of their impact will remain very relevant in future.

Investigations into the selected pharmaceutical substances were carried out in different periods. In order to focus on different groups of pharmaceutical substances, it has been decided to analyze them in phases: first – diclofenac and estradiol investigated in the environment in 2013, then – macrolide antibiotics.

Results of the SFA for the selected pharmaceutical substances

Results of the analysis of diclofenac flows in Lithuania

It was assumed, for the purposes of analytical calculations, that all the medicines purchased were consumed orally. The main processes analyzed include consumption and excretion of the substances, metabolism, accumulation, and dispersion in the environment. The review of the literature led to a conclusion that the SFA system can be divided into smaller study groups for simplification and clarity. Statistics and reports issued by the Environmental Protection Agency (EPA) provide a basis for the application of this SFA. By analyzing and systematizing the EPA data, elements of the SFA system were divided into three interrelated investigation groups: consumption, excretion and dispersion in the environment.

Functional unit is the quantity of the substance investigated, consumed over one year (kg/yr). 2,368.2 kg of diclofenac was consumed in 2013.

An analysis of the diclofenac flows has shown that approx. 92% of DCF gets into households where the majority of the pollution with this pharmaceutical substance is generated.

The results presented in the SFA scheme (see Figure 4) show that as much as 18% of unused medicines end up in landfill sites, part is disposed into sewerage, and only a small part (3%) is incinerated. This waste flow (i. e. 385.25 kg/yr of DCF) could be reduced by means of preventive measures such increasing public awareness in the area of environmental protection.

56.3% of all diclofenac sold goes to sewerage. At present, wastewater before treatment contains as much as 28% of the pollutants under investigation – because of the households not connected to the municipal wastewater collection and removal systems. However, the majority of the pharmaceutical substances (51%) are released to the environment, i. e. through surface water bodies and wastewater treatment facilities. The efficiency of wastewater purification by removing pharmaceutical substances could be improved by applying the cleaner production principle, thus reducing the quantities of residual pharmaceutical substances released to the environment.

The DCF flow analysis has established that households are the main source of pollution and wastewater treatment facilities are the main object through which the majority of pharmaceutical pollutants get into the environment.

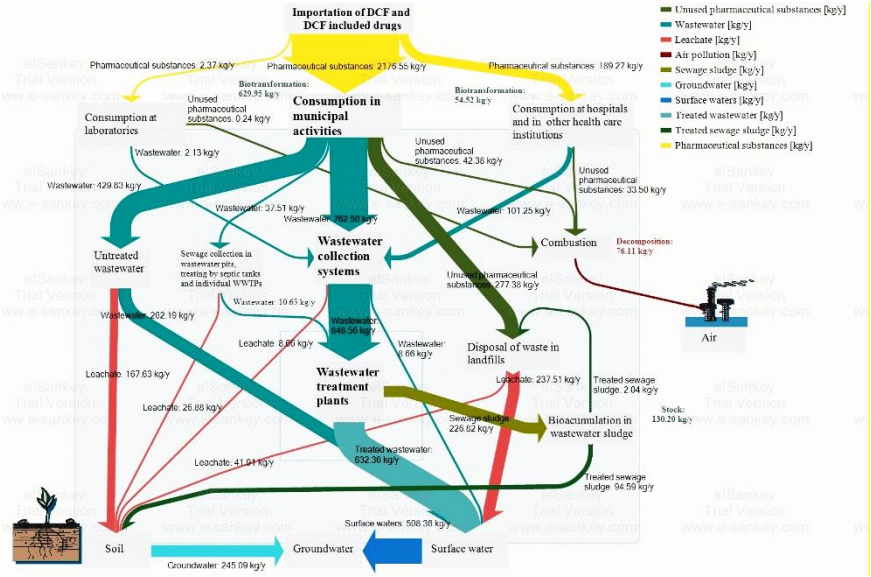


Figure 4. Diclofenac flows in Lithuania. Balance flow chart, 2013.

Results of the analysis of macrolide antibiotics flows in Lithuania

The SFA system for macrolide antibiotics was defined in a manner identical to that for the DC. Data on the total consumption of all the three substances under investigation (kg/yr.) are presented in Table 2.

Table 2. Macrolide antibiotics sales volumes in Lithuania in 2021

Target substance	Year	Quantity sold, kg/yr.	Share, %
Erythromycin	2021	8.3	1.2%
Azithromycin		124.5	17.7%
Clarithromycin		571.0	81.1%
	Total	**703.8**	

The SFA analysis has established that 39.6% of all macrolide antibiotics sold are released to wastewater treatment facilities (private or municipal), are incinerated, or end up in landfills; the remaining share is destroyed by digestion. Most medicinal preparations are released from households (96.3%). Distribution of the macrolide antibiotics flows after the consumption phase is as follows:

- Treated in private wastewater treatment facilities – 17.3%;
- Collected and treated in municipal wastewater treatment facilities – 66%;
- Incinerated – 6.4%;
- Landfilled – 8.2%;
- Released from households directly to surface water bodies – 2%.

The main flows of macrolide antibiotics are released to the environment through water bodies. The distribution of the releases affecting the natural environment is as follows:

- Soil – 40.8%;
- Surface water bodies – 41.4%;
- Full incineration (it is deemed that no active compounds remain upon incineration)– 16.7%;
- Accumulation in leachate at landfills – 1.1% (ending up in soil is probable).

Results of the SFA analysis are presented in Figure 5. The analysis is not focused on groundwater and air pollution, and the persistence of the target substances in the natural environment is not the object of this investigation, therefore, pollutant flows end in soil and surface water systems.

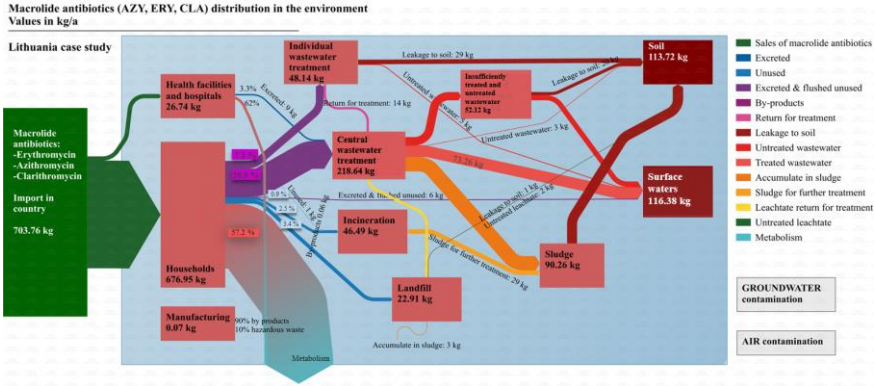


Figure 5. Flows of macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) in Lithuania in 2021

Determination of the pharmaceutical substances (DCF, E1, E2, and EE2) content in municipal wastewater in Kaunas and Marijampolė

Object of investigations. Kaunas city and Marijampolė city were selected for wastewater investigations. In 2013, Kaunas – Lithuania's second largest city had 306,888 inhabitants. Kaunas municipal wastewater treatment plant (WTP), built on the left bank of the Nemunas River, treat 66,400 m^3 of wastewater on average per day. Loading of the facilities is equivalent to pollution from up to 340,000 population equivalent (PE). The WTP employs active sludge technologies. In 2013, Marijampolė had 59,483 inhabitants; it is the 7th largest city of Lithuania. Marijampolė WTP are on the right bank of the Šešupė River; the W treatment technology consists of mechanical and biological treatment facilities with full removal of phosphorus and nitrogen. Capacity of the WTP is 22,000 m^3/d. Loading of the facilities under normal operating conditions is equivalent to pollution from up to 70,000 PE.

Both Šešupė and Nemunas rivers form part of the Nemunas basin. Both WTPs meet set requirements and the treatment is more efficient than required according to Lithuania's Wastewater Treatment Regulations.

Results of DCF, E1, E2, and EE2 analyses in wastewater. An analysis of samples of influent wastewater has established the DCF concentration of 1,590 ng/l for Kaunas WTP and of 1,520 ng/l for Marijampolė. The average DCF removal efficiency was 12.25% at Kaunas WTP, whereas the efficiency at Marijampolė WTP was 2.5 times higher (see Table 3).

Table 3. Results of determining diclofenac concentrations in wastewater

Pharma-ceutical substance	Kaunas WTP			Marijampolė WTP		
	Influent waste-water, ng/l	**Effluent waste-water, ng/l**	**Treatment efficiency, %**	**Influent waste-water, ng/l**	**Effluent waste-water, ng/l**	**Treatment efficiency, %**
DCF	1,590	1,420–1,370	10.7-13.8	1,520	1,060	30.3

Due to insufficient sensitivity of laboratory equipment (62.5–3.4 ng/l limits), it was not possible to determine E2 and EE2 concentrations in both influent and effluent wastewater (see Table 4), however, the concentration of estrone (E1) was determined.

Table 4. Results of determining E1, E2, and EE2 concentrations in wastewater

Kaunas WTP	**Influent wastewater, ng/l**		**Effluent wastewater, ng/l**		**Treatment efficiency, %**
	HK1	**HK2**	**HK1**	**HK2**	
E1	60.54	72.62	<8	<7	<86.8–90.4
E2	Not detected	Not detected	Not detected	Not detected	-
EE2	Not detected	Not detected	Not detected	Not detected	-
E1	9.40	7.10	8.02	7.16	**Detection limits, ng/l**
E2	62.50	18.72	8.48	8.04	
EE2	23.99	13.44	15.04	8.11	
Marijampolė WTP	**Influent wastewater, ng/l**		**Effluent wastewater, ng/l**		**Treatment efficiency, %**
	HM1	**HM2**	**HM1**	**HM2**	
E1	22.07	39.99	<5	<4	<77.3–90.0
E2	Not detected	Not detected	Not detected	Not detected	-
EE2	Not detected	Not detected	Not detected	Not detected	-
E1	5.96	13.60	4.68	3.38	**Detection limits, ng/l**
E2	51.85	16.00	12.76	6.42	
EE2	27.14	34.39	5.68	9.65	

Notes: H – hormone substance, K – sample taken from Kaunas WTP, M – sample taken from Marijampolė WTP.

DCF concentrations in surface water bodies are lower as compared with the environmental quality standards (EQS 100 ng/l according to Loos [17]) – from 19.2 times in the Nemunas River to 56 times in the Šešupė river. It is important that contamination of inflowing wastewater is not taken into account, due to which the concentration of pollutants in the surface water bodies could be higher.

Assessment of the environmental risk posed by the selected pharmaceutical substances

PNEC and PEC concentrations of DCF, E2 and EE2 in 2013

Studies of DCF and estradiols in wastewater were carried out in 2013, therefore, the risk assessment was made on the basis of the data for that year so

that necessary comparisons with PEC and MEC data for the same year could be made.

PEC in the wastewater treatment facilities. It has been established by investigations that 57–65% of the substances under investigation are released, in their active form, by excretion to the environment together with wastewater [18,19,20,21]. This is a theoretical value (**E_j, %)** (see Table 5). The efficiency of removing pharmaceutical substances from wastewater (**R_j, %**) was determined with regard to the wastewater treatment technology [45]. This value signifies the percentage share of the substance removed from wastewater by the methods of sludge adsorption, hydrolysis, and biodegradation (all of them).

Table 5. Consumption of DCF, E2, and EE2 (kg/yr.) in the territory under investigation (2013), influent and effluent wastewater PEC, excretion to the environment and removal efficiency

Pharma-ceutical substance	**Consumption in Kaunas, kg/yr**	**Consumption in Marijampolė, kg/yr**	**$PEC_{j,įt.}$, ng/l**	**$PEC_{j,iš.}$, ng/l**	**E_j, %**	**R_j, %**
DCF	244.318	47.265	7,121.15	5,241.17	65	26.4
E2	1.678	0.325	47.46	17.99	63	62.1
EE2	0.135	0.026	3.44	1.96	57	42.9

*Sources: **E_j (%)**: DCF – [18]; E2 – [20], EE2 – [21]; **R_j (%)** – [19].*

PEC in surface water bodies. On assessment of dilution of wastewater before treatment in the receptacle, an unacceptable theoretical impact of DCF and EE2 concentrations on the environment was established (PEC/PNEC>1) (see Table 6).

Table 6. Predicted concentrations of the pharmaceutical substances in surface water bodies and results of their environmental risk assessment

Pharma-ceutical substance	**PEC_{pav}, ng/l**	**PNEC, ng/l**	**PEC/PNEC, ng/l**
DCF	524.117	100[1]	**5.24**
E2	1.799	2[2]	0.90
EE2	0.196	0.01[2]	**1.96**

Sources: 1 – [22], 2 – [23].

The predicted n-effect concentration (PNEC) was selected under the worst-case scenario; however, a number of investigations shows that the concentration at which no effect is noticed (NOEC) can be much lower. According to the literature, the highest sensitivity was shown by the toxicological test on fish in early life stage (see Table 7).

Table 7. Maximum daily dose of DCF, E2, and EE2 (mg) and toxicological values of the substances

Pharma-ceutical substance	Maximum daily dose, mg	PNEC	Algal growth inhibition test	Daphnia magna reproduction test	Fish, early-life stage toxicity test
DCF	[2]450	[1]0.1 µg/l	[2]NOEC 10 mg/l	[2]NOEC 10 mg/l	[2]0.5 µg/l
E2	[5]0.5	[3]0.002 µg/l	[4]NOEC 80 µg/l	[4]NOEC 100 µg/l	[4]NOEC 40 ng/l
EE2	[2]0.035	[3]0.0001 µg/l	[2]0.84 mg/l	[2]0.1 mg/l	[2]0.001 µg/l

Sources: 1 – [22], 2 – [23]; 3 – [24]; 4 – [25]; 5 – [26].

DCF concentrations at points of release of wastewater after treatments are MEC/PNEC>9, therefore, there is a risk for nearby biota and natural environment (see Table 9). Considering wastewater dilution, however, the DCF concentration is acceptable to the environment.

Table 9. Comparison between measured DCF concentration (MEC) and predicted concentrations (PNEC and PEC) in wastewater

Wastewater type	MEC		MEC/PNEC		PEC/MEC	
	K	M	K	M	K	M
Influent, µg/l	1.59	1.52	15.9	15.2	4.6	4.7
Effluent, µg/l	1.42	1.06	14.2	10.6	3.7	4.9

Note: K – Kaunas city; M – Marijampolė city.

The PEC/MEC ratio is presented in Table 9. This value shows whether the applied evaluation method is accurate and whether the evaluation is adequate [27]. The value for diclofenac in the effluents from Kaunas WTP is PEC/MEC<4, which shows that the evaluation methodology is acceptable with a slight error; at other places PEC/MEC>4, which means a significant error. According to Coetsier set of criteria, when 4 < PEC/MEC < 8, this shows a considerable overestimation of PEC [27].

Discussion of results of DCF, E2, and EE2 environmental hazard assessment

The PEC/PNEC results have shown that diclofenac and ethinylestradiol can pose a significant risk to the environment as PEC/PNEC ratio exceeds 1. If the concentration of E2 and EE2 (MEC) in wastewater after treatment was at least 5 ng/l, compared with the predictable no-effect concentration (PNEC) – E2 and EE2 values (2.5 and 50, respectively) would be deemed to be unacceptable. However, having regard to their dilution in surface water bodies, the MEC/PNEC ratio is below 1, which means a theoretical acceptability of the substances for aquatic environment.

Similarly, a comparison of measured diclofenac concentrations with the predicted no-effect concentration shows that the ratio exceeds 10, which means

that the wastewater after treatment poses a hazard to the water biota at the discharger. Having regard to the WW dilution with the water in the surface body, (D=10) DCF concentration becomes theoretically acceptable.

Based on the risk assessment, the concentrations calculated by means of the risk assessment methodology can be significantly higher in localities with smaller population numbers and, on the contrary, can be acceptable when both population number and density is larger/higher. This can be determined by social characteristics of the locality that determine a higher or lower consumption levels of medicines, such as living standards, prevailing age group, etc.

A comparison between the predicted concentration (PEC) and measured concentration (MEC) with the predicted no-effect concentration has shown that diclofenac is a potential environmental hazard. Both results are comparable, which also testifies to the reliability of the PEC methodology.

PNEC and PEC of AZI, CLA and ERY antibiotics in 2021

Removal (R_j) and excretion (E_j) factors as well as the value of the predicted no-effect concentration (PNEC) were taken from literature. These values are provided in Table 10.

Table 10. Consumption of substances under investigation (kg/yr) in the territory concerned, predicted environmental concentration ($PEC_{(j,iš)}$) in wastewater and in surface water bodies $PEC_{(j,pav)}$, E_j and R_j fractions, and PNEC.

Target pharmaceutical substance	**Sales in Klaipėda, Palanga, Kretinga and Nida, kg/yr**	**$PEC_{j,eff}$, ng/l**	**$PEC_{j,surf}$, ng/l**	**[1] E_j, %**	**[2] R_j, %**	**[3] PNEC, ng/l**
AZI	9.06	17.32	1.73	0.12	0.786	20
KLA	52.89	724.45	72.45	0.4	0.54	70
ERI	1.42	7.42	0.74	0.15	0.533	20

Sources: 1 – [28]; 2 – [29,30,31,32,33]; 3 – [34,35,36].

PNEC values equivalent to values 1,000 times lower than those applied to species investigated during acute toxicity tests were adopted [34,35]. RQ ($PEC_{iš}$/PNEC) for clarithromycin was the highest value in surface water bodies – exceeding 1, which shows that the current clarithromycin consumption level poses an environmental hazard. Whereas clarithromycin's RQ>10 in wastewater at the discharger shows a considerable risk for the natural environment, specifically, biota in the WTP area. For both erythromycin and azithromycin in surface water bodies, RQ<1, which means that, at present, the consumption of these antibiotics should not pose a risk for the environment, however, if consumption growth rate exceeds the rate of increase in the population, RQ should be recalculated in order to verify that the risk remains insignificant. RQ values for effluents ($PEC_{iš}$/PNEC) and surface water bodies (PEC_{pav}/PNEC) are provided in Figure 6.

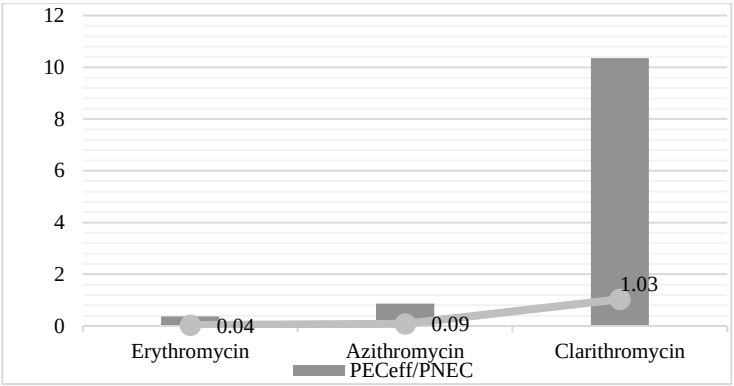


Figure 6. Ratio between the predicted environmental concentrations (PEC) of macrolide antibiotics in wastewater released from wastewater treatment facilities and in surface water bodies in Klaipėda district and the predicted no-effect concentrations (PNEC)

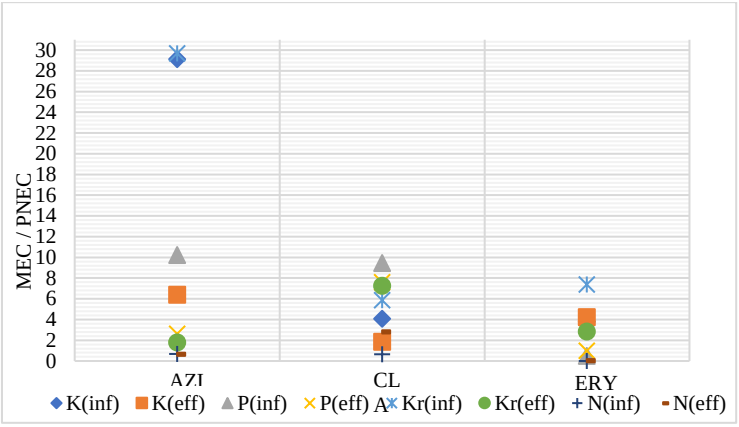
Discussion of the results of the AZI, CLA, and ERY environmental risk assessment

Environmental risk assessments in relation to the presence of antibiotics in surface water bodies were carried out for wastewater treatment facilities in four towns of Klaipėda county that fall within the Nemunas river basin. All four WTPs employ combined mechanical and biological treatment methods, the facilities comply with the standards and their capacity is sufficient for efficient WW treatment according to the Wastewater Treatment Regulations.

The values of antibiotic concentrations in municipal wastewater (before and after treatment) were used for the risk assessment. The concentrations were taken from the latest publicly available data from MORPHEUS project [37].

Concentrations of target pharmaceutical substances in influent and effluent wastewater, measured in winter, were used to determine the MEC/PNEC. The MEC value was considerably higher, probably due to higher consumption of antibiotics in the winter season.

Figure 7 shows the MEC ratio in the influent and effluent wastewater and the values of the predicted no-effect concentrations (PNEC) of the target substances. The PNEC values were used according to [34,35,36,38].



Abbreviations in the figure: K – Klaipėda; P – Palanga; Kr – Kretinga; N – Nida; inf. – influent wastewater; eff. – effluent wastewater.

Figure 7. The ratio between the measured environmental concentrations (MEC) of macrolide antibiotics in the WTP influent and effluent wastewater and the PNEC.

The investigation has shown that all three macrolide antibiotics analyzed potentially pose a risk to the aquatic environment as the values almost always exceed 1. The highest ratios were determined in the influent wastewater in Klaipėda and Kretinga, where the value is near 30 for azithromycin, and in the effluents in Palanga and Kretinga, where the value exceeds 7 for clarithromycin. RQ for clarithromycin exceeds 1 in wastewater after treatment in all four WTP, which potentially poses a threat to the environment, and varies from 1.85 (Klaipėda) and 7.61 (Palanga). RQ < 1 for azithromycin was determined only in the wastewater released from Nida WTP; in other three towns, it varied from 1.80 (Kretinga) to 6.40 (Klaipėda), which also testifies to a potential impact on the environment. RQ > 1 for erythromycin was established in wastewater after treatment in Klaipėda and Kretinga, whereas in Palanga and Nida its RQ < 1.

Table 11 presents the values of the PECj,k / MEC ratio. Reliability of PEC for AZI, CLA, and ERY is acceptable, or acceptable with a slightly exceeded value in three out of four WTPs. Whereas at Nida WTP, PEC values for CLA and AZI in effluents were slightly exceeded, and for ERY – exceeded considerably (see Table 11).

Table 11. PEC reliability values (acceptable, exceeded, and reduced) based on the PEC/ MEC ratio (according to Coetsier set of criteria).

		Klaipėda		Palanga		Kretinga		Nida	
		K_{inf}	**K_{eff}**	**P_{inf}**	**P_{eff}**	**Kr_{inf}**	**Kr_{eff}**	**N_{inf}**	**N_{eff}**
$PEC_{j,k}$/ MEC	**AZI**	0.14	0.12	0.39	0.29	0.14	0.43	5.78	1.20
	CLA	5.49	5.58	2.38	1.36	3.83	1.43	33.51	3.68
	ERY	0.21	0.09	1.59	0.37	0.11	0.13	-	12.37

Note: Abbreviations used in the table: azithromycin (AZI), clarithromycin (CLA), and erythromycin (ERY); inf – influent wastewater, eff – effluent wastewater.

On proper evaluation of the deviations, this risk assessment methodology could be applied in cases when measuring the concentrations of pharmaceutical substances or other pollutants is impossible.

Application of the environmental management system theory to the control of pharmaceutical substance concentrations in wastewater

The substances flow analysis corroborated the statement from the literature to the effect that domestic wastewater from households is the main source of environmental pollution with pharmaceutical substances. Therefore, it is obvious that domestic wastewater should be the main object of investigation for the environmental management system. As shown by the literature review, the share of households not connected to wastewater treatment networks is still large, particularly, in rural areas and city districts. It is estimated that wastewater from such households accounts for 12.6% of total domestic wastewater flows, and ends up in soil untreated. Therefore, as already mentioned, controlling effluents from both municipal wastewater treatment facilities and wastewater from households is important.

Parameters significant for the environmental management system or, in other words, the system's variables include annual consumption of pharmaceutical substances at a national level (kg/yr) and the concentration of such pollutants in wastewater (ng/l) – the main parameter to be controlled in wastewater.

The environmental management system is developed specifically for Lithuania. The purpose of the system expressed as a function is:

$X_{įt}(t) = 0.$

The main strategic solution in the water policy area explaining the function is as follows: gradual reduction of pollution with pharmaceutical substances and termination of their release. With this aim in view, the objective of the system $X_{iš}(t)$ should be implemented by a gradual reduction: by 2025 – $X_{įt.} \rightarrow 1/4\ X_{iš}$; from 2025 until 2030 – $X_{įt.} \rightarrow 1/2\ X_{iš}$; from 2030 until 2035: $X_{įt} \rightarrow 0\ X_{iš}$.

This section of the thesis analyses in detail the main management tools proposed for the system as well as management solutions that support them, disturbances and other factors affecting the system, i. e. all its components. At the same time, each means of control or solution proposes recommendations for the control of environmental pollution with pharmaceutical substances and for consistent reduction of their releases to the environment. Summarizing statements and detailed recommendations are provided in the thesis.

The following are the main realistic controls that would be most efficient in the short term in order to attain the set objective in the wastewater management and water policy area:

a) Integration of most efficient treatment processes in the municipal wastewater treatment facilities in terms of both cost and environmental protection;
b) Separating wastewater flows from healthcare establishments.

To sum up, mechanical and biological treatment processes, mainly the active sludge technology, are used in Lithuania's wastewater treatment facilities. Treatment efficiency is quite high and wastewater after treatment meets set requirements in most cases. However, there is not enough information and too few studies were carried out in the area of removal of pharmaceutical substances from wastewater in order to reduce pollution with such substances. A stage-four treatment technology by adding ozoning or active carbons technologies to the existing ones is proposed [29,39]. On modernization of wastewater treatment facilities, in theory, the direct load of pollutants should be reduced by 51% for diclofenac and by 60–70% for macrolide antibiotics in general [39]. In addition, new advanced wastewater treatment technologies are being developed such as electrochemical treatment and use of ferments, Fenton reaction, fungi, coagulation, or flocculation. Other advanced oxidation technologies can be employed as well. A combined ozoning and filtration system could be used to increase treatment efficiency.

The management system is provided in Figure 8.

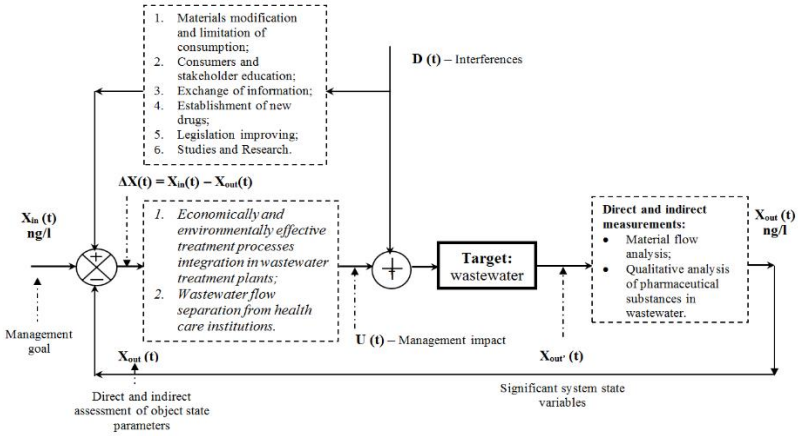


Figure 8. Environmental management system for wastewater containing pharmaceutical substances

CONCLUSIONS

1. From the analysis of the application of substance flow analysis for studies of pharmaceutical substances in the environment, it has been found that the SFA helps to consistently identify residues of pollutants and potential sources of pollution with pharmaceutical substances in the aquatic environment. It has also been found that the substance flow analysis can be applied on a broad scale (i.e. the scale of regions, cities, the state, areas of river basins, etc.) and is suitable for the simulation of the persistence and distribution of chemical substances in the environment. It has been found that there were no studies examining the impact of pharmaceutical substances on the environment with assessment of the full life-cycle of pharmaceutical substances from production to their entry into the environment on a national scale as a result of anthropogenic activity.

2. From the analysis of the consumption of the study pharmaceutical substances, it has been found that the overall demand for medicines increased by 56% in Lithuania in 2009–2021. It has been found that the consumption of diclofenac was very similar during the period from 2009 to 2021, reaching about 20.5 DDD/1000 Lithuanian population/day. During 2017–2021, the average yearly consumption was 2,060 kg. Meanwhile, the consumption of estradiol grew rapidly and changed by 337% during the period from 2009 to 2021. During the study of trends in the consumption of macrolide antibiotics, it was found that the general trend in the consumption of antibiotics was changing with an overall decrease in 2017–2021.

3. According to results of the diclofenac flow analysis in Lithuania, 11.7% of total diclofenac quantity sold in Lithuania end up in landfills, 3.2% are managed as hazardous waste, 28.8% is metabolized in human body, and 56.3% is released into wastewater. 51% of DCF after consumption removal goes to wastewater treatment facilities with wastewater.

   From the analysis of the flows of selected macrolide group substances in Lithuania, it has been found that 96.3% of all the generated pollutants are discharged into the environment through households. It has been found that 71% of all the discharged pollutants enter the environment through wastewater treatment facilities. It has also been found that a large portion of the active substances of medicinal preparations still enters the environment together with untreated wastewater from the city's wastewater treatment facilities. According to the results of the substance flow analysis, 18.7% of the total quantity of antibiotics of the

macrolide group investigated end up in the environment together with untreated wastewater.

4. The risk assessment performed for diclofenac and estradiols has shown that the estimated predicted DCF and EE2 concentration in surface water bodies is unacceptable to the environment (RQ > 1). It has been found that the PEC/PNEC (RQ) and MEC/PNEC are comparable between themselves and measured DCF concentrations in wastewater after treatment constitute a potential environmental hazard in the wastewater treatment facilities of both Kaunas and Marijampolė (MEC/PNEC > 10).

   The risk assessment performed for macrolide antibiotics erythromycin, clarithromycin, and azithromycin has revealed that the predicted concentrations in wastewater can also pose a threat to the aquatic environment based on the level of consumption of these medicines in 2021. For clarithromycin, RQ>10 in effluents and RQ > 1 in surface water bodies was determined, which shows a potential impact of this antibiotic on the environment. A comparison of MEC antibiotics of the macrolides group in wastewater after treatment with the PNEC has shown that all the three substances pose a potential hazard to the environment as the ratio is over 1 in almost all cases.

   In the cases of all the investigated pharmaceutical substances, particularly significant impact on the natural environment may be at points where wastewater after treatment is released.

5. Following the analysis of the investigated pharmaceutical substances, a closed disturbance compensation environmental management system for the management of concentrations in wastewater with integrated recommendations was proposed. The recommendations presented in the created management system are related to modernization of technologies, updating of analyses and investigations, the improvement of legal acts and financing of projects, development of new medical products and raising awareness among consumers. Owing to the implementation and control of the proposed technological management measures, the pollution of surface waters with pharmaceutical substances should decrease by about 71% for azimitrocin, erythrocin, and claritrocin and by about 51% for diclofenac by 2025.

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2. **Baranauskaitė-Fedorova, Inga**; Dvarionienė, Jolanta; Nikiforov, Vladimir A. *Management of pharmaceutical substances in the environment: Lithuanian case study* // Water science and technology. London : IWA Publishing. ISSN 0273-1223. eISSN 1996-9732. **2016**, vol. 74, iss. 6, p. 1255-1265. DOI: 10.2166/wst.2016.289. [Science Citation Index Expanded (Web of Science); Scopus; MEDLINE] [IF: 1,197; AIF: 3,449; IF/AIF: 0,347; Q3 (2016, InCites JCR SCIE);
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CURRICULUM VITAE

Personal information	
Name Surname	**Inga Baranauskaitė-Fedorova**
E-mail	inga.baranauskaite22@gmail.com; inga.baranauskaite@ktu.lt
Date of birth	1989 06 01
Education	
Date	**2014 – 2022**
Qualification	Doctoral studies, Environmental Engineer (04T)
Institution	Kaunas University of Technology, Institute of Environmental Engineering (APINI)
Date	**2012 – 2014**
Qualification	Master of Environmental Protection Engineering
Institution	Kaunas University of Technology, Institute of Environmental Engineering (APINI)
Date	**2008 – 2012**
Qualification	Bachelor of Environmental Protection Engineering
Institution	Kaunas University of Technology, Faculty of Chemical Technology, Department of Environmental Technologies

SANTRAUKA

Temos aktualumas

Paviršinio vandens cheminė tarša kelia grėsmę vandens aplinkai. Jos poveikis gali būti ūmus ir ilgalaikis toksiškumas vandens organizmams, teršalų kaupimasis ekosistemose ir biologinės įvairovės nykimas, taip pat pavojus žmonių sveikatai. 2013 m. direktyvoje 2013/39/EB tarp prioritetinių medžiagų vandens politikos srityje buvo pirmą kartą paminėtos farmacinės medžiagos – diklofenakas, 17-β-estradiolis ir 17-α-etinilestradiolis, siekiant surinkti stebėjimo duomenis, palengvinančius atitinkamų priemonių, skirtų tų medžiagų keliamai rizikai spręsti, nustatymas. 2015 m. Europos Sąjungos (ES) mastu stebimų medžiagų sąrašas buvo papildytas makrolidų grupės antibiotikais – eritromicinu, klaritromicinu, azitromicinu [1]. Pasaulio sveikatos organizacija vertina makrolidus kaip vienus iš svarbiausių antibiotikų žmonių medicinoje pasaulyje. Antibiotikai dažniausiai žinomi kaip vaistai, skirti žmonių ir gyvūnų infekcinėms ligoms gydyti, arba kaip gyvulių augimo stimuliatoriai, naudojami žemės ūkyje ir akvakultūroje [2]. Per didelis ir didėjantis antibiotikų vartojimas ir piktnaudžiavimas šiais vaistais kelia visuomenės susirūpinimą [3]. Didžiausią nerimą kelia tai, kad jų atsiradimas gali paspartinti atsparumo antibiotikams plitimą gamtinėje aplinkoje [4,5], taigi tai turi įtakos žmonėms. Net iki 90 % farmacinių medžiagų į aplinką patenka pradinės formos [6]. Tačiau antibiotikai išsiskiria kaip metabolitai arba pirminiai junginiai, kurie, esant nevisiškam metabolizmui, ne iki galo suskaidomi žarnyne ir, praėję per nuotekų surinkimo ir valymo tinklus, patenka į vandens aplinką ir ekosistemas [7]. Jų likučiai į vandens ir sausumos aplinką patenka įvairiais būdais, tačiau labiausiai paplitęs jų kelias – pasiskirstymas per miesto valymo įrenginius [8].

Labai svarbu paminėti, kad jau daugiau nei kelis dešimtmečius žinoma, kad įprastiniai nuotekų valymo metodai nėra pritaikyti tinkamam jų valymui nuo antibiotikų ar kitų farmacinių medžiagų likučių, tai yra vis dar didelė nerimą kelianti problema [9]. Kaip jau buvo minėta, antibiotikų likučiai vandens telkiniuose kelia didelį susidomėjimą dėl nuolatinio jų atsiradimo, pseudoatsparumo, ekotoksinio poveikio žmogaus sveikatai ir gamtinei aplinkai. Holistiniu požiūriu, atsižvelgiant į farmacinių medžiagų šaltinius, išmetimus ir susijusią riziką aplinkai, labai svarbu nustatyti, stebėti ir valdyti vaistinių medžiagų patekimą į aplinką. Tačiau taip pat svarbu paminėti, kad iki šiol Lietuvoje į stebėsenos sąrašą įtrauktų farmacinių medžiagų tyrimų buvo atlikta labai nedaug.

Remiantis atlikta literatūros analize, medžiagų srautų analizės (MSA) metodas suteikia aiškų pagrindą darniam aplinkos valdymui, leidžiantį kiekybiškai įvertinti medžiagų srautus per socialines ir ekonomines sistemas (pvz.: verslo, pramonės, miesto ar valstybės lygmeniu), todėl valdydami medžiagas jų lygmeniu būtų galima išspręsti išteklių vartojimo ir aplinkos taršos mažinimo klausimus

[10,11]. MSA buvo pasirinkta tyrimui kaip tinkamiausia valdymo priemonė pagrindiniams farmacinių medžiagų šaltiniams bei pasklidimo keliams nustatyti šalies lygmeniu.

Hipotezės:

1. Integruojant farmacinių medžiagų srautų analizę į rizikos aplinkai vertinimo metodiką galima sistemiškai nustatyti valstybės lygiu potencialius taršos farmacinėmis medžiagomis į aplinką šaltinius ir kartu poveikio aplinkai tyrimams tinkamiausią aplinkos terpę ar konkretų objektą.
2. Nuotekų valymo įrenginiai atlieka svarbų vaidmenį valdant farmacinių medžiagų patekimą į vandens aplinką ir labai prisideda kuriant farmacinių teršalų aplinkoje valdymo priemones.

Darbo objektas – farmacinės medžiagos, pagal Komisijos sprendimo (ES) 2015/495, kuriuo sudaromas medžiagų, stebėtinų Sąjungos mastu vykdant vandens politiką pagal Europos Parlamento ir Tarybos direktyvą 2008/105/EB, įtrauktos į sąrašą: diklofenakas (DCF), 17-β-estradiolis (E2), 17-α-etinilestradiolis (EE2), estronas (E1), eritromicinas (ERY), azitromicinas (AZI), klaritromicinas (CLA).

Tyrimo ribos – Lietuvos valstybė.

Darbo tikslas – atlikti 7 farmacinių medžiagų, DCF, E2, EE2, E1, ERY, AZI, CLA, rizikos vandens aplinkai tyrimus, remiantis medžiagų srautų analize.

Darbo uždaviniai:

1. Atlikti medžiagų srautų analizės taikymo farmacinių medžiagų tyrimams aplinkoje analizę;
2. Atlikti tiriamųjų farmacinių medžiagų suvartojimo analizę Lietuvoje;
3. Atlikti pasirinktų farmacinių medžiagų srautų analizę ir sudaryti šių medžiagų balansines srautų schemas Lietuvos lygmeniu;
4. Atlikti tiriamų medžiagų poveikio paviršinio vandens aplinkai rizikos vertinimą;
5. Pasiūlyti tiriamųjų farmacinių medžiagų koncentracijų valdymo nuotekose sistemą su integruotomis rekomendacijomis dėl taršos farmacinėmis medžiagomis prevencijos vandens aplinkoje.

Mokslinis darbo naujumas. Nors vaistuose esančių aktyvių medžiagų keliama rizika aplinkai yra plačiai tiriama ir yra nustatytos ir EB apibrėžtos šių medžiagų leidžiamų koncentracijų paviršiniuose vandenyse ribos, tačiau Lietuvoje atlikta

labai mažai tyrimų ir pateikta duomenų apie farmacinių medžiagų paplitimą, koncentracijas paviršiniuose vandenyse bei taršos prevencijos ir valdymo rekomendacijų. Darbe pirmą kartą Lietuvoje analizuojami diklofenako bei makrolidų grupės antibiotikų medžiagų srautai Lietuvos lygmeniu, pateikiant balansinius modelius nuo medžiagų importo į Lietuvą iki jų patekimo į gamtinę aplinką. Literatūros analizės metu nepavyko surasti tyrimų, taikančių pilną medžiagų srautų analizę valstybės lygiu. Dažniausiai MSA buvo taikytos UBR lygiu ar norint išanalizuoti teorinę farmacinių medžiagų apkrovą NV, tenkančią atskiram technologiniam nuotekų valymo procesui. Sukurta metodika bei pasiūlyta tiriamų medžiagų valdymo aplinkoje sistema ir rekomendacijos galėtų būti taikomos panašių į Lietuvą šalių praktikoje.

Darbo praktinė vertė. Atlikta analizė ir pasiūlyta valdymo sistema farmacinių medžiagų nuotėkiui į aplinką mažinti prisidėtų prie vandens politikos tobulinimo Lietuvoje ir aplinkos apsaugos švietimo tikslais. Siūloma tyrimų metodika gali būti naudojama norint įvertinti numatomas farmacinių medžiagų likučių koncentracijas paviršiniuose vandenyse bei įvertinti jų keliamą riziką aplinkai. Metodika gali būti pritaikyta šalims su panašia sociokultūrine padėtimi, išsivystymo lygiu, panašiomis atliekų tvarkymo ir nuotekų valymo sistemomis. MSA metodas padeda atskleisti pagrindinį taršos šaltinį farmacinėmis medžiagomis ir nustatyti pagrindinį taršos objektą, per kurį ji pasklinda į aplinką.

Darbo aprobacija. Disertacijos tema paskelbtos 3 publikacijos, iš jų dvi leidiniuose, referuojamuose Mokslinės informacijos instituto duomenų bazėje Clarivate Analytics Web of Science, turinčiuose citavimo indeksą, 1 mokslinis straipsnis publikuotas recenzuojamame mokslo leidinyje, referuojamame kitose duomenų bazėse.

Disertacijos tema paskelbti tyrimų duomenys 4 mokslinėse tarptautinėse konferencijose: 2021 m. – „Computational Science and Its Applications“; 2016 m. – „Ecotechnologies for Wastewater Treatment“ – 3-ioji IWA ecoSTP 2016 specializuota konferencija Kembridže, Didžiojoje Britanijoje; 2015 m. – „Micropol & Ecohazard Conference 2015, 9th IWA Specialist Conference on Assessment and Control of Micropollutants and Hazardous Substances in Water“, Singapūre; 2014 m. – „Littoral 2014. Facing Present and Future Coast Challenges“, Klaipėdoje.

Darbo apimtis ir struktūra. Darbą sudaro įvadas ir trys pagrindiniai skyriai, išvados, literatūros sąrašas (151 literatūros šaltiniai, iš jų 127 moksliniai). Darbe taip pat yra santrauka, santrumpų sąrašas, paveikslų ir lentelių sąrašai, kuriuose pateikiama 24 paveikslų ir 18 lentelių. Darbo apimtis 102 lapai.

IŠVADOS

1. Atlikus medžiagų srautų analizės taikymo farmacinių medžiagų tyrimams aplinkoje analizę nustatyta, kad MSA padeda nuosekliai nustatyti teršalų likučius bei potencialius taršos šaltinius farmacinėmis medžiagomis vandens aplinkoje. Taip pat nustatyta, kad medžiagų srautų analizė gali būti taikoma dideliu mastu (t. y. regionų, miestų, valstybės, upių baseinų rajonams ir pan.), yra tinkama cheminių medžiagų aplinkoje išlikimui ir paplitimui modeliuoti. Nustatyta, kad nebuvo atlikta tyrimų, nagrinėjančių farmacinių medžiagų poveikį aplinkai vertinant visą farmacinių medžiagų gyvavimo ciklą nuo gamybos iki jų patekimo į aplinką dėl antropogeninės veiklos visos šalies mastu.

2. Atlikus tiriamųjų farmacinių medžiagų suvartojimo analizę nustatyta, kad nuo 2009 iki 2021 metų bendras vaistų poreikis Lietuvoje išaugo 56 %. Buvo nustatyta, kad dikofenako suvartojimas nuo 2009 iki 2021 metų buvo labai panašus, siekė apie 20,5 DDD/1000 Lietuvos gyventojų/per dieną. 2017–2021 metais suvartojimo vidurkis per metus buvo 2060 kg. O estradiolio suvartojimas stipriai augo ir nuo 2009 metų iki 2021 metų kito 337 %. Makrolidų grupės antibiotikų suvartojimo tendencijų tyrimu metu buvo nustatyta, kad bendra antibiotikų suvartojimo tendencija 2017–2021 metais buvo kintanti, apžvelgiant bendrai – mažėjanti.

3. Atlikus diklofenako srautų Lietuvoje analizę nustatyta, kad į atliekų sąvartynus patenka 11,7 %, sutvarkyta kaip pavojingos atliekos 3,2 %, žmogaus organizme metabolizuojasi 28,8 %, o į nuotekas patenka 56,3 % viso Lietuvoje parduoto DCF. Į nuotekų valymo įrenginius su nuotekomis patenka 51 % viso po vartojimo šalinimo DCF.
   Atlikus pasirinktų makrolidų grupės medžiagų srautų Lietuvoje analizę buvo nustatyta, kad 96,3 % visų generuojamų teršalų į aplinką patenka per namų ūkius. Nustatyta, kad 71 % visų išleidžiamų teršalų į aplinką patenka per nuotekų valymo įrenginius. Taip pat nustatyta, kad vis dar didelė dalis veikliųjų vaistinių preparatų medžiagų patenka į aplinką kartu su nevalytomis nuotekomis iš miesto nuotekų valymo įrenginių. Remiantis medžiagų srautų analize su nevalytomis nuotekomis, į aplinką patenka 18,7 % viso vertinto makrolidų grupės antibiotikų kiekio.

4. Diklofenako bei estradiolių rizikos vertinimo metu buvo nustatyta, kad apskaičiuota prognozuojama DCF ir EE2 koncentracija paviršiniuose

vandenyse yra nepriimtina aplinkai (RQ > 1). Buvo nustatyta, kad PEC/PNEC (RQ) bei MEC/PNEC rezultatai yra palyginami tarpusavyje, kad išmatuotos DCF koncentracijos valytose nuotekose tiek Kauno, tiek Marijampolės nuotekų valyklose taip pat yra potencialiai keliančios riziką aplinkai (MEC/PNEC > 10).
Makrolidų grupės antibiotikų azitromicino, klaritromicino ir eritromicino rizikos vertinimas parodė, kad numatomos koncentracijos nuotekose pagal šių vaistų suvartojimo lygį 2021 metais taip pat gali kelti pavojų vandens aplinkai. Klaritromicino RQ > 10 ištekančiose nuotekose bei RQ > 1 paviršiniuose vandenyse, kas rodo potencialų antibiotiko poveikį aplinkai. Makrolidų grupės antibiotikų MEC valytose nuotekose palyginimas su PNEC parodė, kad visi trys antibiotikai kelia potencialų pavojų vandens aplinkai, nes koeficientas beveik visais atvejais viršija 1.
Visų tirtų farmacinių medžiagų atvejais ypač reikšmingas poveikis gamtinei aplinkai gali būti keliamas vietose, kur yra išleidžiamos valytos nuotekos.

5. Atlikus tiriamųjų farmacinių medžiagų tyrimus pasiūlyta uždaroji trikdžių kompensavimo aplinkos valdymo sistema koncentracijoms valdyti nuotekose su integruotomis rekomendacijomis. Sukurtoje vadybos sistemoje pateikiamos rekomendacijos yra susijusios su technologijų modernizavimu, analizių ir tyrimų atnaujinimu, teisės aktų tobulinimu ir projektų finansavimu, naujų vaistų kūrimu ir vartotojų informuotumo didinimu. Įgyvendinus ir kontroliuojant siūlomas technologines valdymo priemones tarša farmacinėmis medžiagomis azimitrocinu, eritrocinu ir klaritrocinu į paviršinius vandenis iki 2025 metų turėtų sumažėti ~71 %, diklofenaku ~51%.

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Išleido Kauno technologijos universitetas, K. Donelaičio g. 73, 44249 Kaunas
Spausdino leidyklos „Technologija“ spaustuvė, Studentų g. 54, 51424 Kaunas