



Management of Environmental Risks in the Life Cycle of Human Pharmaceuticals in Lithuania

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The paper analyzes and outlines the peculiarities and importance of different stages of the life cycle of human pharmaceuticals in Lithuania with regard to their environmental impact, and points out to the need of risk reduction measures.

Use stage and disposal of unused, unwanted or expired medicines are those stages when the biggest emissions occur and risk management is not adequate yet. Pharmaceuticals consumption distribution profile is presented in the article. Environmental risk assessment was carried out indicating that for Lithuania pharmaceutical substances consumed in amounts over 25 kg/year might be causing a risk to the environment. Three substances have PEC/PNEC ratios above 1 under the worst case calculations. In reality in spite of high environmental load, one of them – amoxicillin – is not likely to pose a risk due to its low environmental stability and high removal rates in WWTPs. The other two substances show a potential of environmental risk even after calculation of the refined PEC/PNEC ratio. The importance of proper wastewater treatment needs to be underlined due to inevitable excretion of pharmaceutical substances from the use phase.

The most popular way to dispose of unused, unwanted or expired medicines in Lithuania is via the household waste. The system for collection of residual medicines is not properly functioning yet. Good management of environmental risk requires establishment of an effective system to collect and destroy pharmaceuticals in an environmentally sound manner.

Key words: pharmaceuticals, life cycle, emissions, disposal.

1. Introduction

Life of modern society is inconceivable without the use of medicines. A vast number of various pharmaceutical substances are synthesized or extracted for their biological effect to cure diseases, fight infections or reduce symptoms. Unfortunately, pharmaceuticals not only ensure the welfare of society. If these substances enter the environment they may have an effect on aquatic or terrestrial organisms due to their biological properties, and some of them may bio-accumulate [1, 2]. Pharmaceuticals may enter the environment during different stages of their life cycle [1, 2, 3, 4]. Some of these stages are more relevant than the others with regard to the ability of pharmaceutical to “escape” to the ambient environment.

The purpose of the current paper is to analyze and outline the peculiarities and importance of different stages of life cycle of human pharmaceuticals in Lithuania with regard to their environmental impact, and to point out the need of risk reduction measures.

2. Life cycle of pharmaceuticals

The life cycle of human pharmaceuticals is briefly presented in Fig.1. Releases to the environment may occur during all stages, requiring implementation of proper risk reduction and management measures.

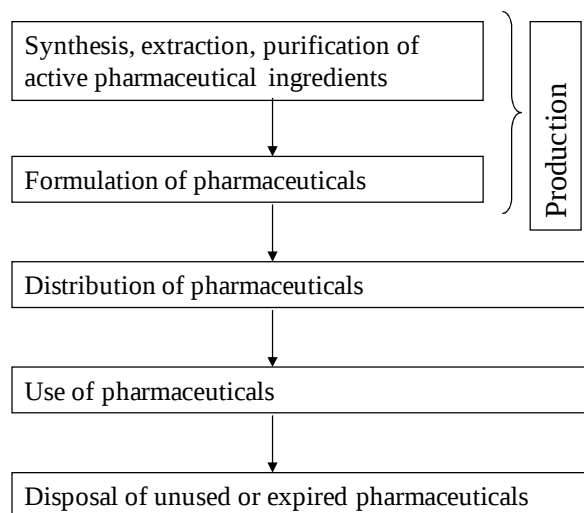


Fig. 1. Scheme of the life cycle of human pharmaceuticals

3. Risk management in life cycle stages

3.1. Production and distribution stages

Currently eight companies hold a membership of Lithuanian Pharmaceutical Manufacturers Association. The largest Lithuania's pharmaceutical company is Sanitas, which produces generic pharmaceutical products. Other companies to mention are a producer of drugs, vitamins and food additives Valentis Ltd, joint-stock company Aconitum, which manufactures herbal and other natural preparations, company Gamtos namai, which produces vitamins and other nutraceuticals, some other manufacturers of herbals and natural products, also modern biotechnology companies Sicor Biotech Ltd and Fermentas Ltd. Lithuanian biotechnology industry is regarded as one of the most sophisticated in Central and Eastern Europe. However, pharmaceutical companies in Lithuania remain very small by industrial standards. It is important to point out to the fact that producers of pharmaceuticals are required to implement standards of Good Manufacturing Practice. Thus, the production phase is well-controlled and emissions of substances to the environment are minimal.

Emissions can also be ruled out during the distribution stage. There are several dozens of wholesalers, and several hundreds of pharmacies in Lithuania. They have developed mechanisms for returning the residual (unsold, outdated) pharmaceuticals back to their producers or to the pharmaceutical waste management company. Distributors are required to have Good Distribution Practice Certificate and to follow the standards of Good Manufacturing Practice.

3.2. Use stage

The use stage is one of those in the life cycle of pharmaceuticals which deserves a particular attention because of possible emissions to the environment. A part of pharmaceuticals used by humans are excreted in the urine and faeces as a mixture of unchanged substances and metabolites. Excretion rates range as wide as from nearly 0% to nearly 100% [5, 6].

The accurate statistics about the use of individual compounds is not readily available because of privacy and industry competition issues. The current analysis was carried out based on sales statistics of 2005, which were made available for scientific purposes by JSC IMS Health [7].

Data were expressed in DOT (days of treatment) units. For risk assessment purposes data must be expressed in mass units. The following formula was used for the calculations:

$$M = \frac{DOT \times DDD}{F} \quad (1)$$

where:

M – consumption of pharmaceutical substance in mass units, kg;

DOT – days (doses) of treatment, absolute for 2005;

DDD – daily defined dose;

F – conversion factor for units adjustment

DDD values were obtained from "ATC/DDD index 2006", available from [8]. Conversion factor was used for obtaining results expressed in kilograms.

The calculation is straightforward in cases, when a substance belongs to one ATC code, and when it is assigned one single DDD. For example, fluoxetine has ATC code N06AB03, and its DDD is 20 mg. Having in mind that the consumption of fluoxetine in Lithuania in 2005 was 968840 DOT, consumption in mass units was calculated as follows:

$$M_{\text{fluoxetine}} = \frac{968840 \times 20\text{mg}}{1000000} = 19.38\text{kg} \quad (2)$$

However, there are many pharmaceutical substances with two or more ATC codes, with two or more different DDD values. In this study the worst case was analyzed by using the highest DDD value for calculations, considering that consumption in mass units might be overestimated in such cases. For example, finasteride can have ATC code D11AX10 with DDD of 1 mg, and it can also have ATC code G04CB01 with DDD of 5 mg. In this case, consumption of finasteride in mass units was calculated as follows:

$$M_{\text{finasteride}} = \frac{746010 \times 5\text{mg}}{1000000} = 3.73\text{kg} \quad (3)$$

It was assumed that sales data equalled consumption.

Total consumption of pharmaceuticals in Lithuania in 2005 included 517 pharmaceutical substances. This variety is still small comparing to the other developed European countries. For example, approximately 2000 different human pharmaceutical substances are registered for use in the UK [9], about 850 active substances for human use in the Netherlands [10].

After exclusion of substances of little interest with regard to the environmental risk (vitamins, microelements, substances synthesized in human body), 438 pharmaceuticals remained. A distribution profile of total consumption in 2005 is presented in Table 1. The majority of pharmaceutical substances (48.2 %) were consumed in amounts between 1 kg and 100 kg. 5 % of substances were consumed in

negligible amounts below 1 g. 4.4 % were consumed between 1 and 10 tons, and only 0.9 % were consumed in more than 10 tons. Among these are aspirin, paracetamol, amoxicillin, and metformin. Similar substances prevail in the other countries as well. For example, the top three compounds prescribed in the UK in 2000 were paracetamol, metformin and ibuprofen [11].

When medicines are consumed, a part of pharmaceutical substances are excreted in the urine and faeces as a mixture of unchanged substance and metabolites [6]. They enter sewage systems and may reach water bodies if not eliminated or degraded. Environmental risk assessment of pharmaceuticals has been carried out for the use phase in order to investigate whether some special environmental risk reduction measures are needed.

Table 1. Human pharmaceuticals consumption distribution profile in Lithuania, 2005

	<0.001 kg	0.001 – 1 kg	1 – 100 kg	100 – 1000 kg	1000 – 10000 kg (1-10 t)	> 10000 kg (> 10 t)
Number	22	108	211	72	21	4
Frequency, %	5.0	24.7	48.2	16.4	4.8	0.9

In the first step potential emissions have been calculated as a worst case scenario, i.e. the potential maximum load to the environment, assuming that 1) the amount sold per year is distributed over the year, and sales figures equal consumption, 2) the medicines are used evenly throughout the country 3) the sewage system is the main gate to the environment, 4) there is no human metabolism or degradation. Emission estimates at the municipality level are illustrated here by total antibiotics and by one particular antibiotic amoxicillin (Fig. 2). The biggest amounts are emitted from the major towns, followed by municipalities in the central part of the country, considering that the greatest load is on the rivers of the Nemunas river basin. Emissions from Klaipėda city go directly to the Baltic Sea. In the worst case, 5791 kg of antibiotics (1800 kg of which was amoxicillin) per year was emitted from Vilnius, and 3812 kg (1184 kg of which was amoxicillin) from Kaunas. Emissions of antibiotics from other big towns Klaipėda, Šiauliai and Panevėžys were in the range of 971-1977 kg (301-614 of them was amoxicillin).

The predicted environmental concentrations (PEC) resulting from the maximum potential load to the environment were calculated according to the EU Guideliness on the environmental risk assessment of medicinal products for human use. The following formula was adopted for calculations [12]:

$$PEC_{SW} = \frac{A}{365 \times P \times Winhab \times D} \quad (4)$$

where:

PEC_{SW} – predicted environmental concentration in surface waters;

A – consumption of active ingredient, kg;
P – number of inhabitants;
 W_{inhab} – volume of wastewater, l inh⁻¹d⁻¹;
D – dilution.

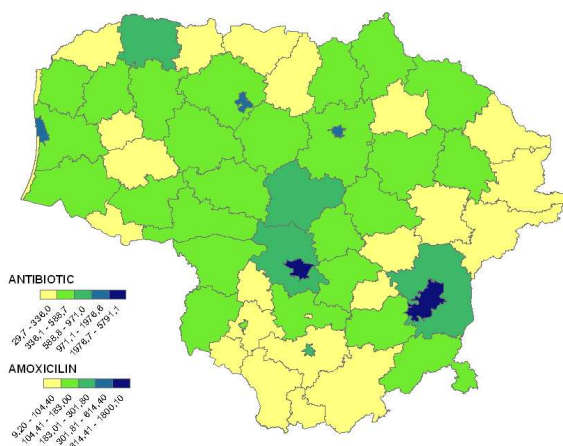


Fig. 2. Emission estimates of total antibiotics and amoxicillin in kg in 2005 (the worst case scenario)

This is likewise “worst case” calculations. They were carried out for Lithuanian population of 3,425 million in 2005, using default EU numbers for wastewater volume (200 l inh⁻¹d⁻¹) and for dilution (factor of 10).

According to the calculations, there might be 170 pharmaceutical substances with environmental concentrations above 0.01 µg/l. Concentration of 0.01 µg/l is agreed as a threshold concentration, considering that if concentration is below 0.01 µg/l, and no other environmental concerns are apparent, it

may be assumed that environmental risk is unlikely. If the concentrations are above 0.01 µg/l, further steps and further information are needed to judge about the possible risks to the environment. For Lithuania, the substances consumed in amounts more than 25 kg/year might be causing a risk to the environment.

According to the proposed EU Guidelines on Risk Assessment, the next step is to calculate the PEC/PNEC ratios of those compounds with PEC values > 0.01 µg/l. PEC/PNEC ratios were evaluated where ecotoxicity data were available. PNEC was calculated from effect concentrations determined as the lowest LC50 or EC50 calculated from a standard acute toxicity test on fish, *Daphnia* and algae, and the assessment factor was set at 1000. The PEC/PNEC ratio was lower than 1 for all pharmaceuticals except three. The exceptions were amoxicillin, ciprofloxacin and spiramycin. All the exceptions are due to their acute toxicity to blue-green algae *Microcystis aeruginosa* [13, 14].

In reality not all the sold and consumed amount of pharmaceutical substances reach water bodies, therefore refinement of emission estimates is required, especially for amoxicillin, ciprofloxacin and spiramycin. Data on metabolism of a substance in human body, on degradation in WWTP, and on practice of waste water treatment are relevant criteria for obtaining the refined emission estimates and predicted environmental concentrations.

For example, 60% [15, 16], or even 80-90% [17] of amoxicillin are excreted unchanged in urine. The median of the removal rate in WWTPs for amoxicillin is 75-100% [20]: it is 49-100% in winter, and 100% in summer. 60% sorption onto sewage sludge is reported for amoxicillin.

Approximately 40 to 50% of an administered dose of ciprofloxacin is excreted in the urine as unchanged drug. 20-35% of a dose is recovered from the faeces [16]. According to [18] the total excretion is approximately 83.7%. Based on the results of WWTP simulation, 65% of ciprofloxacin were eliminated by sorption, and 30% were detected in the effluent [19]. [21] reports that ciprofloxacin is mainly sorbed to sludge, and approximately 4% of the total amount that entered the WWTP were found in the final effluent. According to [20], a removal rate of ciprofloxacin in WWTPs is around 60% (45-78% in summer and 53-69% in winter).

Faecal-biliary elimination is substantial for spiramycin with over 80% of an administered dose excreted in the bile, then enterohepatic recycling may occur. Renal-urinary excretion accounts for 4 to 14% of an administered dose [15]. A removal rate in WWTPs for spiramycin is close to zero (0-11% in winter and 0% in summer time) [20].

About 80% of wastewater in Lithuania is treated biologically, about 60% of it is without additional removal of phosphorus and nitrogen. The rest of the wastewater is treated mechanically, and <1 % is discharged without treatment. In 2005 the city of Kaunas had only mechanical treatment.

Fig. 3 shows results of the refined load on the example of amoxicillin taking into account pessimistic values of the removal rate in WWTPs. Emissions of amoxicillin were estimated to be the highest from Kaunas, Vilnius, Klaipėda, Šiauliai and Panevėžys, and also the districts of Kaunas and Vilnius.

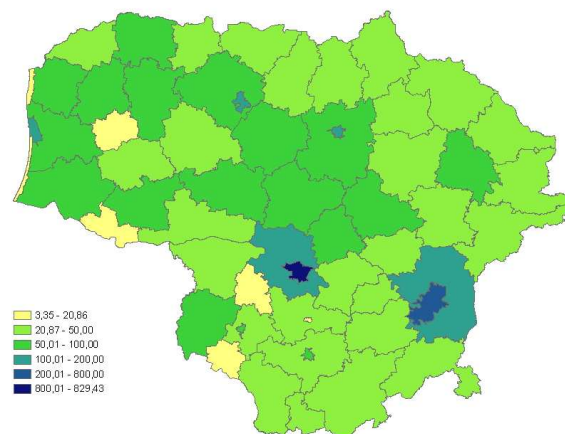


Fig. 3. Emission estimates of amoxicillin in kg in 2005.

Refinement of PEC and recalculation of the PEC/PNEC ratio according to the EU Guideline on the environmental risk assessment did not allow to exclude the possibility of environmental risks from amoxicillin, ciprofloxacin and spiramycin: the recalculated ratio when using the pessimistic values for metabolism and removal in WWTP was still above unity. Even more – PEC for spiramycin might be underestimated due to its veterinary use.

All three substances are antibiotics. Different organisms can differ substantially in their sensitivity to pharmaceutical substances. According to various researchers, blue-green algae seem to be very sensitive to many antibiotics [1]. In our simulation we considered all the toxicological data retrieved, obtaining the PEC/PNEC ratios of more than 1 when using EC50 on algae, but lower ratios using EC50 on the other test organisms. Thus, EC50 values are hardly comparable when derived from tests on different organisms. Nevertheless, algae are the basis of the food chain and a slight decrease in the algal population may affect all the aquatic system.

The measured environmental concentrations would be a great help in judging environmental risks from amoxicillin, ciprofloxacin and spiramycin. However, according to the knowledge of authors, there are no measurements of pharmaceuticals in water bodies of Lithuania. For this reason the research data from the other countries have been consulted.

Amoxicillin was one of the target substances during the assessment campaign in Italy by E. Zuccato and other researchers, but it was not detected in environmental samples [1]. Amoxicillin has a high environmental load but low environmental stability. Also as it has been indicated above, under favourable conditions amoxicillin can be completely removed from WWTP [20]. In such a case the PEC/PNEC ratio

for amoxicillin would be close to zero, indicating no environmental risk.

For both ciprofloxacin and spiramycin, there are cases when they have been detected in water bodies. Maximum ciprofloxacin concentration 26.1 ng/l is reported from Italy [22]. Spiramycin concentration reported from the river Lambro in Italy is 74.2 ng/l, from the river Po – 9.8 ng/l as the median, and 43.8 ng/l as 90 percentile [22].

Prevention of pharmaceuticals entry to the aquatic ecosystems is the best management strategy for facing possible environmental risks. Even from the environmental point of view it is important that patients do not consume excess medicines and that they are instructed to consume medicines in a way, which ensures the best assimilation of pharmaceutical substances in the body. Nevertheless, excretion of certain amounts of pharmaceuticals is inevitable, and here we face the need of proper treatment facilities. According to some researchers, a combination of biological treatment, high sludge residence time, and ozonation of the effluent seem to be the most promising [20]. Currently biological filters and activated sludge are the most efficient for removal of pharmaceuticals [17]. Development of a wastewater collection system and WWTPs has been an important step for Lithuanian environment with regard to reduced load of pharmaceutical substances. In spite of that, WWTPs are still considered “hot spots” of environmental contamination, requiring further research to clarify their capacity to remove a wide range of pharmaceuticals and their metabolites [20]. Tertiary treatments are seldom used, mainly in bigger towns, but are under the extensive investigation for removal of pharmaceutical substances. Certain pharmaceuticals are inclined to be absorbed instead of being degraded [20]. Therefore, spreading of sewage sludge on agricultural land has a potential for environmental contamination with pharmaceutical substances. Such technologies as flocculation, ozonation, advanced oxidation, membrane filtration, and photocatalysis are also possible for removal of pharmaceuticals, however, their costs are to be evaluated [20].

3.3. Disposal

Disposal of unused, unwanted or expired pharmaceuticals is another important route to the environment. In an ideal case all the medicines that have not been consumed should be delivered to waste management companies and destroyed in order to prevent the environmental risk. Certain legal acts are in place at the EU and at national levels in order to organize such a system. In practice, however, the system is not effective yet. The study has been carried out in order to examine the habits of population of disposing of unused, unwanted or expired medicines [23].

The habits vary between residents of different

living places in Lithuania. The most popular way to dispose of medicines is via the household waste (89% in towns, 87% in suburbs and settlements, 50% in country-side). Medicines are sometimes flushed down to the sewage system. 8% of town residents and 6% of those in suburbs and settlements have such a habit. Both methods – flushing medicines down the sewage and throwing them to the garbage – may cause environmental damages, therefore neither of them is preferable. As it has been discussed in the previous section, WWTPs are not designed to remove pharmaceuticals and many medicines may be incompletely eliminated.

Typical of Lithuania if compared to the other West-European countries and the United States is burning of unused, unwanted or expired medicines together with the other household waste. 50% of respondents to the study in country-side did so, as 12.5% in suburbs and settlements, and 2% in towns. In fact, the burned pharmaceuticals do not reach the environment as pharmaceutical substances, nevertheless burning of waste in ordinary household burning facilities produces various other contaminants, causing a risk to human health and the environment.

5% of respondents from towns have tried to deliver medicines to pharmacies, but only 3% succeeded. Another 2% were not successful in finding pharmacies which would have accepted their medicines. Most of the people, who do not return pharmaceuticals to pharmacies, indicate they have never heard about such a possibility and do not know anything about the issue.

It is important to organize a functioning system for collection of residual medicines from the public and dispose of them in environmentally sound manner. This requires implementation of a wide range of measures, such as setting a complete and clear legal basis, institutional responsibilities educating and informing the public (e.g. via mass-media, posters, booklets, together with information on medicines).

4. Conclusions

1. Use stage and disposal of unused, unwanted or expired medicines are those stages of the life cycle of pharmaceuticals when their biggest emissions to the environment occur, and risk management measures are needed.
2. In the worst case, 5791 kg of antibiotics per year could be emitted from Vilnius, and 3812 kg from Kaunas in 2005. Emissions of antibiotics from other big towns Klaipėda, Šiauliai and Panevėžys could be in the range of 971-1977 kg.
3. For Lithuania, pharmaceutical substances consumed in amounts bigger than 25 kg/year have a potential to cause a risk to the environment. Three substances - amoxicillin, ciprofloxacin, and spiramycin – have the PEC/PNEC ratios above 1 under the worst case

- calculations. In reality, amoxicillin is not likely to pose a risk due to its low environmental stability and high removal rates in WWTPs. The other two substances show a potential of environmental risk even after calculation of the refined PEC/PNEC ratio.
4. Development of the wastewater collection system and WWTPs with secondary treatment is an important step in reducing the load of pharmaceutical substances to Lithuanian water bodies. Nevertheless, WWTPs themselves are considered “hot spots” because of incomplete degradation of some pharmaceuticals.
 5. The most popular way to dispose of unused, unwanted or expired medicines in Lithuania is via the household waste (89% in towns, 87% in suburbs and settlements, 50% in country-side). The system for collection of residual medicines is not properly functioning yet. Good management of environmental risk requires establishment of an effective system to collect and destroy pharmaceuticals in an environmentally sound manner.
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Rizikos aplinkai valdymas žmonėms gydyti vartojamų farmacinių medžiagų būvio ciklo etapuose

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Straipsnyje analizuojami farmacinių medžiagų būvio ciklo etapų ypatumai ir jų svarba, atsižvelgiant į šių medžiagų poveikį aplinkai, taip pat nagrinėjamas rizikos valdymo priemonių poreikis.

Didžiausios emisijos į gamtinę aplinką yra iš farmacinių medžiagų vartojimo ir iš nereikalingų ar pasenusių vaistų atsikratymo etapų. Straipsnyje pateikiama farmacinių medžiagų suvartojimo Lietuvoje analizė – kokia jų įvairovė, kokios medžiagos populiariausios, kokiais kiekiais suvartojamos. Remiantis šia analize, atliktas poveikio aplinkai vertinimas, parodęs, kad 2005 m. Lietuvoje suvartota 170 farmacinių medžiagų didesniais nei 25 kg kiekiais. Pagal blogiausio atvejo skaičiavimus tokių medžiagų PEC yra $>0,01 \mu\text{g/l}$. Tačiau tik trims iš tokių medžiagų PEC/PNEC santykis pagal blogiausio atvejo skaičiavimus yra didesnis už vienetą. Viena iš šių medžiagų – amoksicilinas – pasižymi mažu patvarumu aplinkoje, be to, esant palankioms sąlygoms, yra gerai skaidomas valymo įrenginiuose. Todėl amoksicilinas nelaikytinas potencialią riziką keliančia medžiaga, nepaisant didelių jo emisijų. Kitų dviejų medžiagų – ciprofloxacino ir spiramicino – aplinkai keliamos rizikos negalima visiškai paneigti net ir perskaičiavus PEC/PNEC santykį, įvertinant metabolizmą ir pašalinimą valymo įrenginiuose. Abi šios medžiagos yra antibiotikai, kuriems yra labai jautrūs melsvadumbliai. Straipsnyje pabrėžiama, kad nors valymo įrenginiai visiškai nepašalina visų farmacinių medžiagų, vis tik esant tinkamiems valymo procesams farmacinių medžiagų į gamtinę aplinką patenka reikšmingai mažiau. Nuotekų valyklų su antrinio valymo procesais plėtra Lietuvoje yra svarbus žingsnis mažinant farmacinių medžiagų apkrovą iš jų vartojimo etapo, kurio metu dalis medžiagų neišvengiamai pašalinama iš žmogaus kūno.

Nagrinėjant, kaip gyventojai elgiasi su nereikalingais ir pasenusiais vaistais, pabrėžiama, kad kol kas Lietuvoje populiariausia yra vaistus išmesti į buitines atliekas. Atliekamų vaistų surinkimo ir saugaus pašalinimo sistema kol kas tinkamai nefunkcionuoja todėl labai svarbu ją sukurti.