TECHNICAL TRANSACTIONS | **CZASOPISMO TECHNICZNE**
ENVIRONMENT ENGINEERING | ŚRODOWISKO
1-Ś/2014

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OCCURRENCE OF ANTI-CANCER DRUGS IN THE AQUATIC ENVIRONMENT AND EFFICIENCY OF THEIR REMOVAL – THE SELECTED ISSUES

WYSTĘPOWANIE LEKÓW PRZECIWNOWOTWOROWYCH W ŚRODOWISKU WODNYM ORAZ SKUTECHNOŚĆ ICH USUWANIA – WYBRANE ZAGADNIENIA

Abstract

The article discusses the occurrence of selected cytostatic drugs in the aquatic environment. The authors start with a preliminary introduction to the characteristics of the most commonly used cytostatic drugs. Then, based on the review of the literature they show that such drugs occur in small amounts in an aqueous medium and that there is no reliable research data on the long-term exposure of aquatic organisms to cytostatics. Until now, the studies on the stability of some cytostatics showed that these compounds were extremely stable, not only in natural waters, but also at wastewater treatment plants (WWTPs). In spite of the advanced treatment technologies used at wastewater treatment plants, cytostatics pass relatively easily through the treatment line and end up in surface waters, thus posing a threat to water quality.

Keywords: *cytostatic drugs*, *cyclophosphamide*, *ifosfamide*, *5-fluorouracil*, *wastewater*, *surface water*

Streszczenie

W artykule przedstawiono zagadnienia związane z występowaniem wybranych leków cytostatycznych w środowisku wodnym. Dokonano wstępnej charakterystyki najczęściej stosowanych leków cytostatycznych. W oparciu o przegląd literatury wykazano, że związki te występują w środowisku wodnym w niewielkich ilościach i nie ma wiarygodnych badań dotyczących długotrwałego narażenia organizmów wodnych na działanie cytostatyków. Wyniki dotychczasowych badań nad stabilnością wybranych cytostatyków wykazały, że związki te są wyjątkowo stabilne nie tylko w wodach naturalnych, ale także w warunkach panujących w oczyszczalniach ścieków. Mimo stosowania najnowszych technologii w oczyszczaniu ścieków, rozpatrywane cytostatyki, w mniejszym lub większym stopniu, przedostają się przez oczyszczalnie ścieków i trafiają do wód powierzchniowych, stanowiąc zagrożenie dla ich jakości,

Słowa kluczowe: *leki cytostatyczne*, *cyklofosfamid*, *ifosfamid*, *5-fluorouracyl*, *ścieki*, *wody powierzchniowe*

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1. Introduction

The presence of contaminants of pharmaceutical origin in the aquatic environment is not a new issue. In the 1970s, clofibric acid was detected in surface waters in today's Germany. This compound is a metabolite of lipid regulators, including clofibrate and etofibriate. In the 1980s, the presence of thirty-two other different drugs and their metabolites was detected. Up to the year 2007, more than ninety pharmaceuticals have been identified all over the world in the seas, lakes, rivers, groundwater, soil and lake sediments [4]. New developments in medical and pharmaceutical sciences brought along tens of thousands of pharmaceuticals used for the diagnosis, prevention and treatment of numerous diseases and disorders. In many cases, once the drug has been introduced to the human body, it undergoes biotransformation into predominantly hydrophilic forms in the liver; only in the form of metabolites are the drugs excreted by kidneys, which is the major manner of their removal from the body. However, the compounds which are not absorbed from the gastrointestinal tractor readily soluble electrolytes can pass through the body in an unchanged form [25].

Given the continuous growth of the world's population, one can expect a gradual increase in the demand and consumption of pharmaceuticals; it may be associated with the increased presence of these compounds in the aquatic environment. There have been well-known cases with a negative impact of pharmaceuticals on animals, including the impact of diclofenac (from the group of non-steroidal anti-inflammatory drugs) on kidney failure and the death of vultures in Asia [6] or the impact of the synthetic hormone ethinylestradiol (EE2) on changes of the sex of fish [8, 9, 15]. Looking at the growing number of people suffering from cancer, Cytostatic drugs maybe a potential threat to the aquatic environment. This paper attempts to describe the occurrence of some anti-cancer drugs in the environment and estimate the efficiency of their removal in wastewater treatment processes.

2. Characteristic of cytostatics

Cytostatics comprise a group of natural and synthetic compounds used widely in cancer treatment (chemotherapy) and are toxic to rapidly dividing tumor cells. Since they may also be harmful for other rapidly dividing cells (such as bone marrow, hair and mucous membranes), the drugs are highly dangerous with many undesirable side effects, such as anemia, nausea, vomiting and alopecia. Furthermore, cytostatics exhibit carcinogenic, mutagenic and teratogenic effects, and they are therefore considered potentially the most dangerous pollutants in the water environment [11, 12]. Currently, some of the most popular anti-cancer drugs are cyclophosphamide (CP) and ifosfamide (IF), which are alkylating cytostatic agents, and 5-fluorouracil (5-FU), which belongs to a group of antimetabolites.

Cytostatic drugs act differently, depending on the type of drug; but their main role is to inhibit or completely block the replication of DNA in the tumor cell. The above--mentioned cytostatics (cyclophosphamide, ifosfamide, and 5-fluorouracil) are not only used in chemotherapy of different types of cancers, such as cancer of breasts, bronchial, testes, ovaries (CP, IF) and cancer of the digestive system (5-FU) but also in the treatment of leukemia, lymphoma and autoimmune diseases. They are also used for immunosuppression after organ transplantation (CP, IF) [9].

3. Cytostatics in water environment

Pharmacologically active substances present in the environment originate from numerous different sources, as shown in Fig. 1 [16]. Pharmaceuticals, including cytostatics, are not always fully metabolized in the body. The average percentage of original compounds excreted in urine in the case of CP, IF, and 5-FU is 21%, 26% and 18%, respectively [2]. The use of cytostatics in chemotherapy means that the main source of pollution with these compounds is wastewater from hospitals or hospital patients undergoing chemotherapy.

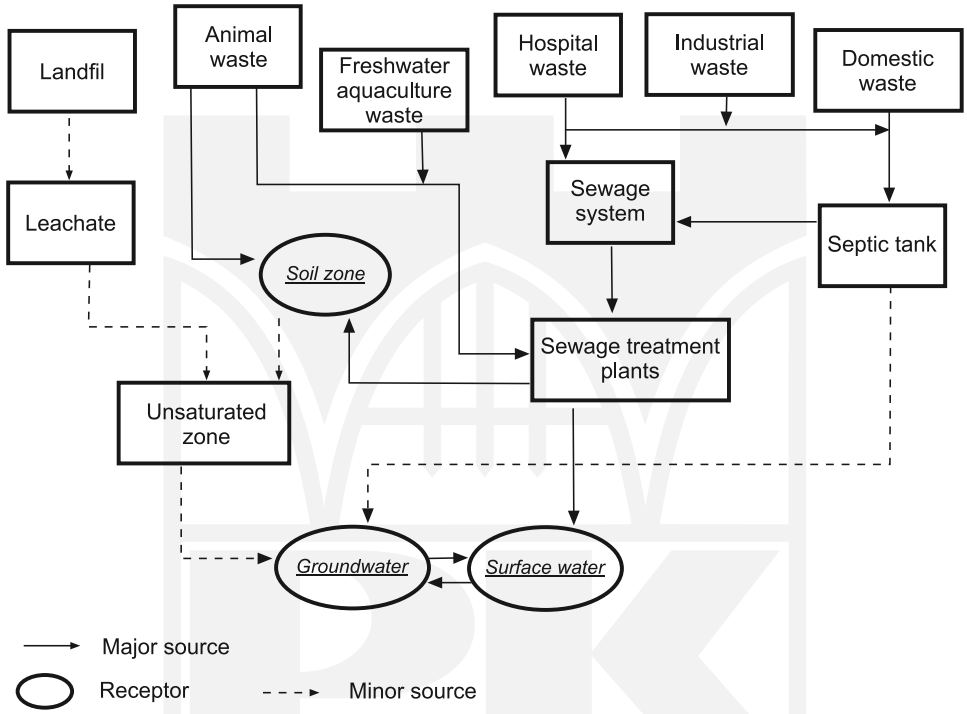

Fig. 1. Potential sources and pathways of pharmaceutical pollution in water and soil

The previous research on biodegradation of alkylating cytostatics (in the 1990s) [1, 5–7] at higher concentrations, as well as the research conducted at lower concentrations in Switzerland in 2006 [3], have demonstrated the exceptional resistance of cyclophosphamide and ifosfamide to biodegradation in activated sludge. This means that the cytostatic drugs pass to the aquatic environment despite the use of advanced treatment technologies. A study conducted in Switzerland indicated the presence of CP in the effluent from the Mannedorf WWTP (CP = 2 ng/l without chemotherapy at a local hospital, and 10 ng/l when such treatment took place) and CP and IF in the effluent from the Zurich WWTP (CP = 2.1–4 ng/l and IF = 1.7–6 ng/l) [3]. The same study showed the presence of these compounds in the river Limmat, downstream from the Zurich WWTP effluent discharge (CP = 0.15–0.17 ng/l and IF = 0.08–0.14 ng/l). Other studies have shown that cyclophosphamide concentrations

in surface water samples reached the level of 64.8 ng/l [21]. However, along with a growing number of cancer cases and a higher consumption of cytostatic drugs, concentrations of these substances in the aquatic environment may also increase. Such a trend has been confirmed by, for example, studies carried out in Spain, where ifosfamide was detected in local surface waters [26]. Cytostatics (CP, IF, 5-FU) were also detected in surface waters throughout Taiwan; water samples were taken from rivers located in the regions of Taipei and Kaohsiung-Pingtung. In the rivers of the Taipei region, the concentrations of 5-fluorouracil, cyclophosphamide and ifosfamide were 5–70 ng/l, 1.9–13 ng/l and 1.9–8.9 ng/l, respectively. However, in the rivers of the Kaohsiung-Pingtung region, the concentrations of these compounds were 35–160 ng/l, 0.9–96 ng/l and 0.1–4.7 ng/l, respectively [17]. Although there are small quantities of these compounds present in the aquatic environment, there is lack of reliable research data on the long-term exposure of aquatic organisms to the cytostatics. In such situations, the best solution seems to be reduced emissions of these compounds into the aquatic environment.

4. Methods

Though cytostatic concentrations in hospital wastewater are sometimes reported at the level of μg/l [17], their actual concentrations at the wastewater treatment plant are much lower due to dilution. Techniques used for the determination of cytostatics include gas chromatography coupled with a mass spectrometer (GC-MS – gas chromatography mass spectrometry) [3] and liquid chromatography coupled with a mass spectrometer (LC-MS – liquid chromatography mass spectrometry). However, sometimes the detection of very low concentrations (ng/l or lower [3, 17]) requires the use of more sophisticated analytical techniques with low limits of quantification like high performance liquid chromatography HPLC-MS. Another common technique is liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS – liquid chromatography-tandem mass spectrometry) [3, 19, 20, 22] and HPLC-MS/MS [18].

5. Treatment efficiency

If chemotherapy were performed only in hospitals, pretreatment of hospital wastewater would sufficiently reduce the amount of anti-cancer drugs discharged to the wastewater treatment plant. However, oral chemotherapy is one of the methods of treatment. Undoubted advantages of this therapy include the comfort of the patient (treatment at home) and no need for continuous hospitalization – this assures a better sense of stability and well-being. On the other hand, a significant disadvantage of this solution is the excretion of metabolites and parent substances of cytostatics with domestic sewage; in such cases, wastewater cannot be pre-treated before its discharge to the treatment plant, this is why it is vital to provide efficient treatment and disposal of cytostatics at the municipal wastewater treatment plant.

The study on the stability of cyclophosphamide and ifosfamide showed that these compounds are extremely stable, not only in natural waters, but also under the

conditions prevailing at the wastewater treatment plants [3, 10, 13, 14, 23, 24]. In the case of 5-fluorouracil [17], the authors report the following results of its biodegradation: in activated sludge – 38% after 3 days and 65% after 4 days; aerobic biodegradation – less than 60% after 50 days. Despite the use of the latest wastewater treatment technologies, cytostatics pass through the plants (to a lesser or greater extent) and end up in surface waters. Table 1 shows cyclophosphamide and ifosfamide concentrations observed in the influents and effluents of sewage treatment plants in the canton of Zurich, Switzerland [3].

Table 1

Concentrations of CP and IF (ng/l) in influents and effluents of treatment plants in the canton of Zurich, Switzerland

WWTP	Sampling time	Cyclophosphamide		Ifosfamide	
		Influent	Effluent	Influent	Effluent
Mannedorf	20–23.09.2002	~4	~2	< 15	< 2
	24–27.09.2002	11	10	< 15	< 2
Zurich	23.03–03.04.2005	5	4	5	6
	18–24.2005	2	2.1	~1.4	1.7

Tests carried out on samples from sewage treatment plants in the region of Taipei in Taiwan [17] confirmed the poor removal of cytostatics in the local sewage treatment plant; concentrations in the plant influent and effluent were as follows: cyclophosphamide 280 ng/l and 80 ng/l; ifosfamide 12 ng/l and 15 ng/l; 5-fluorouracil 8.3 ng/l and 10 ng/l.

Table 2

Degradation of CP and 5-FU [18]

Compound	Initial concentration	Method	Residual concentration [C/C_0]	
			120 min	240 min
5-fluorouracil	200 µg/l	UV	~0.98	~0.99
		UV + ZnO (mg/l)	~0.55	~0.38
		UV + Aldrich-TiO_2 (5 mg/l)	~0.30	~0.10
		UV + Degussa P25 (5 mg/l)	~0.01	~0.00
Cyclophosphamide	27.6 mg/l	UV + Degussa P25 (20 mg/l)	~0.39	~0.05
		UV + Degussa P25 (300 mg/l)	~0.18	~0.00

Since certain cytostatics are resistant to biodegradation, alternative methods of their removal from wastewater and natural waters should be investigated. The latest studies on the photocatalytic oxidation of cyclophosphamide and 5-FU with e.g. UV/TiO2 [18] show the possibility of successful oxidation of these compounds. In this work, the authors used HPLC-MS/MS technique to determine CP and 5-FU concentrations; the results have been summarized in Tab. 2.

6. Conclusions

- Pharmaceuticals are becoming a serious problem for the well-being of organisms living in water that receives the effluent from wastewater treatment plants.
- In many countries, cytostatics have been found in the effluent from wastewater treatment plants and surface waters.
- Poor removal of some cytostatics during the treatment process and their high resistance to biodegradation suggest the need for other methods to eliminate these compounds from wastewater.
- There are no research studies that would clearly indicate the effects of the prolonged exposure of organisms to anti-cancer drugs. Therefore, it is difficult to introduce measures restricting their emissions into surface waters.
- The introduction of regulations defining the allowed and safe maximum concentrations of substances in the aquatic environment seems to be an urgent task for both the European Union and Poland.

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