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THE OCCURRENCE OF SELECTED HYPOLIPIDEMIC DRUGS IN THE AQUATIC ENVIRONMENT

WYSTĘPOWANIE WYBRANYCH LEKÓW HIPOLIPEMICZNYCH W ŚRODOWISKU WODNYM

Abstract

The paper is part of a series of publications discussing the prevalence of pharmaceuticals in the aquatic environment. The paper presents two groups of hypolipidemic drugs (lipid regulators) and their basic parameters. A review of the literature on the occurrence of these compounds in wastewater, surface water and groundwater was made. According to the literature, the presence of various lipid regulators in raw water entering water treatment plants poses a real threat of their penetration into the water supply system, and consequently, to public water intended for human consumption.

Keywords: *lipid regulators*, *lipid–lowering agents*, *wastewater*, *surface water*, *groundwater*, *drinking water*

Streszczenie

Artykuł jest częścią serii publikacji obejmujących zagadnienia występowania farmaceutyków w środowisku wodnym. W pracy przedstawiono dwie grupy leków hipolipemicznych (regulatorów tłuszczu) oraz ich podstawowe parametry. Dokonano przeglądu literatury dotyczącej występowania tych związków w ściekach oraz wodach powierzchniowych i podziemnych. Jak wynika z danych literaturowych, obecność poszczególnych regulatorów tłuszczu w wodzie surowej ujmowanej przez stacje uzdatniania wody stwarza realne zagrożenie ich przenikania do systemu wodociągów, a w następstwie do odbiorców wody przeznaczonej do spożycia.

Słowa kluczowe: *regulatory tłuszczu*, *ścieki*, *wody powierzchniowe*, *wody podziemne*, *woda pitna*

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1. Introduction

The presence of pharmaceuticals in wastewater and the environment has been a controversial issue for many years. The main objective seems to be the possibly most efficient degradation and retention of pharmacologically active substances during wastewater treatment, thus avoiding environmental. The complete elimination of pharmaceuticals present in the raw sewage is not possible. The reason for this could be varying nature and properties of individual groups of pharmaceuticals. Despite the relatively high efficiency of the elimination of ibuprofen in wastewater treatment processes [17], the removal efficiency of cytostatic drugs, which do not show a tendency to biodegradation and adsorption, is very low, and sometimes close to zero [3]. On the other hand, economic factors effectively limit the range of solutions that would ultimately prevent a discharge of drugs and other organic substances into rivers. The application of certain methods used in water treatment would result in the elimination of pharmaceuticals in wastewater treatment, but the risk in this situation is significantly increasing the cost of treating urban wastewater. Thus, papers indicating the presence of specific pharmaceuticals in the aquatic environment are regularly published. According to Wegrzyn et al [24], lipid regulators are found in 6% of environmental samples tested for the presence of pharmaceuticals. If these types of compounds are present in water received by water treatment plants, there is a risk of exposure for drinking water consumers. Lipid regulators, due to their possible harmful side effects, should not be present in water intended for human consumption.

2. Characteristics of lipid regulators

Lipid regulators, or hypolipidemic pharmaceuticals, are a group of natural or synthetic drugs used to reduce the concentration of lipids in the blood. This is one of the methods of reducing the risk of atherosclerosis which is a disease developed by high cholesterol and triglyceride levels [28]. The main reasons for hyperlipidemia are an unhealthy diet, being overweight, having a sedentary lifestyle, smoking, and having a genetic predisposition (ie. congenital hyperlipidemia). The most commonly used pharmaceuticals for lowering the lipid level in blood are statins and derivatives of clofibric acid (fibrates). Due to the serious side effects, lipid regulators should be used only when a change of diet and lifestyle is impossible or insufficient. The most common side effects of statins are muscle problems,

Table 1

Characteristics of selected lipid regulators and clofibric acid [28, 29]

Group	Name	Formula	Molecular mass [g/mol]	CAS	Half–life
Fibrates	**Bezafibrate (BZF)**	$C_{19}H_{20}ClNO_4$	361.819	41859-67-0	1–2 h
	Clofibrate (CLO)	$C_{12}H_{12}ClO_3$	642.699	637-07-0	14–35 h

Fibrates	**Clofibric acid (CFA)**	$C_{10}H_{11}ClO_3$	214.646	882-09-7	10–12 h
	Fenofibrate (FNF)	$C_{20}H_{21}ClO_4$	360.831	49562-28-9	20 h
	Gemfibrozil (GFB)	$C_{15}H_{22}O_3$	250.333	25812-30-0	1.5 h
Statins	**Atorvastatin (ATT)**	$C_{33}H_{34}FN_2O_5$	557.632	134523-00-5	14 h
	Cerivastatin (CET)	$C_{26}H_{34}FNO_5$	459.550	145599-86-6	2–3 h
	Fluvastatin (FLT)	$C_{24}H_{36}FNO_4$	411.466	93957-54-1	3 h
	Lovastatin (LOT)	$C_{24}H_{36}O_5$	404.540	75330-75-5	5 h
	Pitavastatin (PIT)	$C_{25}H_{24}FNO_4$	421.461	147511-69-1	12 h
	Pravastatin (PRT)	$C_{23}H_{36}O_7$	424.528	81093-37-0	77 h
	Simvastatin (SIT)	$C_{25}H_{38}O_5$	418.566	79902-63-9	3 h

increases in liver enzymes and an elevated risk of diabetes; while taking fibrates is associated with a risk of pain and stomach problems, muscle pain, and gallstones. Table 1 shows the basic parameters of the selected statins, fibrates and clofibric acid, which is a metabolite of clofibrate.

3. Occurrence of lipid regulators

Potential sources of pharmaceuticals in wastewater and the water environment are shown in Fig. 1 [8]. Mainly domestic sewage and hospital wastes are transported to municipal treatment plants. In the paper by Al. Aukidy et al [1], the authors present levels of bezafibrate (BZF) and gemfibrozil (GFB) among other pharmaceuticals in hospital wastewater with concentrations of 0.01–7 µg/l for BZF and 0.019–3 µg/l for GFB. Kosma et al [10] published the results of raw sewage and treated wastewater in a hospital treatment plant in Greece. The authors detected two lipid regulators, gemfibrozil and fenofibrate (FNF), the contents of which were 1.1–7.3 μg_{GFB}/l and an average of 0.6 μg_{FNF}/L in raw wastewater and 0.5–1.7 μg_{GFB}/l in the effluent (fenofibrate was not detected). However, due to the character of the compounds and conditions under which they are used (elevated lipid content in the blood and atherosclerotic lesions are treated at the patient's home in most cases), the largest source of these medications in wastewater would be domestic waste. Unfortunately, in contrast to hospital sewage, it is not possible to pretreat the

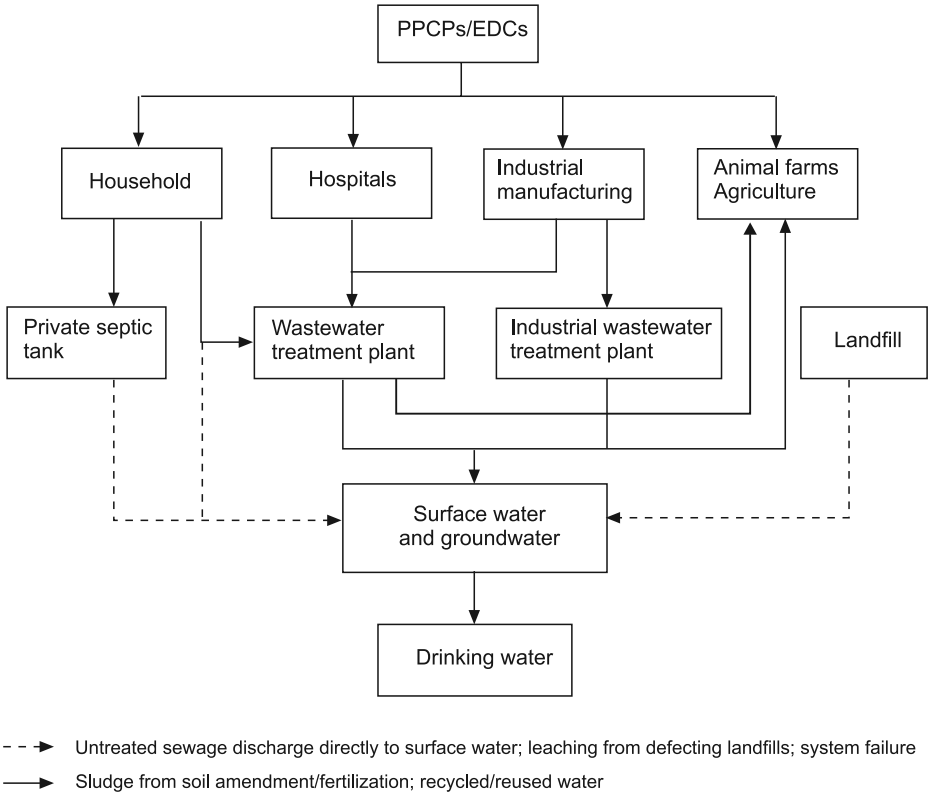

Fig. 1. Potential sources of pharmaceuticals in the aquatic environment [8]

wastewater in every household. Therefore, it seems important to apply the technology to eliminate these compounds in municipal wastewater treatment plants (WWTP). However, taking into account the confirmed reports of the presence of lipid regulators in rivers and groundwater, wastewater treatment efficiency of these pharmaceuticals is not high enough. The concentrations of lipid regulators in the wastewater influents, effluents, surface water and groundwater are presented in Table 2, together with sources of literature.

Lipid regulators are also present in sediments formed in the primary clarifiers. A study published by Martin et al [12] confirms the GFB content in primary sludge from two of the four test WWTPs.

Average concentrations were 1099 and 2026 expressed in µg/kg of dry mass. The susceptibility of gemfibrozil to adsorb on sediments was also confirmed by Yu et al [26]. They showed the presence of GFB and clofibric acid (CFA) in average concentrations of 93.3 and 36.4 µg/kg of dry mass respectively. For this reason, special attention should be paid to the potential presence of pharmaceuticals in sediments before their planned use e.g. in agriculture.

Table 2

Concentrations in ng/l (min–max or mean) of detected lipid regulators in WWTP influent, WWTP effluent surface water and groundwater

Compound	Influent	Effluent	Surface water	Groundwater
Bezafibrate (BZF)	50–1390[11] 420–971[15] 63–120[21] 48–29800[22]	30–670[11] 117–418[15] 11–48[21] 10–3900[22]	202.7[13] 10–90[15] 103–498[18] 3.4[23]	1.2–12.4[5] 112[11] 23–120[18]
Clofibrate (CLO)	–	45–970[22]	–	2900[20]
Clofibric acid (CFA)	1–740[11] 1–651[15] 1–12[21] 12–1040[22] 57–420[26]	300[6] 1–330[11] 75–209[15] 1–6[21] 6–1090[22] 1–81[26]	4–302[15] 10–21[18]	1.43–4210[16] 14[18] 7300[20]
Fenofibrate (FNF)	1–20[21] 80–300[22]	110–2353[9] 1–13[21] 15–190[22]	16–61[18] 0.6[23]	7–27[18] 0.4[23]
Gemfibrozil (GMB)	710[4] 300–700[7] 700–3300[10] 100–17100[11] 1230[12] 1680[12] 2640[12] 2690[12] 160–280[21] 300–17100[22] 430[25] 1090–8500[26]	840–4760[2] 180[4] 220–6050[6] 180–1300[7] 1–1300[10] 2.5–5240[11] 1520[12] 2160[12] 2470[12] 3070[12] 40–170[21] 3–4000[22] 130[25] 1–650[26]	1,7–24[5] 290–194[6] 41–17036[19]	12–574[11]
Atorvastatin (ATT)	1–18[21]	1–6[21]	0.25–1.4[5]	–
Pravastatin (PRT)	80–140[21] 50–1080[22]	40–70[21] 3–20[22]	3–5[5] 1.6[23]	–
Simvastatin (SIT)	7–115[15] 1–4[22]	3–5[15] 1–2[22]	–	–

4. Lipid regulators in drinking water

The presence of pharmaceuticals, including lipid regulators in surface water and groundwater, both of which are sources for water purification plants, pose a risk of the penetration of these compounds into water intended for human consumption. Despite the advanced methods of water purification, lipid regulators are known to occur in finished drinking water. Simazaki et al [18] showed the presence of fenofibrate in purified water in Japan. In six purification plants examined in this study, maximum concentrations of fenofibrate ranged from 6 to 31 ng/l. In the paper of Mompelat et al [14], the authors presented the maximum concentrations of clofibric acid in drinking water samples collected in Italy (5.3 ng/l) and Germany (50–270 ng/l) and also the maximum concentration of bezafibrate in Germany (27 ng/l). Benner et al [5] presented in their review data confirming the presence of the following statins and fibrates in drinking water: atorvastatin (1 ng/l), bezafibrate (1–2.2 ng/l), gemfibrozil (0.8–8 ng/l) and pravastatin (0.2 ng/l).

5. Methods

Though concentrations of lipid regulators in hospital and urban wastewaters are sometimes reported to be at a level of μg/l, their concentrations in natural waters are much lower due to dilution. Because of this, techniques with low levels of detection (LOD) and quantification (LOQ) are needed. For hospital and urban wastewater analysis, sufficient levels of LOD and LOQ can be obtained via gas chromatography coupled with a mass spectrometer (GC-MS – gas chromatography mass spectrometry) [10] and liquid chromatography coupled with a mass spectrometer (LC-MS – liquid chromatography mass spectrometers) [4]. However, sometimes the detection of very low concentrations (ng/l or lower) requires the use of more sophisticated analytical techniques like high performance liquid chromatography HPLC-MS. Another, nowadays very common technique is liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS – liquid chromatography tandem mass spectrometry), which allows obtaining levels of quantification lower than 1 ng/l [5, 23].

6. Conclusions

- Pharmaceuticals, including statins and fibrates are commonly found in wastewater and surface water;
- The presence of lipid regulators in the sediments formed during wastewater treatment requires special attention before application in agriculture;
- There are no conclusive studies on the effects of prolonged exposure of the human body to low concentrations of lipid regulators, and because of this, these compounds should be eliminated from drinking water;
- The constant growth of obesity in developed countries suggests that demand for lipid-lowering drugs will grow steadily, this directly translates into higher levels of these compounds in wastewater;

– The implementation of new technologies in wastewater treatment processes aimed at removing lipid regulators seems to be the only solution for the expected increase in the content of these substances in raw sewage.

References

[1] Al Aukidy M., Verlicchi P., Voulvoulis N., *A framework for the assessment of the environmental risk posed by pharmaceuticals originating from hospital effluents*, Science of the Total Environment, Vol. 493, 2014, 54-64.

[2] Andreozzi R., Raffaele M., Nicklas P., *Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment*, Chemosphere, Vol. 50, 2003, 1319-1330.

[3] Balcerzak W., Rezka,P., *Occurrence of anti-cancer drugs in the aquatic environment and efficiency of their removal – the selected issues*, Technical Transactions, 1-Ś/2014, 11-18.

[4] Bendz D., Paxeus N.A., Ginn T.R., Loge F.J., *Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hoje River in Sweden*, Journal of Hazardous Materials, Vol. 122, 2005, 195-204.

[5] Benner J., Helbling D.E., Kohler H.-P.E., Wittebol J., Kaiser E., Prassem C., Ternes T.A., Albers C.N., Aamand J., Horemans B., Springael D., Walravens E., Boon N., *Is biological treatment a viable alternative for micropollutant removal in drinking water treatment processes?*, Water Research, Vol. 47, 2013, 5955-5976.

[6] Camacho-Munoz D., Martin J., Santos J.L., Aparicio I., Alonso E., *Occurrence, temporal evolution and risk assessment of pharmaceutically active compounds in Doñana Park (Spain)*, Journal of Hazardous Materials, Vol. 183, 2010, 602-608.

[7] Fent K., Weston A.A., Caminada D., *Ecotoxicology of human pharmaceuticals*, Aquatic Toxicology, Vol. 76, 2006, 122-159.

[8] Grassi M., Rizzo L., Farina A., *Endocrine disruptors compounds, pharmaceuticals and personal care products in urban wastewater: implications for agricultural reuse and their removal by adsorption process*, Environmental Science and Pollution Research, Vol. 20, 2013, 3616-3628.

[9] Hernando M.D., Mezcua M., Fernandez–Alba A.R., Barcelo D., *Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments*, Talanta, Vol. 69, 2006, 334-342.

[10] Kosma C.I., Lambropoulou D.A., Albanis T.A., *Occurrence and removal of PPCPs in municipal and hospital wastewaters in Greece*, Journal of Hazardous Materials, Vol. 179, 2010, 804-817.

[11] Luo Y., Guo W., Ngo H.H., Nghiem L.D., Hai F.I., Zhang J., Liang S., Wang X.C., *A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment*, Science of the Total Environment, Vol. 473–474, 2014, 619-641.

[12] Martin J., Camacho-Munoz D., Santos J.L., Aparicio I., Alonso E., *Occurrence of pharmaceutical compounds in wastewater and sludge from wastewater treatment plants: Removal and ecotoxicological impact of wastewater discharges and sludge disposal*, Journal of Hazardous Materials, Vol. 239–240, 2012, 40-47.

[13] Meffe R., de Bustamante I., *Emerging organic contaminants in surface water and groundwater: A first overview of the situation in Italy*, Science of the Total Environment, Vol. 481, 2014, 280--295.

[14] Mompelat S., Le Bot B., Thomas O., *Occurrence and fate of pharmaceutical products and by–products, from resource to drinking water*, Environment International, Vol. 35, 2009, 803–814.

[15] Petrie B., Barden R., Kasprzyk-Hodern B., *A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring*, Water Research, Vol. 72, 2015, 3-27.

[16] Postigo C., Barcelo D., *Synthetic organic compounds and their transformation products in groundwater: Occurrence, fate and mitigation*, Science of the Total Environment, Vol. 503––504, 2015, 32-47.
[17] Rezka P., Balcerzak W., *The occurrence of non–steroidal anti–inflammatory drugs in wastewater and water environment and methods of their removal – selected issues*, Archives of Waste Management and Environmental Protection, Vol. 17(1), 2015, 33-38.
[18] Simazaki D., Kubota R., Suzuki T., Akiba M., Nishimura T., Kunikane S., *Occurrence of selected pharmaceuticals at drinking water purification plants in Japan and implications for human health*, Water Research, Vol. 76, 2015, 187-200.
[19] Spongberg A.L., Witter J.D., Acuna J., Vargas J., Murillo M., Umana G., Gomez E., Perez G., *Reconnaissance of selected PPCP compounds in Costa Rican surface waters*, Water Research, Vol. 45, 2011, 6709-6717.
[20] Stuart M., Lapworth D., Crane E., HartA., *Review of risk from potential emerging contaminants in UK groundwater*, Science of the Total Environment, Vol. 416, 2012, 1-21.
[21] Verlicchi P., Al Aukidy M., Galletti A., Petrovic M., Barcelo D., *Hospital effluent - Investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment*, Science of the Total Environment, Vol. 430, 2012, 109-118.
[22] Verlicchi P., Al Aukidy M., Zambello E., *Occurrence of pharmaceutical compounds in Urban wastewater: removal, mass load and environmental risk after a secondary treatment – a review*, Science of the Total Environment, Vol. 429, 2012, 123-155.
[23] Vulliet E., Cren-Olive C., *Screening of pharmaceuticals and hormones at the regional scale, in surface and groundwaters intended to human consumption*, Environmental Pollution, Vol. 159, 2011, 2929-2934.
[24] Węgrzyn A., Machura M., Żabczyński S., *Możliwości usuwania środków cieniujących ze ścieków*, Ochrona Środowiska, Vol. 37(1), 2015, 55-63.
[25] Yu J.T., Bouwer E.J., Coelthan M., *Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent*, Agricultural Water Management, Vol. 86, 2006, 72-80.
[26] Yu Y., Wu L., Chang A.C., *Seasonal variation of endocrine disrupting compounds, pharmaceuticals and personal care products in wastewater treatment plants*, Science of the Total Environment, Vol. 442, 2013, 310–316.
[27] Zejc A., Gorczyca M., *Chemia leków*, PZWL, Warszawa 2009.
[28] Drugbank, www.drugbank.ca, online: 22.06.2015.