Preliminary assessment of endocrine disruptor compounds in Hungarian surface waters

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Abstract
Many pharmaceuticals with potentially adverse environmental effects along with their metabolites have been detected in surface water samples during the past few decades. Pharmaceuticals have been developed to produce a biological effect, so their residues, metabolites and degradation products in the environment can cause complex ecotoxicological and ecological effects that are difficult to predict, especially in aquatic environments. Nonetheless, concentrations and environmental fate of EDC materials in the aquatic environment are largely unknown. The primary object of this study is to estimate and evaluate the EDC loads into the Hungarian surface waters. Data were collected on the basis of drug consumption figures of the pharmaceutical ingredients and drugs. These first steps of evaluation provide a database from the perspective of aquatic environment to manage EDC materials and to fill the information gap regarding their possible discharges into the surface waters via communal wastewater treatment plants using different technologies.

Keywords
endocrine disrupting compounds, pharmaceuticals, wastewater treatment

INTRODUCTION

Results of national and international surveys conducted into the occurrence and environmental and human health effects of endocrine disrupting compounds (EDCs) in the past few decades resulted in growing concern over these pollutants. EDCs materials can mimic endocrine hormones and adversely interfere with the endocrine system in humans and other higher organisms, even in very low environmental concentrations (typical concentration range in European surface waters is 10^{-9}-10^{-12} g/L). The presence of EDCs in the aquatic environment due to anthropogenic discharges has become a concern in Hungary and other countries as well.

National vital statistics, especially the ones related to fertility parameters and demography have been showing alarming trends in industrialized countries, i.e., the elevated incidence rate of prostate, testis and breast cancer in males, and decreasing number of mobile sperm number regarding the sexually active male population. Amongst the negative environmental effects of EDCs materials the intersex, sterilization, hermaphroditism and feminization of fish and amphibian population was detected at distressing proportions in countries where such surveys were made.

In the EU today approximately 3000 different pharmaceutical ingredients are used including painkillers, antibiotics, antidiabetics, beta-blockers, contraceptives, lipid regulators, antidepressants, antineoplastics, tranquilizers, impotence drugs and cytostatic agents. As these compounds are frequently transformed in the body, a wide range of the original pharmaceuticals and their metabolites are excreted by humans into the waste streams. Pharmaceutical compounds enter into raw wastewater via urine and faeces and by improper disposal. These pharmaceuticals are discharged from private households and from hospitals and eventually reach municipal wastewater treatment plants (WWTPs). [1]

As for the Hungarian surface waters, both the influent treated wastewater and the field monitoring of the sensitive elements of the aquatic environments are entirely missing regarding the effects of EDCs. Only the second Joint Danube Survey (2007) provided some information on selected pharmaceuticals (such as ibuprofen, diclofenac, sulfamethoxazole and carbamazepine) and on phenolic endocrine disrupting compounds and estradiol hormones. [2]

Hence, to give an overall estimate on the total load of EDCs in the influents of domestic WWTPs is necessary to establish a baseline inventory and evaluation their mass balances and fate (transport and degradation) beginning from their consumption until their final emissions into the receiving waters (aquatic environment). The aim of this study is to give preliminary assessment on the concentration of selected pharmaceuticals in Hungarian surface waters based on the consumption figures thereof. These preliminary calculations are also aiming to identify hot-spot locations in Hungary that require further detailed studies to investigate and assess the ambient concentrations and ultimate ecological effects of EDCs.

For calculating the concentrations of selected pharmaceuticals, it is necessary to study their possible pathways from the consumption until the discharges in the aquatic environment. One primary recipient environmental medium of EDCs is the surface water bodies. If the effluent water arrives throughout the soil zone, the pharmaceuticals with high sorption coefficient can adsorb onto the surface of soil particles. In Hungary, rivers are the major recipients of both municipal and industrial wastewater discharges therefore the aquatic ecosystem elements are at risk of exposure. Preliminary assessment regarding the occurrence of the aforementioned pharmaceuticals is necessary to pin-point hot-spot locations in Hungary along the major rivers which are also used as drinking water bases (bank filtered water).

The national boundaries of Hungary are crossed by 24 incoming rivers, bringing 114 km^3 of water annually from abroad. The three major rivers, the Danube, Tisza and Dráva combined discharging annually 120 km^3 water annually. Hungary is highly dependent on upstream countries concerning water resources (dependency ratio is approx. 95%; internal resources are <600 m^3/inhabitant/year). From the viewpoint of hydrology and climate, the country can be divided in two major regions: (i) the area to the west of the Danube and (ii) the larger area to the east which forms part of the Tisza catchment.

The Hungarian Danube section traverses 417 river km. It forms the national border with Slovakia in the north-west and then flows south. The Tisza, a major Danube tributary, flows 595 km down the eastern part of Hungary. The gradient of the major rivers is low, typically 7-8 cm/km for the Danube; 2-5 cm/km for the Tisza; this pinpoint the importance of settling character of suspended solids that are potentially adsorbing EDCs.

Public water utilities supply 560 million m^3 of drinking water per year. 99.4 % of the population is connected to the water supply and 61 % to wastewater collection. A further 9 % live in areas served by wastewater collection but are not connected to the sewerage system yet. 240 million m^3 water are provided for economic and general public use. (Average leakage rate is 19%). Annual industrial and agricultural water abstraction accounts for c. 5000 million m^3 and 680 million m^3 respectively. [3]

METHODS

For the preliminary budgeting of the EDCs, four types of EDCs were selected as representative pharmaceutical: paracetamol, diclofenac, estradiol and ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory drug. It is used for relief of symptoms of arthritis, primary dysmenorrhea, fever, and as an analgeticum (pain-killer). Paracetamol is a widely used analgeticum and antipyretic agent (fever reduction). It is commonly used for the relief of fever, headaches, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. It is normally extensively metabolized to glucuronide and sulphate conjugates and only 3-4% of a therapeutic dose is excreted unchanged in the urine. [4] Diclofenac is a non-steroidal anti-inflammatory drug taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury. Diclofenac is mainly metabolized in humans to its hydroxylated or methoxylated derivatives and further conjugated, mostly to glucuronides. By oral intake, around 95% are excreted in the urine, while after application to the skin, circa % 5 of diclofenac absorb, the rest is washed off. [5] Estradiol is a sexual hormone that represents the major estrogenic compound type in humans. A synthetic form of estradiol, called ethinylestradiol is a major component of hormonal contraceptive devices. In the blood plasma, estradiol is largely bound to globulin and also to albumin, - only a fraction is free and biologically active. Deactivation includes conversion to less active estrogens such as estrone and estriol. Estriol is the major urinary metabolite. Estradiol is conjugated in the liver by sulfate and glucuronide formation and as such excreted via the kidneys. [6]

To estimate environmental releases consumption figures of the aforementioned pharmaceuticals, the annually published database of the Hungarian National Health Insurance Found [7] was used regarding the *de facto* purchased volume of the medicines and the quantity of active ingredient contents of these. The human excretion rate and treatment/removal efficiencies of different types of existing Hungarian wastewater treatment plants were used for calculations to assess final environmental loads. Estimates on EDCs loads and final environmental concentrations do not reflect the purchased but unconsumed pharmaceuticals and the emissions from the unsewered regions. The assessment of the environmental concentrations of the EDCs in Hungarian surface waters was based on the annual mean flow rate of the streams (regarding dilution). Due to insufficient data, the estimates ignored the accumulating and potentially superponating upstream loads (Vienna, Bratislava and other large cities for the Danube River).

As for the database on the consumption figures, we have data mostly on the prescribed medicines. Since almost all types of estradiol containing medicines and the grate number of diclofenac containing medicines are to be prescribed, the following calculations on the consumption figures can be a proper base to estimate their environmental concentrations. Regarding the paracetamol and ibuprofen consumptions, some magnitude of underestimation is envisaged in the calculations because the bulk of these pharmaceuticals can be purchased without medical prescription. As for ibuprofen and paracetamol containing medicines, since 2006 these products can be purchased outside of the pharmacies (in alimentary shops, petrol stations, etc.). According to the Gfk Economy Research Institute, in the field of non prescribed drugs, the leaders are the vitamins (53%), and then the inflammatory drugs (29%) [8] and the cold and flu remedies, like ibuprofen and paracetamol, respectively. According to the analyses of the Hungarian Market Competition Authority, from 2004 May-2005 April approximately 4.7 million box of cold and flu remedies drugs were purchased [9]; and this number is increased after the aforementioned decision of the Hungarian Parliament on the purchase rules of the drugs. Since it is very easy to obtain these drugs, people purchase them without necessity, sometimes only for storing them. These factors were all considered when accuracy of our estimates is discussed.

In Table 1. the excretion rate and removal efficiencies [4] for different types of Hungarian wastewater treatment are given. In this study we do not consider the sorption process onto the activated sludge particles surface.

Table 1. Excretion rate and wastewater treatment removal efficiencies of the selected pharmaceuticals

Pharmaceutical	Diclofenac	Estradiol	Ibuprofen	Paracetamol
Human excretion rate	30%*[6]	60%[10]	15%[10]	5%[5,10]
Mechanical treatment removal eff.	10% [1]	0% [1]	0% [1]	10% [1]
Biological treatment	30% [1]	90% [1]	90% [1]	30% [1]

*Estimated number for the excretion rate both for oral intake and dermal applications after the purchased type of the medicines

Assessment of the final effluent concentration originating from WTTPS, the list (see Table 2. and 3.) was used concerning each WTTP and their particular treatment type (used technology) on the Danube and Tisza rivers as well as their tributaries. The hot-spots regarding the drug consumption are mainly the county capitals and other large cities (Danube and Tisza). Estimate is based on the consumption figures for each county with the hypothesis that the 80% of the purchased drugs was fulfilled in the capitals of each county of Hungary and then emissions from the WTTPs upon various treatment technologies. A multiplying factor of 0.7 was used to take into account the rate by which the total amount of the purchased medicines was really consumed. In Table 2. and 3. the percent of sewered region can also be seen.

Table 2. Treated wastewater discharger location along the Danube basin

	Discharger location	Receiving river	Flow rate m^3/s [11]	Type of the applicated treatments	Discharged water Thousand m^3/yr [12]	Percent estimated sewered region [13]
Pannonian Central Danube Basin	Budapest Nord	Danube		M, B	32100	
	Budapest South	Danube	2740	M, B	20700	93
	Budapest Raw water	Danube		-	138000	
	Budapest Central (Csepel)*	Danube		M, B	109500	
	Budapest Nord	Danube	2740	M, B	32100	98
	Budapest South	Danube		M, B	20700	
	Győr	Mosoni Danube	33	M, B	12500	85
	Zalaegerszeg	Zala		not considered		
	Szombathely	Sorok-Perint, Rába		not considered		
	Székesfehérvár	Gaja Creek		not considered		
	Tatabánya	Általér Creek	1,3	M,B	4350	84
	Dunaújváros	Danube	3100	M,B	3140	90
	Vác	Danube	1920	M, B	4050	87
	Sopron	Ikva Creek		not considered		
	Kaposvár	Kapos Creek	3,5	M, B	3580	99
	Szekszárd	Sió Channel	36	M, B	2010	91
	Veszprém	Veszprémi Séd Creek		not considered		
	Baja	Danube	3300	M, B	3060	70

*The Central WTTPS in Budapest is under construction. During the construction project, the percent of sewer service region will be increased in the capital. Calculations were made for the present and future scenarios.

Table 3. Treated wastewater discharger location along the Tisza basin

	Discharger location	Receiving river	Flow rate m^3/s [11]	Type of the applied treatments	Discharged water Thousand m^3/yr [12]	Percent estimated sewered region [13]
Tisza River Basin	Szeged	Tisza	1160	M, B	14200	100
	Miskolc	Sajó	25	M,B	16800	81
	Szolnok	Tisza	702	M,B	8390	90
	Nyíregyháza	Lónyai Channel	2	M,B	7230	96
	Debrecen	Kösely/Tisza	5	M, B	16600	95
	Békéscsaba	Kettőskörös/Tisza	120	M, B	4660	55
	Kecskemét	Csukás Channel		not considered		
	Eger	Eger Creek		not considered		
	Hódmezővásárhely	Hódtó-Kistisza		not considered		
	Salgótarján	Tarján Creek		not considered		

To calculate the mass flow of the selected pharmaceuticals, the following equation was used:

$$C_{Ph}=\Sigma[E_{Ph}\times 0.7\times Ex_{Hu}\times 0.8\times SEW\times Eff_{rem}]/Q_r$$

Where:
C_{Ph} is the calculated concentration of the selected pharmaceuticals (ng/yr)
E_{Ph} is the amount of the purchased pharmaceutical (kg/yr)
Ex_{Hu} is the human excretion factor of the pharmaceutical (%)
SEW is the percent of sewerage service in a region (%)
Eff_{rem} is the removal efficiency of the particular WTTPS for the selected pharmaceutical (%)
Q_r is the certain river median flow rate (m^3/s)

RESULTS AND DISCUSSION

In this section the annual regional and seasonal distribution of the consumed pharmaceuticals are presented. The former provide the base of the calculations of the emissions these compounds in the aquatic environment. Based on the calculated emissions, ambient environmental concentrations of the selected pharmaceuticals are estimated.

Consumption figures in Hungary on the selected pharmaceuticals

To indentify the hot-spots in Hungary, calculations were made on the consumption of the selected pharmaceuticals in each county of Hungary. On the following map can be seen their annual consumption visualised by circles. For comparing them, the diameter of the circles corresponds the consumed quantity.

Table 4. Consumed quantity of the selected pharmaceuticals in 2008, according to the annual database of the Hungarian National Health Insurance Found

Diclofenac (kg)	6863
Estradiol (g)	2716
Ibuprofen (kg)	n.a.
Paracetamol (kg)	1042

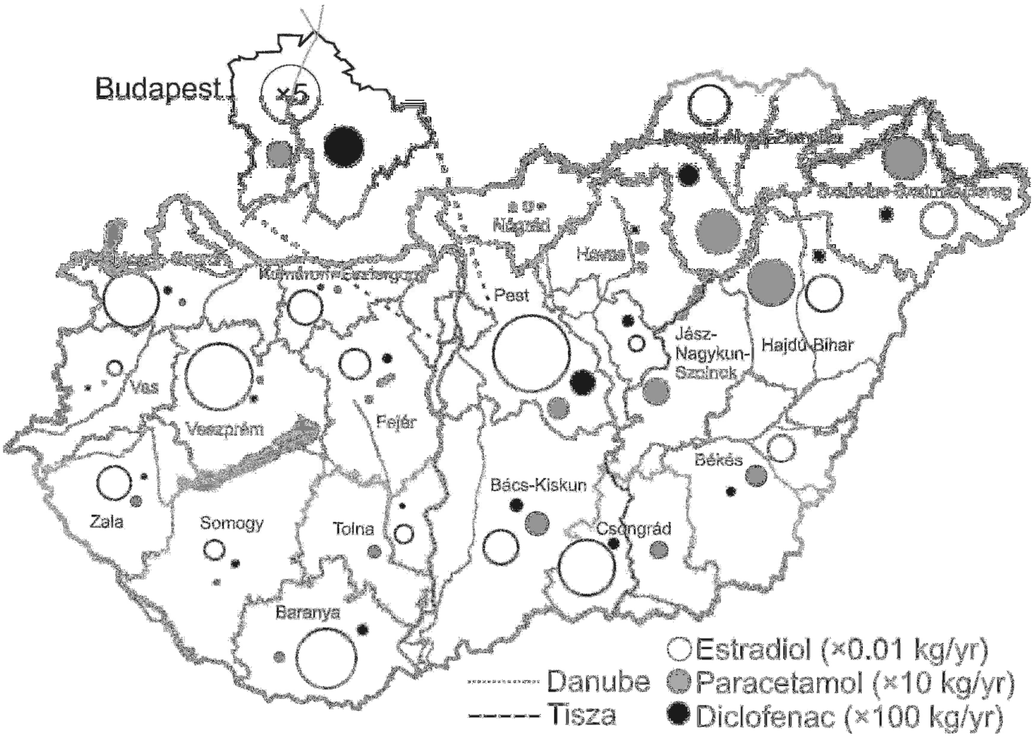

Figure 1. Consumption figures of the selected pharmaceuticals in Hungary for identifying potential hot-spots

In the Table 5. and 6. we divided the counties according the catchments of the Danube and its tributary, the Tisza river. Based on the estimations, some WTTPS were selected, which have as effluent receiving surface water the Danube or the Tisza river.

Table 5. Percent of consumed quantity of the selected pharmaceuticals in the regions on the in the catchment of the Tisza river

Region	**Nord- Hungarian Plain**			**Nord- Hungary**			**South –Hungarian Plain**			**Total**
County	*Hajdú-Bihar*	*Jász-Nagykun-Szolnok*	*Szabolcs-Szatmár-Bereg*	*Borsod-Abaúj-Zemplén*	*Heves*	*Nógrád*	*Bács-Kiskun*	*Békés*	*Csongrád*	
Diclofenac %	5.2	5.0	5.6	8.4	3.5	2.5	5.6	4.0	4.9	**44.7**
Estradiol %	3.7	1.6	3.6	4.2	0.8	0.8	3.6	2.8	5.8	**26.9**
Paracetamol %	**12.7**	7.0	**17.0**	**11.7**	2.9	2.0	6.3	5.7	4.7	**70.0**

Table 6. Percent of consumed quantity of the selected pharmaceuticals in the regions on the in the catchment of the Danube river

Region	**South- Transdanubian Region**			**Central- Transdanubian Region**			**West-Transdanubian Region**			**Central Hungary**		**Total**
County	*Bara-nya*	*Somogy*	*Tolna*	*Fejér*	*Komárom-Esztergom*	*Vesz-prém*	*Győr-Moson-Sopron*	*Vas*	*Zala*	*Buda-pest*	*Pest*	
Diclofenac %	4.5	3.4	2.4	4.0	2.6	3.1	3.4	2.3	2.8	**16.2**	10.6	**55.3**
Estradiol %	6.2	2.1	1.9	3.2	3.6	6.9	5.7	1.5	3.5	**30.6**	7.9	**73.1**
Paracetamol %	2.7	1.3	3.4	1.9	1.7	1.6	1.6	0.9	2.8	6.6	5.5	**30**

Monthly distribution of consumption figures

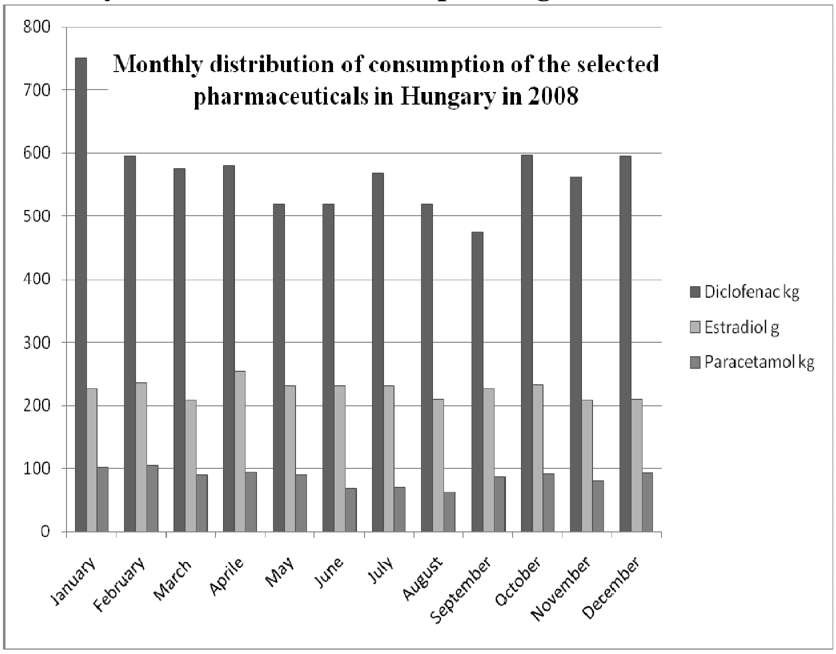

Figure 2. Monthly distribution figures of diclofenac, estradiol and paracetamol in Hungary, 2008

The temporary concentration patterns on the consumption were investigated for the selected pharmaceuticals whose consumption could show seasonal changes depending on the incidence rate of relevant illnesses. As Fig.2 shows in the cold seasons the consumption of diclofenac and paracetamol is increasing, 52% and 54% of these drugs were purchased in autumn and winter, respectively. In winter, from November till February, approximately 36.5% of these two medicines were purchased. For estradiol which is not a drug of seasonal use, these figures are 49 and 32.5 % respectively.

Estimated environmental concentrations of the selected pharmaceuticals

According to the calculation method, emissions from each relevant county were calculated and then summarised for the Danube and for the Tisza catchment. The environmental concentrations are estimated for Nagytétény, 1629.0 river km (downstream of Budapest) for both scenarios, and for Baja (the last large city and discharge upstream of the Serbian state border on the Danube river) and for Szeged (the last large city along the Hungarian Tisza section). (see also Tab.7)

Table 7. Estimated environmental concentration (ng/l) of the selected pharmaceuticals at different rkm sections

Pharmaceutical concentration ng/l	DANUBE			TISZA
	1629.0 rkm Nagytétény (downstream to Budapest-without central WTTP)	1629.0 rkm Nagytétény (downstream to Budapest-with Central WTTP)	1478.7 rkm Baja	180.0 rkm Szeged
Diclofenac	1.8479	1.4832	3.6553	6.3431
Estradiol	0.0023	0.0003	0.0021	0.0005
Paracetamol	0.0028	0.0022	0.0038	0.0033

As for the estimated concentration figures, only the diclofenac is found to be in detectable concentration. Regarding the calculations downstream to Budapest, the results correspond with the finding of the second Joint Danube Survey (JDS2), where the average diclofenac concentration was below 5 ng/l, around 1 ng/l [2]. During this survey, the estradiol concentration was measured as well, but in all samples found to be below the detection limit. As for the Tisza river, respectively large emissions were identified. The average flow rate of Tisza is smaller than the Danubian one, therefore the estimated concentrations for diclofenac and paracetamol are higher than their estimated concentrations in Danube. For the Danube to scenarios were compared: the present situation, without the Central WTTP and the future one with it. Mostly for estradiol, which can be removed particularly effectively by biological treatment discharges will decrease steeply upon the operation of the new Central WTTP.

CONCLUSION

The paper illustrated that calculations regarding to the ambient concentration levels of EDC materials could be reliably based on national drug selling statistics concerning of recipe based pharmaceuticals (i.e., diclofenac). The calculations presented however, biased in some respects particularly the assumptions on the de facto drug consumption figures, the human excretion rates, and sewerage service related numbers (serviced fraction of the population, technological removal efficacy etc.). Upstream discharges (Vienna, Bratislava) were also neglected in this study. Even these preliminary calculations and predictions could serve as a basis in pin-pointing hot-spot locations (spatial distribution) along the river stretch and environmental fate assessment (temporal distribution) as well. The further development and refinement of the presented assessment method provides a firm technical basis in designing a cost effective future monitoring network regarding EDC materials in large rivers.

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