What is at risk? – an environmental health risk assessment related with pharmaceutical substances in drinking water

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Constantly increasing rate of drugs' consumption can be related with environmental abundance of drug substances and their degradation products. Unused and used drugs are often discharged into municipal wastewaters or landfills. Wastewater treatment plants are not able to remove the entire load of drugs. Especially those which occur occasionally or at very low concentrations. Therefore, a variety of pharmaceuticals occur in surface and drinking water sources. A chronic low-level exposure to drugs occurring in a water environment can cause: antibiotic resistance, allergic reactions (eg. Penicillin), cause carcinogenesis (oxytetracycline, furazolidone), nephropathy (gentamicin) and have a negative impact on the natural human intestinal microflora. Therefore, it is not an easy task to assess a common human health effects related with chronic exposure to low doses of active pharmaceutical substances. Nonetheless, such knowledge seems essential in order to undertake preventive actions that would substantially decrease the level of health risk.

Keywords: drinking water, pharmaceuticals, health risk assessment, exposure assessment

Background

According to Polish pharmaceutical law, pharmaceutical substance is: „a substance or mixture of substances having properties that treat or prevent disease in human beings, animals or is administered in order to make a diagnosis or to restore, improve or modify physiological functions of the body by the pharmacological, immunological or metabolic action". [1] In the past few years, a sharp increase in the production of pharmaceuticals and their excessive consumption can be observed. The main reason is the growing number of people requiring care. Especially in high-income countries there is an increasing number of obese and older people with chronic health problems. In Europe, approximately 4,000 different pharmacologically active substances are presently used. Among them dominate analgesics and anti-inflammatory drugs, β-blockers, antibiotics, hormonal agents including steroids, diuretics, lipid regulators and others. Many analgesics are available without prescription. [2,3] Poland is the fifth in Europe in terms of quantities of pain killers and anti-inflammatory drugs sold over the counter. [4]

The increasing drug consumption results in an increase in environmental pollution related with environmental abundance of drug substances and their degradation products. Unused and used drugs are often discharged into municipal wastewaters or landfills. Wastewater treatment plants are not able to remove the entire load of drugs. Especially those which occur occasionally or at very low concentrations. Therefore, some groups of pharmaceuticals occur in surface and drinking water sources. The most common groups of drugs identified in drinking water are: β-blockers, nonsteroidal anti-inflammatory drugs (NSAID), antibiotics, female sex hormones (natural and synthetic), lipid regulators and antiepileptic drugs (Table 1). Table 1 contains a list of pharmaceuticals that according to studies carried out by Nikolaou et al. (2007) predominate in drinking and surface waters. [5] Owing to their variety it is not an easy task to assess a common human health effects related with chronic exposure to low doses of active pharmaceutical substances.

One of the most common hazards to human health related with pharmaceuticals exposure is antibiotic resistance. It is caused by the presence of a large spectrum of antibiotics in drinking water. Involuntarily ingested can induce allergic reactions (eg. Penicillin), cause carcinogenesis (oxytetracycline, furazolidone), nephropathy (gentamicin) and have a negative impact on the natural human intestinal microflora. [6,7,8] A great hazard is also posed by a ethinylestradiol (EE2). EE2 is a hormone and is an ingredient of the contraceptive pill formulations. Hormones are designed in such a way that can cause an effect (deliberate/therapeutic) at very low doses. Therefore, impact of hormones occurring in tap water may cause an estrogenic/androgenic effect to any organism that is exposed to it. [4] The impact on humans is associated with disrupted hormone balance, which in turn leads to an impaired development of secondary sex characteristics, neurodevelop-

Table 1. Pharmaceuticals present in surface and drinking waters

Pharmaceutical substance	Country considered	Type of water sample	Min. concentration [ng/L]	Max. concentration [ng/L]	Average cencentration [ng/L]	Median concentratration [ng/L]	Source
NSAID							
Acetylsalicylic acid	Italy	surface	7,0	200,0	103,5	103,5	[10]
Diclofenac	China	surface	22,8	136,0	169,7	32,5	[11]
	Hungary	surface	24,0	931,0			[12]
	Wales (UK)	surface	9,0	40,0			[5]
	Sweden	surface	25,0	170,0			[13]
	Germany	tap	6,0	35,0	30,2	27,5	[14]
	Brazil	tap	20	60			[15]
Ibuprofen	Poland	surface	50,0	100,0	75,0	75,0	[16]
	United States	tap	1	32	7,9	3,8	[17]
Naproxen	Hungary	surface	5,7	62,0	24,1	14,2	[12]
	China	surface	10,5	18,0			[11]
	United States	tap	8	8	19,0	9,0	[17]
	Brazil	tap	10	50			[15]
Ketoprofen	Sweden	surface	10,0	163,0	306,0	45	[13]
	Poland	surface	6,0	47,0			[16]
	Spain	surface	43,0	1567,0			[14]
Triclosan	Norway	surface	200,0	2400,0	1300,0	1300,0	[18]
Paracetamol	Spain	surface	188,0	2813,0	1500,5	1500,5	[14]
Lipid regulators							
Clofibric acid	Wales (UK)	surface	8,0	11,0	39,5	9,5	[5]
	Poland	surface	1,0	8,0			[16]
	Spain	surface	24,0	185,0			[14]
	Brazil	tap	10	30	20,0	20,0	[15]
Bezafibrate	Sweden	surface	6,0	231,0	467,2	123,5	[13]
	Poland	surface	1,0	16,0			[16]
	Spain	surface	234,0	2315,0			[14]
β-blockers							
Atenolol	Wales (UK)	surface	190,0	560,0	1808,8	439,0	[5]
	Spain	surface	318,0	6167,0			[14]
Metoprolol	Wales (UK)	surface	8,0	11,0	9,5	9,5	[5]
Propranolol	Wales (UK)	surface	9,0	40,0	60,5	27,5	[5]
	Poland	surface	15,0	178,0			[19]
Hormones							
Estrone	France	surface	0,3	3,5	1,8	1,6	[20]
	United States	surface	0,6	2,6			[21]
	Germany	tap	0,3	2,1	1,6	1,7	[22]
	United States	tap	1,1	2,3			[17]
Estriol	United States	surface	0,8	19,0	9,9	9,9	[21]
Estradiol	Germany	surface	0,2	3,6	2,4	2,0	[19]
	Netherlands	surface	0,3	5,5			[19]
Ethinyl estradiol	Germany	surface	0,1	5,1	2,4	2,2	[19]
	Netherlands	surface	0,1	4,3			[19]
Psychotropic drugs							
Carbamazepine	Netherlands	tap	29,0	50, 8	21,6	17,4	[23]
	UK	tap	1,1	5,7			[24]
Meprobamate	UK	tap	1,6	13,0	7,3	7,3	[24]
Antibiotics							
Erythromycin	China	surface	13,0	423,0	140,7	17,0	[25]
	Vietnam	surface	9,0	11,0			[25]
	Japan	surface	21,0	448,0			[25]
	South Korea	surface	0,0	450,0			[25]
	Wales (UK)	surface	11,0	21,0			[5]
	United States	tap	1,3	1,3	1,3	1,3	[17]
Norfloxacin	Switzerland	surface	45,0	120,0	82,5	82,5	[26]
Ciprofloxacin	Switzerland	surface	294,0	405,0	349,5	349,5	[26]
Sulfamethoxazole	China	surface	2,0	165,0	50,7	13,5	[25]
	Japan	surface	4,0	23,0			[25]
	South Korea	surface	0,0	110,0			[25]
	United States	tap	13	80	46,5	46,5	[27]
Trimetoprim	Vietnam	surface	5,0	20,0	34,2	20,0	[25]
	South Korea	surface	10,0	20,0			[25]
	Wales (UK)	surface	30,0	120,0			[5]
Other							
Caffeine	Norway	surface	7,0	87,0	47,0	47,0	[18]
	United States	tap	2,6	83	23	25	[17]

mental disorders, thyroid hormone disorders and infertility. Another undesirable effect of drugs administered together with drinking water is the detrimental effect they may cause on DNA level. This is mainly the case of cytostatic anticancer drugs. It can lead to an increased risk of incidence of testicular cancer and breast cancer. [9]

The aim of the study is to assess an exposure to substances of pharmaceuticals in drinking water and quantify related human health risk. Risk assessment is based on a systematic literature study.

Methods

The methodology of the risk assessment corresponds with the one suggested by US EPA and consist of: risk identification, exposure assessment, toxicity assessment and risk characterization [28, 29]. Whereas, the first three steps rely on collected and analysed data, the risk characterization represents a model-based approach that links and quantizes information derived from the previous steps. Exposure to a given pharmaceutical substances was assessed on the basis of the quantity of drinking water consumed (assumed scenario) and an averaged concentration of a given pharmaceutical substance. The population was divided by age into five groups. The age interval of each group corresponds with an important physiological changes and psycho-behavioural development of humans. Each group is characterized by: body weight, the amount of drank water, exposure frequency and duration (Table 2). Body weight (BW) values are based on individual growth charts and averaged for a given age interval. [30] Drinking water consumption rate (CR_{dw}) was assumed according to authors best regard and knowledge. Exposure frequency (EF) is a default value recommended by US EPA Human Health Risk Assessment Protocol (HHRAP). [31] Exposure duration (ED) was assumed to be 70 years as in this case scenario a life-long exposure is concerned. Knowledge about each parameter was essential for dose daily intake (I_{dw}) calculation (eq.1).

Intake doses were calculated with respect to exposed subpopulation. Calculations incorporated median values of a given pharmaceutical concentration present in tap water.

$$I_{dw} = C_{dw} \times F_{dw} \times CR_{dw} / BW \qquad \text{eq.1}$$

where:
I_{dw} – daily intake of pharmaceuticals from drinking water [mg/kg-day]
C_{dw} – the average concentration of the substance in drinking water [mg/L]
F_{dw} – fraction of drinking water that is contaminated [-] (assumed 1 according to HHRAP)
CR_{dw} – daily consumption of water [L/day],
BW – average body weight [kg]

Table 2. Age-specific anthropometric and exposure parameters

Exposed subpopulation		Parameter			
Group	Age [yrs]	Average body mass (BW) [kg]	Average amount of consumed water (CR_{dw}) [L/day]	Exposure frequency (EF) [days/ yr]	Exposure duration (ED) [yrs]
Toddlers	1-3	12	0,5	350	70
Preschoolers and primary scholars	4-10	25	1	350	70
Preadolescents and adolescents	11-18	50	1,5	350	70
Adults (high activity)	19–40	70	2	350	70
Adults (moderate and low activity)	41–75	70	1,5	350	70

Table 3. Toxicological parameters of chosen pharmaceutical compounds

Lp.	Pharmaceutical substance	LOEC [mg/L]	NOEC [mg/L]	ADI [mg/kg-d]	EC50 [mg/L]
1	Diclofenac	8 [41]	10 [41]	0,0016 [49]	7,5 [32]
2	Ibuprofen	0,0001 [53]	10 [42]	0,11 [50]	7,1 [33]
3	Naproxen	1 [46]	51 [46]	0,046 [49]	35 [34]
4	Clofibric acid	0,15 [52]	0,075 [52]	0,0167 [51]	12,5 [32]
5	Estrone	0,00075 [43]	0,000307 [54]	0,000423 [43]	0,41[35]
6	Carbamazepine	$1 \cdot 10^{-5}$ [41]	0,026 [52]	0,00034 [49]	74,0 [32]
7	Meprobamate	0,002 [45]	0,01 [42]	0,00016 [49]	13,9 [33]
8	Erythromycin	5 [45]	30 [45]	0,04 [50]	280 [35]
9	Sulfametoxazol	50 [45]	300 [45]	0,13 [50]	177,3 [36]
10	Caffeine	9 [42]	12 [42]	0,15 [50]	1,0 [37]

Then, based on the available literature data, a quantitative relationship between the level of exposure (dose) and the resulting of adverse health effects for each compound needs to be derived. The values were collected primarily from toxicological studies carried out on animals (Table 3). For this reason, it is required to carry out an interspecies and high-dose/low-dose extrapolation. The extrapolation is conducted by dividing a toxicological parameter, i.e. NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level) by an uncertainty factor (UF). The UF=300 assumption stays in accordance with US EPA's methodology for UF's estimation. The ratio of NOEAL (LOAEL) to UF is defined as the reference dose (RfD) (eq.2). The RfD values are specific for each chemical compound defined as non-carcinogenic.

$$RfD = NOAEL / UF \quad \text{eq.2}$$

where:
RfD – reference dose [mg kg^{-1}]
NOAEL – no observed adverse effect concentration [mg dm^{-3}]
UF – uncertainty factor [-] (assumed 300).

Subsequently, the hazard quotient (HQ) for each substance was calculated (eq.3).

$$HQ=(I \times ED \times EF)/(RfD \times AT \times 365) \quad \text{eq.3}$$

where:
HQ – hazard quotient [-]
I – daily intake of pharmaceuticals from drinking water [mg/kg-day]
EF – exposure frequency [days/yr]
ED – exposure duration [yrs]
RfD- reference dose [mg/kg-day]
AT – averaging time [yrs] – for noncarcinogens is numerically the same as ED
365 – units conversion factor [day/yr]

To determine the total values specific for each age-group the hazard index (HI) parameter was calculated (eq.4).

$$HI = HQ_1 + HQ_2 + ... + HQ_n \quad \text{eq.4}$$

All equations used by the authors are same with mathematical formulas described in HHRAP.

Results

Based on the amounts of pharmaceuticals present in tap water (Table 1) and age-specific body parameters along with exposure characteristics (Table 2), estimated intake of each drug and for each age group were calculated (Table 4).

The group that collects the highest dose of all of the drugs are toddlers, when compared with other exposed groups. This situation is a direct result of a mathematical relation between the magnitude of an exposure and low body mass. The highest dose of drug collected for all age groups is sulfamethoxazole, and the lowest dose was estrone.

Based on the literature a quantitative relationship between the level of exposure (dose), and the resulting adverse health effects (response) for each compound (Table 5) was assessed.

Analysing the above table it can be seen that the highest RfD (lowest hazard) value has sulfamethoxazole, and the lowest estrone (highest hazard). It illustrated the magnitude of hazard which is inversely proportional to the RfD values. It means that the higher value of RfD is, the lower hazard it poses to human health. For this reason sulfamethoxazole can be regarded as the low hazard posing drug, whereas estrone is defined as the most hazardous.

The final step, yet to be taken in risk assessment, is characterization of risk magnitude. The hazard quotients along with hazard indexes are presented in Table 6.

The results of the absolute risk were neither greater nor equal to one. It indicates that none of these substances poses considerable health risk. These substances do not

Table 4. Intake doses calculated for each drug with respect to an exposed group

n	Pharmaceutical	Exposed subpopulation [yrs]				
		Toddlers [1-3]	Preschoolers and primary scholars [4-10]	Preadolescents and adolescents [11-18]	Adults (high activity) [19-40]	Adults (moderate and low activity) [41-75]
		Estimated intake x 10^{-8} [mg/day-kg]				
1	Diclofenac	34,40	16,52	12,41	11,86	8,84
2	Ibuprofen	4,75	2,28	1,71	1,63	1,22
3	Naproxen	11,30	5,40	4,05	3,86	2,89
4	Clofibric acid	25,00	12,18	9,00	8,57	6,43
5	Estrone	2,13	1,02	0,76	7,29	0,55
6	Carbamazepine	21,70	10,44	7,83	7,46	5,59
7	Meprobamate	9,13	4,38	3,29	3,13	2,35
8	Erythromycin	1,63	0,78	0,58	0,56	0,42
9	Sulfametoxazol	58,14	27,98	20,93	19,93	14,95
10	Caffeine	31,35	15,01	11,35	10,74	8,04

Table 5. The list of reference doses (RfD) of active substances

	Pharmaceutical active ingredient	RfD* [mg/day-kg]	Literature
1	Diclofenac	0,03	[38]
2	Ibuprofen	0,03	[33]
3	Naproxen	0,17	[37]
4	Clofibric acid	0,03	[33]
5	Estrone	0,01	[35]
6	Carbamazepine	0,09	[38]
7	Meprobamate	0,04	[33]
8	Erythromycin	0,10	[33]
9	Sulfametoxazol	1,00	[33]
10	Caffeine	0,04	[33]

*values received as a product of NOAEL/300

Table 6. Hazard quotients and hazard indexes with respect to compound and an exposed population

No	Pharmaceutical active substance	Age group				
		Toddlers [1-3]	Preschoolers and primary scholars [4-10]	Preadolescents and adolescents [11-18]	Adults (high activity) [19-40]	Adults (moderate and low activity) [41-75]
		HQ [x10^{-5}]				
1	Diclofenac	1,15	0,55	0,41	0,40	0,29
2	Ibuprofen	0,16	0,08	0,06	0,05	0,04
3	Naproxen	0,07	0,03	0,02	0,02	0,02
4	Clofibric acid	0,83	0,41	0,30	0,29	0,21
5	Estrone	0,21	0,10	0,08	0,73	0,06
6	Carbamazepine	0,24	0,12	0,09	0,08	0,06
7	Meprobamate	0,23	0,11	0,08	0,08	0,06
8	Erythromycin	0,02	0,01	0,01	0,01	0,00
9	Sulfametoxazol	0,06	0,03	0,02	0,02	0,01
10	Caffeine	0,78	0,38	0,28	0,27	0,20
	HI	**3,75**	**1,80**	**1,35**	**1,94**	**0,96**

have adverse health effects. Diclofenac received the highest HQ values for all the age groups. The second highest was clofibric acid and caffeine. The lowest HQ values are observed for erythromycin, sulfamethoxazole and naproxen. It should be noted that the youngest children aged 1-3 years had the highest hazard index value. It was twice as high as HI derived for preschoolers and primary scholars and four times higher than HI received for adults aged 31-75 years. The latter, were the group that received the lowest HI value from all the other groups.

Discussion

Although, the hazard index values (HI) were far below the 1.0 value it should be kept in mind that many of these biologically active substances may exert an effect on very low doses (for e.g. hormones). Cytostatics, on the other hand, are a group of highly hazardous DNA intercalators and disruptors that have no safe threshold limit value. Table 1 indicates that NSAID are the most abundant group of pharmaceuticals that is quantified in drinking water intakes but at lower concentrations, when compared with surface waters. The same applies to antibiotics. Though, antibiotics median concentrations do not significantly differ from surface water concentrations. Some of the listed pharmaceuticals occur in much higher quantities than other. These are: triclosan and paracetamol (NSAID), benzafibrate (lipids regulator), atenolol (β-blocker) and ciprofloxacin (antibiotic). Although, these drugs occur rather in surface waters, an environmental and health risk should be perceived. For an attention calls increasing occurrence of hormones both in surface waters and water intakes. This situation indicates that environmental biota and humans are equally exposed to biologically active substances that can cause ecological and/or health effect at very low doses. Nonetheless, mentioned in an introductory part health effect do not apply equally to every human exposed to it.

There are at least two groups of people that call for special attention: children and pregnant women. Children are the group of distinctive concern. The environmental exposure to pharmaceuticals may start through mother's womb and eventually continue when the child is born. What mainly distinguishes children from adults is: activity patterns as well as biochemical and physiological parameters. Due to incomplete physiological development, a child ability to metabolize certain chemical agents is strongly reduced. The highest susceptibility to chemical compounds

can be observed in newborns and infants at the first few weeks of life. At the age of 2, child biochemical and physiological characteristics are almost fully developed. However, the differences between a child and an adult do not disappear until the maturity period. The maturation processes of reproductive and endocrine systems along with nervous system happen very slow and remain the most susceptible to pollutants disruptive effect.

For this reason, the assessment of health risk of children exposed to a vast variety of environmental pollutants should be carried out with distinctive caution. This principle should be especially applied when it comes to newborns and infants as their physiological parameters undergo the largest changes over a very short period of time. This may suggest that classical methods and guidelines of risk assessment proposed by US EPA and applied widely may not suite the most vulnerable subgroups. Moreover, the risk assessment procedure is not valid for substances which toxic effect is non-linear and has threshold much below average threshold values of non-carcinogenic substances.

Conclusions

Based on the analysis we can say that every person, regardless the age or origin is exposed to the adverse health effects of substances of pharmaceutical origin. The main route of exposure is the consumption of contaminated drinking water and the use of surface waters. What is more, antibiotics and hormones can be ingested with meat products. The levels of pharmaceuticals assessed in this study were not high enough to pose a significant health hazard. Nonetheless, it should be noted that no chemical substance is indifferent to our body. Especially biologically active one. Even the smallest dose of a drug may impair the work of internal systems. Coming to a conclusion, pharmaceuticals constitute a serious problem to the environment and human health. There are some necessary steps to be taken in order to minimize the threat. It can be achieved by: continuous education and information the whole of society on how to properly use and manage unused or expired drugs, development of a comprehensive system for reporting medication without a prescription and sold through the Internet, environmentally friendly drug design, development and implementation of more effective methods of water treatment as well as introduction of more restrictive regulations limiting drugs and hormone presence in water and food products.

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