EurEau

Outcome of an inquiry on pharmaceutical residues in drinking water resources (European surface waters) among members of the EurEau Commission on Drinking Water

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Residues of pharmaceutical products are known to occur widely in the aquatic environment of industrialized countries. The primary path to the environment for human drugs is domestic wastewater. The drugs are usually not fully broken down after ingestion and are subsequently excreted. Wastewater treatment plants often do not have the capacity to filter out all pharmaceutical residues. Where wastewater treatment plants are absent these substances have a direct pathway into bodies of water, where they cause harm to plants and animals. Veterinary drugs enter soil and water primarily via the slurry and manure of treated animals.

Information on the occurrence of pharmaceutical residues in the environment has become more readily available in recent years. In the last years, a multitude of papers and reviews has been published, describing the detection of various pharmaceutical residues in the European aquatic environment. However, a concise picture on the relevant pharmaceuticals, their prevailing concentrations in the environment and their relevance to drinking water is still elusive.

In 2013, EurEau-commission 1 “Drinking water” (EU1) started a data inquiry among its members concerning the available knowledge on pharmaceutical residues in surface waters used for drinking water abstraction based on national measurements and findings. Numerous responses, providing raw data sets, reports from research projects as well as peer-reviewed articles in journals, were received and evaluated. According to the evaluation of the replies, 186 different pharmaceutical active substances and degradation products have been traced in the European aquatic environment. However, the respective data basis turned out to be quite heterogeneous with respect to locally investigated parameters, water bodies monitored, sampling frequencies and found concentrations per parameter.140 substances were measured in less than three, 46 compounds in three or more member states (see Figure 1).

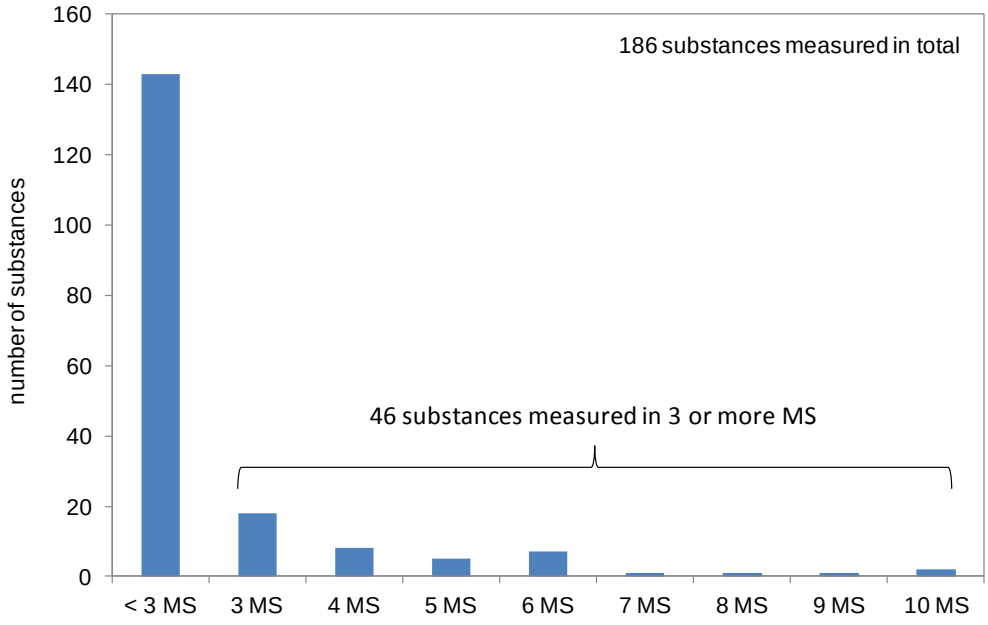

Figure 1: EU1 inquiry: Number of substances from pharmaceutical residues measured in member states (MS).

Based on an evaluation of measurement frequencies, positive findings, as well as levels and concentrations. Table 1 shows the compounds being most often measured and detected in European waters.

Table 2 summarizes substances that were less often measured in member states, but are interesting due to detection at relatively high concentrations when investigated.

Table 1: EU1 inquiry: Substances from pharmaceutical residues most often measured and detected in the aquatic environment of member states.

Diclofenac	Analgesic
Ibuprofen	Analgesic
Carbamazepine	Antiepileptic drug
Naproxen	Analgesic
Atenolol	Beta blocker
Erythromycine	Antihypertensive drug
Bezafibrate	Lipid-lowering drug
Ethinyl estradiol	Estrogen
Ketoprofene	Analgesic
Metoprolol	Beta blocker
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic

Table 2: EU1 inquiry: Substances from pharmaceutical residues less often measured in the aquatic environment of member states, but interesting based on their levels found.

Amidotrizoic acid	X-Ray contrast medium
Caffeine	Alkaloid
Clarithromycine	Antibiotic
Clindamycine	Antibiotic
Iohexol	X-ray contrast medium
Iomeprol	X-ray contrast medium
Iopamidol	X-ray contrast medium
Iopromid	X-ray contrast medium
Metformin	Antidiabetic drug
Paracetamol	Analgesic
Primidon	Anticonvulsant
Sotalol	Beta blocker

Further evaluation of the data sets for the substances of major interest, as presented in table 1 and table 2, in surface waters, preferably those of large river systems which are used directly or indirectly for drinking water purposes, indicated that certain compounds are regularly found in the European aquatic environment in concentrations up to several hundred nanogram per litre. The results are summarized in the annex in table A1, Table 3 displays a smaller selection of the results.

Table 3: EU1 inquiry: Concentration levels of pharmaceutical residues in major river systems in Europe.

river	**Rhine**	**Ruhr**	**Main**	**Lek**	**Bergse Maas**	**Afgedamde Maas**
location	Düsseldorf, km 732,1 r	various locations	Frankfurt, km 37,6	Nieuwegein	Keizersveer, km 865	Brakel, km 840
country	Germany	Germany	Germany	The Netherlands	The Netherlands	The Netherlands
data from	2012	2012	2012	2012	2012	2012
number of measurements	13	161	13	13	13	13
reference	ARW report	Ruhrgütebericht	ARW report	RIWA report	www.riwa-maas.org	www.riwa-maas.org
substance	annual average [ng/L]	annual average [ng/L]	annual average [ng/L]	annual average [ng/L]	annual average [ng/L]	annual average [ng/L]
diclofenac	50	71	70	55	26	6
ibuprofen	10	<25	20	<20	23	<32
carbamazepine	50	70	100	40	<50	27
naproxen	9*	18		40	<20	1
atenolol	10	<25	<10	6	n.a.	5
erythromycine	27*	n.a.	n.a.	n.a.	<20	n.a.
bezafibrate	10	34	30	17	<10	2
ethinyl estradiol	<1**	n.a.	n.a.	n.a.	<500	n.d.
ketoprofene	n.a.	n.a.	<10	<2	<10	<20
metoprolol	60	123	110	29	98	<50
sulfamethoxazole	40	59	60	n.a.	20	13
trimethoprim	<20	n.a.	n.a.	6	<20	2
amidotrizoic acid	210	285	560	251	72	145
caffeine	89*	n.a.	n.a.	69	293	59
clarithromycine	11*	n.a.	n.a.	n.a.	<50	n.a.
iohexol	100	122	130	103	74	78
iomeprol	420	308	430	404	141	186
iopamidol	220	426	590	228	<50	58
iopromid	120	88	340	158	130	127
metformin	n.a.	n.a.	n.a.	646	719*	588
paracetamol	n.a.	11	n.a.	2	2*	<1
primidon	n.a.	n.a.	n.a.	n.a.	<20	6
sotalol	20	59	20	19	<100	15
	* older data from km 757,9 r				* average of 3 measurements ir 2013	
	** older data from 2003					

Based on the relative concentration levels, the most relevant compounds for the investigated rivers that were detected most often and in the highest concentrations were

the X-ray contrast media amidotrizoic acid, iomperol, iopamidol and the antidiabetic drug metformin. For these compounds, maximum concentration levels range up to several hundreds of nanogram per litre. Concentrations of the analgesic drug diclofenac or the antiepileptic drug carbamazepine were significantly lower in each river system.

Several EU1 members also pointed at the results of relevant studies published recently in literature. Some key findings will be summarized in the following.

An European Union-wide survey of polar organic persistent pollutants in European river waters by Loss et al. (2009) investigating more than 100 individual water samples from over 100 European rivers from 27 European countries, also on selected compounds of pharmaceuticals residues, identified caffeine and carbamazepine as those pharmaceuticals being most frequently and at the highest concentration levels detected. X-ray contrast media and the antidiabetic drug metformin were, however, not included in the analytical target spectrum of the compounds analyzed. Concentration levels of substances overlapping with the ones selected in the EurEau inquiry did fit quite well to the findings reported by the EU1 members (Figure 2).

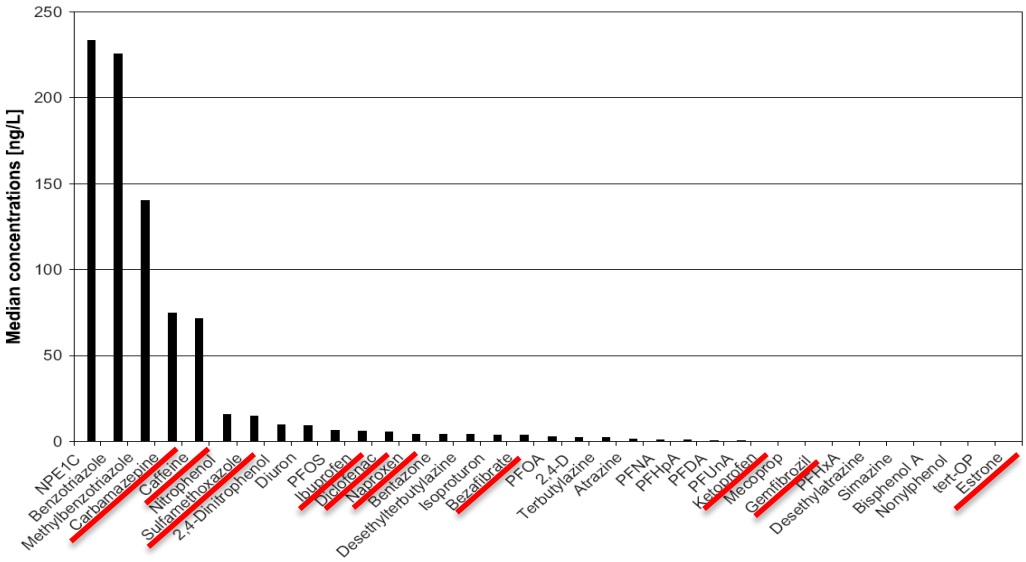

Figure 2: Medium concentrations of organic micropollutants including some pharmaceuticals (underlined by red strokes) as reported by Loss et al. (2009).

Hughes et al. (2013) presented a global-scale analysis of the presence of a whole set of pharmaceuticals across several countries. According to their findings the majority of research effort has focused so far upon just 14 compounds. Data from the 20 most commonly encountered pharmaceuticals in European receiving waters are presented in Figure 3. Similar to the study by Loss et al. (2009) median concentration levels were for most of the substances covered by the analysis below 100 ng/L. However, the compounds highlighted by the EurEau inquiry as being most relevant, were not considered.

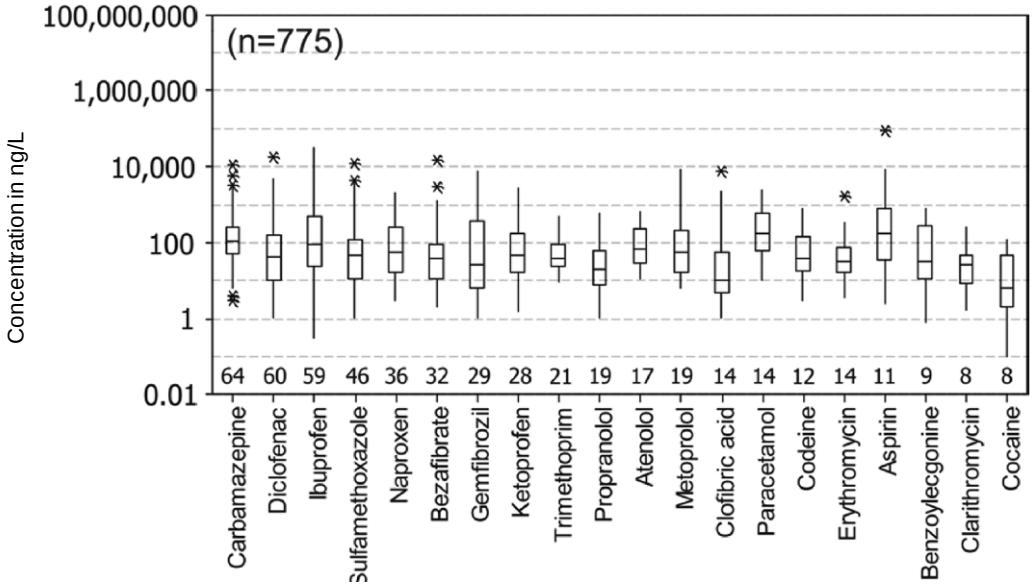

Figure 3: Boxplots of concentration levels of pharmaceutical residues found in European rivers as reported by Hughes et al. (2013).

A study by Sacher et al. (2008) reporting on the results of a one-decade monitoring program on pharmaceuticals in the Rhine River (1997 until 2006) could not identify any significant trend in concentration levels based on an evaluation of the long-term monitoring data. Thus the contamination of the Rhine River by pharmaceutical residues was regarded as almost constant. Quite interestingly, seasonal variations could be detected for bezafibrate, diclofenac and ibuprofen where the concentrations are much lower in the summer months. A more effective removal during wastewater treatment in the warmer periods of the year was stressed as the major reason for those variations. For carbamazepine no comparable seasonal effect was found. Based on the measured concentration levels, also annual transports were calculated. It was found that like the concentrations the transports of the pharmaceutical residues in the Rhine River increased with increasing distance from the river source. In the upper part at Basel, transports for most of the pharmaceuticals were below or close to 0.5 tons per year. Further downstream at Düsseldorf, transports for several compounds raised up to several tons per year with maximum transports for carbamazepine and diclofenac close to 10 tons per year.

Hut et al. (2013) studied the relation between pharmaceutical residues along the Rhine River and the demographic characteristics of the upstream population. By combining environmental water quality data and demographic data some insight was gained in the interplay between humans and their environment, showing the medicinal footprint of the population of the Rhine basin. Total concentrations of the 21 pharmaceuticals measured revealed a contamination of 500-1500 ng/L. A significantly increasing trend was found in measured total concentrations of pharmaceuticals with downstream distance, supporting the fact that the concentration of pharmaceuticals is linked to the number of people in the

upstream catchment. The demographic groups that contribute most per pharmaceutical are shown in Table 4. For 12 of the 21 studied pharmaceuticals, a significant ($p < 0.05$) dominant demographic group could be identified.

Table 4: Main contributing demographic group per pharmaceutical according to Hut et al. (2013).

Pharmaceutical	Therapeutic class	Most contributing group	R^2	p-value
Carbamazepine	Anti-epileptic	Male elderly	0.98	<0.001
Primidone	Antidepressant	Male adults	0.98	<0.001
Temazepam	Psycholeptic	Germans	0.96	<0.001
Bezafibrate	Antilipaemic	Germans	0.97	<0.001
Losartan	Anti-hypertension	Male adults	0.94	<0.001
Sotalol	Beta blocker	Female children	0.97	<0.001
Lidocaine	Analgesic (a.o.)	Female adults	0.94	0.001
Bisoprolol	Beta blocker	Male elderly	0.95	0.003
Hydrochlorothiazide	Diuretic	Germans	0.96	0.004
Sulfamethoxazole	Antibiotic	Male elderly	0.95	0.009
Oxazepam	Psycholeptic	Female children	0.93	0.034
Atenolol	Beta blocker	Swiss	0.84	0.05
Lincomycin	Antibiotic	Germans	0.76	0.065
Metoprolol	Beta blocker	Swiss	0.77	0.077
Iopromide	X-ray contrast agent	Female adults	0.84	0.083
Phenazone	Analgesic	Germans	0.69	0.113
Diazepam	Psycholeptic	French	0.77	0.361
Atorvastatin	Antilipaemic	Swiss	0.60	0.593
Propranolol	Beta blocker	Male children	0.70	0.62
Trimethoprim	Antibiotic	Male adults	0.64	0.824
Metformin	Antidiabetic	Male children	0.79	0.852
Average			0.85	<0.001

Pharmaceuticals are substances that are synthesized to create a biological effect. It is also worth mentioning that several single compounds within this group belong to the same therapeutic class, making possibly a summated evaluation relevant. The data assembled in this document shall serve EurEau members as the basis for further considerations, more concrete discussions and useful tool in prioritizing future studies and investigations on pharmaceuticals in the aquatic environment and drinking water. The results indicate that the pattern of detectable compounds is quite similar all over Europe. Even though the list of possibly occurring pharmaceuticals is long, certain parameters, as given in Table 1 and Table 2, can serve as good indicators to assess the respective contamination degree of the water under investigation. There is proof that pharmaceutical residues in the environment pose a certain problem all over the world. This problem can be solved only on a global scale by promoting international chemicals safety and developing appropriate countermeasures.

References

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