The risk of pharmaceuticals in the aquatic environment

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In a literature review the effects and risks of five human pharmaceuticals in the aquatic environment were examined. These pharmaceuticals, carbamazepine, diclophenac, erythromycin, metoprolol and sulphamethoxazole, have frequently been detected in Dutch surface waters. Four of these five pharmaceuticals, on the basis of risk assessment, represent a risk to the aquatic environment. In concentrations less than one-millionth of a gram (µg or ppm) per litre water these pharmaceuticals harm the liver, kidneys and gills of fish. Moreover at these low concentrations they disturb growth, reproduction and behaviour of animal plankton. The European Parliament is trying to persuade the European Union to place environmental harmful pharmaceuticals on the list of priority substances of the EU Water Framework Directive. This will stimulate the pharmaceutical industry to develop more environmentally friendly medicines. Moreover, governments and other parties will be encouraged to improve wastewater treatment and promote more responsible use of pharmaceuticals.

From a simple painkiller for a headache to medication for heart diseases, almost everyone uses medicines. The total use of pharmaceuticals in the Netherlands during the period 2001-2006 increased by 21.9%[1]. In the body these compounds are not broken down and are excreted. By way of wastewater from households, nursing homes and hospitals, pharmaceuticals end up in sewage treatment plants (STP) where most pharmaceuticals are only partly broken down[2]. Since pharmaceuticals reach the surface, ground and drinking water, there is a potential risk to environment and health. In 2001 the Health Council of the Netherlands established that emission of pharmaceuticals into the environment is undesirable and that opportunities for reduction must be considered[3]. In addition, the European Water Framework Directive (WFD) issued a directive in 2000 that a good chemical and ecological quality of surface water should be achieved in 2015. Since 2006 the European Parliament is trying to persuade the European Union to add several pharmaceuticals to the list of priority substances of the WFD. Once pharmaceuticals are definitely placed on the list, EU Member States have to develop emission reduction measures within five years. This European decision depends to a large extent on a proper risk assessment of the designated chemicals. For a number of pharmaceuticals the effects on soil and water organisms has been investigated, but for many pharmaceuticals information on their fate and environmental effects are not yet available. The Dutch organization Stichting Huize Aarde has commissioned a literature review on the impact of chronic exposure to pharmaceuticals on the environment. For this study five pharmaceuticals were selected which are frequently observed in Dutch surface waters[4] and of which ecotoxicological data are available, see Table 1. The studied compounds are the anti-epilepticum carbamazepine, the painkiller diclophenac, the beta blocker metoprolol and the antibiotics erythromycin and sulphamethoxazole. All five pharmaceuticals are of human origin. Antibiotics in surface water also partly originate from the veterinary sector. In particular sulphamethoxazole is very mobile in the environment, which makes it difficult to determine the human or veterinary origin. In a recent study by the Global Water Research Coalition, these pharmaceuticals have been identified as high priority (Class I), except for metoprolol, which is classified in Class II (normal priority)[5].

Expected effects on aquatic organisms

Pharmaceuticals are designed to cause a targeted effect in the molecular structures of humans and animals. Since receptors, enzymes and certain organs in some aquatic organisms are comparable to those in the human body, it is conceivable that pharmaceuticals may also cause an impact to aquatic organisms[2]. Carbamazepine, for example, imitates the GABA receptor by which the influx of chloride-ions in the brain is halted and an epileptic attack can be prevented. The GABA receptor has also been found in fish[6]. Diclophenac works by inhibiting the cyclooxynase (COX) enzyme and thus suppresses the formation of certain hormone-like chemicals (prostaglandins) that causes pain. Research in fish has shown that the COX enzyme is active in infections[7]. In other vertebrate and invertebrate organisms prostaglandins are also formed. Metoprolol acts on the heart muscle and blocks the beta-adrenaline receptor that among others reduces the heart rate. The beta-adrenaline receptor has been detected in fish, amphibians, mammals and other vertebrate organisms and performs the same function as in humans[8]. By reducing the heart rate, the presence of metoprolol in aquatic organisms could affect growth and flight behavior. In surface water it is possible that the antibiotics erythromycin and sulphamethoxazole eliminate bacteria, thereby disrupting the balance in the ecosystem.

Proven ecotoxicological effects

During previous years several ecotoxicological studies have been published on the five selected pharmaceuticals. In these studies organisms were exposed, during part (semi-chronic) or total lifecycle (chronic), to environmentally relevant concentrations, see Table 1. The lowest measured effect concentration of chronic exposure to **carbamazepine** in two studies was 1.0 µg/L. At this concentration kidney damage in carp was detected[9]; and female water fleas reached maturity earlier and produced more offspring as a result of a stress reaction[10]. In a study in which the acute effect of carbamazepine on the behavior of *Gammarus pulex* was tested, the lowest effect concentration was 0.01 µg/L. At this concentration, the activity of this freshwater amphipod was 30% lower than in the control group[11]. The lowest measured effect concentration for **diclophenac** in trout was 0.5 µg/L[12]. At this concentration kidney, gill and liver damage was observed following a three-week period in which the trout were exposed to different concentrations of diclophenac. In another study of rainbow trout kidney, liver and gill damage was demonstrated in 1.0 µg/L diclophenac[9,13], see Figure 1. A concentration of 1.0 µg/L **erythromycin** reduces the population density of a cyanobacterium by 15%[14]. The lowest measured concentration effect of **sulphamethoxazole** on the cyanobacterium *Synechococcus leopoliensis* was 6.0 µg/L[15]. Besides toxicity the increased bacterial resistance to antibiotics is another indication of an environmental impact and potential risk to public health. The resistance of bacteria to erythromycin and sulphamethoxazole has been studied in three types of E-coli bacteria and an unknown bacterium isolated from a STP. This showed that all bacteria are resistant to erythromycin and one of the bacteria was resistant to sulphamethoxazole[16]. The lowest measured concentration effect of **metoprolo**l for liver and kidney damage in rainbow trout was 1.0 µg/L[9].

Table 1: Measured concentrations in surface water of the Netherlands[4] en lowest measured effect concentrations (µg/L) of the selected pharmaceuticals.

Compound	Total samples	Positive samples	Frequency (%)	Highest concentration	Mean concentration	Lowest measured effect concentration
sulphamethoxazole	133	109	82	0.11	0.028	6.0[15]
(anhydro)erytromycin	106	75	71	0.11	0.020	1.0[14]
carbamazepine	153	99	65	0.26	0.067	1.0[9,10]
diclophenac	172	85	49	0.70	0.033	0.5[12]
metoprolol	120	59	49	0.42	0.023	1.0[9]

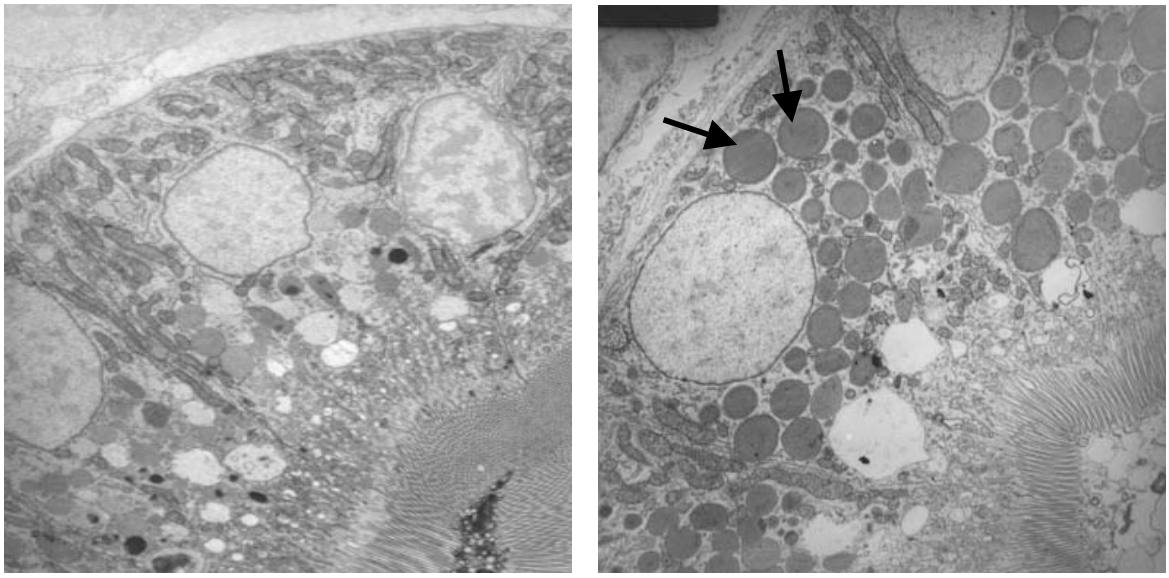

Figure 1. Cross-section of healthy (left) and by diclophenac affected (right) kidney tissue (3700x) of rainbow trout. In the (three) healthy cells round the light coloured nucleus many dark coloured mitochondria (energy supply) are visible. In the (two) affected cells instead of mitochondria many dark grey coloured hyaline droplets are visible (see arrows). Hyaline droplets are filled with proteins and they block the filter function of the kidney. This effect of diclofenac was visible in rainbow trout from 1.0 µg/L[9,13] and from 0.5 µg/L[12]. Dr Rita Triebskorn, Steinbeis-Transferzentrum für Ökotoxikologie und Ökophysiologie, Germany, generously made these pictures available.

Combination toxicity

Water organisms are exposed to a cocktail of different industrial chemicals, including pharmaceuticals. Little research has been conducted on the combined toxicity of pharmaceuticals in surface water. The available research shows that within pharmaceutical groups, like hormones, antibiotics, NSAID-analgesics and beta-blockers, the environmental toxicity is additive[17,18,19,20]. For example, the painkiller diclophenac works additively with ibuprofen[17], see Figure 2, and the beta-blocker metoprolol works additively with propanolol and atenolol[20]. Pharmaceuticals from different groups can also work together. For example, carbamazepine works additively with the cholesterol reducer clofibrate[18]. This means that when chemicals are complementary the combination toxicity is higher than the individual toxicity. Therefore pharmaceuticals in concentrations below their lowest effect concentration, even in non-detectable concentrations, are capable of contributing to overall environmental toxicity. Moreover, the toxicity of biotransformation products (metabolites) is of interest. A metabolite of carbamazepine (carbamazepine-10,11-epoxide), for example, still has 50% to 100% of the biological activity of the original substance. Although metabolites can contribute to the combined toxicity in surface water, and their environmental concentrations could exceed those of the parent compound, little is known about the presence and role of metabolites.

Risk assessments

In order to determine the risk of industrial chemicals in the aquatic environment, a risk assessment is prepared. The risk assessment is based on the quotient of the PEC (predicted environmental concentration) and PNEC (predicted no effect concentration). A PEC/PNEC higher than one means a high risk to the aquatic environment; a PEC/PNEC smaller than one means a low risk. Table 2 summarizes the risk quotients of the selected pharmaceuticals as described in the literature. The quotients may vary per pharmaceutical, as the PEC per country may vary by differences in medicine consumption. The PNEC may vary because use is made of other eco-toxicological data (acute, semi-chronic or chronic) with different targets (endpoints) in the organisms, like growth, reproduction or histology. The table shows that carbamazepine, erythromycin and sulphamethoxazole are classified by most

studies as high risk. Diclophenac is classified by most studies as low risk, however, by one study as very high risk. In this study, malformations in the liver are demonstrated at concentrations of 0.5 µg/L[12]. Metoprolol is assessed by all studies as low risk. It should be noted that metoprolol does not yet have a PEC/PNEC calculation which is derived from the low concentration effect (1.0 µg/L) for liver and kidney damage in fish[9]. Table 2 shows that it is important to know on which endpoint the PNEC is based. From the precautionary principle, our conclusions are based on the highest PEC/PNEC.

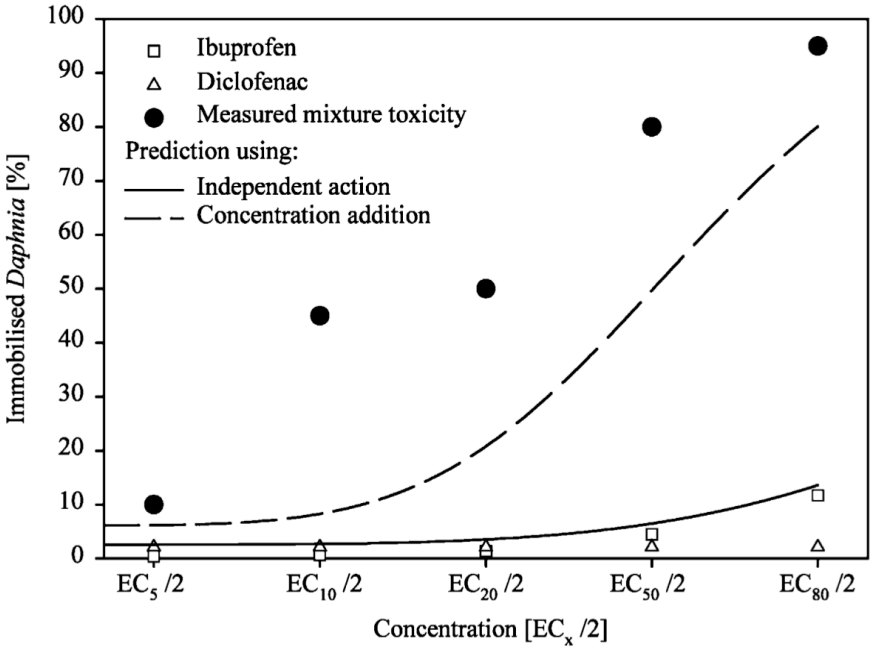

Figure 2. Individual and combined toxicity of diclophenac and ibuprofen in water fleas.
EC = standardized effect concentration. The measured additional effect is higher than the expected additional effect only on the basis of concentration (from Cleuvers, 2003[18]).

Table 2: Published risk quotients of pharmaceuticals in surface water

Compound	PEC/PNEC	Risk	End point	Chronic or acute	Country	Source
sulphamethoxazole	0.1	low	population growth Gammarus pulex	chronic	Italy	21
	1.31	high	immunotoxicty mussel	acute	Canada	22
	11.4 – 59.3	high	growth blue-green algae	semi-chronic	Germany	15
	97 - 101	high	growth blue-green algae	semi-chronic	Norway	23
erytromycin	1.0	high	algae growth	semi-chronic	Italy	21
	2.4	high			Germany	24
carbamazepin	0.017	low	algae growth	semi-chronic	Germany	24
	1.4	high	immunotoxicity mussel	acute	Canada	22
	2.4 – 3.85	high	Reprod. Gammarus pulex	chronic	Germany/ France	15
diclophenac	0.033 – 0.124	low	reproduction Gammarus pulex	chronic	Germany/ France	15
	0.079	low	survival water flea	acute	Germany	24
	0.51 – 5.7	low/ high	reproduction Gammarus pulex	chronic	Norway	23
	100	high	histology liver fish	semi-chronic	Germany	12
metoprolol	0.0016	low	survival fish	acute	Germany	24
	0.029 – 0.032	low	water flea	semi-chronic	Norway	23
	0.28	low	algae growth	semi-chronic	Germany	25

Conclusions and recommendations

Of the selected pharmaceuticals there are, except for sulphamethoxazole, several ecotoxicological studies which demonstrate (semi-)chronic effects in environmental relevant concentrations. The comparison between published lowest concentration effects and measured concentrations in Dutch surface waters (Table 1) shows that for all the studied pharmaceuticals, except sulphamethoxazole, the highest measured concentration in Dutch surface water is close to the lowest measured effect concentration. The effect concentrations of carbamazepine and diclophenac are also close to the average water concentrations by which the possibility of environmental damage by these pharmaceuticals is greatest.
The international risk assessments (Table 2) show that four of the five pharmaceuticals pose a risk to the aquatic environment: carbamazepine, erythromycin, sulphamethoxazole and diclophenac. For diclophenac, the risk assessment is ambiguous, but based on the precautionary principle it must be assumed that this medicine also has a high risk. Metoprolol presumably poses a low risk in the aquatic environment, but the risk assessment has not yet taken into account recent research on organ damage in rainbow trout[9]. Combination toxicity and metabolites have not been taken into account in this risk assessment. The evaluations reconcile with the prioritization of the Global Water Research Coalition[5]. Furthermore, some bacteria in surface water demonstrate resistance to the antibiotics erythromycin and sulphamethoxazole.
The research results indicate that the selected pharmaceuticals may cause effects in the aquatic environment and that measures are urgent. The stream of pharmaceuticals that end up via the STP in surface water is continuously ongoing and all aquatic organisms during their entire life cycle are exposed to a cocktail of different pharmaceuticals. An important step in the right direction would be to place those pharmaceuticals with the greatest risks to the environment on the list of priority substances of the EU Water Framework Directive. This will move the pharmaceutical industry to develop pharmaceuticals that are more environmentally friendly. Moreover, governments and other parties will be encouraged to improve wastewater treatment and develop more responsible use of pharmaceuticals.

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