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Pharmaceuticals in the environment – A short review on options to minimize the exposure of humans, animals and ecosystems

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ABSTRACT

Pharmaceuticals are indispensable for human and animal health. After use, the active agents and their metabolites are excreted and enter the environment via different pathways. For decades, pharmaceuticals and metabolites have been found in the environment, e.g. surface water, groundwater, drinking water, sediment, sewage sludge and manure. About half of the 2300 active ingredients used in Germany are considered to be potentially of environmental relevance. Monitoring in the environment is still under way, but an impact on living organisms has already been detected. There is still a lack of knowledge concerning: quantities of pharmaceuticals entering the environment, origin of the pharmaceutical active agents, metabolism and transformation pathways, the effects of the active substances, metabolites and transformation products on aquatic organisms, as well as their persistence or degradability in the environment. Sporadically, traces of drugs are detected in drinking water. The concentrations are usually far below the μg per liter range and below concentration levels, which might have an effect on humans. Long-term effects cannot be excluded, though, and should be investigated. Moreover, antibacterial agents and antibiotic-resistant bacteria enter the environment in different ways. They are widely distributed. There is an urgent need for concepts and priorities in order to eliminate the exposure by pharmaceuticals in the environment. The authors suggest short-, medium- and long-term measures for the reduction of pharmaceuticals in the environment, with a clear prioritization of preventive measures.

1. Pharmaceuticals in water, soil and air

In 1994, the lipid-lowering pharmaceutical clofibric acid was detected in surface waters in Berlin, Germany (Stan et al., 1994). It became clear to populace and public authority that pharmaceuticals are biologically highly active agents which are on the one hand indispensable for diagnosis and treatment of human and animal diseases but, on the other hand, may have detrimental effects on aquatic living organisms (Triebskorn et al., 2007). Investigations on risk assessment gained in importance.

Today we know that pharmaceuticals are widespread in the global environment: Approximately half of the 2300 APIs approved for human medicine in Germany are considered to be potentially relevant for the environment because they are persistant, bioaccumulative and toxic (Ebert et al., 2014). Veterinary pharmaceuticals, mainly antibiotics and parasiticides, must be added on top. So far, only a limited number of pharmaceuticals have been detected in the environment as more than 600 active pharmaceutical ingredients (API), or their metabolites or transformation products have been detected in 71 countries worldwide (Weber et al., 2014). Traces were most often found in surface waters and sewage effluent, but also in groundwater, manure, soil, and even drinking water (Hamscher et al., 2002; Ratsak et al., 2013). In Germany, as documented by research and monitoring projects by public authorities, more than 150 different APIs have been measured nationwide in different environmental matrices. In surface water, concentrations range from below 0.1 to more than 1.0 μg per liter (Weber et al., 2014). Among the number of these frequently occurring complex organic molecules which can be detected by state-of-the-art techniques, it seems to be rather difficult to identify and detect transformation products that result from biological or physical degradation processes in waters and soil but also in, e.g., waste water treatment plants (Schulz et al., 2008; Wick et al., 2011).

Diclofenac, a heavily used painkiller, and X-ray contrast media show strikingly high concentrations in surface waters (Weber et al., 2014). Lipid-lowering agents, antidiabetic agents and psychotropic drugs were detected in a lower range, but still represent the modern way of life and its consequences to human health. Endocrine-disrupting pharmaceuticals, like the synthetic estrogen 17α-ethinylestradiol used in contraceptives, which may influence

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the development of organisms at the lowest concentrations, receive special attention. In animal husbandry around 0.67 t of hormones are used every year (SRU, 2007). Despite this relatively low volume hormones have a high environmental relevance due to their major ecotoxicological effects. Veterinary medicinal products are of particular concern from the environmental perspective, as the active agents and their degradation products enter the environment directly, never passing through a sewage treatment plant. Moreover, antibiotic substances do not only have direct toxicological effects but also facilitate the development and spread of antibiotic-resistant microorganisms, a severe risk for human health in the long term.

1.1. Emission pathways and occurrence

Taking medication is an everyday occurrence in most lives. As western populations are aging it is expected that the use of pharmaceuticals will even rise in the future: a 20–24 year old man takes 56 defined daily doses on average, while men older than 60 need 649 defined daily doses, almost twelve times as much (Ebert et al., 2014). After ingestion and becoming effective in the body, a part of the API is excreted more or less unmodified or only slightly metabolized and enters the sewage system. In addition to this unavoidable emission, relevant amounts of pharmaceuticals unnecessarily get into the environment because of their inappropriate disposal via sink or toilet (Goetz and Keil, 2007).

Pharmaceuticals can reach water bodies, because they are insufficiently removed by conventional wastewater treatment. After use pharmaceuticals are transferred to the wastewater treatment plant (if available), where a part may adsorb to sewage sludge. However, most APIs remain in liquid form and, to a certain degree, pass through a wastewater treatment plant. Only by using special techniques like membrane filtration, activated charcoal or ozonization can the cleaning capacity of wastewater treatment plants be improved. Having reached water bodies, pharmaceuticals and their metabolites may also get into groundwater, albeit in much lower concentrations. Sporadically, traces of pharmaceuticals have also been found in drinking water (Weber et al., 2014). The concentrations are still very low and direct effects on humans are not expected. However, long-term effects of active compounds in the low range cannot be excluded and should be investigated as disease resistance to pharmaceuticals is favored by low concentration exposure and compounds such as hormones have effects at very low levels (Roig et al., 2010).

A contamination of soils with pharmaceuticals may result if manure or sewage sludge are used as fertilizers. Besides human pharmaceuticals, even veterinary pharmaceuticals carry a significant environmental risk. Residues of veterinary APIs can be found in manure and dung of treated animals in livestock farming. If manure is used to fertilize land, APIs accumulate in soil. Then they can relocate to water bodies and groundwater. The same is true for pharmaceuticals in sewage sludge that is spread on fields. In Germany, about 800,000 t of sewage sludge are applied to fertilize or improve soils (DWA et al., 2015). Another source of veterinary pharmaceuticals in soils is digestate from biogas plants, which often coferment manure. It is mainly antibiotics which spread on soils in large amounts in this manner. It seems possible that these pharmaceuticals pollute food, as it has been shown that plants can take it up from soil (Carter et al., 2014).

An additional pathway of pharmaceuticals into the environment is the airborne input from livestock farming. It has been shown that veterinary pharmaceuticals disperse in the air inside animal husbandry facilities, as drugs are often applied as a powder, and are distributed, together with dust and bioaerosols, in the surrounding area of the facilities with exhaust air (Schulz et al., 2012). That way, APIs may also get into waters and soil or may even be deposited on plants and potentially reach the food chain. Additionally, pharmaceutical aerosols may be inhaled and absorbed by animals and humans working in the stable and may, in the case of antibiotics, enable the development and spread of antibiotic-resistant microorganisms in healthy animals and humans.

2. Risks for organisms, ecosystems and human health

Observations in nature and laboratory investigations provide evidence of health impairment, in particular of aquatic living organisms, through pharmaceuticals in the environment (Kuemmerer, 2004). When released into the environment, the biological activity of agents may affect wildlife, which are non-target organisms, and impair ecosystem health (Weber et al., 2014). A well-known example for unexpected effects on terrestrial organisms occurred in the 1990s. The population of several species of vultures in India collapsed due to feeding on off-lable treated cattle with diclofenac. The rotting carcasses were easily accessible for vultures but still contained diclofenac in an effective concentration. The drug induced kidney failure and reduced one of the populations by 95% in about ten years (Shultz et al., 2004). An impact of active agents on aquatic organisms can occur through a variety of mechanisms, some of which have been demonstrated in laboratory and field observations (Weber et al., 2014), e.g., the antiepileptic agent carbamazepine and the betablocker metoprolol, which evidently damage organs in fish. The synthetic estrogen 17α-ethinylestradiol and the psychotropic oxazepam were shown to affect sexual characteristics of male fish and the behavior of perch, respectively (Oaks et al., 2004; Kidd et al., 2007; Triebskorn et al., 2007). Experts believe that pharmaceuticals in drinking water are below the danger-threshold and do not effect human health, at least not yet (DWA, 2010). An indirect but quite severe impact on human health is predicted for antibiotic agents through antibiotic resistance genes, which get into the environment through wastewater treatment plants and manuring.

2.1. Antibacterial agents, resistance development, and dissemination in the environment

In 2011, the dispensing of 600 t of human antibiotics and 1700 t of veterinary antibiotics was registered in Germany (Kuester et al., 2013). In veterinary medicine the overall amount was reduced to 1300 t up to 2014, but the dispensing of last-resort antibiotics like fluoroquinolone increased by around 4% (BVL, 2015). The Netherlands sold the most veterinary antibiotics among the other European countries (Grave et al., 2010). China, the USA, Brazil, India and Mexico are predicted to be the five largest consumers of livestock antimicrobials in 2030 (Van Boeckel et al., 2015). In the last decade, an emergence of (multi)resistant bacterial strains has been observed. Currently, medical progress in developing new antibiotics is no longer able to keep pace with the spread of antibiotic resistance. There is a high risk that we are running out of effective medical treatment options for many dangerous infectious diseases. Experts predict a higher mortality rate due to infectious diseases by antibiotic-resistant pathogens than by cancer in 2050 (O´Neill, 2014). Moreover, the World Health Organization describes a *post-antibiotic era*, in which common infections and minor injuries can kill humans, as a real possibility for the 21st century, as pathogens have adapted to important antibiotics for human treatment (WHO, 2014). Germany counts up to 600,000 nosocomial infections and 15,000 deaths per year due to infections with resistant pathogens (DAK-Gesundheit, 2014). An increasing proportion of *Enterobacteriaceae* including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* and *Salmonella* has displayed