Antibiotics – The Flipside of the Coin

Antibiotics that are widely used in human and veterinary medicine are detectable today in Swiss waste waters and surface waters. Studies performed at EAWAG show that there are different pathways by which human and veterinary antibiotics find their way into the aquatic environment: human antibiotics are found in the effluents of wastewater treatment plants and in lower concentrations in surface waters; they are not completely removed during the wastewater treatment process. Veterinary antibiotics, on the other hand, are rarely detected in the wastewater effluent, but can be found in specific surface waters. They are carried with animal excreta and liquid manure from the pastures directly into streams. It is not quite clear yet what effects the antibiotics have on ecosystems and humans – particularly with respect to the spread of antibiotic resistance.

Pharmaceuticals are released into the aquatic environment via human and animal excreta and by improper disposal. There are two different pathways (Fig. 1). Human pharmaceuticals originating from private households and hospitals first reach wastewater treatment plants (WWTPs). The pharmaceuticals are only partially removed by the wastewater treatment process and ultimately reach surface waters. With the application of liquid manure or animal excreta, veterinary pharmaceuticals are spread across fields or pastures from where they are washed directly into streams or infiltrate into the soil and reach the ground water. Most pharmaceuticals are found in natural waters in only very low concentrations. Despite this general finding, the question arises whether these traces of pharmaceuticals pose a risk for aquatic ecosystems. Antibiotics are of particular interest because we do not currently know whether their presence in natural waters contributes to the spread of antibiotic resistance in potentially pathogenic microorganisms.

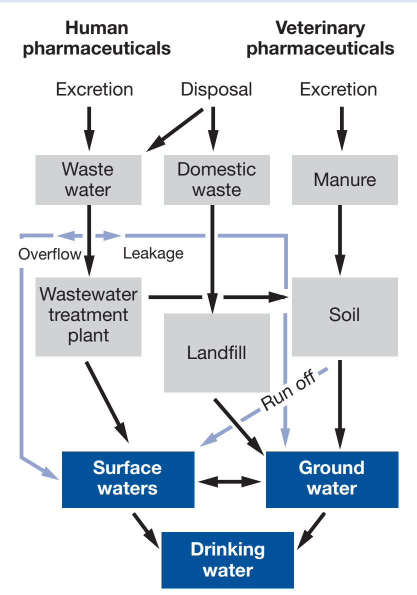

Fig. 1: Human and veterinary pharmaceuticals reach natural waters via different pathways.

Use of Antibiotics in Switzerland

In 1997, approximately 90 tons of antibiotics (including antibacterials like fluoroquinolones and sulfonamides) were used in Switzerland – 38 % in human medicine and 62 % in veterinary medicine [1–3]. In veterinary medicine, antibiotics are used as growth promoters, as prophylactic or therapeutic amendments to animal feed, or for the therapeutic treatment of individual animals. Because of a ban on growth promoters in 1999, they are essentially no longer in use in Switzerland [3]. The volume of antibiotics in feeds has also dropped – by 33 % by the year 2000 – to a level of 17.3 tons annually. Therapeutic use of antibiotics for individual animals, on the other hand, has increased by 27 %, reaching a level of 21.6 tons per year. The volume of antibiotics used annually in human medicine is around 34 tons and has remained fairly constant since 1992. The β-lactam antibiotics which include penicillins and cephalosporins represent the largest fraction of human antibiotics, accounting for approximately 18 tons in 1997. They are followed by 5.5 tons sulfonamides, 4.3 tons macrolides and 3.9 tons fluoroquinolones. Considering the magnitude of these numbers, it is important to know what portion of these antibiotics is actually reaching the environment. A few recent studies in Germany and the U.S. were able to detect antibiotics in surface waters [4–6]. But what is the situation in Switzerland? EAWAG is investigating this question. Since β-lactam antibiotics are chemically unstable, EAWAG has focused on the fate of sulfonamides, macrolides and fluoroquinolones. The study aims at determining environmental pathways for these antibiotics, their mass fluxes, their behavior in wastewater treatment processes and their introduction into natural waters. The first task was to develop analytical techniques for the detection of individual antibiotics.

Sulfonamide and Macrolide Antibiotics

Concentrations of sulfonamide and macrolide antibiotics were determined in 24-hour composite samples from four wastewater treatment plants in Canton Zurich and in random samples from various streams and lakes in the Cantons of Zurich and Lucerne. Antibiotics were enriched by solid phase extraction and analyzed with liquid chromatography directly coupled to mass spectrometry. Figure 2 summarizes the observed concentration ranges. Note that for the veterinary antibiotic sulfamethazine, effluents from WWTPs exhibited lower concentrations than surface waters, indicating that veterinary antibiotics are leached from ani-

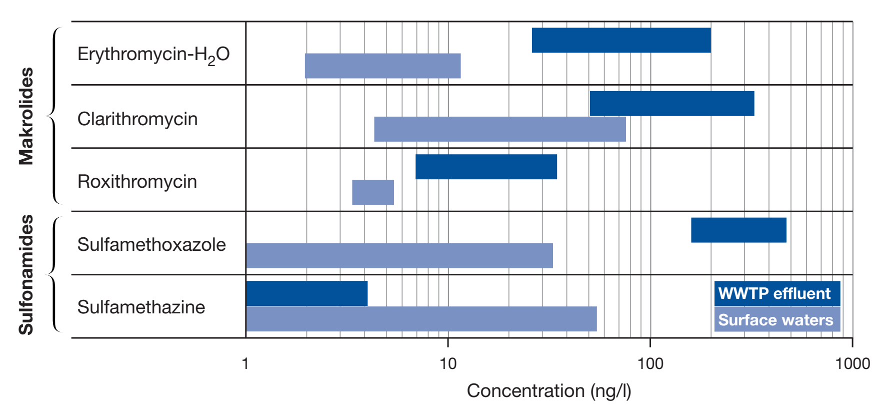

Fig. 2: Sulfonamide and macrolide concentrations in effluents of wastewater treatment plants (WWTPs) and in surface waters of the Cantons Zurich and Lucerne.

mal excreta and are washed directly from the fields into the surface waters. More recent studies performed at EAWAG showed that the antibiotic sulfamethazine could be detected in the liquid manure from selected farms which use this antibiotic as a therapeutic drug for pigs and calves. Sulfamethazine and its metabolite N^4-acetyl-sulfamethazine were found in concentrations of up to 8.7 mg and 2.6 mg, respectively, per kg liquid manure with a dry matter content of 3.3% [7, 8].

In contrast to veterinary antibiotics, antibiotics used in humans showed higher concentrations in the effluents of wastewater treatment plants than in the streams and lakes examined for this study (Fig. 2). The observed concentration differences correspond to dilution factors of 2 to 20. The difference is due to the fact that human antibiotics are first discharged with domestic and hospital waste water into treatment plants; after being partially removed in the WWTP, they are then released into surface waters.

Depending on the catchment area of the wastewater treatment plant, the antibiotic loads can vary dramatically. Daily loads of the macrolide antibiotics erythromycin, clarithromycin and roxithromycin in the effluent of the WWTP Werdhoelzli are 5 to 30 times higher than the loads for these antibiotics in the effluent of the Duebendorf treatment plant. For example, the daily load for clarithromycin at Werdhoelzli was 48 g, while it was only 1.6 g in Duebendorf. This difference can be attributed to the fact that the Werdhoelzli plant serves approximately eight times more people than the Duebendorf plant. Additionally, a large number of commuters work within the catchment area of the Werdhoelzli plant, and most of the hospitals in Zuerich also are located in this area.

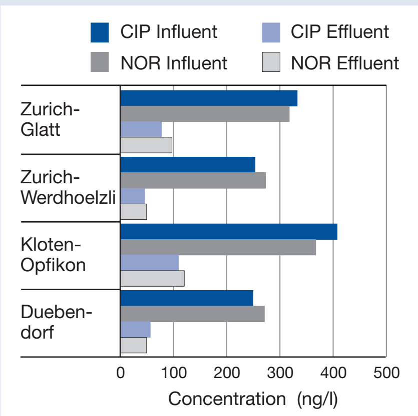

Fig. 3: Concentrations of the fluoroquinolones ciprofloxacin (CIP) and norfloxacin (NOR) in the influent and effluent of wastewater treatment plants in Canton Zurich.

Fluoroquinolone Antibiotics

The two most important fluoroquinolone antibiotics used in human medicine are ciprofloxacin and norfloxacin. In order to follow the fate of these antibiotics, 24-hour composite samples were measured in the influent and effluent of four WWTPs in Canton Zurich [9–11]. Influent samples were taken before the mechanical treatment step; effluent was sampled after biological treatment and filtration. Fluoroquinolones were detected using a new method. After solid phase extraction, they were analyzed by a method coupling liquid chromatography and fluorescence detection. Figure 3 shows that the concentrations of the two fluoroquinolones in the influent are clearly higher than their concentrations in the effluent. Our studies showed that the wastewater treatment plant removes 70–80% of the fluoroquinolones; the remaining 20–30% of the load is discharged into surface waters. In the river Glatt, for example, which receives effluent from several wastewater treatment plants, this leads to ciprofloxacin and norfloxacin concentrations of up to 18 ng/l. Additional investigations on the fate of fluoroquinolones in wastewater treatment plants showed that these compounds were not degraded during the treatment process, but were merely adsorbed to sewage sludge.

Until now, neither fluoroquinolones nor sulfonamides or macrolides have been detected in ground water or drinking water in Switzerland.

EAWAG Projects Investigating the Removal of Antibiotics from Waste Water

Current and future studies at EAWAG are aimed at examining the fate of antibiotics in wastewater treatment plants in more detail and the comparison of different treatment technologies. Within the EU project POSEIDON, different methodologies for the treatment of waste water and drinking water are evaluated with respect to elimination of antibiotics and other pharmaceuticals. Of particular interest is a comparison of newer membrane technologies with conventional activated sludge and fixed bed processes used in wastewater treatment. One advantage of the membrane technology is that higher sludge concentration and sludge age can be achieved. The hope is that microorganisms with slower growth rates can establish themselves in the activated sludge and become specialized in degrading specific contaminants, such as antibiotics. In the interdisciplinary EAWAG project NOVAQUATIS, approaches are explored in which pharmaceuticals or other undesirable compounds are not even released into the wastewater stream, but are collected at the source. In a special no-mix toilet, urine is collected separately, only diluted minimally with flushing water, and then fed into a technical clean-up process.

Risk Assessment

Because of their persistence in water, the assessment of the effects that antibiotics have in the aquatic environment is extremely important. Of particular interest is the

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Antibiotics, a blessing if used appropriately.

spread of resistance to antibiotics. According to our current knowledge, resistance is transferred to humans primarily in hospitals, but possibly also via foods from animal products [12]. In addition the question arises whether antibiotics can contribute to the spread of resistance at concentrations which are found in the environment. This and other aspects related to the widespread occurrence of antibiotic resistance are addressed in the recently launched National Research Program NRP 49 by the Swiss National Science Foundation.

Another effect that is caused by prolonged use of antibiotics is the increased appearance of allergies, which has been observed over the last several years. Allergic reactions to penicillin, for example, may be caused by repeated contact with antibiotics at relatively low concentrations [13].

An assessment of the ecotoxicological effects of antibiotics present in trace concentrations is extremely difficult at this point in time, mostly because we do not have the data to judge the effects. The EU is currently preparing guidelines for the ecotoxicological risk assessment of human pharmaceuticals that will be part of the approval procedure for new drugs. Such guidelines exist for veterinary pharmaceuticals since 1998.

Targeted Use and Proper Disposal

There is no question that antibiotics are indispensable in the medical treatment of humans and animals. The release of these antibiotics into the environment, however, could be minimized by their targeted use and proper disposal. Antibiotics should only be used if they are really needed – and then at the correct dosage and over a sufficiently long time period. It is therefore most important that physicians and patients are informed about the problems. In veterinary medicine, a first step towards reducing the consumption of antibiotics in Switzerland has already been made with the ban of growth promoters. Serious consideration should also be given to avoiding the use of identical or similar preparations in both humans and animals. There is growing evidence for so-called cross-resistance, where the resistance a microorganism has acquired towards a particular antibiotic can also cause resistance to other antibiotics that are chemically similar or are in the same family as the original antibiotic.

Conclusion: There is a major need for research before we can judge how dangerous the antibiotics are that we release into the environment. We need to know more about how antibiotics behave in the environment, their ecotoxicological effects, to what degree they are eliminated in wastewater and in drinking water plants, and how they behave in sewage sludge and in liquid manure.

Acknowledgement

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Additional information is available at:

- www.eu-poseidon.com
- www.novaquatis.eawag.ch
- www.snf.ch/en/rep/nat/nat_nrp_49.asp
- www.emea.eu.int

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