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Article

Antibiotics in Austrian drinking water resources, survey 2014

Antibiotika in österreichischen Trinkwasserressourcen, Monitoring 2014

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Summary

We surveyed antibiotics in drinking water in Austria. Testing for 37 antimicrobials was performed by online solid-phase extraction–liquid chromatography–high-resolution mass spectroscopy method. Selection of sample sites for drinking water resources focused on areas considered susceptible to contamination and on geographic population distribution. Sulfamethoxazole was detected in 10 (5%) of 200 samples collected in 2014. Five samples showed concentrations above the limit of quantification (2.5 ng/l). Concentrations measured were ≤8.9 ng/l, making toxic effects highly unlikely. However, even low-level concentrations of antibiotics could increase bacterial resistance. The presence of antibiotics is presently not regulated. We assume anthropogenic pollution (not animal husbandry) as source and ask for a maximum permissible value of antibiotics in drinking water.

Keywords: Drinking water, antibiotics, anthropogenic, sulfamethoxazole, resistance

Zusammenfassung

Wir haben die Belastung des Trinkwassers durch Rückstände von Antibiotika in Österreich im Jahr 2014 untersucht. Fünfzig Messstellen für Grundwässer, die zur Trinkwassergewinnung verwendet werden, wurden risikobasiert und fünfzig weitere unter Berücksichtigung der regionalen Bevölkerungsverteilung ausgewählt. Mittels einer Online-Festphasenextraktions-Flüssigkeitschromatographie - hochauflösender Massenspektrometrie - Methode wurde auf 37 Wirkstoffe getestet. Sulfamethoxazol wurde in 10 (5%) der 200 Proben nachgewiesen; fünf Proben zeigten Konzentrationen (≤8,9 ng/L) über der Bestimmungsgrenze von 2,5 ng/L. Während eine toxische Wirkung in derartig niedrigen Konzentrationen sehr unwahrscheinlich ist, können selbst extrem niedrige Konzentrationen eine Resistenzinduktion bewirken. Wir gehen nicht von landwirtschaftlicher Verunreinigung, sondern von anthropogener Einbringung als Quelle aus, und halten die Einführung eines Grenzwertes für Antibiotika im Trinkwasser für angezeigt.

Schlagworte: Trinkwasser, Antibiotika, anthropogen, Sulfamethoxazol, Resistenz

1. Introduction

Antibiotic resistance has emerged as a very significant health-care problem because of the extensive use and misuse of antibiotics in human and veterinary medicine and in agriculture (WHO, 2012). On an average 12,500 tons of antibiotics have been used annually within Europe over the past decade leading to an acceleration in the evolution of antibiotic-resistant bacterial strains in surface and ground waters used for supplying drinking water (Gray, 2008). In Austria, in 2012, the respective consumption of antimicrobials by humans and livestock was 37.1 and 53.0 tons, respectively (ECDC, 2015). Therapeutically administered antibiotics are excreted almost quantitatively unchanged via urine or feces. Water can act as a solvent for these antimicrobials, and research has shown that antibiotics can enter the environment, disperse, and persist to a greater extent than originally anticipated (McArdell et al., 2003; Batt et al., 2006; Balzer et al., 2016). An exposition scheme showing the different pathways of antibiotics into water is presented in Figure 1. Surprisingly, little is known about the extent of environmental occurrence of antibiotics in public water supplies. The aim of this study was to provide the first nationwide survey of the occurrence of a broad range of 37 antimicrobials in drinking water resources across Austria.

2. Materials and methods

2.1 Antimicrobials

Thirty-seven commonly prescribed human and veterinary antibiotics were arbitrarily chosen because of their widespread use in Austria and their known persistence

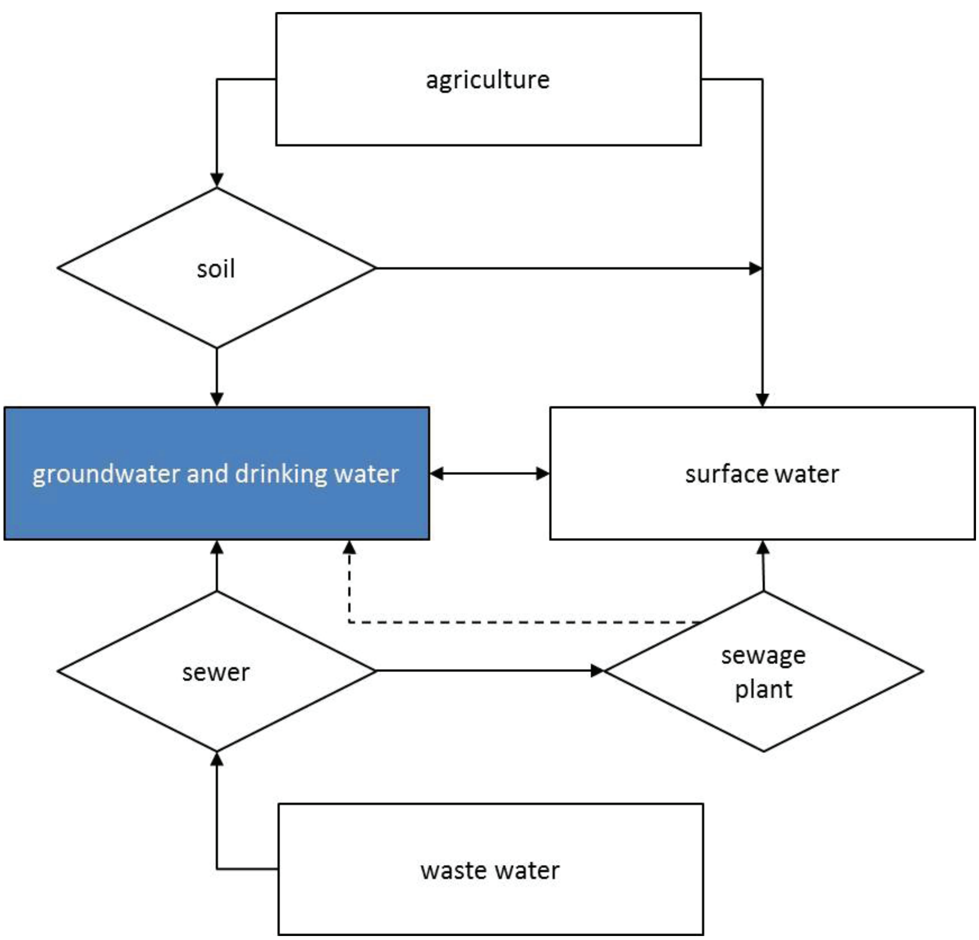

Figure 1. Pathways of pharmaceuticals in groundwater and drinking water
Abbildung 1. Einbringungswege von Arzneistoffen in Grund- und Trinkwasser

in the environment. The testing covered 10 quinolones (ciprofloxacin, danofloxacin, enrofloxacin, marbofloxacin, norfloxacin, difloxacin, flumequin, nalidixic acid, oxolin acid, and sarafloxacin), 7 macrolides (clarithromycin, erythromycin, josamycin, roxithromycin, erythromycin-anhydro, spiramycin, and tylosin), 1 lincosamide (lincomycin), 1 diaminopyrimidine (trimethoprim), 13 sulfonamides (sulfadiazine, sulfadimidine, sulfadoxine, sulfamethoxazole, sulfathiazole, acetyl-sulfamethazine, acetyl-sulfamethoxazole, sulfadimethoxine, sulfamerazine, sulfamethoxypyridazine, sulfamonomethoxine, sulfaquinoxaline, and sulfisoxazole), and 5 tetracyclines (chlortetracycline, epi-tetracycline, oxytetracycline, tetracycline, and doxycycline).

2.2 Site selection and sampling

In Austria, a nationwide groundwater monitoring program has been established in 1991, which provides long-term data about the water quality, including indicators for disturbances by human activity. Based on this information, the selection of sample sites for public drinking water, on the one hand, was focused on areas considered susceptible to contamination from human, industrial, and agricultural wastewater (100 samples). Following a risk-based approach, these water samples were collected from water supplies close to ground water sampling sites indicating anthropogenic influence.

On the other hand, sample sites were chosen using an allocation formula based on the geographic distribution of the Austrian population (e.g., according to the respective number of inhabitants) (100 samples). Anyhow, all samples originated from untreated raw water (predominantly well water) used for drinking water abstraction.

All samples were collected by Austrian Agency for Health and Food Safety GmbH (AGES) personnel using consistent protocols and procedures designed to obtain representative samples. At each site, a composite water sample of 500 ml was collected once during the second quarter of 2014 (time period: May 13 till July 11) and once during the fourth quarter of 2014 (time period: October 13 till December 12), accounting for possible seasonal variation. Following collection, samples were immediately chilled and sent to the AGES laboratory in Linz for testing. Table 1 summarizes the sample sites, and Figure 2 locates the sampling sites (the municipal territories) geographically.

2.3 Analytical Methods

Testing for antimicrobials was performed by an online solid-phase extraction (SPE)–high-performance liquid chromatography (HPLC)–high-resolution mass spectroscopy (HRMS) method (online SPE-HPLC-HRMS method) as previously described by Ali Khan et al. (2012) with modifications reported by Singer et al. (2009) and Westrup et al. (2013). In brief, the test instrumentation combined a Thermo Scientific EQUAN online SPE system for high-volume sampling (injection volume: 2.0 ml), two Thermo Scientific Ultimate 300 Series UHPLC pumps (a load pump and an elution pump), and a Thermo

Table 1. Samples according to site (state) and selection criterion (based on risk versus population distribution)
Tabelle 1. Probenanzahl nach Bundesland und Auswahlkriterium der jeweiligen Messstelle (risikobasiert versus Berücksichtigung gemäß regionaler Bevölkerungsverteilung)

State	Samples from sites chosen according to population distribution	Samples from sites chosen according to the risk of contamination
Burgenland	5	11
Carinthia	7	5
Lower Austria	24	10
Upper Austria	20	23
Salzburg	8	14
Styria	16	20
Tyrol	10	7
Vorarlberg	6	8
Vienna	4	2
Total	**100**	**100**

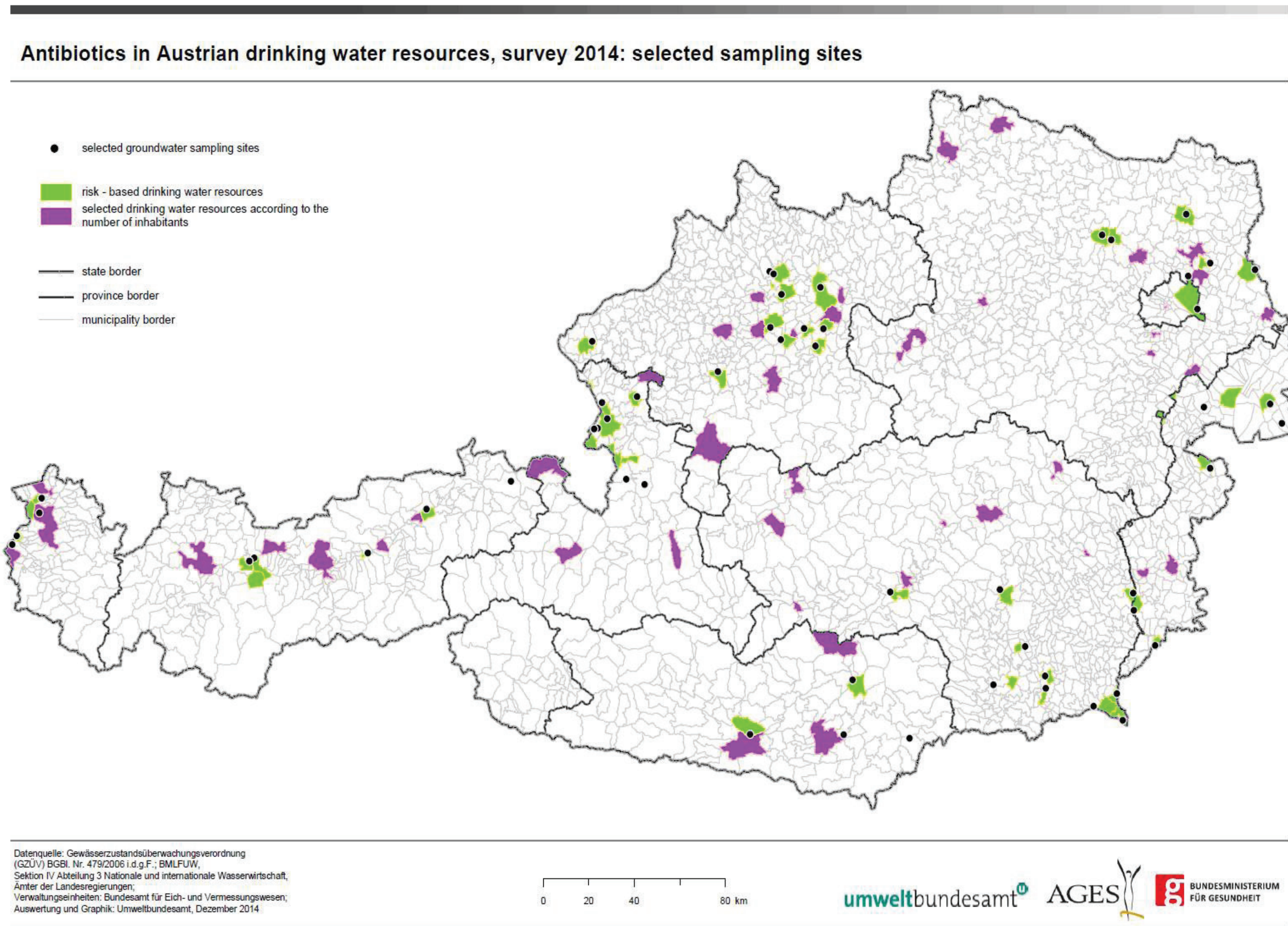

Figure 2. Antibiotics in Austrian drinking water resources, survey 2014: selected sampling sites
Abbildung 2. Antibiotika in österreichischen Trinkwasserressourcen, Monitoring 2014: Probenziehungsorte

Scientific Q-Exactive mass spectrometer. The high-resolution accurate mass spectrometer was operated in full-scan and data-dependent-MS2-mode. SPE was performed using Waters Oasis HLB (20 × 2.1 mm, 15 µm particle size) at pH values of 7.0 or 3.5. Manual sample preparation was reduced to sample filtration, pH adjustment with formic acid buffer solution, and spiking of isotope labeled internal standards. The limits of quantification (LOQs) ranged from 0.5 to 2.5 ng/l.

3. Results

Sulfamethoxazole was detected in 10 (5%) of the 200 drinking water samples tested. The 37 remaining antibiotics were not detected in the samples analyzed.

In total, five samples, three from two sampling sites in Upper Austria and two from one sampling site in Lower Austria, yielded sulfamethoxazole in concentrations above the LOQ (2.5 ng/l). The site in Lower Austria had been chosen according to the criteria based on the population distribution, the two sites in Upper Austria were sites with assumed high risk for contamination. Quantifiable concentrations showed a median of 5.2 ng/l and a mean of 5.8 ng/l (range: 4.4–8.9 ng/l). Occurrence of positive findings showed no significant seasonal variation (Figure 3).

Another total of five samples from four different sampling sites (one sampling site in Upper Austria and one in Lower Austria with one sample from each site; two sampling sites in Salzburg with three samples) yielded sulfamethoxazole in concentrations below the LOQ but above the detection limit of 1 ng/l. One of these sites was positive in the second and fourth quarter, the remaining sampling sites yielded antibiotics (in quantities below LOQ) only in the fourth quarter.

4. Discussion

Antibiotics are powerful drugs needed to treat many life-threatening infections. However, they are specifically designed or discovered by chance to alter biological functions. They can cause chronic toxicity in aquatic species at environmentally relevant concentrations (low to ng/l), and there is the growing issue of antibiotic resistance (Halling-Sørensen et al., 1998; Halling-Sørensen et al., 2000; Kolpin et al., 2002; Enick and Moore, 2007; Halling-Sørensen et al., 2000; Kolpin et al., 2002; World Health Organization, 2011A; Rat der Europäischen Union, 2012). Antibiotics can enter the environment through human and animal excretion and the improper disposal of unused drugs. In ordinary municipal wastewater treatment plants, antibiotics are not or incompletely degraded and thus may enter surface water bodies. Of the 37 antibiotics tested, only sulfamethoxazole was detected in our study. According to official data, approximately 5.6 tons of sulfonamides are sold for animal husbandry in Austria each year (ECDC/EFSA/EMA, 2015), as compared to 0.4 tons for human medicine. Sulfonamides given to animals generate huge amounts of feces and urine that contain residual levels of these compounds. This manure is sprayed on fields as fertilizer and can reach drinking water reservoirs (Sapotka et al., 2007). According to Kolpin et al. (2002), the low frequency of detection for tetracyclines and quinolones, antibiotics also widely used in animal husbandry, is not unexpected, given their apparent affinity for sorption to clay mineral particles.

The concentrations of sulfamethoxazole detected in Austrian drinking water were in the low nanogram per liter range, and it is difficult to quantify the effects at such low levels because of the myriad factors that humans are exposed to in daily life. Also in the Netherlands, sulfamethoxazole was detected in the drinking water supply at concentrations below 50 ng/l, with animal husbandry being considered the major source (Mons et al., 2003). An univariate analysis (details not presented) on the prevalence ratio of sulfamethoxazole in our Austrian drinking water samples showed that samples positive for carbamazepine (a drug used primarily in the treatment of epilepsy and neuropathic pain in humans) were 9.04 times (95% confidence interval [CI]: 2.17–29.82) more often sulfonamide-positive than samples negative for carbamazepine. In contrast, samples yielding nitrate in a concentration greater than 23 mg/l (75 percentile of the median of nitrate tests performed by AGES on drinking water samples in 2014) were only 2.0 times (95 % CI: 0.19–21.0) more often positive for sulfonamide than samples yielding nitrate in concentrations less than 23 mg/l. The significant association of the presence of sulfonamide in drinking water resources with carbamazepine contamination indicates anthropogenic contamination—not antibiotic use in animal husbandry—as the main source of the antibiotics detected in the drinking water supply in Austria. We tested water samples from the river Danube in close vicinity to two of

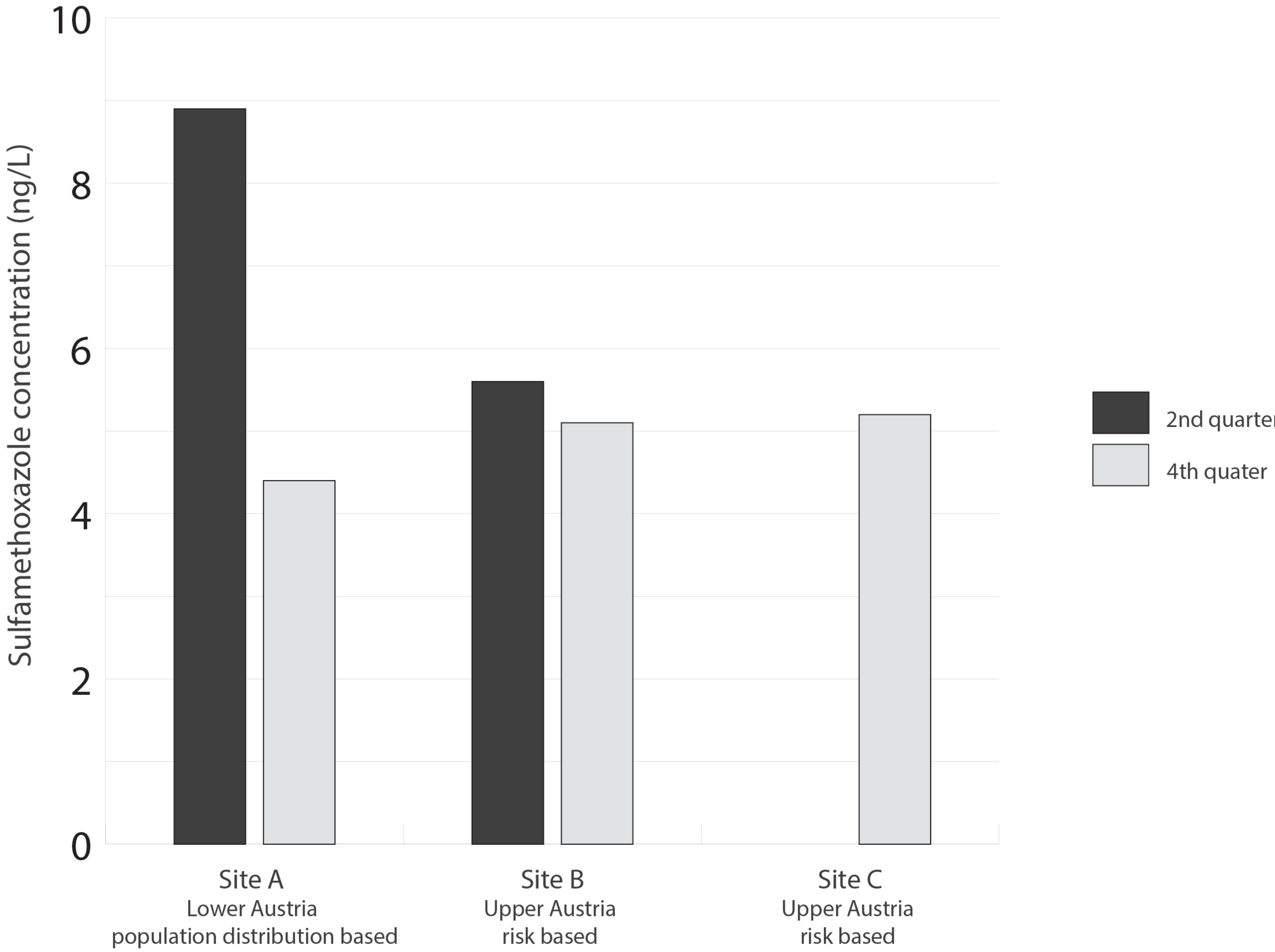

Figure 3. Occurrence of sulfamethoxazole in drinking water resources in concentrations above the limit of quantification (>2.5 ng/l) in 5 of 200 samples.
Abbildung 3. Vorkommen von Sulfamethoxazol in Trinkwasserressourcen in Konzentrationen über der Bestimmungsgrenze von 2,5 ng/L in 5 von 200 Proben.

our three drinking water resources yielding sulfamethoxazole in concentrations above the LOQ (>2.5 ng/l) and repeatedly detected sulfamethoxazole in surface water in concentrations of around 20 ng/l (data not shown). This finding seemingly is in contrast to the fact that in Austria, human medicine officially only uses 0.4 tons sulfonamides per year, as compared to 5.6 tons in animal husbandry (ECDC/EFSA/EMA, 2015). In our view, the Austrian consumption figures grossly underestimate the real use of sulfonamides in human medicine. The official Austrian consumption data rely on data from the association of workers' compensation insurance carriers; however, antibiotics that cost less than the prescription fee ("deductible") usually are paid directly by the patient and, therefore, are not included in the associations' consumption statistics. According to IMS HEALTH Marktforschung GmbH (Vienna; charged inquiry, 10 June 2015), 2.6 tons of sulfonamides were delivered in Austria in 2014 (2,482.7 kg for outdoor patients and 118.5 kg for hospitalized patients), a number 6.5 times higher than officially postulated. Sulfamethoxazole accounted for 247.3 kg (212 kg for outdoor patients and 35.3 kg for hospitalized patients). While there are only few data on the occurrence of antibiotics in drinking water resources, results from a variety of studies have demonstrated contamination with sulfamethoxazole in ground waters in concentrations of 0.22

(Lindsey et al., 2001) to 0.41 µg/L (Sacher et al., 2001). A Swiss study sampling 100 sites in 2006 showed 20% of the ground water samples to be contaminated with sulfamethoxazole, concentrations were at 35 ng/l and below (Hanke et al., 2007). An Austrian study sampling ground water from 50 sites twice (second and fourth quarter) in 2008 found antibiotics in 8 of the 100 samples (Clara et al., 2010). Three ground water samples of the second quarter yielded clarithromycin (12 ng/l), erythromycin (49 ng/l), and trimethoprim (below LOQ of 4.7 ng/l). Five ground water samples of the fourth quarter had danofloxacin (below LOQ of 4 ng/l), erythromycin (59 ng/l), sulfadimidine (22 ng/l), and sulfamethoxazole (below LOQ of 10 ng/L). In Germany, a study was performed in 2012 and 2013, sampling 48 ground water sites in areas with intensive animal husbandry. In 2012, four sites (8%) yielded antibiotics: sulfadiazine and sulfadimidine in maximal concentrations of 11 ng/l and sulfamethoxazole at a concentration of 230 ng/l. In 2013, again only sulfonamides were detected as contaminants (eight sites): sulfadiazine and sulfadimidine at concentrations of up to 6 ng/l; sulfamethoxazole was found at two sampling sites in concentrations of above 200 ng/l (maximum 950 ng/l) (Hannappel et al., 2014).

In 2013, the European Medicines Agency Committee for Medicinal Products for Veterinary Use (CVMP) drafted a "*Concept paper on assessing the toxicological risk to humans and the environment of veterinary pharmaceuticals in groundwater*." The committee recommended developing a guideline outlining the methodology to perform risk assessment for both human health and the environment in cases where the concentration of residues of veterinary medicinal products in groundwater was estimated to be above a trigger value of 0.1 µg/l (CVMP, 2013). In Germany, the German Federal Environment Agency (Umweltbundesamt) recommends the introduction of a threshold value for antibiotics in ground water of 100 ng/L (Umweltbundesamt, 2014).

Antimicrobial resistance (AMR) is not a recent phenomenon but has become a critical health issue today. The widespread use of antibiotics causes selection of a variety of resistance mechanisms that seriously challenge our ability to treat bacterial infections. Resistant bacteria can be selected by the high concentrations of antibiotics used therapeutically. However, the role in selection by the much lower antibiotic concentrations present in many environments remains largely unclear. There is also an increasing evidence that subinhibitory concentrations of antibiotics interfere with host–parasite interactions (Ohlsen, 1998). Gullberg et al. (2011) showed that the selection of resistant bacteria can occur even at extremely low concentrations of streptomycin, tetracycline, and ciprofloxacin, that is, at levels several hundred-fold below the minimal inhibitory concentration of susceptible bacteria and similar to those found in natural environments. Their results suggest that release of antibiotics into the environment might considerably contribute to the emergence and maintenance of resistance and they emphasized the importance of introducing measures to reduce antibiotic contamination (Gullberg, 2011). The continued growth in the human population has created an increasing demand for natural resources, specifically placing a strain on the limited supply of fresh water. Thus, protecting the integrity of drinking water sources is one of the most important issues of the 21st century.

Exposure to antibiotics through drinking water is an unintended and involuntary exposure over potentially long periods of time. Given the low likelihood of human health risk, World Health Organization (WHO) does not consider it necessary to implement routine monitoring programs (WHO, 2011B), and most countries (if any) have no monitoring programs to routinely test for antibiotics in drinking water (WHO, 2011B). In Europe, and therefore, in Austria too, the occurrence of antibiotics in drinking water is presently not regulated by legal provisions. The concentrations measured in our study were generally low, and the risk of acute toxic effects with the current use of water is highly unlikely. However, more subtle, chronic effects from low-level environmental exposure to antibiotics appear to be of concern. Even low-level concentrations of antibiotics in the environment could increase the rate at which pathogenic bacteria develop resistance to these compounds (Gullberg et al., 2011). Therefore, respective policy development must heed the precautionary principle.

Antibiotics are a precious commodity, and we should do what we can to preserve the activity of antimicrobials to treat human infections. Rational antibiotic usage policies suggest curtailing the unnecessary use of antibiotics in situations such as animal husbandry and human medicine (Opal, 2015). As our study reveals, this approach might also be indispensable for keeping our drinking water free from contamination by antimicrobials. The role of antibiotic use in human medicine as a source of environmental contamination must be critically appraised.

Acknowledgment

The complete data of this study is available in German as an original report entitled "Monitoringprogramm von Pharmazeutika und Abwasserindikatoren in Grund- und Trinkwasser" at http://www.bmg.gv.at/cms/home/attachments/1/3/5/CH1254/CMS1449665508835/monitoringprogramm_von_pharmazeutika_und_abwasserindikatoren_in_grund-_und_trinkwasser.pdf

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