Journal of Hazardous Materials 196 (2011) 1–15

Contents lists available at SciVerse ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Review

Effects of the presence of sulfonamides in the environment and their influence on human health

Wojciech Baran[a], Ewa Adamek[a,*], Justyna Ziemiańska[b], Andrzej Sobczak[a,b]

[a] Silesian Medical University, Department of General and Analytical Chemistry, Jagiellońska 4, 41-200 Sosnowiec, Poland
[b] Institute of Occupational Medicine and Environmental Health, Kościelna 13, 41-200 Sosnowiec, Poland

ARTICLE INFO

Article history:
Received 10 March 2011
Received in revised form 22 July 2011
Accepted 31 August 2011
Available online 6 September 2011

Keywords:
Sulfonamides
Biotransformation
Ecotoxicity
Environmental risk
Drug resistance

ABSTRACT

World production and consumption of pharmaceuticals has been steadily increasing. Anti-infectives have been particularly important in modern therapy of microbial infection. Sulfonamides have been widely used for a long time as anti-infectives and are still widely prescribed today. This review presents the most common types of sulfonamides used in healthcare and veterinary medicine and discusses the problems connected with their presence in the biosphere. Based on the analysis of over 160 papers, it was found that small amounts of sulfonamides present in the environment were mainly derived from agricultural activities. These drugs have caused changes in the population of microbes that could be potentially hazardous to human health. This human health hazard could have a global range, and administrative activities have been ineffective in risk reduction.

Contents

1. Introduction

World production and consumption of pharmaceuticals has been steadily increasing at a rate higher than the rate of global population growth. After use, large amounts of drugs have been discharged into the environment in the form of human and animal excretions and unused waste [1]. The persistence of pharmaceuticals in the environment, the rate of their spreading and their ability to accumulate in the biosphere has differed. However, their high biological activity indicates that these drugs, even in trace amounts, could cause significant changes in the biosphere. An example of such changes in the last decade of the 20th century is

* Corresponding author. Tel.: +48 032 364 15 62.
E-mail address: ewa.adamek11@wp.pl (E. Adamek).

0304-3894/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jhazmat.2011.08.082

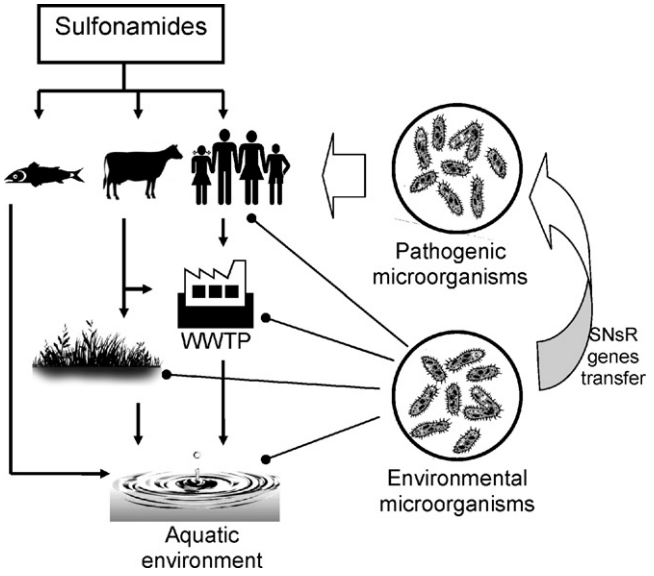


Fig. 1. The possible fates of SNs residues and resistance genes (SNsR) in the environment.

the phenomenon of feminization of fish by sex hormones caused by anthropogenic pollution of European rivers [2]. For these reasons, pharmaceuticals have been classified as particularly dangerous pollutants for the environment. As a result, research and multinational projects (e.g., REMPHARMAWATER [3], POSEJDON [4], KNAPPE [5], ERAPHARM [6], and ECO-SENS [7]) have been carried out to find answer to the following questions:

- Which pharmaceuticals have the greatest environmental risk?
- How can we effectively control the amounts and effects of drugs on the environment?
- How can we successfully reduce their release into the environment?

Antibiotics are a group of pharmaceuticals with effects on the environment that could be particularly harmful to human health. Unfortunately, their frequency in environmental samples is very high [1,5,8–18].

Historically, sulfonamides (SNs) have been used as synthetic antibiotics the longest. Recently the large quantities of SNs are used in animal husbandry in particular as veterinary medicines. Based on these drugs, we can obtain a reliable estimation of the effects and consequences of prolonged use of anti-infectives on people's health and on the environment. A report for State Office for Nature, Environment and Consumer Protection of North Rhine-Westphalia (Germany) published in 2007 has been presented the literature review on effects of the introduction of SNs to the environment [1]. In the majority of published articles, the authors assessed the risk caused by SNs almost exclusively on the basis of their use, toxicity, and removal efficiency from the environment. The data presented in this context led to the conclusion that the presence of drugs in the environment was a negligible problem regarding quality of life. However, in the majority of articles, the effect of anti-infectives in the generation of drug resistance in microbes was not considered.

The effect of antibiotics occurring in the environment to the generation and prevalence of drug-resistant microorganisms is essential from the human health point of view (Fig. 1.). This influence has been much more widespread in the last decades due to the globalization process.The aim of the work is to show that:

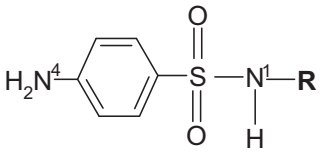


Fig. 2. Chemical structure of SNs with bacteriostatic properties.

- excessive amounts of SNs are introduced to the biosphere (a common practice is illegal and/or without control administration of SNs to healthy farm animals),
- a local concentration of SNs in the environment and risk associated with this issue are very high,
- SNs can remain in the environment for a long time,
- SNs present in the environment are active in the generation of drug resistance in bacterial cells (including cross resistance to drugs).

2. Physicochemical properties of SNs

Since the early 1940s, over 150 SNs, sulfanilamide derivatives, have been applied in human and veterinary medicine as antibacterial drugs [19].

The formula of structure presented in Fig. 2 corresponds to the synthetic antimicrobial agents that contain the sulfonamide group. Such a molecule should have a free amino group ($-N^4H_2$) at one end.

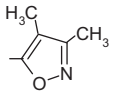
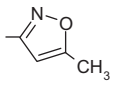
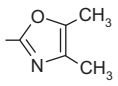
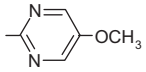
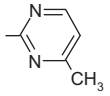
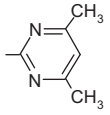
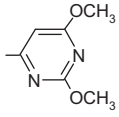
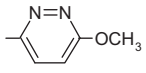
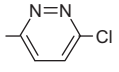
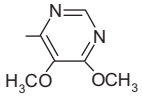
SNs are a group of synthetic bacteriostatic drugs classified by the Anatomical Therapeutic Chemical (ATC) classification index as a group of antibacterial drugs for systemic use (the subgroup J01E) [20]. Many SN derivatives have also been used as antiprotozoal agents [21] and herbicides [19], and complexes of SNs with Ag^+ and Zn^{2+} have been used as antifungals [22]. Moreover, SNs have been the most commonly used components of more composite drugs with trimethoprim (TMP). The characteristics of commonly used SNs are presented in Table 1.

SNs are polar molecules with amphoteric properties. Their amino nitrogen (N^4) is protonated at pH 2–3, while the amide nitrogen (N^1) is deprotonated at pH 4.5–11 [10,23]. The SNs presented in this text are small molecules (molar mass 177–300 g mol^{-1}), are water soluble (with the exception of SGM and sulfasalazine) and have low Henry's constant (1.3×10^{-12}–1.8×10^{-8}) values [9,10,24]. They are slightly sorbed by soil (the soil partition coefficient values are 0.6–7.41 kg^{-1}) [9]. Thus, these SNs are easily and quickly spread in the environment, but their properties should limit their accumulation in defined biotopes. SNs do not easily adsorb onto activated carbon [1,4]. They are classified as photo- and thermally stable substances at the degradation half-life (DT_{50}) >1 year [24]. They can undergo alkaline hydrolysis and coupling reactions with phenols and amines and easily react with the hydroxyl radical HO$^\bullet$ [10,11,25].

3. Mechanism of antibacterial activity of SNs

As shown in Fig. 3, antibacterial SNs act as competitive inhibitors of the enzyme dihydropteroate synthease (DHPS) which catalyses the conversion of para-aminobenzoate (PABA) to dihydropteroate (AHHMD), a precursor of folate synthesis. Tetrahydrofolic acid (THF) participates in the synthesis of nucleic acids that are essentials as building blocks of DNA and RNA.A mechanism of action of herbicidal SNs is similar.As a result, it is possible to inhibit the synthesis of nucleic acids and thus proteins [18,27]. SNs also inhibit the permeability of the bacterial cell wall for glutamic acid, which is also an essential component in folic acid synthesis. However, SNs do not inhibit the growth of microorganisms that:

Table 1
Common names, CAS number and structure of selected SNs.

Common name of SNs	CAS number	ATC classification index	Abbreviation	–R
Sulfanilamide	63-74-1	J01EB06, D06BA05, QJ01EQ06	SAD	–H
Sulfacetamide	144-80-9	S01AB04	SCT	$-COCH_3$
Sulfacarbamide	547-44-4	J01EC20 (with SDZ and SDM)	SC	$-CONH_2$
Asulam (herbicide)	3337-71-1	–		$-COOCH_3$
Carbutamide	339-43-5	A10BB06		$-CONH(CH_2)_3CH_3$
Sulfathiourea	515-49-1	J01EB08	STU	$-CSNH_2$
Sulfaguanidine	57-67-0	A07AB03	SGM	$=C(NH_2)_2$
Sulfathiazole	72-14-0	D06BA02, J01EB07, QJ01EQ07	STZ	
Sulfafurazole, Sulfisoxazole	127-69-5	J01EB05, S01AB02, QJ01EQ05	SSZ	
Sulfamethoxazole	723-46-6	J01EC01, QJ01EQ11	SMX	
Sulfamoxole	729-99-7	J01EC03	SMM	
Sulfapyridine	144-83-2	J01EB04, QJ01EQ04	SPY	
Sulfadiazine	68-35-9	J01EC02, QJ01EQ10	SDZ	
Sulfamethoxine, Sulfamethoxydiazine	651-06-9	J01ED04	SMO	
Sulfamerazine	127-79-7	J01ED07	SMR	
Sulfamethazine, Sulfadimidine	57-68-1	J01EB03, QJ01EQ03, QP51AG01	SDM	
Sulfadimethoxine	122-11-2	J01ED02, QJ01EQ09, QP51AG02	SDT	
Sulfamethoxypyridazine	80-35-3	J01ED05, QJ01EQ15	SMP	
Sulfachloropyridazine	80-32-0		SCP	
Sulfadoxine	2447-57-6	QJ01EQ13	SDX	

- need the presence of folic acid in the environment,
- possess a high concentration of PABA, or
- have modified metabolic pathways (drug resistance).

4. Use of SNs

SNs are active against a broad spectrum of Gram-positive and many Gram-negative bacteria including species of the genus Streptococcus, Staphylococcus, Escherichia, Neisseria, Shigella, Salmonella, Nocardia, Chlamydia and Clostridium. Moreover, SNs have used against protozoa (e.g., *Toxoplasma gondii*), parasites (e.g., *Plasmodium malariae*), and fungi (e.g., *Pneumocystis carinii*).

SMX, SCT or sulfasalazine belong to SNs commonly used in human medicine while SDM, SDT, SMR, SDZ, STZ are used most frequently in veterinary medicine (different SNs have been used in different countries). Moreover, SNs have been added to animal feed

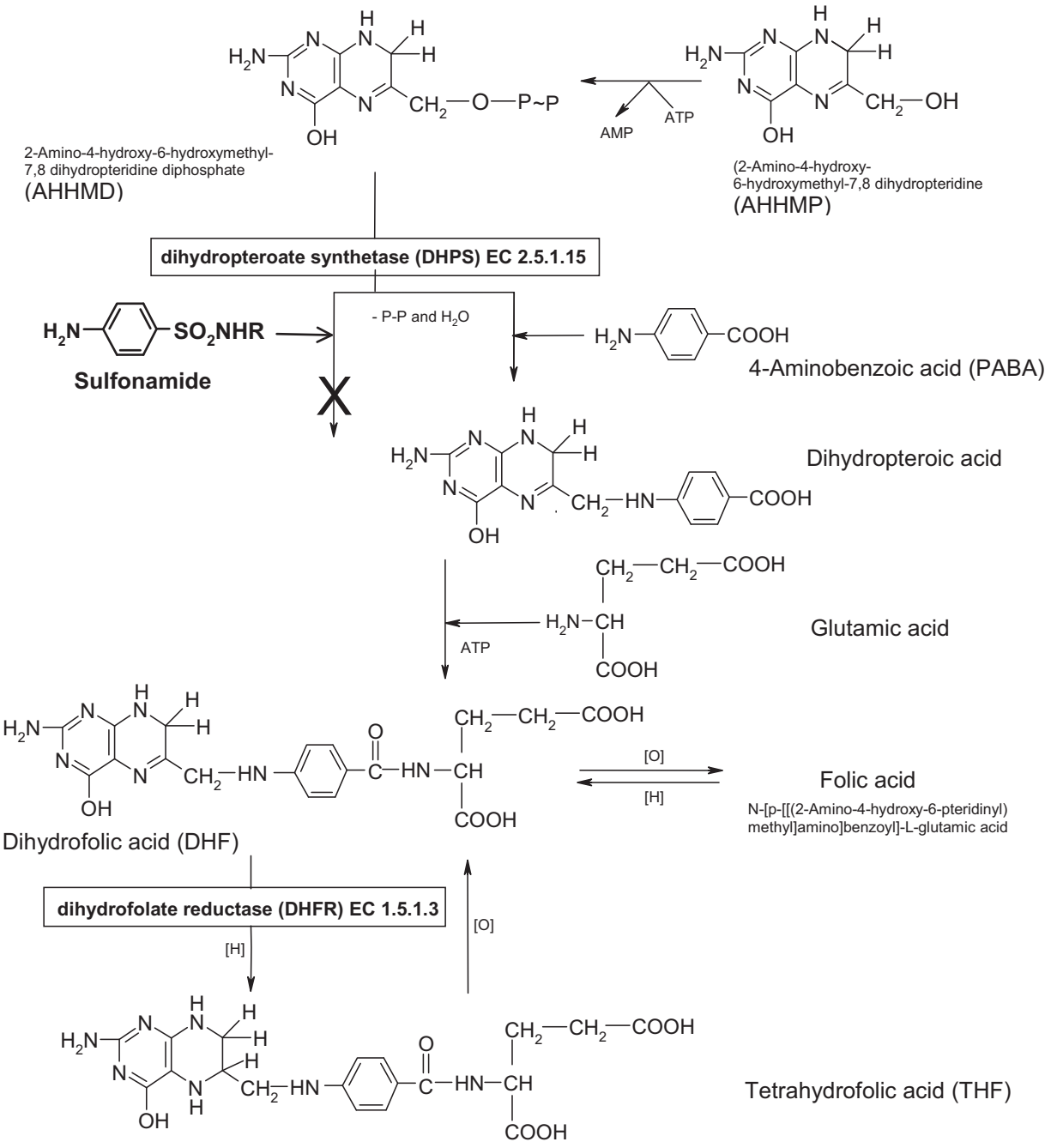


Fig. 3. The schema of SNs pathways, based on Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry [26].

premix used in young animals feeding. For example in Denmark in 2009 the consumption of SNs with TMP per kg of meat produced was as follows [28]:

- pigs 4.82 mg,
- cattle 17.2 mg,
- broilers 0.033 mg,
- farmed fish (aquaculture) 58.5 mg.

Moreover, SNs can be used in commercial beekeeping (they protect honey bees against bacterial diseases e.g., American foulbrood).

In agriculture, sulfonamide Asulam has been widely used as a herbicide. It is effective against dicotyledonous weeds e.g., barnyard grass (*Echinochloa crus-galli*), velvet grass (*Holcus lanatus*), wild oat (*Avena fatua*) and broadleaf dock (*Rumex obtusifolius*). However, the use of Asulam could lead to the contamination of honey with SNs residues [29]. In 2008, it has been withdrawn from use in the EU countries.

5. Estimated usage of SNs

An accurate assessment of the global consumption of all drugs would be difficult, if not impossible. The authors of the KNAPPE project have estimated that the global consumption of pharmaceuticals used in human and veterinary medicine has reached 100,000 tonnes per year [5]. Based on information from the Union of Concerned Scientists, Sarmach et al. indicated that, at the beginning of the 21st century, Americans consumed 16,000 tonnes of antibiotics per year [9]. SNs used in veterinary medicine accounted for approximately 2.3% of the total amount of antibiotics. In European

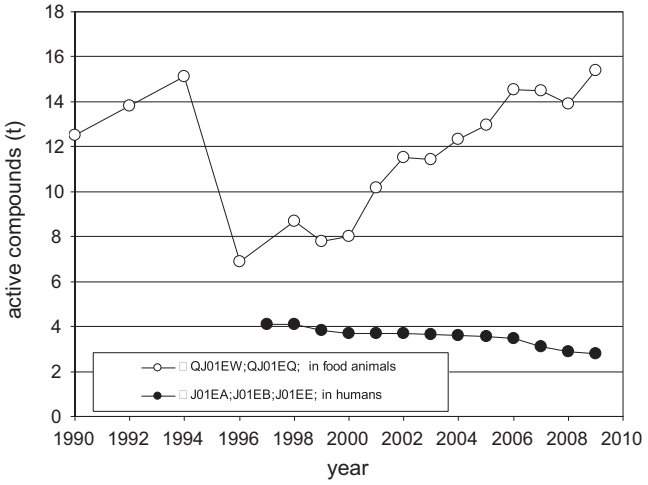


Fig. 4. The dynamics of consumption of SNs and TMP in Denmark in the years 1990–2009 [28,31].

countries, this value ranged from 11 to 23% [9]. According to other authors, the worldwide consumption of antibiotics (anti-infective drugs) ranged from 100,000 to 200,000 tonnes per year, including 50–75% that were used in veterinary medicine and animal husbandry [1,24]. It has been possible that each year more than 20,000 tonnes of SNs, with bacteriostatic properties, have been introduced into the biosphere (not counting drugs introduced as herbicides).

Since the end of 20th century, Scandinavia and other countries in Europe and North America have imposed restrictions on the use of antibiotics (including SNs) in animal husbandry. The use of antibiotics as growth promoters in animal husbandry in the European Union has been banned since January 1, 2006 [30]. However, reports on the consumption of pharmaceuticals in different countries have not shown a reduction in the use of these drugs.

Fig. 4 presents the dynamics of SN with TMP consumption in Denmark in the years 1990–2009 [28,31]. A decrease in the use of SNs in animal husbandry occurred in the mid-1990s and is associated with the introduction of administrative restrictions related to the application of these drugs in animal feed. Although the ban has been still in place, the use of SNs in agriculture is similar as in 1994. In our opinion, the plots in Fig. 4 illustrate global trends in consumption of SNs in livestock farming and medicine.

6. Occurrence of SNs in the environment and food

The first publication containing quantitative data about the presence of SNs in river water was published in 1982 [9]. However, systematic studies on the quantitative determinations of SNs in environmental matrices became possible after the development of highly sensitive analytical methods. According to data from the U.S. Environmental Protection Agency the limit of detection during routine analytical procedures using SPE/HPLC-MS/MS techniques for the selected SNs was below 10^{-9} g l^{-1} (e.g., for SDT, the limit of detection was 1×10^{-10} g l^{-1}). A detailed statement of the analytical techniques and limits of detection of drugs (including SNs) in environmental samples has been discussed by García-Galán et al. [18] and Seifrtová et al. [32]. At the described level of detection, SNs were detected in 27% of rivers and streams in the USA [11], in almost all surface waters in France and Tajwan [33,34], and in 100% of wastewater samples [13,35,36]. According to Vulliet and Cren-Olivé, in the Rhônee Alpes region of Frances the frequencies of SMX in surface and groundwater were 37 and 66%, respectively [37]. In commercially available, Italian natural mineral water the frequency of SNs was 50% (in 4 of the 8 investigated samples) [38]. García-Galán et al. [36] described in detail the frequency of occurrence of 19 selected SNs in wastewater. Moreover, metabolites of SNs, mainly N^4-acetyl sulfonamides (N^4-AcSNs), were also identified in environmental samples [11,39]. SNs concentrations in the environment underwent significant fluctuations, which were mainly dependent on the type of matrix and the type of SN [36]. Additionally, the results obtained may have depended on the sampling site, the day of the week [40] and even the time of day [41]. However, it was important to note that the data concerning the determination of SNs in environmental samples could contain significant errors. The cause of this may be imperfection of the analytical procedure used and the incorrect (incomplete) extraction of samples. For example, the recovery of SNs from soil samples ranged from 5 to nearly 294% but the authors have found that the "presented method is characterized by good selectivity" [42]. The recovery efficiency depends on various parameters including extraction/purification strategies [43] and the type of matrix [44].

A summary of the occurrence of SNs, depending on the matrix, is shown in Fig. 5, and the maximal values are given in Table 2. The presented data are based on the maximum values described in the literature.

SNs concentrations in samples increased as follows: seawater < ground water < surface water < treated sewage < untreated (raw) municipal sewage < hospital sewage < activated sludge < soil < runoff from farmland < leachates from landfill < manure. Due to the low concentrations and low abundance of SNs, the presence of trace amounts of these drugs in drinking water was not considered a significant problem. The maximum concentrations were found in freshly removed bedding [58] and manure from pigs fed diets that contained SNs, mainly SDM [59]. This SN occurred in almost 50% of samples (the average concentration of the drug was 7 mg kg^{-1}). Additionally, other SNs were identified in tested samples (e.g., for SDZ, the maximum concentration was 35.2 mg kg^{-1}). Fortunately, even short-term storage of manure could result in a significant reduction in the concentration of SNs [58].

The highest allowed concentrations of SNs in food were established in administrative regulations. The European Union adopted a maximum SN concentration of 100 μg kg^{-1} in animal foodstuffs [61]. In Poland, the maximum permitted concentration of Asulam in fruits and vegetables is 0.5 mg kg^{-1} [62].

The occurrence of SNs in tissues of farmed fish has been incidental, e.g., in Slovenia, SNs residues were found in 14 of the 2363 samples [63]). SNs residues in edible marine food were detected rarely, however the concentration of SNs in tissue of common eel (*Anguilla anguilla*) was above 5 mg kg^{-1} [64].

In EU countries, the occurrence of SNs residues in edible tissues of farm animals has been insignificant. According to "Report for 2006 on the results of residue monitoring in food of animal origin in the Member States" SNs, at concentrations above their maximum allowed limits, were detected in 0.006, 0.05, 0.08, 0.97 and 3.86% of samples of poultry, bovines, pigs, eggs and rabbits, respectively [65]. Although the use of SNs in beekeeping is banned in the EU, the frequency of these drugs in honey samples is high. In Poland, it has been estimated that almost 10% of honey samples contain excessive amounts of SNs i.e., above the allowed maximum concentration.

The results reported by the Chinese researchers are much less optimistic. High concentrations of SNs were determined in pig offal (almost 74 mg kg^{-1} of SDT and 73 mg kg^{-1} of STZ) and poultry offal (46 mg kg^{-1} of SDZ) [66]. Even more worrying is the fact that 75% of meat samples contained SNs at the total concentration >100 μg kg^{-1} [67].

SNs could be absorbed and accumulated by plants fertilized with manure (the highest concentrations of SNs are determined in roots and leaves [9,68–71]. For example, the maximum concentration

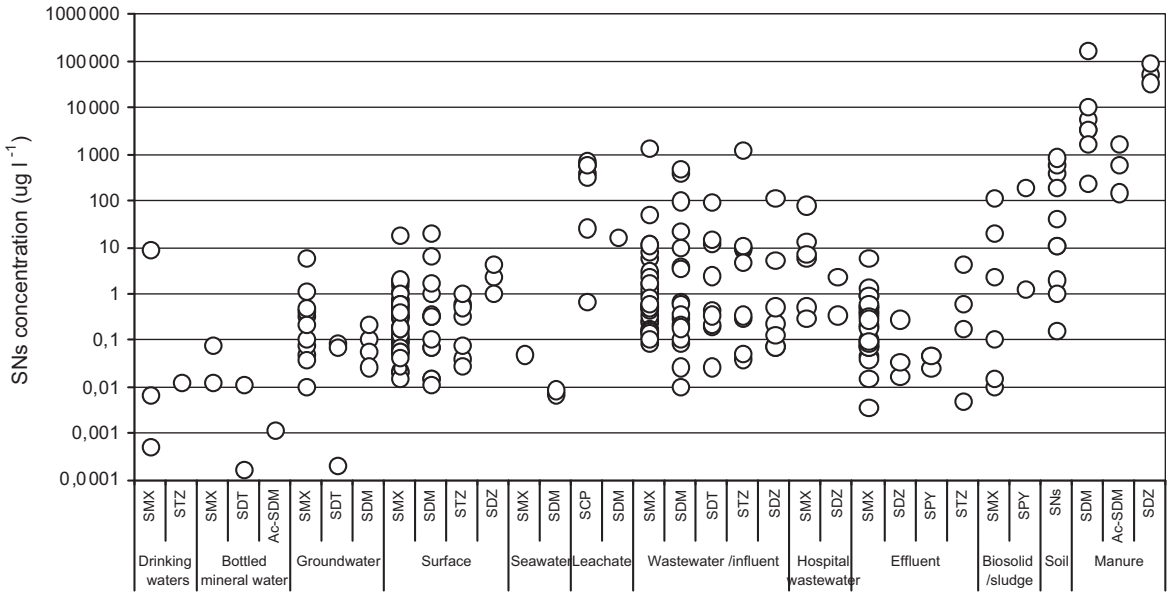


Fig. 5. Occurrence of the selected SNs depending on the matrix.

of SDM determined in corn, tomatoes and lettuce was 0.1 mg kg^{-1} [69]. Migliore et al. [71] reported that cosmopolitan weeds (*Amaranthus retroflexus* and *Plantago major*) showed a high tendency to bioaccumulate. In the tissues of these plants cultured in the medium containing SDT the accumulation rates were 2314 and 6065 mg kg^{-1}, respectively [71].

In our opinion, although the data presented in this section are based on the maximum values, it is possible that they can be underestimated. A commonly routine practice is the excessive and prophylactic use of antibiotics in animal husbandry and the use of manure as a fertilizer. Therefore, the local real concentrations of SNs in the biosphere are much higher. Additionally, this effect is difficult to control due to the high mobility of SNs in the environment. For these reasons, the excessive use of manure containing SNs as fertilizer should be banned.

7. Ecotoxicity of SNs

The toxicity of SNs to higher organisms (vertebrates) is not high. According to the EU directive 93/67/EEC, SNs under investigation can be classified as non-toxic or harmful [72]. The results described in the literature indicate that SNs do not exhibit mutagenic or

Table 2
Concentrations of SNs in the environment.

Matrix	Mean[a]/the most described SNs	n[b]	Maximal values
Drinking waters	2.1 (0–8.5 [8]) μg l^{-1} (SMX); 0.011 μg l^{-1} (SMX) [37]	4	8.5 μg l^{-1} (PEC[c] for SMX) [8]
Bottled mineral water	0.164 ng l^{-1} (SDT) [38] 0.047 (0.013–0.080) μg l^{-1} (SMX) [38]	2	0.080 μg l^{-1} (SMX) [38]
Ground water	0.80 (0.0099–1.11 [14]) μg l^{-1} (SMX)	11	3.461 μg l^{-1} (SCT) [45]
	0.053 (0.0002–0.09148 [45]) μg l^{-1} (SDT)	3	<1.11 μg l^{-1} (SMX) [14]
Surface water	0.87 (0.015–18 [8]) μg l^{-1} (SMX)	39	19.2 μg l^{-1} (SDM) [46]
	2.26 (0.0108–19.2 [46]) μg l^{-1} (SDM)	12	>25 μg l^{-1} (all SNs) [43]
Sea water	0.0475 μg l^{-1} (SMX) [47]	1	0.0475 μg l^{-1} (SMX) [47]
Drainflow/leachate	379.78 (0.66–703.2 [48]) μg l^{-1} (SCP)	7	703.2 μg l^{-1} (SCP) [48]
Influent/wastewater	46.58 (0.05–1340 [33]) μg l^{-1} (SMX)	31	1340 μg l^{-1} (SMX; from pharmaceutical production) [33]
	61.11 (0.0269–500 [49]) μg l^{-1} (SDM)	17	1158.68 μg l^{-1} (STZ; agricultural wastewater) [50]
Hospitals wastewater	17.78 (0.3–79.9 [51]) μg l^{-1} (SMX)	6	12.8 μg l^{-1} (SMX) [52]
	1.28 (0.353–2.2 [51]) μg l^{-1} (SDZ)	2	PEC 92.8 μg l^{-1} (all SNs) [51]
Effluent (after WWTP)	0.517 (0.00366–6.0 [53]) μg l^{-1} (SMX)	30	6.0 μg l^{-1} (SMX) [53]
	1.26 (0.005–4.27 [50]) μg l^{-1} (STZ)	4	4.27 μg l^{-1} (STZ; effluent of agricultural WWTP) [50]
Sludge (after WWTP)	22.56 (0.01–113 [54]) μg kg^{-1} (SMX)	6	197 μg kg^{-1} dw[d] (SPY) [54]
	99.1 (1.2–197 [54]) μg kg^{-1} (SPY)	2	31 μg kg^{-1} (SDM) [55]
Soil	211.6 (0.16–860 [56]) μg kg^{-1} (SNs)	10	400 μg kg^{-1} (STZ; agricultural soil) [57]
			PEC 860 μg kg^{-1} (SCP; soil pore water estimation) [56]
Manure	27.30 (0.23–167 [1]) mg kg^{-1} (SDM)	7	395.730 mg kg^{-1} (SDT; in bedding – day 0) [58]
	59.07 (35.2–91 [1]) mg kg^{-1} (SDZ)	3	167 mg kg^{-1} (SDM) [59]
Waste landfill			1600 μg l^{-1} (all SNs) [60]

[a] Calculated based on maximal values given in tables.
[b] Number of papers.
[c] Predicted environmental concentration.
[d] Dry weight.

carcinogenic (teratogenic) activity [73]. On the other hand, in the report "Environmentally Classified Pharmaceuticals 2009", SNs were considered as highly toxic drugs [74]. The discrepancies between these reports probably result from different criteria used to define a risk. Directive 93/67/EEC is based on the environmental risk posses by pharmaceutical substances while "Environmentally Classified Pharmaceuticals" report assesses both environmental risk (based on the acute toxic risk to the aquatic environment) and additionally persistence and bioaccumulation of SNs in the environment (based on the information published by the Swedish Association of the Pharmaceutical Industry [74]).

Fig. 6 illustrates the toxicity of SMX to selected test organisms.

Important data on the SNs ecotoxicity were summarized in articles by García-Galán et al. [18] and Isidori et al. [73]. SNs are practically non-toxic to most microorganisms tested [4,18,73,75], including selected strains of bacteria, such as *Vibrio fischeri, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. For example, the L(E)C_{50} values determined using the Microtox® test (*V. fischeri*) ranged from 16.9 to 118.7 mg l^{-1} (for SMX) to >1000 mg l^{-1} (for STZ) [73,76,77]. Strong bacteriostatic properties caused by the SNs could significantly change the functioning of microorganisms living in the environment, for example a significant reduction of their microbial activity [78]. Additionally the number of less sensitive (resistant) strains has increased and the number of strains sensitive to SNs has decreased. Thiele-Bruhn and Beck showed that the disposing of urine that contained even a low concentration of SPY (0.02 mg kg^{-1}) into the soil resulted in a significant reduction of microbial activity [78]. It was found that, in the case of SPY, the EC_{10} values for soil organisms ranged from 0.00014 to 0.16 mg kg^{-1} (the microbial $Fe^{(III)}$ reduction test) and from 0.0071 to 0.056 mg kg^{-1} (the substrate-induced respiration test) [79].

However, the most sensitive assays for the presence of SNs are bioindicators containing chlorophyll [9,18,73]. A highly toxic effect of SMX on *Synechococcus leopoliensis* (EC_{50} = 0.0268 mg l^{-1}) was described by Ferrari et al. [77]. In the case of SMX, the no observed effect concentrations (NOECs) for algae (*Pseudokirchneriella subcapitata* and *S. leopoliensis*) and gibbous duckweed (*Lemna gibba*) were 0.090 [77], 0.0059 [77] and 0.01 mg l^{-1} [4], respectively. This indicates that even low concentrations of SNs may significantly affect the growth and development of plants.

SNs can accumulate in various organisms in the food chain, and this accumulation could lead to a local increase in toxic effects induced by these drugs [9,10,70,71]. In addition, the toxic effects of SNs and other pollutants could exhibit a synergism [11,80,81]. At environmental exposure levels (samples contained 13 micropolutans, including SMX at the concentration of 46 ng l^{-1}) the drug mix inhibited the growth of human embryonic cells HEK293, with the highest effect observed as a 30% decrease in cell proliferation compared to controls [81].

Since there has not been sufficient extensive experiments in patients with a single overdose of SNs the maximum tolerated dose in humans are unknown [82]. In laboratory experiments, acute oral overdoses of SNs in animals (LD_{50}) were as follows:

- in rats 10,000 mg kg^{-1} (SSZ),
- in rabbits 2000 mg kg^{-1} (SSZ),
- in mice 5700 mg kg^{-1} (SSZ), 16,500 mg kg^{-1} (SCT), 3700–4200 mg kg^{-1} (SAD), 4500 mg kg^{-1} (STZ) [83].

Exemplary adverse effects associated with overdosage of SNs in humans include nausea and cutaneous hypersensitivity reactions. Other adverse effects e.g., stomatitis, hemolysis, methemoglobinemia, hepatotoxicity and renal toxicity occur rarely. SNs can cause interaction with other drugs, for example with methotrexate, sulfonylureas, wafarin, mercaptopurine, cyclosporine or didanosine [84].

In our opinion, direct toxic effects caused by SNs occurring in the environment do not appear to be a significant threat to public health. Potential possible cases of direct toxic effects of SNs on human may be sporadic. On the other hand, the occurrence of SNs residues in food, particularly in the case of illegal or improper use of these drugs, can be a more serious problem. According to Dolliver et al., SNs residues in food products do not pose a threat and/or adverse effect to human health but "development and spread of antibiotic resistance, which is a major problem globally" [69].

8. Degradation of SNs in organisms and in the environment

Possible products of the biotransformation and degradation of SNs are shown in Fig. 6. A detailed discussion of these processes is presented in the next sections.

8.1. Metabolism of SNs in mammals

A large part of the SNs dose is excreted from organisms as unchanged compounds. For example, 75% of SMR could be excreted from the body in its parent form [1]. However, in general, over 80% of an SN dose undergoes biotransformation in mammals. The degree of transformation of each SN depends both on its type and the features of the organism. Biotransformation of SNs is mainly based on oxidation, acetylation or hydroxylation at the N^4-nitrogen atom or glucuronidation of the N^1- or N^4-nitrogen atoms [1,10,11]. It is assumed that, after oral administration, 50–70% of the dose is excreted in urine as N^4-AcSNs, and 15–20% as N^1-glucuronides [1,10]. The metabolites of SNs do not possess high biological activity as unchanged SNs. However, this activity could be easily restored during *in vitro* conditions [11,85]. The concentrations of metabolites other than those listed above are small and are likely not significant in the environment. Reviews of possible paths of SNs biotransformation were described in the papers of Sukul and Spiteller [10] and García-Galán et al. [11].

8.2. Biodegradability of SNs

The opinions of researchers on the biodegradability of SNs have been divided [1,4,10,17,24,86]. The cause of this may be the differences in microbial activity of the matrix, the inoculum used, and the applied methods used to assess SN degradation (Table 3). The stability of various SNs is also different; for example, SDM is more (10x) resistant to biodegradation than STZ.

The results of standardized tests, such as the ISO 11734:1995 and OECD 301D, and the assessment of soil microbial activity suggest that most of the SNs do not undergo natural biodegradation. One of the most often described SNs in the literature is SMX, which has been regarded as a non-biodegradable compound (in pure water, seawater, natural water and wastewater or active sludge) in 9 of 24 articles [1,4,24,86,89,91,97–99]. According to Weifen et al. [114], in the presence of shrimp (*Penaeus chinensis*), the DT_{50} value for SMX is 5.68 h. Ingerslev and Halling-Sørensen [92] found that, in the presence of microorganisms in activated sludge, the DT_{50} of SNs is only ~7 h. De Liguoro et al. [58] stated that, in the case of SDT, the DT_{50} for microbial degradation in fresh bedding is ~1 day. Similarly, equally rapid degradation of SDT has been described by Wang et al. [87]. These authors have observed an increase in the DT_{50} value with increasing initial concentrations of SDT in fresh and sterile manure. In these cases, most of the SNs were incorporated into microorganisms and/or underwent only reversible transformations, such as acetylation [11,85]. The rapid disappearance of SNs in soil and manure could be an effect of binding between SNs and organic or mineral particles [85,88,93] or could be caused by

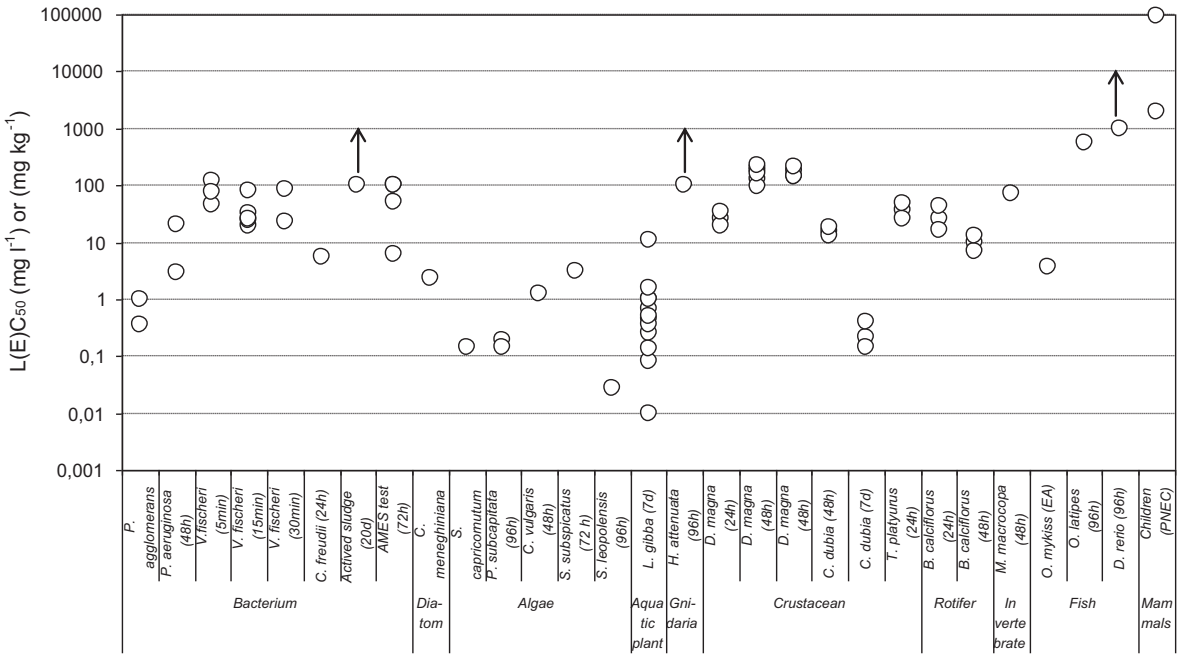


Fig. 6. Comparison of SMX toxicity to selected test organisms.

photochemical processes (on the soil surface, in the presence of Fe compounds and nitrates) [107,115]. Most researchers recognized SNs as poor or non-biodegradable compounds in the environment (in pure water, surface water and in soil with a DT_{50} > 30 days) [24,74]. The fact that SNs occurred so often in test samples could also be considered as evidence of their persistence in the environment.

In our unpublished study on the biodegradation of SAD, STZ, SMX and SDZ applied to natural matrices, we found that, in individual cases (STZ under aerobic conditions, in wastewater and water from the swamp), the DT_{50} was less than 2.5 days. In the remaining cases, the DT_{50} values for SDZ, SAD and SMX were >5, >8 and ≫31 days, respectively.

In our opinion the read stability data related to SNs residues in the environment (especially for SMX) are generally much higher than the data reported by other researchers in the cited articles. The above-described high frequency of SNs in environmental samples can confirm this assumption.

8.3. Physicochemical methods of degradation of SNs

The efficiency of SNs degradation using the most commonly used chemical and physicochemical methods is presented in Table 3. The high degradation efficiency of SNs in wastewater was obtained using various advanced oxidation processes (AOP) [1,4,101,105,108,116,117], such as the use of O_3, Cl_2, and ClO_2 [1,101,116–118], the Fenton reaction [105,116] or photocatalytic processes [85,105,116,117]. Unfortunately, the application of these methods is costly and could be harmful to the environment due to the formation of highly toxic intermediates [118]. Moreover, a decrease in the efficiency of AOP with an increase in overall wastewater pollution was observed [108]. This fact made it difficult to apply these methods directly to remove SNs from manure. In Table 3, examples of other methods used to remove contaminants from the aquatic environment without their degradation or transformation (non-destructive methods) are presented. SNs can be removed from wastewater with nearly 100% efficiency by reverse osmosis [1,4,24,109,110]. However, with this method, there could be a problem with wastewater containing concentrated solutions of toxins (including SNs) [110]. In the case of substances resistant to biodegradation, there could be a local, risky increase in the concentration of these toxins in a small area [119].

The physico-chemicals methods (particularly AOP) can be effective and very useful in the degradation of SNs. In our opinion, it is not excluded that their environmental degradation is the result of photochemical reactions initiated by sunlight in the presence of natural photosensitizers, and not only of biodegradation processes.

9. Removal of SNs from wastewater

Opinions on the efficiency of SN removal in conventional biological-mechanical treatment plants are divergent. Similar differences occur during the assessment of the biodegradability of drugs (Table 3). Onesios et al. [120] analyzed 49 cases of the removal of SDZ, SDM, SMX and SPY from wastewater in wastewater treatment plants (WWTPs). Based on the analysis of recent publications, −280 to 100% of SNs were removed using activated sludge (AS) (Table 4). The mean degree of SN removal in these cases was ∼24%.

According to the data published in 2010, SMX was removed from the selected WWTPs in Spain in the range of 30–92% [35]. However, there are also cases in which the concentration of SNs in effluent was higher than that in the influent [4,86,134,138]. This effect was described in a pilot WWTP in Austria [90] and in Switzerland [138]. This effect is likely caused by hydrolysis of the N^4-AcSNs present in wastewater to the parent SNs [11].

A conclusion of this problem may be found in the data from the study by Turkdogan and Yetilmezsoy [109]. These authors have estimated that 80% of used antibiotics enter the environment despite the use of various processes in WWTPs (based on the data from Turkey, without regard to SNs). Importantly, a large part of SNs may be adsorbed in WWTPs by biomass [132] and could return again to the environment.

10. The environmental risk assessment

The majority of researchers have used the method recommended by the European Medicines Evaluation Agency (EMEA) for environmental risk assessment. This method uses the results of

Table 3
Biotransformation, degradation and other methods of SNs removal.

Matrix	Methods	Efficiency	DT_{50}
Biotransformation			
Human		<90% (SNs) [1,11]	
Animal		50–90% (SNs) [11]	
Manure		0% after 28 days (SDZ) [1]; 10% after 11 weeks (SDM) [1]; 25% after 15 days (SDT)	>30 days (SNs) [1] 1.36–2.56 days (SDT) [87]; 7 days (SDM) [1]; 61 days (SDT) [58], 127 days (SCP) [88]
Bedding		99.5% after 28 days (SDT) [58]	1 day (SDT)[58]
Wastewater		41 (0–90)% (SNs) [1,89]	
	Membrane bioreactor	70–90% (SMX) [1,90]	
Activated sludge		42 (−138 to 99)% (SMX) [86,91] k_{biol} = 0.1–10 l g SS^{-1} d^{-1} (SMX)[a] [4]	0.3–4.1 days (SNs) [92]
Soil		0% after 28 days (SDZ) [1]; 0.2–0.3% after 64 days (SDM) [1]	2.8–21.3 days (SCP) [88,93]; <10 days (SDM) [1]; <15 days (SDZ) [1]
Sediment		0–90% after 28 days (SDZ) [1,94]; 20% after 180 days (in marine sediment) [1]	0.7 day (SDM) [94]; 4.9–10.1 days (SMX) [94]
Surface water		24 (0–82)% (SNs) [95,96]; practically non-biodegradable (SMX) [1,91,97]	
Pond water			15.8 (1.7–47.6) days (SNs) [94]
	OECD 301D test	Non-biodegradable after 40 days [1,98]; non-biodegradable in manure (SDT) [97]; 4% after 28 days (SMX) [24]; BOD_5/TOD <1.5% (SNs) [99] BOD_5/COD ≈ 0 (SMX) [89]	
Physicochemical degradation			
Pure water	Photolysis	>90% (at 254 nm; 2768 mJ cm^{-2}) [100]	
	HClO		6–181 s [101]
	$Fe^{(VI)}$		91–241 s [101]
	ClO_2	k = 2.2–103 l mol^{-1} s^{-1} [101]	
	Cl_2	<88% after 2 h; k = 0.00025–0.0347 s^{-1} [102]	
	$HO^{\bullet}$	k = 3.7–7.1 10^9 l mol^{-1} s^{-1} (SNs) [25]	
	O_3	>90% (SMX) [1]; <99% after 60 min [103]; k = 2.5–106 l mol^{-1} s^{-1} [101]	
	O_3/H_2O_2	<99% after 20 min [104]	
	Photo Fenton	<100% (at 5 Einstein m^{-3}) [89]	
	Fenton	>90% after 10 min (SNs) [105]	
Pure water	TiO_2	∼100% after 180–300 min (SNs) [99]; 88% after 360 min [106];	∼20 min (SAD)[107]
Wastewater		15–30% after 60 min (SNs) [108]	
Pure water	$TiO_2/FeCl_3$	<90% after 90 min (SAD) [107]	∼4 min (SAD) [107];
Wastewater		62–84% after 60 min (SNs) [108]	11–42 min (SNs) [108]
Non-destructive methods			
Permeate	Reverse osmosis	∼100% [109,110]	
Concentrate		−58% [110]	
	Microfiltration	−18% [109]; 0–90% (SMX) [1]	
	Bank filtration	25% (SMX) [111]	
	Adsorption	89–98% Micelles; 45–58% Activated carbon [112]; ∼0% [1,4]	
Hospitals wastewater	Coagulation $Al_2(SO_4)_3$	∼0 (−50 to 21.3)% [112]	
Pure water	Ionic treatment	>90% (SNs) [113]	
Effluent	MIEX® resin	40–90% (SNs) [113]	

[a] k_{biol} kinetic constant for pseudo first order biodegradation (l gSS^{-1} d^{-1}), suspended solids concentration (g$SS\,l^{-1}$) [4].

toxicological studies and is based on calculating the hazard quotient (HQ) as the ratio of the PEC value to the predicted no-effect concentration (PNEC) [1,4,13,17,18,24,72–76,109,141]. The method for the determination of these values was described in detail by Koschorreck et al. [24], Park and Choi [75], Kim et al. [76] and Lopes de Souza et al. [141]. A similar method is based on a calculation of the MEC/PNEC ratio in which MEC is the maximum environmental concentration [1,8,35,73,75]. Typically, values of HQ < 1 indicate that the substance analyzed could be considered environmentally safe.

A comprehensive review of the data on the HQ values for 5 selected SNs was published by García-Galán et al. [18]. Although the presented HQ values were mainly obtained for SMX, they are significantly different. The selected data on the HQ values calculated based on the available literature and this review [18] are shown in Table 5.

However, the maximum HQ values have probably negligible importance. According to Schwab et al. [8], the concentrations of SNs in the environment do not pose a risk to human health. Moreover, according to Environmentally Classified Pharmaceuticals (2009), the environmental risk of SNs is specified as insignificant [74]. On the other hand, data on the quantity of these drugs in matrices such as manure, wastewater from agricultural fields and pharmaceutical industries indicate that, in these cases, SNs could cause serious problems for the environment. The potential negative effects on the soil microorganisms of SNs present in manure and bedding are especially alarming (Table 5). Moreover, changes in the genotypes of microorganisms are often not taken into account. In contrast to the toxic effects, these changes could easily be transferred, even to species in other biocenoses.

11. Generation of drug resistance

In populations of bacteria that are sensitive to specific antibiotics, there are intrinsically occurring strains that are resistant to at least one drug (natural resistance). As a result, these resistant bacteria can survive, multiply and spread to others in the family [7,9,12,30]. In Nicole Kemper's article [12] on the influence of veterinary antibiotics on the environment, the author formulated

Table 4
Efficiency of WWTPs (full scale, pilot and lab scale).

WWTP	SNs	Influent ($\mu g\,l^{-1}$)	Efficiency (%)	Ref.
Guangzhou, China (AS, F, S or Cl_2)	SDZ	5.10–5.15	~100	[121]
	SMX	5.45–7.91		
Wisconsin, USA (AS)	SDM	0.11; 0.21	~100	[122]
	SMX	0.13–1.25	17.8–100	
Fort Collins, USA (Drake water reclamation facility)	SDM	0.52	>93	[123]
	SMX	0.68	38	
Taiwan (AS or trickling filter, Cl_2 or UV)	SNs/SDZ	0.06–0.51	20–82	[124]
	SMX	0.179–1.760	26–88	
Laboratory scale up-flow bio-reactors	SDT	10	66	[125]
	SDM		46	
	SMX		76	
	SDT	2	93	
	SDM		72	
	SMX		90	
Terrassa, Spain (CAS, MBR)	SMX	0.25–1.3	74 ± 13	[126]
Japan (AS, Cl_2)	SMX	0.18	26	[127]
		0.44	26	
	SDT	0.07	62	
Erie County, USA (extended aeration; rotating contactors; pure oxygen aeration)	SMX	0.72–0.88	36–77	[128]
Pearl River Delta, South China, (AS, oxidation ditch, Cl_2, UV)	SMX	0.01–0.118	0–64	[55]
	SDZ	0.072	50	
	SDM	0.696	50	
Čakovec, Croatia	SMX	0.3	2	[129]
		0.7	92	
Braunschweig, Germany (AS)	SMX	0.82	24	[130]
Slaughterhouse, Beijing, China, (anaerobic–anoxic–oxic or anaerobic–oxic processes)	SAD	max 1.2	54–91	[131]
	SMO	max 0.215	60–89	
	SCP	max 0.057	60–82	
	Sulfaquinoxaline	max 0.103	73–85	
Brisbane, Australia (CAS, advanced wastewater treatment)	SNs	0.362	25	[110]
Northwest Ohio, USA, Tokyo, Japan, (AS)	SDT	0.0047	>67	[132]
	SPY	0.495	4.6	[133]
	SMX	0.104	62	
AS+F	SPY	0.495	18.6	
	SMX	0.104	72	
As+F+O_3	SPY	0.495	95	
	SMX	0.104	96	
Austria (MBR pilot plant or CAS)	SMX		−280 to 61	[90]
Kloten/Opfikon or Altenrhein Swiss, (MBR pilot plant or CAS)	SMX		0–91	[134]
CAS ($n = 20$)	SMX		−138 to 99 (33)	[86]
MBR ($n = 3$)			57–90 (73)	
CAS	N^4-AcSMX		$k_{biol} = 5.9–7.6\,l\,gSS^{-1}\,d^{-1}$	[135]
MBR			$k_{biol} = 3.2–5.0\,l\,gSS^{-1}\,d^{-1}$	
CAS and MBR	SMX/SDM		$k_{biol} < 0.1\,l\,gSS^{-1}\,d^{-1}$	
Spain (AS or biologic filters)	SDZ		43–98 (69)	[35]
	SMX		30–92 (74)	
Jamaica Bay	SMX		62	[136]
Albuquerque, USA	SMX		27	[137]
Turkey (CAS)	SNs		25	[109]
Swiss (CAS)	SPY	0.06–0.15	−107 to 72	[138]
	SMX	0.23–0.57	−138 to 60	
	N^4-AcSMX	0.85–1.6	85–96	
(Fixed-bed reactor)	SPY		41; 52	
	SMX		−61; 29	
	N^4-AcSMX		81; 86	
(Sand filtration)	SPY/SMX		−21 to 0	
(Primary wastewater treatment)	SPY/SMX		−29 to 21	
	N^4-AcSMX		9–21	
Stanley and Shatin, Hong Kong	SMX	0.1465	68.2	[139]
		0.3555	95.7	
	SDZ	0.0730	72.8	
Luxemburg	SMX	max = 0.155	75	[140]

AS, activated sludge; CAS, conventional activated sludge; F, filtration; S, sedimentation; Cl_2, chlorination; MBR, membrane bioreactor; O_3, ozonation; UV–UV illumination.

Table 5
Ecotoxicological data on the HQ[a] value (based on the available literature).

Matrix	Maximal values of HQ calculated based on data from Table 2	Maximal values of HQ presented in the literature (only for SMX)	Comments
Drinking water	8.5[b]/0.05[c] = 170 (SMX)	0.0097 [8]	For child drinking water and fish consumption, US
Surface water	18/0.05[c] = 360 (SMX) 19.2/201[d] = 0.9552 (SDM)	59.30 [77]	Acute toxicity test, Germany
Wastewater	1340/0.05[c] = 26800 (SMX)	22.96 [35]	For algae, Spain
Aquatic environment	–	6.3 [76]	The PEC of test pharmaceuticals was estimated based on several conservative assumptions, Korea
Hospital wastewater	12.8/0.05[c] = 256 (SMX)	15.1 [51]	For hospital effluent, Germany
Soil	395.73[e]/0.00014[f] ≅ 2.8×10^6		

[a] HQ = P(M)EC/PNEC.
[b] PEC.
[c] PNEC = NOEC/10 for *S. leopoliensis.*
[d] For *D. magna.*
[e] SDT; in fresh bedding.
[f] The microbial $Fe^{(III)}$ reduction test for SPY.

the following thesis: "Resistance is provoked by repeated exposition of bacteria to sub-lethal dosages of antibiotics, as realized by continuing manuring with contaminated faeces on land used agriculturally". Although the natural resistance to pathogenic bacteria has not been transferred between strains, the formation of drug resistance by the transfer of "resistance" genes between bacterial cells belonging to different strains, or even genera, during one recombination process (horizontal gene transfer) may have contributed to the dissemination of drug-resistant bacterial species on a large scale. As a result, these strains may occur in ecosystems theoretically not exposed to chemotherapeutics [142–144]. For example, Pallecchi et al. described the occurrence of drug resistance in 67% of members of the Guaraní Indian community of Alto Los Athletic (Bolivia) [143]. Drug resistance against one group of drugs may favour the generation of drug resistance to other drugs or disinfectants [145]. Due to the importance of pathogenic resistance to human health, programs for monitoring microorganism resistance in Europe and the Americas have been implemented [7,142,146]. For example, the ECO-SENS project has collected and analyzed drug resistance data in 17 European and American countries since the 1960s [7,142].

The resistance of pathogenic bacteria to SNs may be due to structural changes in dihydropteroate synthase (DHPS, Fig. 3) that are the effect of point mutations in the DHPS gene (*folP*) [147]. Thus, these mutations affect the expression of the DHPS enzyme with has a lower affinity for SNs. The spontaneous mutants of *E. coli*, showing resistance to SNs as a result of the substitution of one or more base pairs in the DHPS gene have been isolated in laboratory [147].

SNs resistance may be also distributed on mobile genetic elements, such as plasmids, transposons and integrons [148,149]. There have been three known genes encoding resistance to SNs [144]. The *sul1* gene is usually located on the 3′ conserved region of class 1 integrons, which are a part of large conjugative plasmids and Tn21-like transposons. The dissemination of this gene increased with the prevalence of class 1 integrons in bacterial pathogens. The *sul2* gene was first identified on the RSF 1010 plasmid in *E. coli*. It is frequently located on large conjugative plasmids, e.g., pGS05,

Table 6
Dissemination of SNs resistance genes (*sul1, sul2 and sul3*).

Matrix	SNs-resistant isolates positive for *sul1-3* genes (%)		SNs-resistant isolates (%)	Ref.
Pigs	11-84(*sul1*), 19-54(*sul2*), 3-46(*sul3*)		50–97	[152]
Swine			81	[153]
Cattle			22	
Dogs and cats			20	
Laying hens			26	
Pigs	18(*sul1*), 20(*sul2*), 18(*sul3*)		50	[154]
Wild small mammals	5(*sul1*), 1(*sul2*)		6	
Danish broiler faeces, and meat	11(*sul1*), 82–100(*sul2*)		15–18	[155]
Broiler meat	26(*sul1*), 61(*sul2*), 8(*sul3*)		45	
Foodstuffs	69.8(*sul1*), 36.9(*sul2*), 1.4(*sul3*)		92.5	[156]
Wastewater directly from swine farms	92	(total of SNs resistant isolates positive for *sul* genes)		[157]
Shrimp ponds	43			
City canal/fish ponds	72			
Water-sediment and Manure	14(*sul1*), 96(*sul2*)			[158]
Faecal samples	100(*sul1–3*)			[159]
Urine				
UK 1991	43		39.7	[160]
UK 1999	53.9		46	
UK 2004	57.5		45.5	
Europe before 1990			0–5	[142]
Europe 1999–2000			9–26	
Healthy humans	33(*sul1*), 91(*sul2*), 5(*sul3*)			[155]
Humans	16(*sul1*), 97.5(*sul2*)		74	[143]
Animal, food and human			100	[31]

and on small non-conjugative plasmids, such as pBP1, pHD148 and RSF 1010. The last two plasmids also carried genes associated with resistance to streptomycin, and therefore, the resistance to SNs and streptomycin are strongly linked together [150,151]. The *sul3* gene has been found in pathogenic *E. coli* isolated from swine. The dissemination of each *sul1-3* gene depends on the location of sampling sites and bacterial species. Among Gram-negative isolates resistant to SNs, mainly *E. coli* and *Salmonella*, the *sul1* and *sul2* genes are often found at almost an equal frequency [144]. Resistant bacterial species commonly carried single genes, but in recent years, an increased number of pathogens that possess three SNs-resistant genes have been observed (Table 6).

In environmental matrices, the presence of organisms resistant to SNs could be determined by detection of the genes described above. Most often, bacterial resistance to SNs has been described in *E. coli*, *Salmonella enterica* and *Shigella* spp. from the manure of farm animals, from meat and meat products, from healthy humans with urinary infections and from wastewater (Table 6). However, all SNs-resistant bacterial species positive for the *sul* genes and plasmids mentioned above were identified and classified as belonging to thirteen genera, namely *Acinetobacter, Aeromonas, Arthrobacter, Bacillus, Brachybacterium, Cellulosimicrobium, Enterobacter, Escherichia, Pseudoalteromonas, Pseudomonas, Shigella, Vitreoscilla* and *Wautersiella* [157].The most important facts related to drug-resistance include the following:

- the use of antibiotics in veterinary medicine increases the drug-resistance of microorganisms, including cross-resistance [9,161],
- the presence of SNs in the environment increases the antimicrobial resistance of microorganisms [9,12],
- the number of bacterial strains resistant to SNs increases systematically in recent years [7,160],
- SNs have shown the highest drug resistance, almost twice as high as tetracyclines and many times higher than other antibiotics [153].

12. Conclusions

- Antibacterial SNs are a group of drugs still commonly used in human and veterinary medicine. Used SNs could be spread into the environment in an almost entirely biologically active form or could recover activity.
- Opinions on the possibility of SNs removal in conventional WWTPs are divergent. There are known technologies that could completely degrade SNs in WWTP. However, nearly 80% of used SNs have reached the biosphere. This indicates that some existing, modern technologies are not able to manage the degradation of SNs.
- SNs introduced into the environment likely remain there for a long time and could spread easily and infiltrate groundwater.
- The frequency of SNs in tested environmental samples is very high.
- SNs have a very low toxicity to higher organisms (vertebrates) and are highly toxic to microorganisms, algae and certain plants.
- SNs occurring in the environment favour the generation of drug resistance. SNs resistance genes may be transferred into the environment.

High concentrations of SNs in the environment occur incidentally (in manure from livestock), but due to a gene transfer process, their relevance to the global change of drug resistance may be much larger than expected. The risk caused by the generation of drug resistance by anti-infectives drugs is much higher than the risk caused by their toxicity.

These facts indicate that the problem presented here has a serious global importance in ecology, and limitations of antibiotic consumption in individual countries will not solve this problem. The data also pointed to the need to search for effective and inexpensive methods of removing pollutants from the environment.

Acknowledgements

This work was supported by Medical University of Silesia in Katowice (Poland), Contract No. KNW-1-015/10.

References

[1] Eintrag von Arzneimitteln und deren Verhalten und Verbleib in der Umwelt, Literaturstudie Fachbericht 2, Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen, Recklinghausen, 2007. Available from: http://www.lanuv.nrw.de/veroeffentlichungen/fachberichte/fabe2/lanuvfabe2.pdf.
[2] L.B. Christiansen, M. Winther-Nielsen, C. Helwig, Feminisation of fish. The effect of estrogenic compounds and their fate in sewage treatment plants and nature, Danish Environmental Protection Agency, 2002. Available from: http://www.mst.dk/udgiv/publications/2002/87-7972-305-5/html/default_eng.htm.
[3] ENVIRPHARMA, B. Ferrari, J. Garric, N. Paxéus, A. Pollio, Ecotoxicity of 6 pharmaceuticals found in effluents of Sewage treatment plants and surface water in Europe, Lyon, France, 14–16 April 2003.
[4] POSEIDON, Assessment of technologies for the removal of pharmaceuticals and personal careproducts in sawage and drinking water facilities to improve the indirect portable water reuse: detailed report, 2005. Available from: http://poseidon.bafg.de/servlet/is/2888/.
[5] KNAPPE, Ch.G. Daughton, I.S. Ruhoy, Knowledge and need assessment on pharmaceutical products in environmental waters, 2008. Available from: http://www.knappe-eu.org.
[6] ERAPharm, Environmental Risk Assessment of Pharmaceuticals, Publishable final activity report, 2007. Available from: http://www.erapharm.org.
[7] G. Kahlmeter, The ECO-SENS Project: a prospective, multinational, multicentre epidemiological survey of the prevalence and antimicrobial susceptibility of urinary tract pathogens—interim report, J. Antimicrob. Chemother. 46 (2000) 15–22.
[8] B.W. Schwab, E.P. Hayes, J.M. Fiori, F.J. Mastrocco, N.M. Roden, D. Cragin, R.D. Meyerhov, V.J. D'Aco, P.D. Anderson, Human pharmaceuticals in US surface waters: a human health risk assessment, Regul. Toxicol. Pharm. 42 (2005) 296–312.
[9] A.K. Sarmah, M.T. Meyer, A.B.A. Boxall, A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment, Chemosphere 65 (2006) 725–759.
[10] P. Sukul, M. Spiteller, Sulfonamides in the environment as veterinary drugs, Rev. Environ. Contam. Toxicol. 187 (2006) 67–101.
[11] M.J. García-Galán, S. Díaz-Cruz, D. Barceló, Identification and determination of metabolites and degradation products of sulfonamide antibiotics, Tr. Anal. Chem. 27 (2008) 1008–1022.
[12] N. Kemper, Veterinary antibiotics in the aquatic and terrestrial environment, Ecol. Indic. 8 (2008) 1–13.
[13] A.Y.-Ch. Lin, T.-H. Yu, Ch.-F. Lin, Pharmaceutical contamination in residential, industrial, and agricultural waste streams: risk to aqueous environments in Taiwan, Chemosphere 74 (2008) 131–141.
[14] K.K. Barnes, D.W. Kolpin, E.T. Furlong, S.D. Zaugg, M.T. Meyer, L.B. Barber, A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States – I groundwater, Sci. Total Environ. 402 (2008) 192–200.
[15] P.A. Segura, M. François, Ch. Gagnon, S. Sauvé, Review of the occurrence of anti-infectives in contaminated wastewaters and natural and drinking waters, Environ. Health Perspect. 117 (2009) 675–684.
[16] S. Mompelat, B. Le Bot, O. Thomas, Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water, Environ. Int. 35 (2009) 803–814.
[17] K. Kümmerer, Antibiotics in the aquatic environment – a review – Part I, Chemosphere 75 (2009) 417–434.
[18] M.J. García-Galán, S. Díaz-Cruz, D. Barceló, Combining chemical analysis and ecotoxicity to determine environmental exposure and to assess risk from sulfonamides, Tr. Anal. Chem. 28 (2009) 804–819.
[19] A.E. Smith, L.J. Milward, Thin-layer chromatographic detection of the herbicide asulam in soils and the identification of sulphanilamide as a minor soil degradation product, J. Chromatogr. A 265 (1983) 378–381.
[20] WHO, Anatomical Therapeutic Chemical classification index. Available from: http://www.who.int/entity/classifications/atcddd/en/.
[21] J.P. Dubey, D.S. Lindsay, A review of Neospora caninum and neosporosis, Vet. Parasitol. 67 (1996) 1–59.

[22] A. Mastrolorenzo, C.T. Supuran, Antifungal activity of Ag(I) and Zn(II) complexes of sulfacetamide derivatives, Met. Based Drugs 7 (2000) 49–54.
[23] Z. Qiang, C. Adams, Potentiometric determination of acid dissociation constants (pK_a) for human and veterinary antibiotics, Water Res. 38 (2004) 2874–2890.
[24] J. Koschorreck, S. Lehmann, A. Naulin, Arzneimittel in der Umwelt -Zu Risiken und Nebenwirkungen fragen Sie das Umweltbundesamt, Umweltbundesamt, Texte 29/05, Dessau 2005.
[25] A.L. Boreen, W.A. Arnold, K. Mc Neill, Photochemical fate of sulfa drugs in the aquatic environment: sulfa drugs containing five-membered heterocyclic groups, Environ. Sci. Technol. 38 (2004) 3933–3940.
[26] J.M. Beale Jr., Anti-infective agents, in: Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 11th ed., Lippincott Williams & Wilkins, Baltimore, 2004, pp. 271–274 (Chapter 8).
[27] M.W. Valderas, B. Andi, W.W. Barrow, F. Paul, P.F. Cook, Examination of intrinsic sulfonamide resistance in Bacillus anthracis: a novel assay for dihydropteroate synthase, Biochim. Biophys. Acta 1780 (2008) 848–853.
[28] Danmap, Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark, 2009. Available from: http://www.danmap.org/pdfFiles/Danmap_2009.pdf.
[29] A. Kaufmann, A. Kaenzig, Contamination of honey by the herbicide asulam and its antibacterial active metabolite sulfanilamide, Food Addit. Contam. 21 (2004) 564–571.
[30] Narodowy Program Ochrony Antybiotyków na lata 2006–2010 (National Programme for Protection of Antibiotics), Minister of Health (Poland). Available from: http://www.mz.gov.pl/wwwfiles/ma_struktura/docs/zal_ochr_antybiotyk_26032007.pdf.
[31] DANMAP, Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark, 2004. Available from: http://www.danmap.org/pdfFiles/Danmap_2004.pdf.
[32] M. Seifrtová, L. Nováková, C. Lino, A. Pena, P. Solich, An overview of analytical methodologies for the determination of antibiotics in environmental waters, Anal. Chim. Acta 649 (2009) 158–179.
[33] A.Y.-Ch. Lin, Y.-T. Tsai, Occurrence of pharmaceuticals in Taiwan's surface waters: impact of waste streams from hospitals and pharmaceutical production facilities, Sci. Total Environ. 407 (2009) 3793–3802.
[34] F. Tamtam, F. Mercier, B. Le Bot, J. Eurin, Q. Tuc-Dinh, M. Michel Clément, M. Chevreuil, Occurrence and fate of antibiotics in the Seine River in various hydrological conditions, Sci. Total Environ. 393 (2008) 84–95.
[35] M. Gros, M. Petrović, A. Ginebreda, D. Barceló, Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes, Environ. Int. 36 (2010) 15–26.
[36] M.J. García-Galán, M.S. Díaz-Cruz, D. Damià Barceló, Determination of 19 sulfonamides in environmental water samples by automated on-line solid-phase extraction-liquid chromatography–tandem mass spectrometry (SPE-LC–MS/MS), Talanta 81 (2010) 355–366.
[37] E. Vulliet, C. Cren-Olivé, Screening of pharmaceuticals and hormones at the regional scale, in surface and groundwaters intended to human consumption, Environ. Pollut. 159 (2011) 2929–2934.
[38] D. Perret, A. Gentili, S. Marchese, A. Greco, R. Curini, Sulphonamide residues in Italian surface and drinking waters: a small scale reconnaissance, Chromatographia 63 (2006) 225–232.
[39] K. Stoob, H.P. Singer, Ch.W. Goetz, M. Ruff1, S.R. Mueller, Fully automated online solid phase extraction coupled directly to liquid chromatography–tandem mass spectrometry Quantification of sulfonamide antibiotics, neutral and acidic pesticides at low concentrations in surface waters, J. Chromatogr. A 1097 (2005) 138–147.
[40] Ch. Wu, J.D. Witter, A.L. Spohgberd, K.P. Czajkowski, Occurrence of selected pharmaceuticals in an agricultural landscape, western Lake Erie basin, Water Res. 43 (2009) 3407–3416.
[41] W. Xu, G. Zhang, S. Zou, X. Li, Y. Liu, Determination of selected antibiotics in the Victoria Harbour and the Pearl River, South China using high-performance liquid chromatography–electrospray ionization tandem mass spectrometry, Environ. Pollut. 145 (2007) 672–679.
[42] A. Białk-Bielińska, J. Kumirska, R. Palavinskas, P. Stepnowski, Optimization of multiple reaction monitoring mode for the trace analysis of veterinary sulfonamides by LC–MS/MS, Talanta 80 (2009) 947–953.
[43] M.S. Díaz-Cruz, M.J. García-Galán, D. Barceló, Highly sensitive simultaneous determination of sulfonamide antibiotics and one metabolite in environmental waters by liquid chromatography–quadrupole linear ion trap–mass spectrometry, J. Chromatogr. A 1193 (2008) 50–59.
[44] S. Wang, H.Y. Zhang, L. Wang, Z.J. Duan, I. Kennedy, Food analysis of sulphonamide residues in edible animal products: a review, Addit. Contam. 23 (2006) 362–384.
[45] M.J. García-Galán, T. Garrido, J. Fraile, A.M. Ginebreda, M.S. Díaz-Cruz, D. Barceló, Simultaneous occurrence of nitrates and sulfonamide antibiotics in two ground water bodies of Catalonia (Spain), J. Hydrol. 383 (2010) 93–101.
[46] S. Managaki, A. Murata, H. Takada, B.C. Tuyen, N.H. Chiem, Distribution of macrolides, sulfonamides, and trimethoprim in tropical waters: ubiquitous occurrence of veterinary antibiotics in the Mekong Delta, Environ. Sci. Technol. 41 (2007) 8004–8010.
[47] T.B. Minh, H.W. Leung, I.H. Loi, W.H. Chan, M.K. So, J.Q. Mao, D. Choi, J.C.W. Lam, G. Zheng, M. Martin, J.H.W. Lee, P.K.S. Lam, B.J. Richardson, Antibiotics in the Hong Kong metropolitan area: ubiquitous distribution and fate in Victoria Harbour, Mar. Pollut. Bull. 58 (2009) 1052–1062.
[48] P. Kay, P.A. Blackwell, A.B.A. Boxall, Transport of veterinary antibiotics in overland flow following the application of slurry to arable land, Chemosphere 59 (2005) 951–959.
[49] S. Babić, D. Ašperger, D. Mutavdžić, A.J.M. Horvat, M. Kaštelan-Macan, Solid phase extraction and HPLC determination of veterinary pharmaceuticals in wastewater, Talanta 70 (2006) 732–738.
[50] K.-J. Choi, S.-G. Kim, C.-W. Kim, S.-H. Kim, Determination of antibiotic compounds in water by on-line SPE-LC/MSD, Chemosphere 66 (2007) 977–984.
[51] K. Kümmerer, A. Henninger, Promoting resistance by the emission of antibiotics from hospitals and households into effluent, Clin. Microbiol. Infect. 9 (2003) 1203–1214.
[52] R. Lindberg, P.-A. Jarnheimer, B. Olsen, M. Johansson, M. Tysklind, Determination of antibiotic substances in hospital sewage water using solid phase extraction and liquid chromatography/mass spectrometry and group analogue internal standards, Chemosphere 57 (2004) 1479–1488.
[53] A.L. Batt, I.B. Bruce, D.S. Aga, Evaluating the vulnerability of surface waters to antibiotic contamination from varying wastewater treatment plant discharges, Environ. Pollut. 142 (2006) 295–302.
[54] A. Göbel, A. Thomsen, C.S. McArdell, A.C. Alder, W. Giger, N. Theiß, D. Löffler, T.A. Ternes, Extraction and determination of sulfonamides, macrolides, and trimethoprim in sewage sludge, J. Chromatogr. A 1085 (2005) 179–189.
[55] W. Xu, G. Zhang, X. Li, S. Zou, P. Li, Z. Hu, J. Li, Occurrence and elimination of antibiotics at four sewage treatment plants in the Pearl River Delta (PRD), South China, Water Res. 41 (2007) 4526–4534.
[56] A. Boxall, P. Blackwell, R. Cavallo, P. Kay, J. Tolls, The sorption and transport of sulphonamide antibiotic in soil systems, Toxicol. Lett. 131 (2002) 19–28.
[57] A. Karcı, I.A. Balcıoğlu, Investigation of the tetracycline, sulfonamide, and fluoroquinolone antimicrobial compounds in animal manure and agricultural soils in Turkey, Sci. Total Environ. 407 (2009) 4652–4664.
[58] M. De Liguoro, C. Poltronieri, F. Capolongo, C. Montesissa, Use of sulfadimethoxine in intensive calf farming: evaluation of transfer to stable manure and soil, Chemosphere 68 (2007) 671–676.
[59] C. Winckler, H. Engels, K. Hund-Rinke, T. Luckow, M. Simon, G. Steffens, Verhalten von Tetrazyklinen und anderen Veterinärantibiotika in Wirtschaftsdünger und Boden. Band 44/00, Umweltbundesamt (Hrsg.), Berlin, 2004.
[60] J.V. Holm, K. Ruegge, P.L. Bjerg, T.H. Christensen, Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grindsted, Denmark), Environ. Sci. Technol. 29 (1995) 1415–1420.
[61] Commission Regulation (EU) No. 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin, 2009. Available from: http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf.
[62] Regulation of the Minister of Health of 16 May 2007, Poland (Journal of Laws No. 171, Item 1225).
[63] K. Šinigoj-Gačnik, D.Z. Doganoc, Contamination of farm animals and fishes from slovenia with heavy metals and sulfonamides, Bull. Environ. Contam. Toxicol. 64 (2000) 235–241.
[64] S.Y. Won, Ch.H. Lee, H.S. Chang, S.O. Kim, S.H. Lee, D.S. Kim, Monitoring of 14 sulfonamide antibiotic residues in marine products using HPLC-PDA and LC–MS/MS, Food Control 22 (2011) 1101–1107.
[65] Commission staff working document on the implementation of national residue monitoring plans in the Member States. Report for 2006 on the results of residue monitoring in food of animal origin in the Member States, Brussels 2008. Available from: http://ec.europa.eu/food/food/chemicalsafety/residues/workdoc_2006_en.pdf.
[66] Q. Chu, D. Zhang, J. Wang, J. Ye, Multi-residue analysis of sulfonamides in animal tissues by capillary zone electrophoresis with electrochemical detection, J. Sci. Food Agric. 89 (2009) 2498–2504.
[67] K.-H. Lu, Ch.-Y. Chen, M.-R. Lee, Trace determination of sulfonamides next term residues in meat with a combination of solid-phase microextraction and liquid chromatography–mass spectrometry, Talanta 72 (2007) 1082–1087.
[68] G. Brambilla, C. Civitareale, L. Migliore, Experimental toxicity and analysis of bacitracin, flumequine and sulphadimethoxine in terrestrial and aquatic organisms as a predictive model for ecosystems damage, Quim. Anal. 13 (1994) 114–118.
[69] H. Dolliver, K. Kumar, S. Gupta, Sulfamethazine uptake by plants from manure-amended soil, J. Environ. Qual. 36 (2007) 1224–1230.
[70] L. Migliore, G. Brambilla, P. Casoria, C. Civitareale, S. Cozzolino, L. Gaudio, Effect of sulphadimethoxine contamination on barley (*Hordeum distichum* L., Poaceae, Liliopsida), Agric. Ecosyst. Environ. 60 (1996) 121–128.
[71] L. Migliore, C. Civitareale, G. Brambilla, S. Cozzolino, P. Casoria, L. Gaudio, Effects of sulphadimethoxine on cosmopolitan weeds (*Amaranthus retroflexus* L., *Plantago major* L. and *Rumex acetosella* L.), Agric. Ecosyst. Environ. 65 (1997) 163–168.
[72] Technical guidance document in support of Commission Directive 93/67/EEC on risk assessment for new, Notified substances and commission. Regulation (ec) no. 1488/94 on risk, Assessment for existing substances. Part II, Brussels Luxembourg, 1996.
[73] M. Isidori, M. Lavorgna, A. Nardelli, L. Pascarella, A. Parrella, Toxic and genotoxic evaluation of six antibiotics on non-target organisms, Sci. Total Environ. 346 (2005) 87–98.
[74] Environmentally Classified Pharmaceuticals, Stockholm County Council, 2009. Available from: http://www.janusinfo.se/environment.

[75] S. Park, K. Choi, Hazard assessment of commonly used agricultural antibiotics on aquatic ecosystems, Ecotoxicology 17 (2008) 526–538.
[76] Y. Kim, K. Choi, J. Jung, S. Park, P. Kim, J. Park, Aquatic toxicity of acetaminophen, carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risks in Korea, Environ. Int. 33 (2007) 370–375.
[77] B. Ferrari, R. Mons, B. Vollat, B. Fraysse, N. Paxeus, R. Lo Giudice, A. Pollio, J. Garric, Environmental risk assessment of six human pharmaceuticals: are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? Environ. Toxicol. Chem. 23 (2004) 1344–1354.
[78] A. Kotzerke, S. Sharma, K. Schauss, H. Heuer, S. Thiele-Bruhn, K. Smalla, B.M. Wilke, M. Schloter, Alterations in soil microbial activity and N-transformation processes due to sulfadiazine loads in pig-manure, Environ. Pollut. 153 (2008) 315–322.
[79] S. Thiele-Bruhn, I.-C. Beck, Effects of sulfonamide and tetracycline antibiotics on soil microbial activity and microbial biomass, Chemosphere 59 (2005) 457–465.
[80] M. De Liguoro, B. Fioretto, C. Poltronieri, G. Gallina, The toxicity of sulfamethazine to Daphnia magna and its additivity to other veterinary sulfonamides and trimethoprim, Chemosphere 75 (2009) 1519–1524.
[81] F. Pomati, S. Castiglioni, E. Zuccato, R. Fanelli, D. Vigetti, C. Rossetti, D. Calamari, Effects of a complex mixture of therapeutic drugs at environmental levels on human embryonic cells, Environ. Sci. Technol. 40 (2006) 2442–2447.
[82] US National Institutes of Health; DailyMed, Current Medication Information for Sulfisoxazole, 2008. Available from: http://dailymed.nlm.nih.gov/dailymed/.
[83] TOXNET – Databases on toxicology, hazardous chemicals, environmental health, and toxic releases. Available from: http://toxnet.nlm.nih.gov/.
[84] P.O. Anderson, J.E. Knoben, W.G. Troutman (Eds.), Handbook of Clinical Drug Data, 10th ed., McGraw-Hill, Medical Publishing Division, 2002.
[85] A. Göbel, A. Thomsen, C.S. McArdell, A. Joss, W. Giger, Occurrence and sorption behaviour of sulfonamides, macrolides, and trimethoprim in activated sludge treatment, Environ. Sci. Technol. 39 (2005) 3981–3989.
[86] J. Sipma, B. Osuna, N. Collado, H. Monclús, G. Ferrero, J. Comas, I. Rodriguez-Roda, Comparison of removal of pharmaceuticals in MBR and activated sludge systems, Desalination 250 (2010) 653–659.
[87] Q.-Q. Wang, S.A. Bradford, W. Zheng, S.R. Yates, Sulfadimethoxine degradation kinetics in manure as affected by initial concentration, moisture, and temperature, J. Environ. Qual. 35 (2006) 2162–2169.
[88] P.A. Blackwell, A.B.A. Boxall, P. Kay, H. Noble, Evaluation of a lower tierexposure assessment model for veterinary medicines, J. Agric. Food Chem. 53 (2005) 2192–2201.
[89] O. Gonzalez, C. Sans, S. Esplugas, Sulfamethoxazole abatement by photo-Fenton. Toxicity, inhibition and biodegradability assessment of intermediates, J. Hazard. Mater. 146 (2007) 459–464.
[90] M. Clara, B. Strenn, O. Gans, E. Martinez, N. Kreuzinger, H. Kroiss, Removal of selected pharmaceuticals, fragrances and endocrine disrupting compounds in a membrane bioreactor and conventional wastewater treatment plants, Water Res. 39 (2005) 4797–4807.
[91] B. Halling-Sörensen, S. Nors Nielsen, P.F. Lanzky, F. Ingerslev, H.-C. Holten Lützhoft, S.E. Jorgensen, Occurrence, fate and effects of pharmaceutical substances in the environment – a review, Chemosphere 36 (1998) 357–393.
[92] F. Ingerslev, B. Halling-Sørensen, Biodegradability properties of sulfonamides in activated sludge, Environ. Toxicol. Chem. 19 (2000) 2467–2473.
[93] C. Accinelli, W.C. Koskinen, J.M. Becker, M.J. Sadowsky, Environmental fate of two sulfonamide antimicrobial agents in soil, J. Agric. Food Chem. 55 (2007) 2677–2682.
[94] H.-T. Lai, J.-H. Hou, Light and microbial effects on the transformation of four sulfonamides in eel pond water and sediment, Aquaculture 283 (2008) 50–55.
[95] R. Alexy, T. Kümpel, K. Kümmerer, Assessment of degradation of 18 antibiotics in the Closed Bottle Test, Chemosphere 57 (2004) 505–512.
[96] B.T. Lunestad, O.B. Samuelsen, S. Fjelde, A. Ervik, Photostability of eight antibacterial agents in seawater, Aquaculture 134 (1995) 217–225.
[97] P.K. Jjemba, The potential impact of veterinary and human therapeutic agents in manure and bio solids on plants grown on arable land: a review, Agric. Ecosyst. Environ. 93 (2002) 267–278.
[98] A. Al-Ahmad, F.D. Daschner, K. Kümmerer, Biodegradability of Cefotiam, Ciprofloxacin, Meropenem, Penicillin G, and Sulfamethoxazole and inhibition of wastewater bacteria, Arch. Environ. Contam. Toxicol. 37 (1999) 158–163.
[99] W. Baran, J. Sochacka, W. Wardas, Toxicity and biodegradability of sulfonamides and products of their photocatalytic degradation in aqueous solutions, Chemosphere 65 (2006) 1295–1299.
[100] I. Kim, N. Yamashita, H. Tanaka, Performance of UV and UV/H_2O_2 processes for the removal of pharmaceuticals detected in secondary effluent of a sewage treatment plant in Japan, J. Hazard. Mater. 166 (2009) 1134–1140.
[101] V.K. Sharma, Oxidative transformations of environmental pharmaceuticals by Cl_2, ClO_2, O_3, and Fe(VI): kinetics assessment, Chemosphere 73 (2008) 1379–1386.
[102] E. Chamberlain, C. Adams, Oxidation of sulfonamides, macrolides, and carbadox with free chlorine and monochloramine, Water Res. 40 (2006) 2517–2526.
[103] R.F. Dantas, S. Contreras, C. Sans, S. Esplugas, Sulfamethoxazole abatement by means of ozonation, J. Hazard. Mater. 150 (2008) 790–794.
[104] A.Y.-Ch. Lin, Ch.-F. Lin, J.-M. Chiou, P.K.A. Hong, O_3 and O_3/H_2O_2 treatment of sulfonamide and macrolide antibiotics in wastewater, J. Hazard. Mater. 171 (2009) 452–458.
[105] W. Ben, Z. Qiang, X. Pan, M. Chen, Removal of veterinary antibiotics from sequencing batch reactor (SBR) pretreated swine wastewater by Fenton's reagent, Water Res. 43 (2009) 4392–4402.
[106] M.N. Abellan, B. Bayarri, J. Gimenez, J. Costa, Photocatalytic degradation of sulfamethoxazole in aqueous suspension of TiO_2, Appl. Catal. B: Environ. 74 (2007) 233–241.
[107] W. Baran, E. Adamek, A. Sobczak, J. Sochacka, The comparison of photocatalytic activity of Fe-salts, TiO_2 and TiO_2/$FeCl_3$ during the sulfanilamide degradation process, Catal. Commun. 10 (2009) 811–814.
[108] J. Ziemiańska, E. Adamek, A. Sobczak, I. Lipska, A. Makowski, W. Baran, The study of photocatalytic degradation of sulfonamides applied to municipal wastewater, Physicochem. Probl. Miner. Process. 45 (2010) 127–140.
[109] F.I. Turkdogan, K. Yetilmezsoy, Appraisal of potential environmental risks associated with human antibiotic consumption in Turkey, J. Hazard. Mater. 166 (2009) 297–308.
[110] A.J. Watkinson, E.J. Murby, S.D. Costanzo, Removal of antibiotics in conventional and advanced wastewater treatment: implications for environmental discharge and wastewater recycling, Water Res. 41 (2007) 4164–4176.
[111] T. Heberer, G. Massmann, B. Fanck, T. Taute, U. Dünnbier, Behaviour and redox sensitivity of antimicrobial residues during bank filtration, Chemosphere 73 (2008) 451–460.
[112] S. Suarez, J.M. Lema, F. Omil, Pre-treatment of hospital wastewater by coagulation–flocculation and flotation, Bioresour. Technol. 100 (2009) 2138–2146.
[113] K.-J. Choi, H.-J. Son, S.-H. Kim, Ionic treatment for removal of sulfonamide and tetracycline classes of antibiotic, Sci. Total Environ. 387 (2007) 247–256.
[114] W. Weifen, L. Hong, X. Changhu, K. Jamil, Elimination of chloramphenicol, sulphamethoxazole and oxytetracycline in shrimp, Penaeus chinensis following medicated-feed treatment, Environ. Int. 30 (2004) 367–373.
[115] R. Andreozzi, M. Raffaele, P. Nicklas, Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment, Chemosphere 50 (2003) 1319–1330.
[116] M. Klavarioti, D. Mantzavinos, D. Kassinos, Removal of residual pharmaceuticals from aqueous systems by advanced oxidation processes, Environ. Int. 35 (2009) 402–417.
[117] F.J. Beltran, A. Aguinaco, J.F. Garcia-Araya, A. Oropesa, Ozone and photocatalytic processes to remove the antibiotic sulfamethoxazole from water, Water Res. 42 (2008) 3799–3808.
[118] M.C. Dodd, Ch. Huang, Transformation of the Antibacterial Agent sulfamethoxazole in reactions with chlorine: kinetics, mechanism, and pathways, Environ. Sci. Technol. 38 (2004) 5607–5615.
[119] W. Baran, E. Adamek, J. Sochacka, A. Sobczak, A. Makowski, Forecast of accumulation of pollutants resistant to biodegradation in leachates from landfill, Proc. ECOpole 3 (2009) 121–125.
[120] K.M. Onesios, J.T. Yu, E.J. Bouwer, Biodegradation and removal of pharmaceuticals and personal care products in treatment systems: a review, Biodegradation 20 (2009) 441–466.
[121] X. Peng, Z. Wang, W. Kuang, J. Tan, K. Li, A preliminary study on the occurrence and behavior of sulfonamides, ofloxacin and chloramphenicol antimicrobials in wastewaters of two sewage treatment plants in Guangzhou, China, Sci. Total Environ. 371 (2006) 314–322.
[122] K.G. Karthikeyan, M.T. Meyer, Occurrence of antibiotics in wastewater treatment facilities in Wisconsin, USA, Sci. Total Environ. 361 (2006) 196–207.
[123] S. Yang, K. Carlson, Evolution of antibiotic occurrence in a river through pristine. Urban and agricultural landscapes, Water Res. 37 (2003) 4645–4656.
[124] A.Y.-Ch. Lin, T. Yu, S.K. Lateef, Removal of pharmaceuticals in secondary wastewater treatment processes in Taiwan, J. Hazard. Mater. 167 (2009) 1163–1169.
[125] T. Yu, A.Y.-Ch. Lin, S.K. Lateef, Ch.-F. Lin, P. Yang, Removal of antibiotics and non-steroidal anti-inflammatory drugs by extended sludge age biological process, Chemosphere 77 (2009) 175–181.
[126] J. Radjenovič, M. Petrovič, D. Barcelò, Fate and distribution of pharmaceuticals in wastewater and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor (MBR) treatment, Water Res. 43 (2009) 831–841.
[127] G.C. Ghosh, T. Okuda, N. Yamashita, H. Tanaka, Occurrence and eliminationof antibiotics at four sewage treatment plants in Japan and their effects on bacterial ammonia oxidation, Water Sci. Technol. 59 (2009) 779–786.
[128] A.L. Batt, S. Kim, D.S. Aga, Comparison of the occurrence of antibiotics in four full-scale wastewater treatment plants with varying designs and operations, Chemosphere 68 (2007) 428–435.
[129] S. Terzić, I. Senta, M. Ahel, M. Gros, M. Petrović, D. Barcelo, J. Müller, T. Knepper, I. Martí, F. Ventura, P. Jovančić, D. Jabučar, Occurrence and fate of emerging wastewater contaminants in Western Balkan Region, Sci. Total Environ. 399 (2008) 66–77.
[130] T.A. Ternes, M. Bonerz, N. Herrmann, B. Teiser, H.R. Andersen, Irrigation of treated wastewater in Braunschweig. Germany: an option to remove pharmaceuticals and musk fragrances, Chemosphere 66 (2007) 894–904.
[131] B. Shao, D. Chena, J. Zhang, Y. Wu, Ch. Sun, Determination of 76 pharmaceutical drugs by liquid chromatography–tandem mass spectrometry in slaughterhouse wastewater, J. Chromatogr. 1216 (2009) 8312–8318.
[132] A.L. Spongberg, J.D. Witter, Pharmaceutical compounds in the wastewater process stream in Northwest Ohio, Sci. Total Environ. 397 (2008) 148–157.

[133] N. Nakada, H. Shinohara, A. Murata, K. Kiri, S. Managaki, N. Sato, H. Takada, Removal of selected pharmaceuticals and personal care products (PPCPs) and endocrine-disrupting chemicals (EDCs) during sand filtration and ozonation at a municipal sewage treatment plant, Water Res. (2007) 4373–4382.
[134] A. Joss, E. Keller, A.C. Alder, A. Göbel, Ch.S. McArdell, T. Ternes, H. Siegrist, Removal of pharmaceuticals and fragrances in biological wastewater treatment, Water Res. 39 (2005) 3139–3152.
[135] A. Joss, S. Zabczynski, A. Göbel, B. Hoffmann, D. Löffler, Ch.S. McArdell, T.A. Ternes, A. Thomsen, H. Siegrist, Biological degradation of pharmaceuticals in municipal wastewater treatment: proposing a classification scheme, Water Res. 40 (2006) 1686–1696.
[136] M.J. Benotti, B.J. Brownawell, Distributions of pharmaceuticals in an urban estuary during both dry- and wet-weather conditions, Environ. Sci. Technol. 41 (2007) 5795–5802.
[137] K.D. Brown, Pharmaceutically active compounds in residential and hospitaleffluent, municipal wastewater and the Rio Grande in Albuquerque. New México – a review, Water Resources Program, The University of New Mexico, Albuquerque, 2004. Available from: http://www.unm.edu/~wrp/wrp-9.pdf.
[138] A. Göbel, Ch.S. McArdell, A. Joss, H. Siegrist, W. Giger, Fate of sulfonamides. macrolides and trimethoprim in different wastewater treatment technologies, Sci. Total Environ. 372 (2007) 361–371.
[139] B. Li, T. Zhanga, Z. Xu, H.H.P. Fang, Rapid analysis of 21 antibiotics of multiple classes in municipal wastewater using ultra performance liquid chromatography–tandem mass spectrometry, Anal. Chim. Acta 645 (2009) 64–72.
[140] J.-Y. Pailler, A. Krein, L. Pfister, L. Hoffmann, C. Guignard, Solid phase extraction coupled to liquid chromatography-tandem mass spectrometry analysis of sulfonamides, tetracyclines, analgesics and hormones in surface water and wastewater in Luxembourg, Sci. Total Environ. 407 (2009) 4736–4743.
[141] S.M. Lopes de Souza, E. Carvalho de Vasconcelos, M. Dziedzic, C.M. Ribas de Oliveira, Environmental risk assessment of antibiotics: an intensive care unit analysis, Chemosphere 77 (2009) 962–967.
[142] M.T. Blahna, C.A. Zalewski, J. Reuer, G. Kahlmeter, B. Foxman, C.F. Marrs, The role of horizontal gene transfer in the spread of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* in Europe and Canada, J. Antimicrob. Chemother. 57 (2006) 666–672.
[143] L. Pallecchi, C. Lucchetti, A. Bartoloni, F. Bartalesi, A. Mantella, H. Gamboa, A. Carattoli, F. Paradisi, G.M. Rossolini, Population structure and resistance genes in antibiotic-resistant bacteria from a remote community with minimal antibiotic exposure, Antimicrob. Agents Chemother. 51 (2007) 1179–1184.
[144] K.G. Byrne-Bailey, W.H. Gaze, P. Kay, A.B.A. Boxall, P.M. Hawkey, E.M.H. Wellington, Prevalence of sulfonamide resistance genes in bacterial isolates from manured agricultural soils and pig slurry in the United Kingdom, Antimicrob. Agents Chemother. 53 (2009) 696–702.
[145] D.C. Bean, D.M. Livermore, I. Papa, L.M.C. Hall, Resistance among *Escherichia coli* to sulphonamides and other antimicrobials now little used in man, J. Antimicrob. Chemother. 56 (2005) 962–964.
[146] P. Boerlin, R. Travis, C.L. Gyles, R. Reid-Smith, Antimicrobial resistance and virulence gene of *Escherichia coli* isolates from swine in Ontario, Appl. Environ. Microbiol. 71 (2005) 6753–6761.
[147] G. Swedberg, C. Fermér, O. Sköld, Point mutations in the dihydropteroate synthase gene causing sulfonamide resistance, Adv. Exp. Med. Biol. 338 (1993) 555–558.
[148] C.A. Liebert, R.M. Hall, A.O. Summers, Transposon Tn21, flagship of the floating genome, Microbiol. Mol. Biol. Rev. 63 (1999) 507–522.
[149] A. Carattoli, Importance of integrons in the diffusion of resistance, Vet. Res. 32 (2001) 243–259.
[150] V.I. Enne, P.M. Bennett, D.M. Livermore, L.M.C. Hall, Enhancement of host fitness by the sul2-coding plasmid p9123 in the absence of selective pressure, J. Antimicrob. Chemother. 53 (2004) 958–963.
[151] P. Radstrom, G. Swedberg, RSF1010 and a conjugative plasmid contain sulII, one of two known genes for plasmid-borne sulfonamide resistance dihydropteroate synthase, Antimicrob. Agents Chemother. 32 (1988) 1684–1692.
[152] F. Anthony, J. Acar, A. Franklin, R. Gubata, T. Nicholss, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren, D.G. White, Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine, Rev. Sci. Tech. Off. Int. Epiz. 20 (2001) 829–839.
[153] R. Lanz, P. Kuhnert, P. Boerlin, Antimicrobial resistance and resistance gene determinants in clinical *Escherichia coli* from different animal species in Switzerland, Vet. Microbiol. 91 (2003) 73–84.
[154] G.K. Kozak, P. Boerlin, N. Janecko, R.J. Reid-Smith, C. Jardine, Antimicrobial resistance in *Escherichia coli* isolates from swine and wild small mammals in the proximity of swine farms and in natural environments in Ontario, Canada, Appl. Environ. Microbiol. 75 (2009) 559–566.
[155] M. Trobos, L. Jakobsen, K. Pedersen, K.E.P. Olsen, N. Frimodt-Møller, A.M. Hammerum, Y. Agersø, L.J. Porsbo, J.E. Olsen, Prevalence of sulphonamide resistance and class 1 integron genes in *Escherichia coli* isolates obtained from broilers, broiler meat, healthy humans and urinary infections in Denmark, Letters to the Editor, Int. J. Antimicrob. Agents 32 (2008) 363–371.
[156] A. Miko, K. Pries, A. Schroeter, R. Helmuth, Molecular mechanisms of resistance in multidrug-resistant serovars of Salmonella enterica isolated from foods in Germany, J. Antimicrob. Chemother. 56 (2005) 1025–1033.
[157] P.T.P. Hoa, L. Nonaka, P.H. Viet, S. Suzuki, Detection of the sul1, sul2, and sul3 genes in sulfonamide-resistant bacteria from wastewater and shrimp ponds of north Vietnam, Sci. Total Environ. 405 (2008) 377–384.
[158] Y. Agerso, A. Petersen, The tetracycline resistance determinant Tet 39 and the sulphonamide resistance gene sulII are common among resistant Acinetobacter spp. isolated from integrated fish farms in Thailand, J. Antimicrob. Chemother. 59 (2007) 23–27.
[159] G. Peirano, Y. Agerso, F.M. Aarestrup, D. dos Prazeres Rodrigues, Occurrence of integrons and resistance genes among sulphonamide-resistant Shigella spp. from Brazil, J. Antimicrob. Chemother. 55 (2005) 301–305.
[160] V.I. Enne, D.M. Livermore, P. Stephens, L.M. Hall, Persistence of sulphonamide resistance in *Escherichia coli* in the UK despite national prescribing restriction, Lancet 357 (2001) 1325–1328.
[161] K.A. DeFrancesco, R.N. Cobbold, D.H. Rice, T.E. Besser, D.D. Hancock, Antimicrobial resistance of commensal *Escherichia coli* from dairy cattle associated with recent multi-resistant salmonellosis outbreaks, Vet. Microbiol. 98 (2004) 55–61.