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# ASSESSMENT OF SULFONAMIDES OCCURRENCE IN THE BIOSPHERE

## OCENA WYSTĘPOWANIA LEKÓW SULFONAMIDOWYCH W BIOSFERZE

**Abstract:** Sulfonamides, derivatives of $p$-aminobenzenesulfonic acid, have been used in the treatment of patients with bacterial diseases since 1940s. According to the Anatomical Therapeutic Chemical Classification (ATC) they are included in a group of antibacterial agents, intended mainly for internal use, commonly known as antibiotics. Sulfonamides are also used as herbicides and feed additives in agriculture. It is estimated that their annual world consumption in veterinary medicine only can be up to 15 thousand Mg (tons).

At present, sulfonamides are detected in almost 100 % of environmental samples which are checked from the point of view of antibiotics contents. Typically, the determined concentrations of sulfonamides are lower than $\mu g \cdot dm^{-3}$ but in liquid manure they were even detected at the 100 $mg \cdot kg^{-1}$ level. An environmental risk caused by sulfonamides, estimated based on their ecotoxicity, is not great. However, there are evidences that they take part in generating drug resistance of microorganisms. Newly arisen drugresistance genes can be transferred between different strains of bacteria, $eg$ by conjugation. As a result, these genes may occur in pathogenic bacteria present in the ecosystems that have not previously been exposed to antibiotics.

The aim of this paper was to present the problems connected with the occurrence of sulfonamides in different ecosystems. Based on the available literature from 2004 to 2010 the characterization of the potential resistance of sulfonamides in the environment and their ecotoxicity was carried out. Moreover, the problems of drugresistance to sulfonamides and the risk assessment with allowing their antimicrobial activity were presented.

**Keywords:** sulfonamides, ecotoxicity, drugresistance

## Introduction

The global increase in human prosperity and a general fear of a pandemic have caused that the world consumption of drugs has increased systematically. Unfortunately,

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Poland is one of the leaders in this field. After use, large amounts of drugs are discharged into the environment with human and animal excretions as well as unused waste [1]. A persistence of pharmaceuticals in the environment, the rate of their spreading and their ability to accumulate in the biosphere are different. However, their high biological activity indicates that drugs, even in trace amounts, can cause significant changes in the biosphere. An example of such changes can be widely described in the last decade of the 20th century the phenomenon of feminization of fish caused by anthropogenic pollution of European rivers by sex hormones or increasing frequency of zoonotic infection (*ie* human diseases acquired from vertebrate animals) [2]. For these reasons, pharmaceuticals are currently classified as particularly dangerous pollutants for the environment. In result, researches and multinational projects (*eg* REMPHARMA-WATER, Poseidon, Knapp, ERAPHARM) are carried out to find answer to the following questions:

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

Antivirotics (antibiotics) are a group of pharmaceuticals, whose effect on the environment can be particularly harmful from human health viewpoint. In almost 100 % of environmental samples tested for the content of antibiotics traces of tetracyclines and sulfonamides were detectable [1–16]. The aim of the present study was to discuss problems and issues related to the occurrence of sulfonamides in the environment. The potential risk assessment on the environment and effect of sulfonamides on human health were considered as particularly important. It was used also the data of the ecotoxicity of sulfonamides and information relating to drug resistance.

## Structure and physicochemical properties of sulfonamides

Since the early 1940s, over 150 substances, sulfanilamide derivatives have applied in human and veterinary medicine (Fig. 1). They have a free amino group ($-N^4H_2$) at one end and a substituted, amide nitrogen atom ($N^1$) at second end.
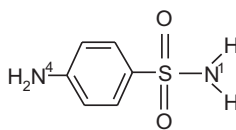


Fig. 1. Sulfanilamide

Common names of selected sulfonamides, sulfanilamide derivatives and their chemical structure are presented in Table 1.
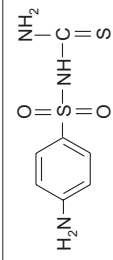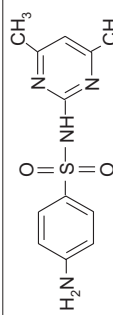
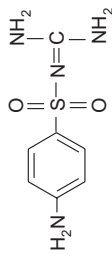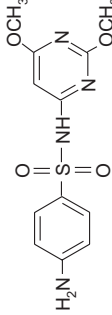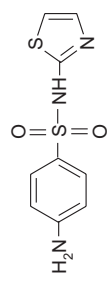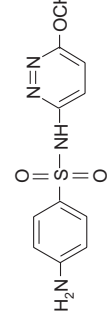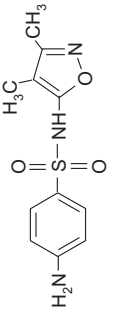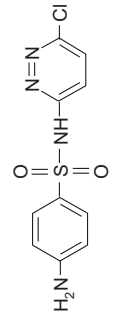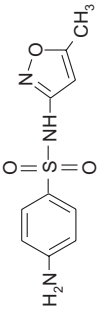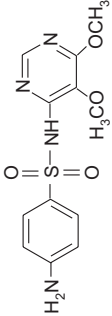Sulfonamides are amphoteric and polar molecules (Fig. 2). Their amino nitrogen ($N^4$) is protonated at pH 2–3 while the amide nitrogen ($N^1$) is deprotonated at pH 4.5–11 [7, 17].

Sulfonamides presented in text (except sulfaguanidine and sulfasalazine) are small molecules (molar mass 177–300 g · mol$^{-1}$), soluble in water (7.5–1500 mg · dm$^{-3}$), and

Table 1

Common (non-systematic) names and structure of selected sulfonamides

| Name of sulfonamide/ CAS number | Abbreviation | Chemical structure | Name of sulfonamide/ CAS number | Abbreviation | Chemical structure |
|---|---|---|---|---|---|
| Sulfanilamide 63-74-1 | SAD |  | Sulfamoxole 729-99-7 | SMM |  |
| Sulfacetamide 144-80-9 | SCT |  | Sulfapyridine 144-83-2 | SPY |  |
| Sulfacarbamide 547-44-4 | SC |  | Sulfadiazine 68-35-9 | SDZ |  |
| Asulam 3337-71-1 | |  | Sulfamethoxine 651-06-9 | SMO |  |
| Carbutamide 339-43-5 | |  | Sulfamerazine 127-79-7 | SMR |  |

Table 1 contd.

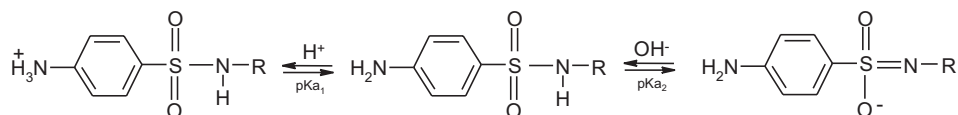| Name of sulfonamide/ CAS number | Abbreviation | Chemical structure | Name of sulfonamide/ CAS number | Abbreviation | Chemical structure |
|---|---|---|---|---|---|
| Sulfathiourea 515-49-1 | STU | (chemical structure) | Sulfadimidine/ Sulfamethazine 57-68-1 | SDM | (chemical structure) |
| Sulfaguanidine 57-67-0 | SGM | (chemical structure) | Sulfadimethoxine 122-11-2 | SDT | (chemical structure) |
| Sulfatiazole 72-14-0 | STZ | (chemical structure) | Sulfamethoxy-pyridazine 80-35-3 | SMP | (chemical structure) |
| Sulfafurazole 127-69-5 | | (chemical structure) | Sulfachloro-pyridazine 80-32-0 | SCP | (chemical structure) |
| Sulfamethoxazole 723-46-6 | SMX | (chemical structure) | Sulfadoxine 2447-57-6 | SDX | (chemical structure) |

Fig. 2. Acid-base dissociation constants of sulfonamide

with low value of Henry's constant ($1.3 \cdot 10^{-12}$–$1.8 \cdot 10^{-8}$) [6, 7, 18]. They are only slightly sorbed by soil (soil partition coefficient values are 0.6–7.4 $dm^3 \cdot kg^{-1}$ [6]). This is the reason that sulfonamides are easily and quickly spread in the environment but it should limit their accumulation in defined biotopes. Sulfonamides practically do not adsorb onto activated carbon [1, 3]. They are classified as photo- and thermally stable substance ($DT_{50} > 1$ year) [18]. They can undergo alkaline hydrolysis, coupling reaction with phenols and amines and can react easily with the hydroxyl radicals $HO^{\bullet}$ (k = = 5.8–7.1 $\cdot 10^9$ $mol^{-1} \cdot s^{-1}$) [7, 8, 19, 20]. Possible ways of decomposition of sulfonamides were described in detail by Garcia-Galan et al [8].

## Antibacterial activity of sulfonamides

The discussed sulfonamides are a group of synthetic bacteriostatic drugs classified by the WHO to the group of antibacterial drugs for systemic use (the subgroup J01E) [21]. They cause inhibition of proliferation of microorganisms (bacteria) that produce folic acid. The mechanism of this process is based on competitive antagonism of sulfonamide with *p-aminobenzoic acid* (PABA). During the biosynthesis of folic acid, PABA bonds with dihydropteridine, and then with glutamic acid. Sulfonamides, due to their similarity in structure, can replace PABA and to block the biosynthesis of PABA and folic acid in bacterial cells. In result, it is possible the inhibition of nucleic acids synthesis and, in consequence, proteins [16, 22]. Sulfonamides inhibit also the permeability of bacterial cell wall for glutamic acid which is also essential component in the folic acid synthesis. However, they do not inhibit the growth of microorganisms that:
  – need the presence of folic acid in the environment,
  – possess a high concentration of PABA or
  – have modified metabolic pathways (drug resistant).
Biotransformation of sulfonamides is mainly based on their acetylation or glucuronidation [7, 8]. The metabolites of sulfonamides do not possess their biological activity. However, it can be easily restored *in vitro* conditions [23].

## Biodegradability of sulfonamides

The opinions of researchers on the biodegradability of sulfonamides are divided [1, 3, 7, 15, 18]. The cause of this may be, for example, differences in microbial activity of matrix, stability of various sulfonamides, inoculum used, and applied methods to assess their degradation [1].

The results of standardized tests such as the ISO 11734:1995 and OECD 301D and the assessment of soil microbial activity suggests that most of the sulfonamides do not

undergo natural biodegradation [18, 24, 25]. Probably the best described sulfonamide in the literature namely sulfamethoxazole was practically regarded as a non-biodegradable compound in the eight of the twenty three articles describing its resistance to biodegradation: 3 in pure water, 1 in seawater, 2 in natural water and 3 in wastewater or active sludge). According to Weifen et al, in the presence of shrimp (*Penaeus chinensis*) the $DT_{50}$ value for sulfametoxazole was 5.68 h [26] and Ingerslev and Halling-Sorensen have determined that the presence of microorganisms in activated sludge the $DT_{50}$ for sulfonamides can be only 0.3 day [27]. It is not excluded that in these cases most of the sulfonamides may be incorporated in microorganisms and /or undergo only slight reversible transformations such as acetylation [8, 23]. It was also describes the rapid disappearance of sulfonamides in soil and manure however, it may be an effect of binding between sulfonamides and organic or mineral particles [23, 28, 29] or be caused by photochemical processes [30, 31].

Reassuming, most researchers recognize sulfonamides as poorly or non-biodegradable compounds values in the range from a few to tens of days) [32]. Sulfamethoxazole, sulfadiazine and sulfachloropyridazine are considered as more resistant to biodegradation while sulfathiazole or sulfamethazine are less resistant. Moreover, sulfonamides may also bioaccumulation [1, 6].

## Ecotoxicity of sulfonamides

Toxicity of sulfonamides to higher organisms is not high. According to the EU directive 93/67/EEC sulfonamides under investigation can be classified as non-toxic or harmful [33]. However, according to "Environmentally Classified Pharmaceuticals 2009" they are highly toxic drugs [32].

Sulfonamides are practically non-toxic to most microorganisms tested [3, 16, 34], including selected strains of bacteria such as *Vibrio fischeri*, *Enterococcus feacalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, or *Staphylococcus aureus*. For example, the $L(E)C_{50}$ values determined using the Microtox ® test (*Vibrio fischeri*) ranged from 16.9–78.1 mg · dm$^{-3}$ (for sulfamethoxazole) to > 1000 mg · dm$^{-3}$ (for sulfathiazole) [34, 35]. A highly toxic effect of sulfomethoxazole on *Vibrio fischeri* ($EC_{50}$ = 0.083 mg · dm$^{-3}$) has been described by Ferrari et al [36].

Strong bacteriostatic properties cause that sulfonamides can significantly change the functioning of non-selected organisms living in the environment [36]. Thiele-Bruhn and Beck have showed that the pouring out of urine, containing even a very low concentration of sulfapirydine (0.0071–0.056 mg · kg$^{-1}$), into the soil results in a significant reduction in microbial activity [37]. It was found that in the case of sulfapirydine the EC10 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) [38].

However, the most sensitive to the presence of sulfonamides were bioindicators containing chlorophyll [6, 16, 34]. In the case of sulfamethoxazole, the NOEC values for algae (*Pseudokirchneriella subcapitata* and *Synechococcus leopolensis*) and gibbous duckweed (*Lemna gibba*) were 0.09 [36, 39], < 0.0005–0.103 [36, 40] and 0.01

mg · dm$^{-3}$ [3], respectively. It means that even very low concentrations of sulfonamides may significantly affect the growth and development of plants. Results described in the literature indicate that sulfonamides do not exhibit mutagenic or carcinogenic (terato-genic) activity [34].

It is not excluded that sulfonamides may accumulate in the various organisms in the food chain, and then it may lead to a local increase in toxic effects induced by these drugs [6, 7]. In addition, toxic effects of sulfonamides and other drugs can exhibit a synergism [39, 40]. Particularly large data on the sulfonamides ecotoxicity are summarized in articles by Garcia-Galan et al [16] and Isidori et al [34].

## Estimated usage of sulfonamides

The accurately assessment of the global consumption of all drugs is difficult or even impossible. The authors of the Knappe project (*Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters*) estimate that global consumption of pharmaceuticals used in human and veterinary medicine rises and reaches 100,000 Mg (tons) per year. In turn, based on the Union of Concerned Scientists information, Sarmach et al have indicated that at the beginning of the 21$^{st}$ century Americans consumed 16000 Mg of antibiotics per year. Sulfonamides used in veterinary medicine accounted for approximately 2.3 % of the total amount of antibiotics. In European countries, this value ranged from 11 to 23 % [6]. According to other authors, the all world consumption of antibiotics belonging to group J01 alone (antibacterial for systemic use) was ranged from 100000 to 200000 Mg per year, including from 50 to 75 % were used in veterinary medicine and animal husbandry [1, 18]. Reassuming, it is possible that each year even more than 20000 Mg of sulfonamides having bacteriostatic properties is introduced into the biosphere (without drugs introduced as herbicides).

Since the end of 20$^{th}$ century, Scandinavia and other countries in Europe and North America have imposed restrictions on the use of antibiotics (including sulfonamides) in animal husbandry. Among other, the use of antibiotics as growth promoters in animal husbandry in the European Union [41] has banned since January 1, 2006. However, reports on the consumption of pharmaceuticals in different countries do not showed the reduction in their use. For example, in Denmark in the years from 1990 to 2004, the consumption of antibiotics in veterinary medicine has increased from 53.4 to 112.5 Mg [42].

## Removal of sulfonamides from wastewater

A part of sulfonamides used in veterinary medicine reaches (in manure) directly into the soil. However, the great majority of these compounds enter wastewater. Opinions on the effectiveness of sulfonamide removal in conventional biological-mechanical treatment plants are divergent. Similar differences occur during the assessment biodegradability of drugs [1, 3, 14, 15, 18, 23, 27, 30, 43]. Based on the analysis of recent publications on this subject it shows that most of the sewage treatment plants using activated sludge remove 25 to 90 % of sulfonamides from wastewater. For example, according to the data published in the 2010, sulfamethoxazole was removed from the selected *sewage*

*treatment plants* (STPs) in Spain in the range 30–92 % [43]. However, there were also described cases in which the concentration of sulfonamides in effluent was higher than in influent [3, 44, 45]. For example, in a pilot STP in Austria the efficiency of removal of sulfamethoxazole ranged from – 280 to 61 % [44].

It is also important that a large part of sulfonamides may be adsorbed in STPs by the biomass [46]. Obviously, the high degradation efficiency of sulfonamides in wastewater was obtained using the various *advanced oxidation processes* (AOP) [1, 3, 47–51] such as the use of $O_3$, $Cl_2$, $ClO_2$ [1, 47–49, 52], Fenton reaction [47, 50] or photocatalytic processes [23, 47, 49, 50]. Unfortunately, the application of these methods is costly and can also be harmful to the environment due to the formation of highly toxic intermediates [52]. Sulfonamides can be removed from wastewater by nanofiltration and reverse osmosis with nearly 100 % efficiency but in these cases then there may be a problem with wastewater containing concentrated solutions of toxins (including sulfonamides) [1, 3, 18, 53, 54].

A conclusion of this problem may be the data from the article by Turkdogan and Yetilmezsoy [53]. The authors have estimated that 80 % of used antibiotics enter the environment despite the use of various processes in STPs (based on the data from Turkey, without regard to sulfonamides).

## Occurrence of sulfonamides in the environment

The first information containing quantitative data about the presence of sulfonamides in river water was published in 1982 [6]. However, systematic studies on the quantitative determinations of sulfonamides in environmental matrices became possible after the development of the highly sensitive analytical methods. According to *American Environmental Protection Agency* (EPA) data, the limit of detection during the routine analytical procedures using SPE/HPLC-MS/MS technique for the selected sulfonamides is below the $10^{-9}$ g · dm$^{-3}$ (*eg* for sulfadimethoxine, the limit of detection is $1 \cdot 10^{-10}$ g · dm$^{-3}$). A detailed statement of analytical techniques and limits of detection of drugs (including sulfonamides) in environmental samples has been discussed by Garcia-Galan et al [16] and Seifrtova et al [55]. At such a level of detection, sulfonamides are detected practically in all of the surface water [56, 57] and wastewater samples [10, 43, 58]. Sulfonamides concentrations in the environment undergo significant fluctuations which are mainly dependent on the type of matrix and the type of sulfonamide. Sulfamethoxazole is a sulfonamide mostly detected in the environment (40–50 % of described results). Garcia-Galan et al [58] have described, in detail, the frequency of occurrence of 19 selected sulfonamides in wastewater. According to Bialk-Bielinska et al [59], the literature data concerning the determination of sulfonamides in environmental samples may contain significant errors. For example, the recovery of sulfonamides from soil samples may be in the range from about 5 to nearly 294 %. Additionally, the results obtained may depend on the sampling site, day of the week [60] and even on the time of day [61]. A summary of the occurrence of sulfonamides depending on the matrix is given in Table 2. The presented data are based on some the selected review articles [1, 12, 15] and values described in the literature.

Table 2

Some data on the occurrence of sulfonamides in the environment

| Matrix | Mean¹/ the most of ten described sulfonamides (Based on our literature studied) | $n^2$ | Mean¹ [1] | $n^2$ | Mean [12] | $n^2$ | Mean [15] | $n^2$ | Maximal values | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Drinking waters | 2.1 (0–8.5) µg·dm⁻³ (Sulfamethoxazole) | 4 | | | | | | | 8.5 µg·dm⁻³ (PEC for Sulfamethoxazole) | [5] |
| Bottled mineral water | 0.164 ng·dm⁻³ (Sulfadimethoxine) | 1 | — | | 0.4 ng·dm⁻³ | 5 | — | | 1.1 ng·dm⁻³ (N₄-acetylsulfamethazine) | [62] |
| Ground water | 0.80 (0.0099–1.11) µg·dm⁻³ (Sulfamethoxazole) | 11 | 0.167 (0.017–0.47) µg·dm⁻³ | 12 | | | 0.183 µg·dm⁻³ | 6 | 3.461 µg·dm⁻³ (Sulfacetamide) | [63] |
| Ground water | 0.053 (0.0002–0.09148) µg·dm⁻³ (Sulfadimethoxine) | 3 | | | | | | | < 1.11 µg·dm⁻³ (Sulfamethoxazole) | [11] |
| Surface water | 0.87 (0.015–18) µg·dm⁻³ (Sulfamethoxazole) | 38 | 0.156 (0.004–1) µg·dm⁻³ | 51 | 66.53³ (max 1600) µg·dm⁻³ | 60 | 0.339 µg·dm⁻³ | 9 | 19.2 µg·dm⁻³ (Sulfamethazine) | [64] |
| Surface water | 2.26 (0.0108–19.2) µg·dm⁻³ (Sulfamethazine) | 12 | | | | | | | > 25 µg·dm⁻³ (all sulfonamide) | [62] |
| Sea water | 0.0475 µg·dm⁻³ (Sulfamethoxazole) | 1 | — | — | — | — | — | — | 0.0475 µg·dm⁻³ (Sulfamethoxazole) | [65] |
| Drainflow/ leachte | 379.78 (0.66–703.2) µg·dm⁻³ (Sulfachloropyridazine) | 2 | — | — | — | — | — | — | 703.2 µg·dm⁻³ (Sulfachloropyridazine) | [66] |
| Influent/ wastewater | 46.58 (0.05–1340) µg·dm⁻³ (Sulfamethoxazole) | 31 | 1.485 (0.02–9) µg·dm⁻³ | 15 | 11.972 (max 1158.68) µg·dm⁻³ | 57 | — | — | 1340 µg·dm⁻³ (Sulfamethoxazole; from pharmaceutical production) | [56] |
| Influent/ wastewater | 61.11 (0.0269–500) µg·dm⁻³ (Sulfamethazine) | 17 | | | | | | | 1158.68 µg·dm⁻³ (Sulfathiazole; agricultural wastewater) | [67] |

Table 2 contd.

| Matrix | Mean¹/ the most of ten described sulfonamides (Based on our literature studied) [1] | $n^2$ | Mean¹ [1] | $n^2$ | Mean [12] | $n^2$ | Mean [15] | $n^2$ | Maximal values | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Hospitals wastewater | 17.78 (0.3–79.9) µg · dm⁻³ (Sulfamethoxazole) | 6 | | | | | | | 12.8 µg · dm⁻³ (Sulfamethoxazole) | [68] |
| | 1.28 (0.353–2.2) µg · dm⁻³ (Sulfadiazine) | 2 | | | | | | — | PEC 92.8 µg · dm⁻³ (all sulfonamides) | [69] |
| Effluent | 0.517 (0.00366–6) µg · dm⁻³ (Sulfamethoxazole) | 30 | | | | | 1.123 µg · dm⁻³ | | 6.0 µg · dm⁻³ (Sulfamethoxazole) | [70] |
| | 1.26 (0.005–4.27) µg · dm⁻³ (Sulfathiazole) | 4 | 1.189 (0.0632–4.7) µg · dm⁻³ | 21 | | | | 3 | 4.27 µg · dm⁻³ (Sulfathiazole; effluent of agricultural STP) | [67] |
| Sludge (after WWTP) | 22.56 (0.01–113) µg · kg⁻¹ (Sulfamethoxazole) | 6 | | | | | | | 197 µg · kg⁻¹ (Sulfapyridine) | [71] |
| | 99.1 (1.2–197) µg · kg⁻¹ (Sulfapyridine) | 2 | 68 20 µg · kg⁻¹ | 1 | — | — | — | — | 31 µg · kg⁻¹ (Sulfamethazine) | [72] |
| Soil | 211.6 (0.16–860) µg · kg⁻¹ (Sulfonamides) | 10 | 837.74 (1–9520) µg · kg⁻¹ | 12 | — | — | — | — | 400 µg · kg⁻¹ (Sulfathiazole; agricultural soil) | [73] |
| | | | 48.45[4] (1–304) µg · kg⁻¹ | 11 | — | — | — | — | PEC 860 µg · kg⁻¹ (Sulfachloropyridazine; soil pore water estimation) | [74] |
| Manure | 27.30 (0.23–167) mg · kg⁻¹ (Sulfamethazine) | 7 | 32.803 (0.020–167) mg · kg⁻¹ | 13 | — | — | — | — | 395.730 mg · kg⁻¹ (Sulfadimethoxine; in bedding-day 0) | [75] |
| | 59.07 (35.2–91) mg · kg⁻¹ (Sulfadiazine) | 3 | | | — | — | — | — | 167 mg · kg⁻¹ (Sulfamethazine) | [76] |
| Waste landfill | | | — | — | — | — | — | — | 1600 µg · dm⁻³ (all sulfonamides) | [77] |

[1] Calculated on maximum values given in tables; [2] n-number of papers; [3] natural waters; [4] without a soil sample containing 9520 µg · kg⁻¹ sulfadiazine (immediately after application).

Sulfonamide concentrations in samples increase as follows: seawater < ground water < surface water < raw municipal sewage < treated sewage < hospital sewage < activated sludge < soil < runoff from farmland < leachates from landfill < manure. In our opinion, due to the very low concentrations of sulfonamides and small number of positive tests, the presence of trace amounts of these drugs in drinking water is not a significant problem. Their maximum concentrations were found in fresh removed bedding [75] and manure from pigs fed diets with the addition of sulfonamides, mainly sulfamethazine [76]. However, as we consider the more worrying is the fact that this sulfonamide occurred in almost 50 % of samples (the average concentration of drug was $7 \text{ mg} \cdot \text{kg}^{-1}$). Additionally, sulfadiazine was also determined in tested samples (max $35.2 \text{ mg} \cdot \text{kg}^{-1}$). It is important, that even short-term storage of manure can result in a significant reduction in concentrations of sulfonamides [75].

## Generation of drug resistance

In populations of bacteria that are sensitive to specific antibiotics can also intrinsically occur strains resistant to at least one drug. In consequence, these resistant bacteria can survive, multiply and be spread to others in the family. A potentially possible correlation between the presence of anti-infectives in the environment and drug resistance was observed in the 20th century [6, 78]. For example, the ECO-SENS project has collected and analyzed the drugs resistance data in 17 European and American countries, since 1960. In Nicole Kemper's article on the influence of veterinary antibiotics on the environment the author has formulated 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" [9]. Moreover, the generation of drug resistance as a result of the transfer of "resistance" genes (horizontal gene transfer) in the environment has also significance [79–81]. In this case, resistant strains may occur in ecosystems theoretically not exposed to chemotherapeutics. For example, Pallecchi et al have described the occurrence of drug resistance in 67 % of members of the Guarani Indian community of Alto Los Athletic (Bolivia) [80]. There is also the possibility that drug resistance against one group of drugs may favour the generation of drug resistance to other drugs or disinfectants [82]. Due to the high importance of pathogens' resistance to human health, a program of monitoring for microorganisms resistance in Europe and the Americas was implemented [79, 83].

A significantly increased resistance against sulfonamides was observed in these bacteria strains that have in cells:
  – overproduction of glutamic acid, or (PABA),
  – overproduction of *dihydropteroate synthase* (DHPS) coded by plasmid DNA,
  – increased activity of *dihydrofolate reductase* (DHFR),
  – a reduction in the permeability of bacterial cell wall,
  – there is no synthesis of folic acid (it is taken with food),
  – a synthesis of the modified DHPS enzyme having no affinity for sulfonamide.

In environmental matrices the presence of organisms resistant to sulfonamides can be determined by detection of specific resistance-genes sul1, sul2, and sul3 or plasmids R388, RSF1010, pUVP4401 [84–86]. The most often, the mechanism of bacterial resistance to sulfonamides has been described in isolates of *Escherichia coli*, *Salmonella enterica*, *Shigella* spp from manure of farm animals, from meat and meat products, from healthy humans and urinary infections, and wastewater. The available data on the bacterial resistance to sulfonamides are presented in Table 3.

Table 3

Dissemination of sulfonamide resistance genes (sul1, sul2 and sul3) in the environment

| Matrix | Total of sulfonamide-resistant isolates positive for sul1-3 genes [%] | Total of sulfonamide--resistant isolates [%] | References |
|---|---|---|---|
| Pigs | 11–84 (sul1), 19–54 (sul2), 3–46 (sul3) | 50–97 | [84] |
| Swine | | 81 | [87] |
| Cattle | | 22 | |
| Dogs and cats | | 20 | |
| Laying hens | | 26 | |
| Pigs | 18 (sul1), 20 (sul2), 18 (sul3) | 50 | [88] |
| Wild small mammals | 5 (sul1), 1 (sul2) | 6 | |
| Danish broiler faeces, and meat | 11 (sul1), 82–100 (sul2) | 15–18 | [89] |
| Broiler meat | 26 (sul1), 61 (sul2), 8 (sul3) | 45 | |
| Foodstuffs | 69.8 (sul1), 36.9 (sul2), 1.4 (sul3) | 92.5 | [86] |
| Wastewater directly from swine farms | 92 (Σ sul1, sul2, sul3) | | [90] |
| Shrimp ponds | 43 (Σ sul1, sul2, sul3) | | |
| City canal/fish ponds | 72 (Σ sul1, sul2, sul3) | | |
| Water-sediment and Manure | 14 (sul1), 96 (sul2) | | [91] |
| Faecal samples | 100 (Σ sul1, sul2, sul3)) | | [92] |
| Urina UK 1991 | 43 (Σ sul1, sul2, sul3) | 39.7 | [85] |
| UK 1999 | 53.9 (Σ sul1, sul2, sul3) | 46 | |
| UK 2004 | 57.5 (Σ sul1, sul2, sul3) | 45.5 | |
| Healthy humans | 33 (sul1), 91 (sul2), 5 (sul3) | | [89] |
| Human | 16 (sul1), 97.5 (sul2) | 74 | [80] |
| Animal, food and human | | 100 | [42] |

Some most important facts related to drug-resistance:

– the use of antibiotics in veterinary medicine increases the drug-resistance of microorganisms including also cross-resistance [6, 94],

– the presence of sulfonamides in the environment increases the antimicrobial resistance of microorganisms [6, 9],

– number of bacterial strains resistant to sulfonamides increases systematically in recent years [78, 85],

– sulfonamides have shown the highest drug resistance, almost twice higher than tetracyclines and many times higher than other antibiotics [87].

## The environmental risk assessment

The majority of researchers have used the method recommended by the *European Medicines Evaluation Agency* (EMEA) for the environmental risk assessment. This method uses the results of toxicological studies and is based on the calculation the *Hazard Quotient* (HQ) as the ratio of *predicted exposure concentration* (PEC) to the *predicted no-effect concentration* (PNEC) [1, 3, 10, 15, 16, 32, 34, 54, 95]. The way of determination of these values described in detail by Koschorreck et al, Kim et al and Lopes de Souza et al [18, 35, 95]. A similar method base on calculation of the MEC/PNEC ratio where MEC is the measured environmental concentration [1, 5, 34, 43, 96]. Typically, value of the HQ < 1 indicate that substance analyzed can be considered as environmentally safe. According to Environmentally Classified Pharmaceuticals (2009) the risk is specified as:

– insignificant if PEC/PNEC < 0.1,

– low if PEC/PNEC ratio 0.1–1,

– moderate if PEC PNEC 1–10,

– high if PEC/PNEC  > 10 [32].

A comprehensive review of the data on HQ values for 5 selected sulfonamides are shown in the article by Garcia-Galan et al [16]. Although the presented HQ values are mainly obtained for sulfamethoxazole however they significantly differ among themselves. The selected data on the HQ value made based on the available literature and the above-cited article [16] are shown in Table 4.

Theoretically, for the sulfadimethoxine; in bedding-day 0 and Lemna gibba ($MEC_{max} = 395.73 \text{ mg} \cdot \text{kg}^{-1}$ [75], $EC_{50}$ 0.248 $\text{mg} \cdot \text{dm}^{-3}$ [16]), $HQ_{max} = 1.6 \cdot 10^{6}$ where $HQ_{max} = MEC_{max}/PNEC$ and $PNEC = EC_{50}/1000$.

However, the discussed-above maximum HQ values have probably negligible importance. According to Schwab et al [5] the present concentrations of sulfonamides do not pose a risk to human health. Moreover, according to Environmentally Classified Pharmaceuticals (2009) environmental risk of sulfonamides is specified as insignificant [32]. On the other hand, data on the quantity of these drugs in matrices such as manure, wastewater from agricultural fields and pharmaceutical industry indicate that in these cases sulfonamides can cause serious problems for the environment. Moreover, often it does not take into account changes in the genotype of microorganisms. In contrast to the toxic effect, these changes can easily be easily transferred, even to species in other biocenosis.

Table 4

Ecotoxicological data on the HQ value (based on the available literature)

| Matrix | Mean for all sulfonamides | n[1] | Mean for all sulfonamides [16] | n[1] | Maximum values calculated based on data from Table 2 $HQ_{max} = MEC_{max}/PNEC$ | Maximum values presented in the literature | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Values | Comments | References |
| Drinking water | 0.0097 (0.001–22.96) ... | 1 | — | — | $8.5^2/0.05^3 = 170$ (sulfamethoxazole) | 0.0097 (sulfamethoxazole) | HQ = PEC/PNEC for children, for combined drinking water/wsh consumption | [5] |
| Surface water | 6.256 (0.002–59.3) | 15 | 11.116 (0.002–59.3) | 8 | $18/0.05^3 = 360$ (sulfamethoxazole) $19.2/201 = 0.9552$ (for sulfamethazine and *Daphnia magna*) | 59.30 (sulfamethoxazole) | HQ = PEC/PNEC Acute toxicity test on surface waters in Germany | [36] |
| Wastewater | 2.916 (0.001–22.96) | 9 | — | — | $1340/0.05^3 = 26800$ (sulfamethoxazole) | 22.96 (sulfamethoxazole) | HQ = MEC/PNEC algae | [43] |
| Aquatic environment | 2.114 (0.00089–6.3) | 3 | 1.464 (0.03–6.3) | 7 | — | 6.3 (sulfamethoxazole) | HQ = PEC/PNEC The PEC of test pharmaceuticals was estimated based on several conservative assumptions in Korea | [35] |
| Hospital sludge | 3.278 (0.03–15.1) | 7 | — | — | $12.8/0.05^3 = 256$ (sulfamethoxazole) | 15.1 (sulfamethoxazole) | HQ = PEC/PNEC for hospital effluent in Germany | [69] |

[1] n–number of data; [2] PEC; [3] PNEC = NOEC/10 for *Synechococcus leopolensis*.

## Conclusion

Antibacterial sulfonamides are a group of drugs still commonly used in human and veterinary medicine.

1. The used sulfonamides can be spread almost entirely into the environment in biologically active form or can recover the activity.

2. Probably sulfonamides introduced into the environment remain there for a long time and can spread easily in it and infiltrate even the groundwater.

3. Attendance of sulfonamides in tested environmental samples is very high.

4. The highest concentrations of sulfonamides are found in manure from livestock.

5. Opinions on the possibility of sulfonamides removing in conventional sewage treatment plants (STPs) are divergent.

6. Effective methods for the elimination of sulfonamides can be: nanofiltration, reverse osmosis and AOP.

7. Sulfonamides have very low toxicity to higher organisms, and from this point of view they are not a really threat to people's health.

8. Sulfonamides are highly toxic for microorganisms, algae and certain plants.

9. Sulfonamides occurring in the environment favour the generation of drug resistance.

10. Sulfonamide resistance genes may be transferred in the environment.

According to the authors of the National Programme for Protection of Antibiotics [41], microorganisms with relatively low pathogenic risk due to acquired resistance mechanisms may be the major factors threatening the health and human life. In result, it can lead to the spreading of diseases which are commonly considered to be "overcome." These facts indicate that the presented problem has a serious global importance in ecology and the limitations of antibiotic consumption in individual countries do not solve it.

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## OCENA WYSTĘPOWANIA LEKÓW SULFONAMIDOWYCH W BIOSFERZE

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**Abstrakt:** Sulfonamidy, pochodne kwasu *p*-aminobenzenosulfonowego są znanymi od lat 30. XX w. lekami przeciwbakteryjnymi. Według klasyfikacji anatomiczno-terapeutyczno-chemicznej (ATC) zaliczane są do grupy leków przeciwbakteryjnych do stosowania wewnętrznego powszechnie nazywanych antybiotykami.

Mają one również właściwości roślinobójcze oraz są wykorzystywane jako dodatki do pasz w rolnictwie. Szacuje się, że jedynie w weterynarii ich roczne światowe zużycie może wynosić nawet 15 tys. Mg (ton).

Obecnie w niemal 100 % próbek środowiskowych badanych pod kontem zawartości antybiotyków wykrywane są sulfonamidy. Zazwyczaj ich oznaczane stężenia są niższe niż 1 µg · dm$^{-3}$, niemniej w gnojowicy wykrywano sulfonamidy w ilościach przekraczających nawet 100 mg · kg$^{-1}$. Ryzyko środowiskowe powodowane przez sulfonamidy oceniane na podstawie ich ekotoksyczności nie jest wielkie. Jednak istnieją dowody na to, że biorą one udział w generowaniu lekooporności mikroorganizmów. Takie geny lekooporności mogą być przenoszone pomiędzy różnymi szczepami bakterii, np. na drodze koniugacji. W rezultacie geny te mogą się pojawić u bakterii chorobotwórczych obecnych w ekosystemach uprzednio nie narażonych na kontakt z antybiotykami.

Celem pracy jest omówienie problematyki występowania sulfonamidów w poszczególnych ekosystemach. Na podstawie dostępnej literatury obejmującej ostatnią dekadę dokonano charakterystyki potencjalnej trwałości w środowisku i ekotoksyczności sulfonamidów. Omówiono również problematykę lekooporności na sulfonamidy i dokonano oceny ryzyka z uwzględnieniem ich działania przeciwbakteryjnego.

**Słowa kluczowe:** sulfonamidy, ekotoksyczność, lekooporność