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Chapter 23

Exposure and Hazard Identification of Sulphonamides in the Terrestrial Environment

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Additional information is available at the end of the chapter

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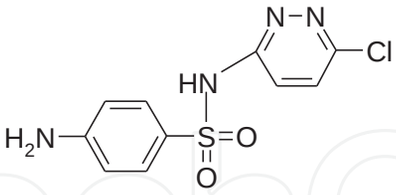
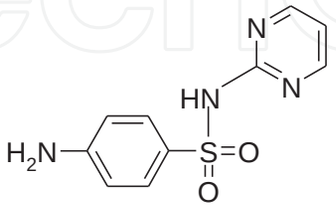
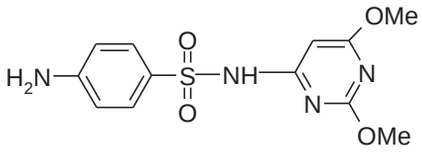
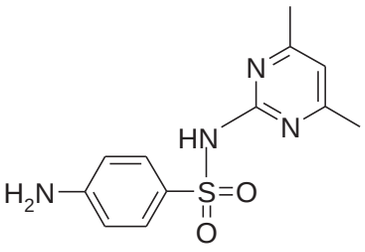
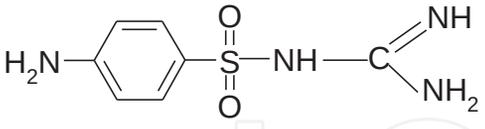
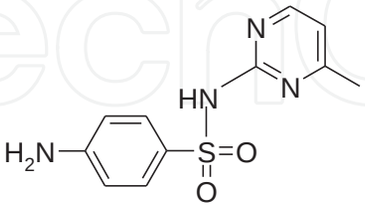
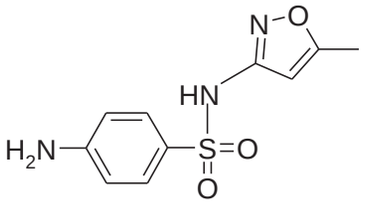
1. Introduction

For ten years now, interest has been increasing in research focused on pharmaceutical residues in the environment. Special attention has been given to the residues of antimicrobials, since it has been demonstrated, that due to the formation of the dangerous phenomenon of bacterial resistance, these substances could pose a real threat not just to ecosystems, but also to human health. Most antimicrobial agents are used in large quantities for different purposes in veterinary medicine.

Various antibiotics are commonly used in this field, but we shall concentrate on sulphonamides (SAs). The physicochemical properties and chemical structures of selected SAs are presented in Table 1.

Having been used for more than fifty years, SAs are among the oldest groups of veterinary chemotherapeutic substances. They are inexpensive and offer a broad spectrum of activity for the prevention and treatment of bacterial infections. After tetracyclines, they are the most commonly consumed veterinary antibiotics in the European Union [1,10]. However, as animals do not completely metabolize these compounds, a large fraction of them is being excreted unchanged in faeces and urine. Therefore, both the unmetabolized drugs and their metabolites are discharged to the environment, mainly to the soil component, either directly by grazing animals or indirectly during the application of manure [11]. Once in the soil, they and their transformation products are distributed among its different compartments and can be transported to the surface and ground waters. The physicochemical properties of these compounds, the applied dosage and the nature of the environmental compartment where they are released and further interact, comply the whole process.

Substance [CAS] Abbreviation	Chemical structure	Selected physicochemical properties
Sulphachloropyridazine [80-32-0] SCP		M = 284.7 g mol^{-1} pK_{a2} = 1.72 pK_{a3} = 6.39 logP = 0.71
Sulphadiazine [68-35-9] SDZ		M = 250.3 g mol^{-1} pK_{a2} = 1.98 pK_{a3} = 6.01 logP = -0.09
Sulphadimethoxine [122-11-2] SDM		M = 310.3 g mol^{-1} pK_{a2} = 2.5 pK_{a3} = 6.0 logP = 1.63
Sulphadimidine (sulphamethazine) [57-68-1] SDMD (SMZ)		M = 278.3 g mol^{-1} pK_{a2} = 2.46 pK_{a3} = 7.45 logP = 0.27
Sulphaguanidine [57-67-0] SGD		M = 214.2 g mol^{-1} pK_{a2} = 2.8 pK_{a3} = 12.0 logP = -1.22
Sulphamerazine [127-79-7] SMR		M = 264.3 g mol^{-1} pK_{a2} = 2.16 pK_{a3} = 6.80 logP = 0.11
Sulphamethoxazole [723-46-6] SMX		M = 253.3 g mol-1 pK_{a2} = 1.81 pK_{a3} = 5.46 logP = 0.89

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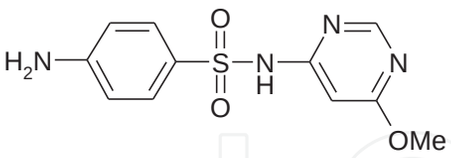
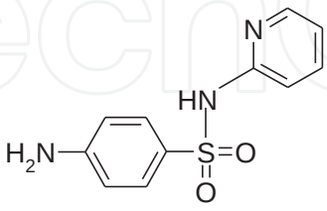
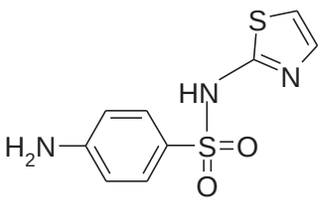
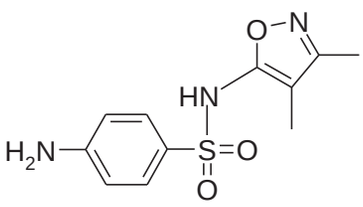
Substance [CAS] Abbreviation	Chemical structure	Selected physicochemical properties
Sulphamonomethoxine [1220-83-3] SMM		M = 280.3 g mol^{-1} pK_{a2} = 1.73 pK_{a3} = 6.22 logP = -0.04
Sulphapyridine [144-83-2] SPY		M = 249.2 g mol^{-1} pK_{a2} = 2.37 pK_{a3} = 7.48 logP = 0.03
Sulphathiazole [72-14-0] STZ		M = 255.3 g mol^{-1} pK_{a2} = 2.06 pK_{a3}= 7.07 logP = -0.04
Sulphisoxazole [127-69-5] SSX		M = 267.3 g mol^{-1} pK_{a2} = 2.15 pK_{a3}= 5.00 logP = 1.01

Table 1. The structures and physicochemical properties of the sulphonamides discussed in this chapter (according to [1-9])

SAs are fairly water-soluble, polar compounds, however quite persistent - resistant to biodegradation [10,12-13] and hydrolysis [3]. This goes a long way to explaining why they have been regularly detected in both aquatic and terrestrial environments in the last ten years [1,10-11]. Although SA concentrations in environmental samples are relatively low (at the ppb or ppt level), they are continuously being released, so ultimately they may pose an elevated risk. SAs are designed to specifically target the biosynthetic pathway of folate (an essential molecule required by all living organisms) by competitively inhibiting the conversion of *p*-aminobenzoic acid (pABA); hence, they not only target bacteria but can also elicit hitherto unknown effects in environmentally relevant, non-target organisms like invertebrates and plants [14-16]. As they belong to different trophic levels, these taxonomic groups may be exposed to SAs to various extents.

So far only a small number of studies concerning the presence and effects of SAs in the soil environment have been carried out. Hence, there are a number of very pertinent questions that

need to be addressed, for example: (i) What is the fate of these compounds in the terrestrial environment? (ii) What are the effects of their presence in the soil environment? (iii) Do they pose a risk to different soil organisms and also to human health?

For these reasons, the aim of this chapter is to review and summarize existing knowledge of the fate and effects of SA residues in the terrestrial environment.

Conventionally, the environmental fate of antimicrobials in the soil ecosystem is assessed with respect to their persistence and sorption onto soil. In the case of SAs, as they are very stable, only photodegradation process could have recognizable influence on their elimination from the environment [1,10]. However this process in the soil ecosystem is of lesser importance. Therefore, sorption processes influence the environmental behaviour of SAs to the greatest extent, so it is these that we shall be discussing in detail.

Although a few review papers have been published summarizing the available ecotoxicity data of pharmaceuticals, including some SAs [14-15,17-18], they focus on aquatic organisms rather than soil. In this chapter, therefore, we shall discuss the available data on SA toxicity towards different soil organisms on various trophic levels like bacteria, invertebrates and plants. These results will be discussed with respect to the existing requirements for the environmental risk assessment of veterinary pharmaceuticals (VICH, 2000 [19]; VICH, 2004 [20]; EMEA, 2007 [21]; EMEA, 2008a [22]; EMEA, 2008b [23]). In addition, we shall identify some areas where future work is warranted as well as the needs for further investigations.

2. Fate of SAs in the terrestrial environment

2.1. Basic concept of sorption modelling studies

Sorption is defined as a phenomenon during which chemicals become associated with solid phases. Immensely important, this process affects the fate of chemicals in the environment [24-25]. Adsorption/desorption experiments are useful for generating essential information on the mobility of various contaminants and their distribution in the soil, water and air. Assessing the distribution of a chemical between the soil and aqueous phases is not a straightforward process, however. It depends on various factors, such as the chemical nature of the substance and the characteristics of the soil (*e.g.* pH, organic matter (OM) content, clay fraction content). Furthermore, climatic factors such as rainfall, temperature, sunlight intensity and wind, which can affect the strength of sorption, also have to be taken into consideration. Thus, the numerous phenomena and mechanisms involved in the adsorption of a chemical by soil cannot be completely defined by simple laboratory models. Nevertheless, such investigations can provide valuable information on the environmental relevance of the adsorption of chemicals [26].

Laboratory sorption experiments can be carried out under static (batch) and dynamic (column) conditions. Static tests are commonly used when the aim of the study is to calculate the distribution coefficient (Eq. 1), in equilibrium time, which is specific to every chemical. Column tests, on the other hand, enable time-dependent monitoring of contaminant

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leaching from soil and waste materials; in addition, the flow-through pattern of such tests resembles actual environmental conditions. Therefore, the release of a contaminant depending on local equilibrium time and advection conditions can be evaluated based on column testing systems [27].

Both column and batch tests can be used to assess the possible leaching/release potential of contaminated materials on the soil – ground water pathway [28-30]. The release potential of water-soluble contaminants can be assessed as an expression of the source term, which gives an indication of their bioavailability. In this case a batch test provides a snapshot of a particular liquid-to-solid ratio. This type of test focuses on constituent solubility and release over a range of conditions by varying a single parameter (e.g. final extract pH, liquid-to-solid (LS) ratio) [27].

The common approach for modelling sorption results involves using only the initial linear part of the isotherm, plotted as c_w and c_s:

$$c_s = K_d \cdot c_w \tag{1}$$

where: K_d is the partition coefficient; c_s is the content of test substance adsorbed on the soil at adsorption equilibrium (mg kg^{-1}); c_w is the mass concentration of test substance in the aqueous phase at adsorption equilibrium (mg L^{-1}).

The sorption isotherm can be also mathematically described by the Freundlich or Langmuir model.

The Langmuir equation is written as:

$$c_s = \frac{c_{\max} \cdot K_L \cdot c_w}{1 + K_L \cdot c_w} \tag{2}$$

where: c_s is the content of test substance adsorbed on the soil at adsorption equilibrium (mg kg^{-1}); c_w is the mass concentration of test substance in the aqueous phase at adsorption equilibrium (mg L^{-1}); c_{max} is the maximum sorption capacity of the sorbent; K_L is the Langmuir constant.

The linear form of this equation is:

$$\frac{1}{c_s} = \frac{1}{K_L c_{\max} c_w} + \frac{1}{c_{\max}} \tag{3}$$

In the Langmuir model the mass of solute sorbed per unit mass of sorbent (c_s) increases linearly as the solute concentration increases. The model is based on three main assumptions:

- the sorption energy is the same for all sites and is independent of the degree of surface coverage;

- sorption occurs only at localized sites, with no interaction between adjoining sorbed molecules;
- the sorption maximum (c_{max}) represents a monolayer coverage.

Based on these findings, it is justified that the Langmuir isotherms are observed only very rarely in case of sorption of when organic compounds are sorbed in such a complex and heterogeneous sorbent as soils [31].

The Freundlich model takes the following form:

$$c_s = K_F \cdot c_w^{1/n} \tag{4}$$

where: c_s is the content of test substance adsorbed on the soil at adsorption equilibrium (mg kg^{-1}); c_w is the mass concentration of test substance in the aqueous phase at adsorption equilibrium (mg L^{-1}); K_F is the Freundlich adsorption coefficient; n is the regression constant

Based on the value of $1/n$, which describes the relative magnitude and diversity of energies associated with sorption, the mechanism of this process can be defined more accurately [31-36]. If $1/n = 1$, adsorption is linear, which indicates the occurrence of homogeneous energy sites on the sorbent. This type of adsorption is generally typical at very low solute concentrations with many sites on the sorbent still available for possible interaction with the adsorbate. A value of $1/n > 1$ indicates a concave, upward-curving isotherm, which is sometimes referred to as a solvent-affinity type isotherm (S-type), where the sorption energy increases with increasing surface concentration. However, phenomena unrelated to the sorption of the analyte to the sorbate surface, such as strong adsorption of the solvent, strong intermolecular attraction within the adsorbent layers, penetration of the solute in the adsorbent, and the monofunctional nature of the adsorbate, can also affect the shape of the isotherm [31]. When $1/n < 1$, the isotherm is of the convex, downward-curving Langmuir-type (L-type), where the marginal sorption energy decreases with increasing surface concentration. This may occur when the competition of solvent for sites is minimal or the absorbate is a planar molecule [36].

In order to calculate the Freundlich factors as $1/n$ or K_F, Eq. 4 can be linearized by a logarithmic transformation:

$$\log c_s = 1/n \log\ c_w + \log K_F \tag{5}$$

It has been shown that the sorption of pharmaceutical compounds (PCs) to soils is influenced by solution chemistry and the type of mineral and organic sorbents [24,25,37]. Pharmaceuticals can exist as either neutral or charged species (e.g. cations, anions, zwitterions) [24], depending on the pH. Various adsorptive forces may therefore be acting. Whereas neutral molecules partition to solid matrices via relatively weak van der Waals and electron donor-acceptor interactions, charged species can interact via stronger electrostatic mechanisms, such as cation exchange, cation-bridging and complexation. The acid-base equilibrium of sulphonamides

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resulting from either the loss or the gain of a proton is similar for all sulphonamides apart from sulphaguanidine (see Białk-Bielińska et al. [3]). The basic properties are due to the aniline group present in all SAs and specific to each SA heterocyclic base. SAs can thus be described by three dissociation constants. Nevertheless, since the presence of the protonated form of the heterocyclic functional group is extremely unlikely, only two of the possible ionized functional groups existing in the structure of SA molecules are taken into consideration – during sorption experiments [38-45]. Hence, K_{a2} is the dissociation constant for the equilibrium between the positively charged, protonated amino group of a SA and its electrically neutral conjugate base, whereas K_{a3} refers to the equilibrium involving the loss of the SA proton to yield its negatively charged conjugate (Figure 1) [7].

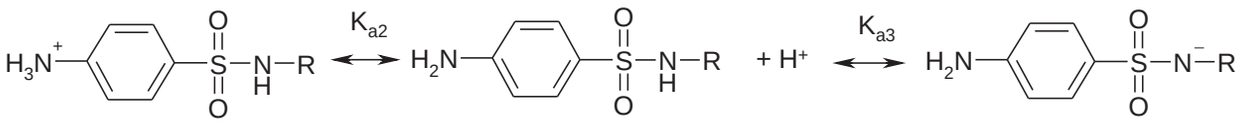

Figure 1. Dissociation equilibrium of sulphonamides [7]

Assessing the sorption of veterinary pharmaceuticals in soils is extremely important for estimating the risk of the large-scale usage of veterinary medicines to human health and environmental matrices, because this affects the fate and transport of chemicals in ground water.

2.2. Sorption potential of SAs to soils

Although SA sorption is quite a common topic of investigation, authors generally focus on just a few SAs, so that knowledge of the sorption behaviour of some of them (e.g. sulphaguanidine, sulphisoxazole) is still limited. So far, only a few review papers have been published describing the sorption of SAs to soils [16,46-49]. However, they cover a wide range of pharmaceuticals, so SAs are inadequately reviewed. Furthermore, since 2011 (when the last review on SA sorption was published), new data have been published, which are included in the present review. The available information on the sorption of the most commonly investigated compounds will therefore be discussed in depth.

The most widely investigated SA is sulphamethazine (SMZ). The level to which its undergoing sorption onto soils was investigated already more than thirty years ago by Langhammer [50]. That author calculated adsorption coefficients for four different soils, differing in pH and OM content. Based on the values of the distribution coefficients (from 1.0 to 3.1 L kg $^{-1}$), this drug can be considered as a very mobile chemical. These results are in accordance with the investigations of other researchers, such as Thurman et al. [51] and Tolls et al. [52], who reported low sorption coefficients for SMZ (0.6 L kg $^{-1}$ and 3.0 L kg^{-1} respectively) or Thiele-Bruhn et al. [53], who gave a K_d value of 2.4 L kg^{-1} for humus-rich soil. This was also supported by Lertpaitoonpan et al. [54], who examined this SA in terms of the distribution in soils varying in OM content (K_d lies between 0.2 and 3.9 L kg^{-1} depending on the physicochemical parameters of soils). However, Fan et al. [55] reported a higher sorption potential of the polar metabolite

of SMZ (*N*4-acetyl-SMZ) during a miscible-displacement experiment (column test). The K_d values obtained by these authors range from 7.5 andto 206.2 L kg^{-1} and are much higher than previous data for the native compound. However, this may well be due to the polar functional group present in *N*4-acetyl-SMZ, which could enhance the association of this compound to the negatively charged soil surfaces via cation bridging or complexes. The high mobility of SMZ was also reported by Kurwadkar et al. [41], who observed a 50-90% release of SMZ from a soil column system. The most recent studies presented by Leal et al. [56] underscore the concern regarding the possible occurrence of this compound in the environment. These authors investigated a number of different Brazilian soils, finding a tendency for SMZ to leach from soil matrices.

Much attention has also been given to calculating the sorption potential of sulphadiazine (SDZ). Just recently, Doretto et al. [45] reviewed the available literature data through Freundlich sorption coefficient (K_F) for SDZ. On this basis they concluded that the potential of SDZ to interact with soil particles is relatively low and depends on the type of soil, thus on the physicochemical properties of the sorbent. In another work, these authors demonstrated the weak interaction of SDZ with binding sites on the soil surface (K_F values from 0.4 to 2.6 $\mu g^{1-1/n}(cm^3)^{1-1/n}g^{-1}$). The column studies of Wehrhan et al. [57] showed that the amount of leached SDZ depends strongly on the duration of the process. The eluted mass fraction was considerably higher in long-pulse experiments (83 and 61% respectively) than in short-pulse ones, during which only 18% was leached. Furthermore, these authors recorded the highest concentrations at the top of the column, with concentrations steadily decreasing towards the bottom. In the column with the short pulse application, solute concentrations were relatively uniformly distributed. Environmental conditions like rainfall can therefore affect the distribution of contaminants in soil.

It was also observed that SDZ exhibits, for example, a lower tendency to be retained in solid matrices than SMZ [53,56], with respective K_d values for SDZ and SMZ varying from 2.0 to 2.4 L kg^{-1} as reported by Thiele-Bruhn et al. [53], and from 5.2 to 10.5 L kg^{-1}, as obtained by Leal et al. [56].

Although sulphachloropyridazine (SCP) is not as widely studied a sulphonamide as SMZ or SDZ, this drug has been extensively examined using various tests besides batch or laboratory column tests. The data available in the literature show a sorption potential in soil similar to that of other SAs. For example, Boxall et al. [58] reported low sorption coefficients for SCP in soil and a soil/slurry mixture ranging from 0.9 to 1.8 L kg^{-1}. They also confirmed the high mobility of SCP in field studies, demonstrating the rapid transport of SCP to surface waters for concentrations as high as 590 $\mu g\ L^{-1}$. Other studies are also consistent with this statement [38,44,52,56], giving K_d values from 0.7 to 70.1 L kg^{-1}.

Blackwell et al. [59], who also examined the leaching of SCP under field conditions, detected this compound in surface run-off samples even at a concentration of 25.9 $\mu g\ L^{-1}$ following application at a rate of 1.18 kg ha^{-1}. These authors reported the occurrence of SCP in soil water samples at a concentration of 0.8 $\mu g\ L^{-1}$ at 40 cm depth as long as 20 days after treatment. On the basis of their results the authors concluded that SCP poses a moderate risk of contaminating ground or surface water but that its potential to accumulate in soils is low. Further lysimeter-

http://dx.doi.org/10.5772/57265

based studies by Blackwell et al. [60] sporadically detected SCP in leachate at levels from 0.7 to 8.5 μg L^{-1}, depending on the irrigation conditions. SCP was applied in slurry (197 mL per lysimeter), which corresponds to a SCP application rate of 5.2 mg (1.18 kg ha^{-1}). The authors concluded that this compound has the potential to reach ground and surface waters. On the basis of a lysimeter study, field investigations and laboratory column tests, Kay et al. [61,62,63] pointed out that soil tillage prior to slurry application can significantly reduce losses of SCP to tile drainage systems, thereby reducing the risk of surface water contamination by SCP residues in the slurry. The observed losses of SCP in a soil column with a soil surface broken as a result of tillage fell from 54.6 % of the applied amount to zero [62].

Studies of sulphamethoxazole (SMX) have reported a similar sorption potential to that of SMZ [40]. With some exceptions, Leal et al. [56] recorded similar values of the distribution coefficient K_d for both SMX and SMZ in an examination of thirteen soils. The results obtained by Yu et al. [64] are in agreement with that. These authors calculated a K_d of 18.9 L kg^{-1} for one of three investigated soils. Their aim was to assess the suitability, inter alia, of SMX as a wastewater indicator. However, owing to the formation of non-extractable residues, such an application of SMX was regarded as limited. On the basis of a few investigations into the sorption of SMX to activated sludge, we can state that the sorption potential of sulphonamides to this sorbent is much greater than to soils [65-69]. Hrsing et al. [65] presented K_d values for SMX ranging from 280 to 370 L kg^{-1}, depending on the type of activated sludge. The results are consistent with the investigations of Hyland et al. [66], who studied the sorption of 75 pharmaceuticals onto activated sludge, obtaining a K_d value of 269 L kg^{-1}, or with those of Göbel et al. [67], who obtained a similar value of K_d for SMX. In contrast, Yang et al. [68] reported a lower sorption of SMX to activated sludge (K_d = 28.6 L kg^{-1}). However, these differences may have arisen, for example, from the different methodologies used in the tests. Nevertheless, Yang et al. [68, 69] concluded that sorption of SAs to activated sludge is highly reversible (the amount retained after desorption is 0.9% of the original dose of 100 μg L^{-1}). Therefore, the use of sewage sludge as fertilizer may constitute an additional source of SAs in ground and surface waters. Moreover, since SAs may be taken up by farmland crops, as demonstrated by Li et al. [70], the use of sewage sludge as fertilizer poses a serious risk to human health as well.

Knowledge of the sorption potential of other SAs like sulphathiazole (STZ), sulphapyridine (SPY), sulphamerazine (SMR), sulphadimethoxine (SDM), sulphamonomethoxine (SMM), sulphaguanidine (SGD) or sulphisoxazole (SSX) is very limited. In the literature there are only a few reports dealing with the sorption of these pharmaceuticals. K_d for STZ adsorption onto soil particles ranges from 1.0 to 62.5 L kg^{-1} depending on soil properties [56]. In the case of SDM, Sanders et al. [71] pointed out that the linear sorption coefficient for SDM differs somewhat, ranging from 0.4 to 25.8 L kg^{-1} as a single solute and from 2.5 to 22.1 L kg^{-1} as a co-solute with ormetoprim, another antimicrobial. Moreover, the sorption of SDM was less linear in combination with ormetoprim. In turn, Maszkowska et al. [72] did not determine the influence of the co-solute on sulphonamide release. SDM exhibited a similar leaching behaviour from the soil when it was tested alone or in a mixture with SGD. Nevertheless, these authors also reported the considerable mobility of three SAs (SDM, SGD, SSX) in three different soils; SDM was released the slowest from the soil column. These results are consistent with

those published previously by Białk-Bielińska et al. [43], who showed that SDM had a greater sorption potential than SGD (K_d = 0.3 – 107.5 L kg^{-1} for SDM, 1.0 – 31.0L kg^{-1} for SGD). SDM was also found to have the strongest tendency of all the SAs investigated to interact with activated sludge [68,69]. In addition, these authors investigated the sorption strength of sulphamonomethoxine (SMM) on activated sludge, finding a lower affinity of SMM than of SDM for activated sludge particles. Jin et al. [73] demonstrated the relatively high mobility of SDM in soil, obtaining a K_d of 18.9 L kg^{-1}. These authors also highlighted the influence of different co-contaminants on adsorption. They concluded that anionic surfactants and urea could adversely affect the sorption potential of SDM, whereas cationic surfactants could improve the retention of SDM on soil particles. Figueroa-Diva et al. [40] found that SMR exhibited the lowest level of sorption of the four SAs (SDM, SMX, SMZ and SMR) that they examined. According to Thiele-Bruhn et al. [53], SPY was the most strongly retained SA in the soil matrix, with K_d higher than that of SMZ, SDZ and SDM.

Summing up, the available data indicate that determining the environmental fate of SAs in soils is not an easy task, as this depends largely on the physicochemical properties of soils and the chemical structures of the SAs. Nevertheless, one can infer from these results that these pharmaceuticals will tend to leach into ground or surface water rather than persist in soils. These data also show, however, that a certain amount of the SAs entering the soil can be retained there for quite a long time. Furthermore, their sorption to soils can increase or decrease depending on a number of different factors, which are discussed below.

2.3. Factors influencing sorption of SAs to soils

2.3.1. Influence of the organic/mineral composition of soil

Soils can be regarded as mixtures of mineral and organic fractions. The differences in their texture, structure, consistency, colour, chemical, biological and other characteristics arise from the type of parent material. Soils are therefore diverse matrices in which different sorption mechanisms can occur. The organic matter (OM) content undoubtedly plays a critical role in the sorption capacity of soils [74]. Overall, in accordance with the available literature data, it has been shown that OM positively affects sorption strength of organic compounds. Figueroa-Diva et al. [40] reported values of K_d for all examined SAs increasing in the same sequence as the organic carbon content (f_{OC}) in the soils they investigated. Białk-Bielińska et al. [43] pointed out that SAs predominantly interact with soil OM by nonbonding van der Waals interactions and hydrogen bonding. Furthermore, such weak bonding forces are susceptible to desorption, resulting in the free release of SAs following their prior surface adsorption, an observation previously made by Thiele-Bruhn et al. [53]. The authors indicated that the influence of soil OM on adsorption depends not only on the organic carbon content, but also on its composition. Sukul et al. [39] demonstrated increased sorption of SDZ in soils in the presence of manure compared to soil without manure, which greatly emphasizes the role of dissolved OM and organomineral soil particles in SDZ sorption. On the basis of original research and literature available data, Hou et al. [75] demonstrated a positive relationship between K_d and the organic carbon content (f_{OC}) for SMX sorption on soils/sediments with f_{OC} > 2%. However, for

http://dx.doi.org/10.5772/57265

adsorbents with f_{OC} < 2%, a lower f_{OC} could result in increased sorption, suggesting competition between SMX and organic matter on mineral particles. Hyland et al. [66] confirmed the positive influence of organic matter on SA sorption. The high values of K_d for SMX sorption onto activated sludge are fully justified, due in great part to the organic carbon (average f_{OC} = 44.1%) in the sorbent. Leal et al. [56] analysed the influence of the OM and clay content on the sorption of several SAs, concluding that hydrophobic partition was important in SA sorption. Nevertheless, they also found that non-hydrophobic interactions with organic and/or mineral surfaces, mainly with Al and Fe oxides and hydroxides (abundant in the investigated soils) were also important in SA retention in soils. Boxall et al. [58] determined the influence of the type of mineral fraction in soil (clay or sand) on K_d. Their results showed that clay had a greater sorption capacity for SCP than sand. The same was reported by Ter Laak et al. [38], whose K_d value for soil with greater amount of clay was twice as high as that for sandy soil. During field studies, however, Boxall et al. [58] reported faster leaching of SCP to ground water from a clay site than from a sandy site, an observation corroborated by Fan et al. [55]. The K_d values for SMZ were positively related to the OM content in case of sorbents without sand. However, the latter authors' K_d value was higher for sand (%OM=0) than for soil containing OM. They explained this as having resulted from the transport of SAs on mobile colloids (< 2 μm, dissolved organic matter and clay-sized materials) in accordance with EPA [76], which resulted in faster elution from a soil column with OM content than from sand.

2.3.2. Influence of pH

In the context of the acid-base equilibrium of SAs, pH can strongly affect sorption. This has been confirmed in many investigations. The overall trend presented in the literature indicates decreasing sorption of SAs with increasing pH. This is explained by the amphoteric nature of SAs, which consequently can occur in cationic, anionic or neutral form. The strongest possible interactions (ion-exchange mechanism) arise from competition for negatively charged sites on the soil surface between a cationic analyte and other cations present in the solute. Nevertheless, the existence of cationic SAs is limited due to the relatively low pK_{a2} value. Cation exchange is therefore not regarded as a favourable mechanism for SA sorption to soil matrices [39]. Although decreasing SA sorption is observed at high pH, Sukul et al. [39] achieved relatively strong adsorption in the case of one soil at a pH where the anionic form of SDZ was dominant, claiming that this was due to possible partition to the positively charged surfaces of pedogenic oxides, very abundant in the clay fraction [39,53]. Kim et al. [42] and Białk-Bielińska et al. [43] also observed a negative correlation between K_d and pH. The former authors considered that the changes were better evident for soil with a greater OM content. Pinna et al. [77], in turn, did not observe such a strong dependence on OM content. The addition of cow manure (f_{OC} = 30.58) did not significantly affect antibiotic sorption to one of the investigated soils, but did increase the extent of sorption to another soil about three times, even though larger amounts of manure had been added to the first soil than to the second one. These authors concluded that the greater sorption to the second soil prior to the addition of cow manure was most probably due to the low pH of the soil suspension rather than to its high organic carbon content. On the other hand, the high pH of the first soil suspension (7.8) could have been responsible for the reduced sorption, despite the considerable amount of OM in this amended soil.

2.3.3. Influence of ionic strength

Another environmentally important factor that can affect SA sorption is ionic strength. But this has not been examined extensively. Ter Laak et al. [38] carried out sorption studies of SCP, among other compounds. Generally speaking, they did not observe any significant influence of ionic strength, except in the case of one soil (clay loam), in which sorption doubled when the $CaCl_2$ concentration was raised from 0.006 to 0.2 M. The authors concluded that this increase in sorption was probably due to the neutral form of SCP increasing from 3.3 to 8.3% because of the decreasing pH. Protons are displaced from the cation-exchange sites by the addition of Ca^{2+} cations, which are ultimately responsible for the decrease in pH. Elevated cation concentrations near negatively charged soil surfaces, resulting in a decrease in the electrostatic repulsion of negatively charged sorbate molecules and soil particles, is another explanation considered by those authors. Srinivasan et al. [44] reported the different behaviour of SMX under conditions of increasing ionic strength. They explained the increasing K_d for SMX in the case of one soil as being due to cation bridging. Since positively charged calcium ions are present in the solution, bonding of anionic SMX to calcium is possible. In addition, the occurrence of a salting out effect, reducing the solubility of SMX in the salt solution so that it precipitates in the soil, was taken into consideration as a possible reason for the increase in sorption. The positive influence of ionic strength on sorption can also be attributed to the replacement of protons from the soil surface as the ionic strength increases, causing a slight reduction in pH, and shifting acidic SMX towards neutral forms that are more strongly sorbed than the anionic forms. Two other soils examined by Srinivasan et al. [44] exhibited an opposite and irregular trend in sorptive affinity of SMX, with elevated ionic strengths resulting in decreased sorption coefficients of SMX in the case of both soils. A slight decrease in sorption with increasing ionic strength of solute was also observed by Białk-Bielińska et al. [43] in the case of SDM and SGD and three soils. Srinivasan et al. [44] concluded that the ionic composition plays an important role in the sorption of ionizable organic compounds. Nevertheless, they, too, highlighted the necessity for further research in view of the conflicting results published in the literature.

2.4. Available data on the presence of SAs in soils

Although many methods have been developed in the past decade for the analysis of SAs in aqueous matrices, only a few are described in the literature for the determination of these contaminants in soil matrices. This is because the chemical analysis of pharmaceuticals from soil matrices is complicated by the need for extraction. Hence, our knowledge about the quantity of SAs in solid matrices is still limited. Nevertheless, the available literature data indicate their occurrence in agricultural soils after conventional fertilization. In a two-year monitoring study Höper et al. [78] determined SMZ at a concentration of 11 μg kg^{-1}. Pawelzick et al. [79] reported a maximum concentration of 4.5 μg kg^{-1} for SMZ; these results are in agreement with Hu et al. [80], who demonstrated the occurrence of SMX (0.03 – 0.9 μg kg^{-1}) and SCP (0.18 – 2.5 μg kg^{-1}). Karcı et al. [81] found three SAs in agricultural soils in Turkey at concentrations even two orders of magnitude higher than those reported in previous studies: STZ (0.05 – 0.4 mg kg^{-1}), SCP (0.05 – 0.1 mg kg^{-1}) and SMX (0.05 – 0.1 mg kg^{-1}). There are some

http://dx.doi.org/10.5772/57265

discrepancies in the available literature data, which may be due to differences in the physico-chemical properties of the solid samples examined. They may also stem from the intensity of fertilization and the initial quantities of SAs applied in animal husbandry. Nevertheless, even low concentrations of SAs reported in soil samples may contaminate other environmental compartments as a result of release via desorption.

In general, concentration limits of antibiotics in the environment are not regulated, even though growing public concern has been taken into account in the prescription of environmental risk assessments of veterinary pharmaceuticals in the USA and Europe [19-23]. For these reasons, it is still necessary to develop analytical methods for the quantitation of the most important SAs in soil samples: this will help to estimate the exposure potential as well as the concentration of these substances in the terrestrial environment. Nevertheless, for a full risk assessment of these compounds not only is an exposure assessment necessary but also a hazard characterization, which addresses the question whether a substance has the potential to cause harmful effects. This will be discussed below.

3. Effects of sulphonamides in the soil environment

3.1. Introduction to soil ecotoxicology

SAs are commonly present in agricultural soils, though in fairly low concentrations (ppb and ppt levels), and are continuously being released into the environment via several routes (e.g. grazing animal faeces, manure spreading, WTP effluents). Such a state of affairs requires an Environmental Risk Assessment investigation, which should answer the basic question of whether the presence of SAs in soils poses a hazard. Ecotoxicology is the discipline that addresses this issue. It encompasses the study of organisms, populations, communities and ecosystems in terms of exposure to chemical agents, i.e. their transfer from the environment to organisms and their toxic effects. Simply put, it is the science of assessing the effects of toxic substances on ecosystems in order to protect these as a whole, rather than particular compartments, such as populations or organisms. In a practical manner, besides toxic effects, ecotoxicology explores the occurrence, distribution, accumulation and dissipation of anthropogenic toxic substances in ecosystems. The fundamental tools for this kind of research are ecotoxicological tests [82-83].

3.1.1. Ecotoxicological tests

These tests are a special group of quantitative research methods based on a thorough assessment of the impact of toxic substances (single or mixtures) on living organisms. Quantification of the results enables us to estimate the cumulative toxicity and the interactions between the introduced substances [82]. Obtaining such data enables scientists to extrapolate the results and define safe concentration levels in the ERA process (which is described in greater detail in Section 4 of this chapter).

In order to prepare valid ecotoxicity tests numerous factors need to be considered, the main ones being exposure time (acute or chronic), type of medium used, target species, toxic

substance concentration range and choice of endpoint (e.g. mortality, growth inhibition, respiration).

Some 60 years ago scientists realized the need to establish uniform, standard test procedures in order to increase the repeatability and comparability of data obtained from tests. Researchers publish their own designs for tests together with results, enabling others to mimic the conditions for further experiments and allowing a better comparison of the results. Until now many standardized test procedures have been established by various environmental and governmental organizations/institutions. The best-known of these are the Organization for Economic Cooperation and Development (OECD), International Standards Organization (ISO), American Public Health Association (APHA), Environmental Protection Agency (EPA), American Society for Testing and Materials (ASTM) and International Seed Testing Association (ISTA), as well as many others from non-English speaking countries, like the the German Institute for Standardization (Deutsches Institut für Normung – DIN) and Polish Norms (Polskie Normy – PN). With this in mind it is common practice to perform tests strictly according to a chosen norm, or to modify just some aspects of a method as and when the conditions require this [82,84].

3.1.2. Soil organisms in ecotoxicological studies

The guidelines for ecotoxicological tests recommend using the best suited organisms. If the species stipulated in a guideline is unavailable, a similar one can be chosen, but it is important to select species that are extensively described in the literature. As species usually differ between ecosystems, their choice should take account of specific local conditions [82]. It is very important to realize that no single species is representative of all ecosystems; several single-species and multispecies tests have to be carried out in order to evaluate the behaviour of a toxic substance in an ecosystem.

Three main groups of organisms are evaluated in soil ecotoxicology: plants, microorganisms (microfauna) and animals (pedofauna). In the case of pedofauna, most ecotoxicological studies of soils are based on invertebrates and focus on worms, collembolans or enchytraeids because of their rapid reproduction times and easy maintenance. The most often examined endpoints here are weight change, survival, reproduction and behaviour (e.g. avoidance). Spermatophytes are the most popular plants, in which the measured effects usually relate to physiological disorders, growth inhibition and seed germination. Microorganisms constitute a very sensitive indicator of chemical stress as there are many parameters that can be evaluated: the usual ones are respiration, nitrification and growth. However (as in the case of SAs), microorganisms are also regularly evaluated for the occurrence and magnitude of increasing resistance towards pharmaceutical compounds [82-84].

3.2. Available data on sulphonamide soil ecotoxicology

An extensive literature review of data on SA soil toxicity has shown that there is a considerable gap in knowledge concerning the effects of these substances towards soil organisms. The vast majority of publications are dedicated to the analysis of microorganisms, followed by a small number of works on plants and just a few on pedofauna. Investigations involving the determination of quantified dose-response data (such as EC_{50} – the median effective concentration)

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are rare. However, rather more experiments have been done to detect the ecotoxicity of SAs (e.g. effects observed at a single concentration). Several investigations into the accumulation of these drugs in plants and the problem of bacterial resistance have also been done and are summarized below.

3.2.1. Toxic effects of sulphonamides towards soil organisms

Literature results in the form of a dose-response relationship concerning soil organisms affected by SAs are relatively scant in comparison to the numbers available for aquatic organisms. Nonetheless, such material as has been gathered does allow us to establish some basic trends and consider the potential risk posed by SAs in the soil environment. Table 2 lists effective concentrations of SAs towards soil organisms determined for different taxonomic groups. Some of the endpoints deemed less relevant have not been included in Table 2, but they will nevertheless be mentioned in the following section.

To make the results presented in Section 3.2. more transparent, all cited concentrations have been recalculated into ppm units. However, it is of paramount importance to bear in mind that each individual study was designed separately; this implies, for example, differences between the media (soil or liquid) used. Careful thought is therefore advisable in this respect as one could grossly over- or underestimate the inferences drawn from the results. On that account, for a more detailed inquiry, we recommend that the reader refer to the original versions of the cited papers.

The pedofauna is the most understudied group of soil organisms mentioned in the literature: there have been just a handful of studies. Very interesting experiments using SMX, SDZ, SPY and SMZ were conducted on the nematode *Caenorhabditis elegans*, where several kinds of effects were evaluated (behavioural – movement, and growth – body length) during 24 – 96 hours. The second generation, not exposed to SAs, was examined in the same manner. The results showed that SAs affected growth and behaviour in all the exposed nematodes in a time- and concentration-dependent way. Also, as one might expect, behavioural effects were more sensitive than growth in all cases. Interestingly though, transgenerational effects were observed: the unexposed progeny of the examined nematodes exhibited significant toxic effects. This was speculated to correspond to the ability of SMX, SDZ, SPY to penetrate the placenta and the secretion of SDZ, SPY and SMZ in maternal milk [85-86]. A different study group evaluated the effects of SCP in a multispecies soil system, where one of the examined endpoints was the mortality of earthworms *Eisenia fetida*. In this case no effect was observed for up to 21 days of exposure to SCP at concentrations reaching 100 ppm [87].

Two independent groups performed studies of the potential impact of SMX and SMZ towards plant growth and soil quality. The plants investigated were rice *Oryza sativa* L., cucumber *Cucumis sativus* L., endive *Cichorium endivia* [88], lettuce *Lactuca sativa*, alfalfa *Medicago sativa* L. and carrot *Daucus carota* [89]. There are several differences between the approaches of the two groups, such as the time of exposure, range of concentrations or the types of tests used. Despite this, the results are comparable and some conclusions are shared. In all the investigations SMX and SMZ were deemed to have the potential to affect soil organisms in environmentally relevant concentrations. Seed germination was found to be an insensitive endpoint. One of the groups [88] evaluated seed germination using the root length of seedlings in order

to obtain better results. In nearly all cases SMX was found to be more effective than SMZ. Rice and carrot were found to be the most sensitive organisms with respective EC_{10} values of 0.1 ppm and 0.011 ppm [88-89]. Additionally, one group explored soil respiration and soil phosphatase activity: in these cases the respective EC_{10}s for SMX were 7 ppm and 1 ppm [88]. The inference to be drawn here is that antibiotic residues in manure and soils may affect soil microbial and enzyme activities.

A relatively original investigation was performed to assess the impacts of anthropogenic stressors (i.a. SAs) on symbiotic plant-microbe relationships [90]. The authors studied the effects of SMX on the arbuscular mycorrhizal fungus *Glomus intraradices* grown on carrot *D. carota* root-organ cultures. The assay endpoints were root length (carrot), hyphae growth and spore production (fungus). The exposure period lasted up to 28 days and the highest concentration tested was 1 ppm. SMX was found to be effective at low concentrations towards both organisms: the respective EC_{50}s for carrot and fungus (hyphae growth) were 0.0454 and 0.0451 ppm. Assessment of the endpoints was as follows: root lengths responded quickly to the presence of phytotoxic pharmaceuticals in the culture medium; hyphae length was a sensitive endpoint after 21 days' exposure; spore production required 28 days' exposure before significant differences could be detected [90].

The toxicity of STZ towards soybean (*Glycine max* (L.) Merr.) was evaluated as a potential nitrification inhibitor [91]. The effects were measured according to the growth of these plants. Fresh weight and dry weight of roots and plant tops were measured. The concentration range for STZ reached 200 ppm. STZ drastically reduced both main root elongation and lateral root development, the suppression increasing concentration-wise. Effects on soybean plants were detectable but statistically non-significant at a concentration of 10 ppm. STZ EC_{50} for dry root yield was equal to 29.5 ppm. It is worth noting that STZ inhibited root growth more than top growth.

The effects of sulphamonomethoxine sodium (SMM-Na) and sulphadiazine sodium (SDZ-Na) were investigated in three plant species: wheat *Triticum aestivum* L., Chinese cabbage *Brassica campestris* L. and tomato *Cyphomandra betacea* [92]. All of the plants exhibited linear correlations between the effects (root and shoot elongation) and SA concentrations. Seed germination was also considered, but was not sensitive to toxicity within the chosen range of SA concentrations. The tests were conducted over 2-5 days. The data acquired showed that wheat was the plant most sensitive to the toxicity of SDZ-Na with an IC_{50} = 28.1 ppm and that cabbage was the most sensitive to SMM-Na with an IC_{50} = 27.1 ppm. Worthy of note is the fact that in this study root and shoot elongation of the three crops exhibited different sensitivities, depending on the particular drug and plant species [92].

A study was developed specifically for SAs; it attempted to assess different susceptibility patterns of soil bacteria *Pantoea agglomerans* and standard antibiotic test bacteria *Pseudomonas aeruginosa*, depending on intercellular and environmental pH [93]. The results of the study revealed the effects at low concentrations (max. 20 ppm) of 8 SAs (SMX, STZ, SDZ, SDM, SMZ, SCP, SPY and SGD) at different pH values (from 5 to 8). The effects corresponding to the most sensitive pH values are listed in Table 2. The brief conclusion of this work is that the effects of SAs on microbial soil populations may depend closely on the ability of the bacteria to regulate their intercellular pH [93].

http://dx.doi.org/10.5772/57265

Substance	Type of test	Species	Critical effect	Time	Toxicity [ppm]	Ref.
SMX	tailored design	nematode *Caenorhabditis elegans*	body length *	24 h	EC_{10} > 100	[85]
				48 h	EC_{10} = 1.02	
				72 h	EC_{10} = 0.0302	
				96 h	EC_{10} = 0.00131	
	ISTA 1985	rice *Oryza sativa* L.	root length (seed germination)	4-5 d	EC_{50} = 8 NOEC = 1	[88]
		cucumber *Cucumis sativus* L.			EC_{50} > 300 NOEC = 1	
		endive *Cichorium endivia*			EC_{50} = 69 NOEC = 0.1	
	OECD 1984 (modified)	rice *Oryza sativa* L.	root length (plant growth)*	20 d	EC_{50} = 13 NOEC = 1	
		cucumber *Cucumis sativus* L.			EC_{50} > 300 NOEC = 100	
	tailored design	soil microbe	soil respiration	2 d	EC_{50} = 7	
	ASTM 2003	lettuce *Lactuca sativa*	root length*	5 d	EC_{50} > 10 EC_{10} = 1.367	[89]
		alfalfa *Medicago sativa* L.			EC_{50} > 10 EC_{10} > 10	
		carrot *Daucus carota*		7 d	EC_{50} = 0.06 EC_{10} = 0.011	
	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} = 2.98	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 0.34	
	tailored design	carrot *Daucus carota*	root length	14 d	EC_{50} = 0.0627 LOEC = 0.01	[90]
				21 d	EC_{50} = 0.0612 LOEC = 0.03	
				28 d	EC_{50} = 0.0454 LOEC = 0.01	
		mycorrhizal fungus *Glomus intraradices*	hyphae length*	14 d	EC_{50} = 0.5029	
				21 d	EC_{50} = 0.0749 LOEC = 0.3	
				28 d	EC_{50} = 0.0451 LOEC = 0.3	
STZ	tailored design	soybean *Glycine max* (L.) Merr.	growth reduction – fresh weight	61 d	ED_{50} = 42	[91]

Substance	Type of test	Species	Critical effect	Time	Toxicity [ppm]	Ref.
			growth reduction – dry yield top		ED_{50} = 33.5	
			growth reduction – dry yield root		ED_{50} = 29.5	
	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} = 5.47	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 0.77	
SDZ	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} = 2.85	[12]
		bacteria *Pantoea agglomerans*			EC_{50} = 0.5	
SDZ-Na	OECD 1984	wheat *Triticum aestivum* L.	root elongation inhibition *	2 d	IC_{50} = 28.1	[92]
		cabbage *Brassica campestris* L.		3 d	IC_{50} = 31.3	
		tomato *Cyphomandra betacea*		5 d	IC_{50} = 92.9	
SMM-Na	OECD 1984	wheat *Triticum aestivum* L.	root elongation inhibition *	2 d	IC_{50} = 120.7	[92]
		cabbage *Brassica campestris* L.		3 d	IC_{50} = 27.1	
		tomato *Cyphomandra betacea*		5 d	IC_{50} = 88.0	
SDM	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} > 20	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 2.05	
SDMD (SMZ)	ISTA 1985	rice *Oryza sativa* L.	root length (seed germination)	4-5 d	EC_{50} = 45 NOEC = 1	[88]
		cucumber *Cucumis sativus* L.			EC_{50} > 300 NOEC = 1	
		endive *Cichorium endivia*			EC_{50} = 37 NOEC = 0.1	
	OECD 1984 (modified)	rice *Oryza sativa* L.	root length (plant growth)*	20 d	EC_{50} = 43 NOEC = 1	
		cucumber *Cucumis sativus* L.			EC_{50} > 300 NOEC = 100	
	tailored design	soil microbe	soil respiration	2 d	EC_{50} = 13	

Substance	Type of test	Species	Critical effect	Time	Toxicity [ppm]	Ref.
	ASTM 2003	lettuce *Lactuca sativa*	root length*	5 d	EC_{50} >10 EC_{10} = 0.851	[98]
		alfalfa *Medicago sativa* L.			EC_{50} > 10 EC_{10} = 5.336	
		carrot *Daucus carota*		7 d	EC_{50} >10 EC_{10} = 0.065	
	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} > 20	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 1.14	
SCP	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} = 7.08	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 0.48	
SPY	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} > 20	[93]
		bacteria *Pantoea agglomerans*			EC_{50} = 2.22	
SGD	DIN 58959-7	bacteria *Pseudomonas aeruginosa*	growth inhibition	24 h	EC_{50} > 20	[93]
		bacteria *Pantoea agglomerans*			EC_{50} > 20	

* this author also examined the results for several other endpoints – see Section 3.2.1.

Table 2. Sulphonamide soil ecotoxicology – literature review

3.2.2. Other relevant soil ecotoxicology data

Several publications by Migliore et al. have shed much light on the toxicity and bioaccumulation of SDM for different terrestrial plants [94-98]. The species included in the research belonged to two groups:

- crop plants *Panicum miliaceum* L., *Pisum sativum* L., *Zea mays* L. and *Hordeum distichum* L.
- weeds *Amaranthus retroflexus* L., *Plantago major* L., *Rumex acetosella* L and *Lythrum salicaria* L.

All the plants exhibited bioaccumulation and toxicity during post-germinative development at concentrations of 300 ppm, though of course to different extents. *Lythrum salicaria* L., exposed to lower concentrations, demonstrated a hormetic response. Crop plants accumulated SDM at dissimilar rates but always higher in roots than in foliage. In order to present the versatility of these results, those of additional research using other SAs and terrestrial plants are listed in Table 3.

Substance	Organism	Observed effects	Ref.
SDM	*Panicum miliaceum* L., *Pisum sativum* L., *Zea mays* L., *Hordeum distichum* L., *Amaranthus retroflexus* L., *Plantago major* L., *Rumex acetosella* L. and *Lythrum salicaria* L.	accumulation, growth inhibition, hormesis	[94-98]
SDZ SDM SMZ	*Salix fragilis* L., *Zea mays* L., *Hordeum vulgare* L.	accumulation, toxic effects (root physiology impairment)	[101-103]
SDZ SMX	*Brassica rapa* L. and *Lumbricus terrestris* (p), activated sludge (sm)	non-extractable residues – low uptake by organisms	[104]
SDZ	soil microorganisms	respiration inhibition, adaptation	[105]
SDZ	*Eisenia fetida* (p)	no accumulation (uptake detected)	[106]
SDM	*Rhizobium etli* (sm)–*Phaseolus vulgaris* L. symbiosis	growth inhibition of both organisms	[107]
SDZ SMZ SMX	*Brassica chinensis* L. and soil microorganisms	accumulation, soil microbial biomass inhibition - higher effects for combined pollution	[70]
12 SAs	*Arthrobacter globiformis* (sm)	no effect in t = 4 h	[100]
SMX	*Salmonella typhimurium* (sm)	mutagenic activity	[108]
SDZ	*Zea mays* L. and soil microorganisms	molecular-chemical pattern changes	[109]
SDZ	soil microorganisms	soil respiration and bacterial community structure were influenced only after the addition of glucose	[110]
SDZ	soil microorganisms	soil community structure shift	[111]
SDZ	*Triticum aestivum* L.	accumulation (mainly in roots)	[112]
SMZ	*Lupinus luteus*, *Pisum sativum* L., *Lens esculenta* Medik., *Glycine max* (L.) Merr., *Vigna angularis*, *Medicago sativa* L.	root growth inhibition, necrotic changes, cytochrome c oxidase activity shifts	[113]
SDM SMX	*Pisum sativum* L., *Cucumis sativus* L.	accumulation (mainly in roots)	[114]
SMX	*Brassica campestris* L.	minimal accumulation	[115]
SMZ	*Lolium perenne* L., *Poa pratensis* L., *Poa trivialis* L., *Nasturtium officinale* R. Br.	accumulation	[116]
SDM SMR	*Solanum tuberosum* L., *Daucus carota*, *Zea mays* L., *Lycopersicon esculentum* Mill.	accumulation	[117]
SDZ	*Lactuca sativa*, *Daucus carota*	not detected in subject plants	[118]

All organisms in Table 3 belong to one of three groups: soil microorganisms **(sm)**, pedofauna **(p)** or terrestrial plants.

Table 3. Simplified list of published SA soil ecotoxicology research

As stated before soil microbiota is sensitive and easy to evaluate; hence, it is often examined for several target effects. In some cases, however, the results are closely dependent on incubation time – OECD 209 guidelines recommend relatively short exposure times – which can lead to underestimated results. This issue has been mentioned by authors working with SAs [99-100]. Moreover, microorganisms are often not the primarily evaluated body in a test design. In fact effects on microbe communities are sought as additional results, helpful in monitoring the conditions in the test environment. Some research papers covering the soil ecotoxicity of SAs (not mentioned hitherto) are very briefly summarized in Table 3.

3.2.3. Development of resistance of soil microorganisms to sulphonamides

The current increasing interest in research into pharmaceutical residues in the environment has drawn the attention of scientists to the causation of bacterial resistance by antimicrobial residues. As the case of SA residues in terrestrial compartments is no exception, relevant research results have been published by several authors.

The effect of SCP together with pig slurry was examined during a three-week exposure, using Biolog® multiwall plates to determine pollution-induced community tolerance (PICT). Several physiological processes were monitored as well as community-level physiological profiling (CLPP) [119]. As a result of the tests it was established that the soil microbial community's tolerance increased as soon as 7 days following exposure. Indeed, a SCP concentration of 7 ppm was sufficient to trigger the first effects. An increase in tolerance has been reported for a procedure comparable to normal agricultural practice [119].

Several investigations have been conducted with SDZ in manure. It was established that such a combination synergistically increased antibiotic resistance in bacteria. Some of the explored variations of the tests included the use of a multispecies system (microcosm) with soil bacteria, the preparation of tests on different kinds of soil and multiple amendment with pig manure. SA resistance genes were detected using hybridization and the polymerase chain reaction (PCR). In all cases there was a significant increase in resistance, though differing in extent depending on the test design. Following amendment, the bacterial populations carrying the SA resistance genes introduced to the soil declined strongly in the first weeks; nonetheless, they have the potential to be present for several months [120-122].

Sulphamethoxazole (SMX) was also examined with respect to its effect on soil bacteria. Two methods were used to assess PICT: leucine incorporation and Biolog® plates. Community structure was assessed using phospholipid fatty acid (PLFA) analysis, CLPP and bacterial growth. No effect was seen at 1 ppm SMX. At higher concentrations (20 – 500 ppm) effects were significant but relatively small (a ca twofold increase in community tolerance). Nonetheless, the impact of SMX on soil reflected both the direct inhibition of bacterial growth rates and changes in community structure [123].

4. Environmental risk assessment of veterinary pharmaceuticals (VPCs) in soil ecosystems

Guidelines describing how the environmental risks of veterinary products should be assessed for a range of countries have been published [22]. The approach used in Europe is based on the recommendations of the International Co-operation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH), which has attempted to harmonize the environmental risk assessment requirements of veterinary products in the USA, Europe and Japan. The approach is a two-phase process [19-20,22]. According to these guidelines for the environmental risk assessment (ERA) of VPCs, the ERA process starts with an initial exposure assessment (Phase I). With some exceptions, a fate and effects analysis (Phase II) is only required when exposure-based thresholds, the so-called action limits, are exceeded in different environmental compartments. Thus, risk assessment, described by the Risk Quotient (RQ), is carried out by calculating the ratio of the predicted (or measured) environmental concentration (PEC or MEC respectively) and the predicted biological non-effective concentrations (PNEC) on non-target organisms. The PNEC is ultimately derived from the toxicity data by applying an assessment factor (AF), usually calculated as the ratio of EC_{50} or NOEC to AF. The assessment factor (in the range from 10 to 1000) takes into account interspecies variation, acute/subchronic to chronic extrapolation and laboratory data to field impact extrapolation. For example, for acute toxicity tests its value is 1000. Nevertheless, if RQ is less than one, no further testing is recommended. Calculations of environmental concentrations rely on information on treatment dosage and intensity along with default values for standard husbandry practices and are based on a total residue approach reflecting worst-case assumptions. No fate and effects analysis is required for VPCs if the predicted environmental concentration in soil (PEC_{soil}) is < 100 μg/kg dry weight of soil. In this case the ERA is brought to a close. However, if PEC_{soil} is higher than the action limit, then Phase II, divided into two parts, comes into play: Tier A, in which the possible fate of the pharmaceutical or its metabolites and its effects on earthworms (mortality) and plants (germination and growth) as well as the effects of the test compound on the rate of nitrate mineralization in soil are determined; and Tier B, in which only effect studies are recommended for affected taxonomic levels (when RQ > 1 or in the case of soil microorganisms an effect > 25 %); no further guidance on Tier B testing is provided. There are no requirements regarding the species of organisms that should be used at this stage apart from the statement that the study using terrestrial plants should be repeated on two additional species from the most sensitive species category in the Tier A study, in addition to repeating the study on the most sensitive species. However, if after Tier B testing RQ is still > 1, more studies may be needed in order to further elucidate the effects on terrestrial ecosystems [19-23].

The main problem associated with this approach is the fact that the no actual sales figures or measured environmental concentrations are at hand when a risk assessment is conducted. Therefore, only crude PEC calculations are performed [124]. Moreover, the (eco)toxicity tests in Phase II are carried out only for single compounds and on a limited range of species. As these compounds occur in natural media not as single, isolated drugs but usually together with

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other compounds of the same family or the same type, accumulated concentrations or synergistic-antagonistic effects need to be considered. For these reasons, Schmitt et al. suggested checking whether the current action limits are sufficiently protective for aquatic and terrestrial organisms by at least performing limit tests to confirm the absence of effects due to pharmaceuticals with PECs below the action limits [125]. Therefore, it seems to very important to check whether other pharmaceuticals do not also pose a threat to such organisms. In addition, it must be highlighted that contaminants in ecosystems can cause adverse effects, and that the severity of such effects is not dependent on the total substance concentration but on the bioavailable concentration of the xenobiotics. Therefore, the central concept for an assessment of soils should be the bioavailability representing the link between exposure and effect of contaminants. As a consequence a "bioavailability concept" was developed, which links environmental chemistry and ecotoxicology. According to Frische et al. [126] "bioavailability describes the complex processes of mass transfer and uptake of contaminants into soil-living organisms which are determined by substance properties, soil properties, the biology of organisms and climatic influence. The bioavailable contaminant fraction in soil represents the relevant exposure concentration for soil organisms". For these reasons, risk assessments and subsequent regulatory measures (permission to use chemicals, threshold values and redemption goals in soils) are particularly subject to considerable uncertainties as long as nominal and measured total concentrations are the basis of exposure assessment [126]. Owing to necessary extrapolations, the present non-consideration of bioavailability in practice can result in both over- and underestimating the risks posed by chemicals to soils, which is why it should be included in such an ecotoxicological test. To date, only a few authors have investigated the ecotoxicity potential of pharmaceuticals with respect to their bioavailability in soil samples (e.g. [127]).

5. Risk assessment of sulphonamide residues in soil ecosystems

The approach to risk evaluation of sulphonamides in the terrestrial environment, based on the discussed issues, is presented in Figure 2.

Although, as stated in Section 2, available studies have demonstrated that the sorption potential of SAs is low, this feature, along with their mobility, is strongly influenced by the physicochemical properties of soils, the ionic strength of soil solutions as well as the physicochemical properties of the drug itself. Hence, even a slight change in these parameters can greatly increase the immobilization of SAs in soil. Furthermore, it must be emphasized that SAs are continuously being released into terrestrial ecosystems; therefore, the kind of exposure of soil organisms may be subjected to will resemble that of traditional pollutants (e.g. pesticides, detergents), even those of limited persistence. Consequently, SAs (like other pharmaceuticals) may be considered pseudo-persistent, which explains why they are detected in soils, even at such high concentrations. For all the above reasons, the ERA of SAs is a very complex and difficult process. The simple approach defined in the available guidelines, while undoubtedly useful, may not be sufficient. In accordance with existing requirements [19-23] we present a calculation of RQ for three SAs, assuming the worst case scenario; maximum reported

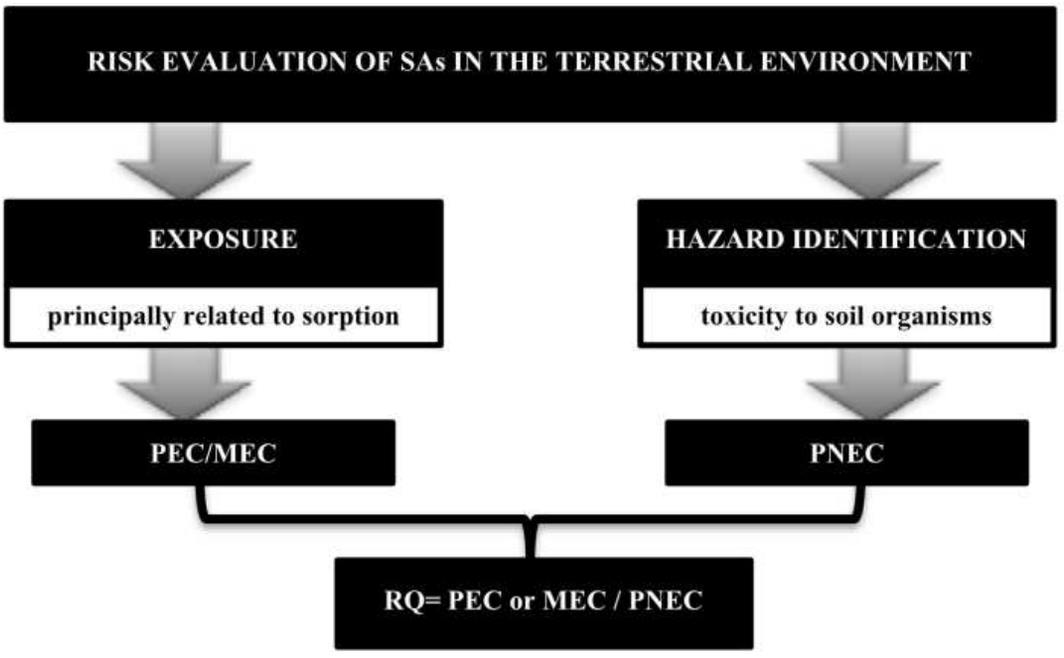

Figure 2. Risk evaluation of sulphonamides in the terrestrial environment

concentrations (Section 2.4) were used for the MEC value, PNEC was calculated on the basis of the data presented in Table 2, and AF was set at 1000 to ensure reliability (see Table 4).

Substance	MEC_{soil} [(μg kg^{-1}]	Organism	$PNEC=EC_{50}/AF$ (AF=1000) [μg kg^{-1}]	RQ=MEC/PNEC
SMX	100	rice *Oryza sativa* L.	13	**7.7**
		soil microbe	7	**14.3**
	0.9	rice *Oryza sativa* L.	13	0.07
		soil microbe	7	0.13
STZ	400	soybean *Glycine max* (L.) Merr.	42	**9.5**
SMZ	11	rice *Oryza sativa* L.	43	0.25
		soil microbe	13	0.84
	4.5	rice *Oryza sativa* L.	43	0.10
		soil microbe	13	0.35

Table 4. RQ calculations for three SAs (RQs >1 are presented in bold)

The data presented in Table 4 support our above statement, as different RQs were obtained, depending on the data used in this evaluation. It seems that a single environmental concentration, which can differ in time and place, as well as the PEC values, which may also differ in different countries, can lead to the over- or underestimation of the risk posed by these

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compounds. Hence, in our opinion, more realistic (reliable) approaches should be incorporated that are based on data obtained from longer term monitoring studies in each country.

6. Conclusions

Our knowledge of the presence of SAs in soils is increasing, but information in the peer-reviewed literature regarding the fate and ecotoxicological effects is still limited.

As sorption to the soil matrix governs the transport, persistence and (bio)availability of these chemicals in the environment, it can be assumed that low K_d values, together with the physicochemical properties of these compounds, indicate that they are highly mobile, readily bioavailable and easily transported from soil surfaces to aquifers, causing surface- and groundwater contamination. Being readily bioavailable to micro-organisms, plants and animals, SAs can affect these directly; indeed, they have the potential to affect entire terrestrial ecosystems. The literature records the effects of many SAs on soil organisms, although these are mainly microorganisms and plants; as there are few data on pedofauna, it is impossible to form any clear judgment in this respect. SAs have been detected in soils, and the evidence points to possible effects on soil organisms at environmentally relevant concentrations. Furthermore, SAs can be accumulated by several terrestrial plants, such as the willow *Salix fragilis* L., which could be employed for the phytoremediation of SA-contaminated soils. However, some vegetables are also reported to accumulate SAs, which could lead to adverse effects along the food chain, ultimately affecting human health. Nevertheless, research into bioaccumulation as well as the phytoremediation of these compounds is still needed.

The most and least sensitive endpoints in plant studies are root length and seed germination respectively. The effects of SAs on microorganisms have been studied in many ways, e.g. with single species and multispecies designs, and different endpoints. Most of the available data show a strongly dose-dependent relationship for the explored endpoints. Moreover, their toxicity can be strongly influenced by the pH in the environment and organisms. Furthermore the issue of microorganisms developing antibiotic resistance is related to SAs. Especially when SA-contaminated manure is used, there is a noticeable increase in resistance genes.

Hardly any information has been found concerning the toxicity of SA mixtures in soils. Since these compounds are almost always present in the form of mixtures in the environment, this issue is one to be addressed in the future. Furthermore, there is a lack of data relating to the long-term exposure of non-target organisms, and especially how continuous exposure for several generations may affect a whole population.

In conclusion, the presented data on the fate and potential effects of SAs in the terrestrial environment appear to indicate a possible negative impact on soil ecosystems and imply a threat to public health. However, further studies are necessary to characterize the risk completely.

Abbreviations

Abbreviation	Full name	Abbreviation	Full name
AF	Assessment Factor	**PICT**	Pollution-induced Community Tolerance
APHA	American Public Health Association	**PN**	Polish Norms (Polskie Normy)
ASTM	American Society for Testing and Materials	**PNEC**	Predicted Non-Effective Concentrations
CLPP	Community-level Physiological Profiling	**RQ**	Risk Quotient
DIN	German Institute for Standardization (Deutsches Institut für Normung)	**SA(s)**	Sulphonamide(s)
EC_{50}	Effective Concentration	**SCP**	Sulphachloropyridazine
ED_{50}	Effective Dose	**SDM**	Sulphadimethoxine
EMEA	European Medicines Evaluation Agency	**SDMD (SMZ)**	Sulphadimidine (Sulphamethazine)
EPA	Environmental Protection Agency	**SDZ**	Sulphadiazine
ERA	Environmental Risk Assessment	**SGD**	Sulphaguanidine
IC_{50}	Inhibitory Concentration	**SMM**	Sulphamonomethoxine
ISO	International Organization for Standardization	**SMR**	Sulphamerazine
ISTA	International Seed Testing Association	**SMX**	Sulphamethoxazole
LOEC	Lowest Observed Effect Concentration	**SPY**	Sulphapyridine
MEC	Measured Environmental Concentration	**SSX**	Sulphisoxazole
NOEC	No Observable Effect Concentrations	**STZ**	Sulphathiazole
OECD	Organization for Economic Cooperation and Development	**VICH**	Veterinary International Conference on Harmonization
OM	Organic Matter	**VPCs**	Veterinary pharmaceuticals
pABA	*p*-aminobenzoic acid	**WTP**	Wastewater Treatment Plant
PEC	Predicted Environmental Concentration	**f_{oc}**	Organic Carbon Content

Table 5. List of abbreviations used in the text

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