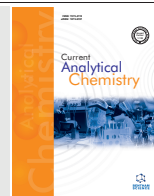


## The Occurrence of Veterinary Pharmaceuticals in the Environment: A Review



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**Abstract:** It is well known that there is a widespread use of veterinary pharmaceuticals and consequent release into different ecosystems such as freshwater bodies and groundwater systems. Furthermore, the use of organic fertilizers produced from animal waste manure has been also responsible for the occurrence of veterinary pharmaceuticals in agricultural soils. This article is a review of different studies focused on the detection and quantification of such compounds in environmental compartments using different analytical techniques. Furthermore, this paper reports the main challenges regarding veterinary pharmaceuticals in terms of analytical methods, detection/quantification of parent compounds and metabolites, and risks/toxicity to human health and aquatic ecosystems. Based on the existing literature, it is clear that only limited data is available regarding veterinary compounds and there are still considerable gaps to be bridged in order to remediate existing problems and prevent future ones. In terms of analytical methods, there are still considerable challenges to overcome considering the large number of existing compounds and respective metabolites. A number of studies highlight the lack of attention given to the detection and quantification of transformation products and metabolites. Furthermore more attention needs to be given in relation to the toxic effects and potential risks that veterinary compounds pose to environmental and human health. To conclude, the more research investigations focused on these subjects take place in the near future, more rapidly we will get a better understanding about the behavior of these compounds and the real risks they pose to aquatic and terrestrial environments and how to properly tackle them.

**Keywords:** Animal husbandry, antibiotics, metabolites, veterinary pharmaceuticals, waste manure.

### 1. INTRODUCTION

The widespread use of large quantities of veterinary pharmaceuticals and respective release into different environmental compartments resulting in environmental and ecological impacts has brought serious concerns in the last years [1, 2]. [1] stated that even though the global pharmaceutical market has grown twice during the last decade, there are possibilities that the amounts of veterinary drugs released into the environment were much higher due to the lack of control in relation to types and amounts of drugs in use mainly when considering countries such as China or other Southeast Asia Nations [3]. For example the European Federation of Animal Health (FEDESA) estimates the consumption of approximately 4700 tons in veterinary medicine back in the year of 1999 in the European Union [4]. [4] have reported that one-third of antibiotics consumption in Europe is related to veterinary use with the main uses reported by poultry and pigs livestock.

Veterinary pharmaceuticals are classified as either for therapeutic use or non-therapeutic use and depending on the different groups of animals, the same compound can be used

for different purposes [5]. According to [4, 6, 7], veterinary pharmaceuticals/antibiotics are widely used in livestock production for disease prevention and growth promotion with significant quantities of antibiotics used as a feed supplement for growth enhancement of food animals. Furthermore, [8] state that veterinary medicines also prevent economical losses and help ensure a safe food supply for human population. In the European Union, veterinary pharmaceutical use for growth promotion is banned making the major environmental load of such chemicals originated from prophylactic treatment. Based on [3], among the total use of antibiotics in Australia, 8% is used for veterinary purposes and 56% is mixed into stock feed. [6] have reported a summarized table which shows the worldwide variation of approximate amounts of veterinary antibiotics used on the basis of sold amounts and USA and Korea were the countries in the top of the list with 11,148 tons year<sup>-1</sup> and 1,533 tons year<sup>-1</sup> sold respectively. These amounts were significantly higher in comparison to countries within European Union suggesting that prohibition of using supplements for growth promotion in 1998 resulted in significant reduction of veterinary antibiotics use.

According to [9], veterinary pharmaceuticals are “emerging contaminants” since such class of chemicals have not been included in any monitoring program (national or inter-

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national) and established as parameters to be controlled in environmental-quality regulations, even though have been continuously introduced into the environment.

Among the veterinary products that have been raising concerns, ionophore antibiotics (IPAs) are antimicrobial agents widely used by the livestock industry and ranked as one of the highest priority groups to be investigated due to the lack of a comprehensive understanding of their environmental occurrence and fate [10]. Anthelmintics are drugs that act against helminthic infections (i.e. caused by parasitic worms) and administrated to wide range of important veterinary animals in agriculture and aquaculture, and comprise a large sector of the animal pharmaceutical industry [9]. Azole substances are widely used as antifungal agents in veterinary pharmaceuticals, agricultural fungicides, and biocides in various products and the massive usage may therefore lead to substantial amounts of azole residues in the environment [11]. Azoles are suspected to potentially affect endocrine systems of aquatic vertebrates [11].

Therefore, it is already widely known that veterinary pharmaceuticals have been introduced into different environmental compartments in metabolized and un-metabolized forms. According to [12] the contamination of soil, surface water and groundwater has raised serious concerns because even though in low levels, antibiotics favor the appearance and development of antibiotic-resistance microorganisms due to their continuous exposure to such chemicals. The authors state an increased emergence of resistant strains of pathogenic bacteria that can bring serious impacts to human health [12] due to the fact that resistance genes could be transferred to other bacteria living in ground water, drinking water or plants and thus to humans [13]. [14] has highlighted the effects of veterinary antibiotics in terrestrial ecosystems such as adverse effects on nitrifying bacteria and growth inhibition of crop plants and weeds through bioaccumulation processes. As soon as such chemicals are released into an environmental compartment, their persistence/availability/ transformation will be determined by steric characteristics, chemical composition, and other parameters including biodegradability, cometabolism, sorption or chemical oxidation which are strongly dependent on the interactions between released compounds and the environment making the process very complex [15]. Moreover, some physicochemical properties play important roles on the potential impacts caused by VPs such as water solubility, octanol/water partitioning coefficient, the acid dissociation constant and others [16].

In the recent years, the number of research and publications on the occurrences of veterinary pharmaceuticals in different environmental matrices has been increasing remarkably. There is no doubt that considerable attention needs to be paid in the coming future due to this type of contamination which justifies the publication of review papers focusing on the occurrence and future challenges such pharmaceuticals will bring to the society. Therefore this current manuscript presents a review of the scientific literature that reports the occurrence of these chemicals in environmental matrices. The main idea is to make available the current

status of studies and knowledge in relation to veterinary pharmaceuticals in environmental compartments. The main subjects of concern presented in the current manuscript are as follows: 1) the most commonly studied veterinary pharmaceuticals, 2) the main sources of veterinary pharmaceuticals and their pathways into the environment, 3) occurrence of veterinary pharmaceuticals in the aquatic environment, 4) occurrence of veterinary pharmaceuticals in terrestrial environment and 5) current and future challenges to tackle the problems of such contaminants in order to prevent future impacts on the environment and human health. In Table 1, some of commonly studied veterinary pharmaceutical compounds can be seen.

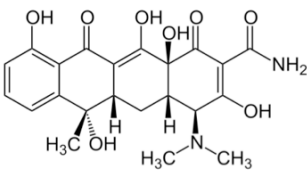
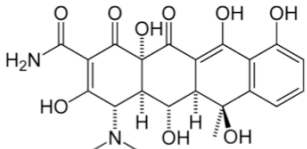
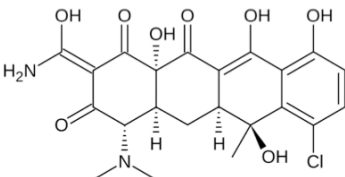
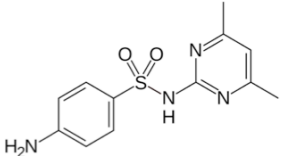
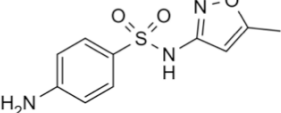
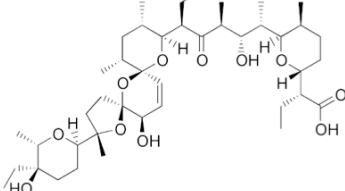
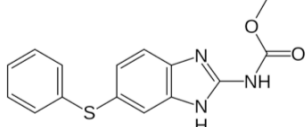
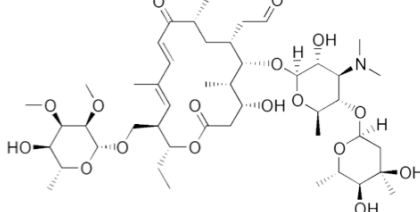
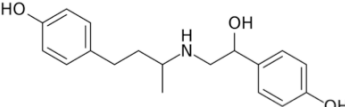
## 2. SOURCES OF CONTAMINATION AND PATHWAYS OF INTRODUCTION INTO THE ENVIRONMENT

It has been reported in the literature that main sources of veterinary pharmaceuticals to the environment are intensive livestock activities and farming practices [2, 6, 17]. [18] mentioned that such chemical compounds are frequently released into the environment either as active metabolites or completely un-metabolized. Veterinary antibiotics are often present as supplements in animal feed as growth promoters being then commonly excreted directly through urine and feces of grazing animals in livestock farms [1, 6, 19], pasture [20] and aquaculture [1, 16]. Indirect release has been related to the use of such excreted organic by-products as alternative fertilizers [1, 6, 20], drifting from manuring processes [21], disposal of sewage from intensive livestock farming and effluents from aquaculture systems [2]. According to [22], land applications of recycled organic manures are increasing in the world and therefore the manure produced from these feces might be a considerable source of environmental/ecological impacts. Manure is regarded as a very valuable fertilizer, as it contains essential nutrients for plant growth such as nitrogen, phosphorous, organic carbon, potassium etc. The extensive use of manure from medicated animals in crop fields is among the major routes by which veterinary antibiotics enter the environment and, eventually, ground water systems and surface waters through percolation and runoff respectively [23].

[18] have also highlighted risks of expired pharmaceuticals being released into the environment due to improper disposal. Another issue that has been recently emphasized in the literature is the potential impacts in natural water recipients originating from land burial of cattle carcasses [24]. The authors have stated that few studies have documented the impacts of carcass burial on groundwater quality in terms of veterinary pharmaceuticals, and the existing ones have focused on poultry carcass disposal and contaminants such as ammonia, nitrate, chloride and fecal pathogens [24].

Even though the sorption of veterinary pharmaceuticals on soil has been reported by [6], depending on the interaction between antibiotics and soil such compounds can be easily transported to groundwater and surface water bodies through surface runoff, infiltration/percolation [6, 20] and land erosion [19]. The application of waste lagoon waters to fields as

Table 1. Some of the veterinary pharmaceuticals reported in the literature.

Class	Compound	CAS-Nr	Structure	Formula
Antibiotics	Tetracycline	60-54-8		$C_{22}H_{24}N_2O_8$
	Oxytetracycline	79-57-2		$C_{22}H_{24}N_2O_9$
	Chlortetracycline	57-62-5		$C_{22}H_{23}ClN_2O_8$
	Sulfamethazine	57-68-1		$C_{12}H_{14}N_4O_2S$
	Sulfamethoxazole	723-46-6		$C_{10}H_{11}N_3O_3S$
	Salinomycin	53003-10-4		$C_{42}H_{70}O_{11}$
Anthelmintic	Fenbendazole	43210-67-9		$C_{15}H_{13}N_3O_2S$
Feed additives	Tylosin	1401-69-0		$C_{46}H_{77}NO_{17}$
	Ractopamine	97825-25-7		$C_{18}H_{23}NO_3$

fertilizers and possibilities of accidental overflow and leakages from such storage lagoons and tanks likely contribute to the release of veterinary drugs into the environment [16]. The main concerns are the complexities that one needs to overcome to have a better understanding of the final fates of veterinary pharmaceuticals since as soon as they reach the environment, their fate will be governed by different factors [20]. One important issue that has been highlighted in the literature is that differently than other general commercial chemicals, pharmaceuticals are designed to have biological effects and be bioavailable resulting in potential effects on aquatic organisms and human health [17].

### 3. OCCURRENCE OF VETERINARY PHARMACEUTICALS IN AQUEOUS MATRIX

During the last decade, a number of studies that have addressed the occurrence of veterinary pharmaceuticals in different aquatic environments, either natural such as lakes, rivers and groundwater or of anthropogenic origin, such as wastewater of different types and landfill leachates. In the following sections, different aquatic environments and respective literature regarding the occurrences of veterinary pharmaceuticals will be presented separately. A summary of the veterinary compounds reported in the different studies, concentration ranges and respective analytical methods is given in Table 2.

#### 3.1. Wastewater Treatment Plants – Inlet/Outlet

Differently than pharmaceuticals for human use that are usually monitored in municipal wastewater treatment plants, the occurrence of pharmaceuticals in the environment is more related to diffuse pollution rather than point sources and not many studies in wastewater treatment plants have been done. However, [25] have studied the presence and concentration of pharmaceuticals in effluents of Canadian sewage treatment plants (STPs) and compared their findings with the maximum concentrations observed in other countries. A diverse number of antibiotics were detected; although most of them were related to human consumption, an antibiotic of exclusive use for veterinary applications, sulphamethazine, was detected in concentrations up to 3.278 µg/L [25]. Whereas municipal wastewater treatment plants are not receiving loads of veterinary pharmaceuticals, wastewater impoundments at concentrated animal feeding operations (CAFOs) represent a potential source of veterinary pharmaceuticals to the environment [26], reason why an investigation regarding the occurrence of seventeen VPs in lagoons at operating swine and beef cattle facilities was carried out [26]. VP compounds detected in samples obtained from cattle facilities included sulfamerazine, sulfamethazine, erythromycin, monensin, tiamulin, and sulfathiazole. Lincomycin, ractopamine, sulfamethazine, sulfathiazole, erythromycin, tiamulin and sulfadimethoxine were detected in wastewater samples obtained from swine facilities making the authors conclude that groundwater underlying livestock wastewater impoundments was highly susceptible to contamination originated from the studied wastewater lagoons. Similar studies were carried out by [15] in Korea, where the authors have taken wastewater samples from 11 different livestock wastewater treatment plants (LWTs) and detected nine antibiotics and two analgesics in the samples. The compounds that were detected in high concentrations were chlor-

tetracycline, oxytetracycline and acetylsalicylic acid, and it was emphasized that the high amounts of such antibiotics detected in LWTs were highly correlated to the annual amount manufactured of each antibiotic [15]. Furthermore the authors have highlighted the correlation between frequency of detection and concentrations since those compounds detected in high concentrations (chlortetracycline, oxytetracycline, and acetylsalicylic acid) were the ones that were frequently detected in the studied samples. [27] reported the presence of VPs in LWTs, and very high levels of the anthelmintic fenbendazole (from 3.85 to 241 µg/L) and its metabolites fenbendazole sulfone (0.283 – 93.9 µg/L), amino fenbendazole (0.554-94.1 µg/L) and p-hydroxyfenbendazole (0.693 – 92.7 µg/L) were detected at the inlet of LWTs, suggesting the wide use of this compound for various livestock. Furthermore, [27] also highlighted the occurrence of fenbendazole (0.018 – 0.533 µg/L) in influent waters of domestic sewage treatment plants, emphasizing the use of veterinary anthelmintics in households (e.g. pets) and consequent discharge into treatment plants.

[28] have detected a wide occurrence of sulfamethazine in the Mekong Delta, Mekong River, Vietnam in extremely high concentrations (19200 and 18500 ng/L) in pig farm wastewater, highlighting the large number of pigs in this region and potential environmental impacts. The authors mentioned that based on an evaluation of commercial drugs and interview with pharmacists, this is solely used for veterinary purposes in Vietnam, suggesting the use of sulfamethazine as an indicator of livestock waste and widespread inputs of veterinary medicines in the Mekong Delta. However, [28] emphasize that the use of this medicine as a specific to livestock wastes should be carefully evaluated since human use can also contribute to environmental contamination of the region. [29] studied the occurrence of oxytetracycline, one of the most widely used veterinary pharmaceuticals, in a small Japanese drainage basin influenced by many livestock farms, including beef cattle, dairy cattle, swine and chicken farms and concentrations broadly ranging between 2 ng/L up to 68 µg/L of the studied antibiotic were detected. The authors also found that winter seasons characterized by higher loads of oxytetracycline that was due to a very common veterinary practice of using higher dosages as prophylaxis against respiratory infections and diarrhea in the winter when the animals are more vulnerable [29]. Interestingly, no negative effects were observed after rainfall event, suggesting that land application of manure in the catchment area was not the main source of oxytetracycline.

In the USA, pharmaceutical testing on samples taken from the CAFO waste lagoon in Washington, Idaho, was previously conducted by the Idaho State Department of Agriculture (ISDA) and concentrations of sulfamethazine and sulfadimethoxine of 43.35 µg/L and 2.03 µg/L were reported [12]. The authors highlighted that such sulfonamides are not approved for human usage and therefore their detection is an indication of contamination from animal sources. A study conducted by [16] was focused on the occurrence of three ionophore compounds in a mixed-landscape watershed characterized by urban and agricultural landscapes, more precisely along the Cache La Poudre River in Northern Colorado, USA.

**Table 2. Summary of the veterinary pharmaceuticals reported in the aqueous matrix, respective concentration ranges and analytical methods used to detect and quantify.**

Name	Concentration reported	Analytical Methods	Location	Sources	Reference
<b>Wastewater Treatment Plants</b>					
Sulphamethazine	3.278 µg/L	-	Municipal WWTP	-	[25]
Sulfamerazine, sulfamethazine, erythromycin, monensin, tiamulin, sulfathiazole, lincomycin, ractopamine, sulfamethazine, sulfathiazole and sulfadimethoxine	-	Solid phase extraction (SPE) followed by LC-MS/MS	Waste Lagoons	Swine and Cattle beef facilities	[26]
Chlortetracycline, oxytetracycline, and acetylsalicylic acid	-	LC-MS/MS with electrospray ionization (ESI)	Livestock WWTP	-	[15]
Fenbendazole Fenbendazole sulfone Amino fenbendazole P-hydroxyfenbendazole	3.85 – 241 µg/L 0.283 -93.9 µg/L 0.554 -94.1 µg/L 0.693-92.7 µg/L	SPE followed by HPLC-MS/MS and negative/positive ESI	Livestock WWTP	Livestock farms	[27]
Fenbendazole	0.018 µg/L	SPE followed by HPLC-MS/MS and negative/positive ESI	Municipal WWTP	Veterinary from households	[27]
Sulfamethazine	18500-19200 ng/L	HPLC and triple-quadrupole MS with ESI	River Waters	Pig farms	[28]
Oxytetracycline	2 ng/L - 68 µg/L	LC/MS with a positive ESI (LC/MS-APCI(+))	River Waters	Beef cattle, dairy cattle, swine and chicken farms	[29]
Sulfamethazine Sulfadimethoxine	45.35 µg/L 2.03 µg/L	SPE followed by LC-MS/MS	CAFO waste lagoons	-	[12]
<b>Landfill/manure leachate</b>					
monensin	191 – 11980 ng/L	SPE followed by LC-MS/MS -ESI	Carcass burial leachate	On-farm animal carcass burial	[24]
<b>Groundwater</b>					
Sulfamethazine Sulfadimethoxine Sulfacetamide	- 3460 ng/L (All sulfonamides detected)	On-line SPE followed by LC-MS/MS	Groundwater	-	[23]
Erythromycin Monensin Ractopamine Sulfamethazine Sufamethazole Sulfathiazole	72 -2380 ng/L 180-2350 ng/L 50 ng/l	SPE followed by LC-MS/MS	Groundwater	Swine and cattle CAFO facilities	[26]
Sulfamethazine Sulfadimethoxine	0.076-0.22 µg/L 0.046-0.068 µg/L	SPE followed by LC-MS/MS	Private wells for drinking water purpose	Beef cattle CAFO facilities	[12]

(Table 2) contd....

Name	Concentration reported	Analytical Methods	Location	Sources	Reference
<b>Freshwater Bodies</b>					
Tetracyclines Sulfonamides	-	HPLC-MS/MS	River Water	Swine Manure composting facility	[31]
Fenbendazole	0.006 – 1.31 µg/L	SPE followed by HPLC-MS/MS and negative/positive ESI	River water	Municipal WWTP	[27]
Sulphasalazine Oxytetracycline	202-321 ng/L 109-423 ng/L	SPE followed by LC/MS positive ESI (+)	Creeks and river waters	Dairy farms	[32]
Monensin Salinomycin Narasin	0.036 µg/L 0.007 µg/L 0.038 µg/L	SPE followed by HPLC-MS/MS	River water	Agricultural activities including chicken farm	[33]
Tetracyclines Sulfonamide Macrolides	-	HPLC followed by a duo ion trap MS with ESI	River waters	CAFO's, Dairy farms, horse farms, cattle breeding	[16]
Tetracycline Sulfonamides Quinolones Macrolides	210 ng/L – 0.47 µg/L	SPE followed by HPLC-MS/MS	River waters	Swine farms, fishponds and dairies	[34]
Anthelmintics	0.32 – 39.43 ng/L	Ultra HPLC coupled to quadrupole linear ion trap mass spectrometry (UHPLC-QqLIT-MS)	River waters	Pig farms	[35]
Progestin medroxyprogesterone	< 1 ng/L	SPE followed by GC-MS/MS	Surface waters	Dairy cattle	[36]
Sulfamethoxazole Sulfamethazine Trimethoprim Erythromycin-H <sub>2</sub> O	20 to 174 ng/L 15 to 328 ng/L 7 to 44 ng/L 9 to 41 ng/L	HPLC and triple-quadrupole MS with ESI	River waters	CAFOs, pig and chicken farms, poultry birds	[28]
Oxytetracycline	2 ng/L – 68 µg/L	LC/MS with a positive electrospray (LC/MS-APCI(+))	River waters	Beef cattle, dairy, swine and chicken farms	[29]
Lincomycin Sulfamethazine	0.006 µg/L	SPE followed by LC and both positive and negative ESI with MS/MS	Creek waters	CAFOs	[37]
Sulfadimidine Tylosin	Up 7 ng/L 90 ng/L	SPE followed by HPLC-MS/MS and ESI	Riverbanks	Agricultural activities	[21]

### 3.2. Landfill Leachates/Manure Leachate

The specific literature regarding the occurrence of veterinary pharmaceuticals in different types of leachates is still scarce and there is a clear need of studies addressing such environmental media in order to bring a better understanding and prevent future environmental and public health impacts.

The presence of veterinary pharmaceuticals in leachate can be related to one of the most conventional disposal

methods for livestock mortalities, on-farm burial. However, the potential water quality impacts of animal carcass burial are not yet well understood [24]. According to [24], on-farm burial pits are constructed without liners and any leachate produced in the process along the years percolates through the soil and infiltrates into groundwater. Due to this reason, [24] investigated the occurrence of veterinary antimicrobials in carcass burial leachate for a period of 20 months and monensin, which is widely used in ruminant animal feed,

was detected in concentrations ranging between 191 and 11,980 ng/L. The authors suggested that high concentrations of monensin in some burial pits could have been related to the very low volumes of leachate making the antimicrobial to be highly concentrated [24]. The total mass load of veterinary antimicrobials on the basis of unit mass of buried carcass ( $\mu\text{g}/\text{Kg}$ ) was also calculated in this study, and an average 1.01  $\mu\text{g}$  of monensin per Kg of cattle carcass buried was reported.

### 3.3. Groundwater

Groundwater provides the most reliable perennial source of freshwater on earth and the contamination of groundwater resources by different types of contaminants is a growing concern, although it is relatively poorly studied and understood in comparison to freshwater resources [30]. Nowadays, the occurrence of contaminants has been much better characterized in wastewater and surface water bodies, which is not different when considering the occurrence of veterinary pharmaceuticals even though some studies are available in the scientific literature.

The occurrence of 19 selected sulfonamides was investigated in groundwater samples taken from two groundwater bodies that are designated as nitrate vulnerable zones in Catalonia, Spain. The results have shown a wide range of sulfonamide concentrations (0.01 ng/L up to 3460 ng/L) being sulfacetamide the one detected with the highest concentration even though it was not frequently detected (20.5% detection frequency) [23]. Sulfamethazine and sulfadimethoxine were the sulfonamides more frequently detected with an average frequency of 90% considering all samples. Interestingly, the authors did not find any correlation between the concentrations of sulfonamides and nitrates, which was explained by the release and transport to groundwater from different sources. Whereas nitrates are originated from the application of fertilizers in the region, sulfonamides were specifically related to animal origin [23].

[26] investigated the release of VPs from CAFOs in different environment compartments and pharmaceuticals such as erythromycin and monensin were consistently detected in groundwater connected to cattle and swine CAFO facilities. The concentrations of erythromycin and monensin ranged from 72 to 2380 ng/L and 180 to 2350 ng/L, respectively [26]. Furthermore, sulfonamides such as sulfamerazine, sulfamethazine, sulfamethazole and sulfathiazole were detected in groundwater samples. High concentrations in groundwater as observed in this study might be related to anaerobic conditions that was indicated by high contents of ammonia and also sandy soil, which facilitates the transport of contaminants from overland activities [26]. The authors have highlighted the presence of certain pharmaceuticals specific to a particular type of animal agriculture in groundwater underlying CAFO facilities since monensin was detected in cattle CAFO facilities while ractopamine (50 ng/L) was detected in swine facilities.

The presence of sulfonamides in private water wells used as drinking water sources in Washington County, Idaho, USA, influenced by a nearby beef cattle CAFO facility was also reported by [12]. The groundwater samples were contaminated by the two veterinary antimicrobials sul-

famethazine and sulfadimethoxine with concentrations ranging between 0.076 to 0.22  $\mu\text{g}/\text{L}$  and 0.046 to 0.068  $\mu\text{g}/\text{L}$ , respectively [12].

### 3.4. Freshwater Bodies

A number of studies addressed to detect pharmaceuticals in different freshwater bodies have been published suggesting this has been the most common subject reported in the literature in comparison to other environmental aqueous matrices.

[31] studied the occurrences and respective seasonal variation of antibiotics close to a swine manure composting facility in Korea, more precisely in surface waters along the Naerincheon River. The authors found that antibiotics such as tetracyclines and sulfonamides had high concentrations in dry season in comparison to the rain season, which was explained by either dilution by rainwater or readily transportation due to intensive energy of raindrop. Furthermore, the lower temperatures in the dry season could have led to lower biodegradation rates of the studied antibiotics making them to be in higher concentrations. The study that antibiotics were transported downstream from the swine manure composting facility through the water flow resulting in increased concentrations when increasing the distance between the sampling point and the manure composting facility [31].

[27] have reported very low concentrations (0.006 – 1.31  $\mu\text{g}/\text{L}$ ) of the anthelmintic fenbendazole and metabolites in Korean river waters located downstream from municipal wastewater treatment indicating the influence of household use of veterinary anthelmintics in Korean river systems.

[32] studied the fate of penicilins, sulphonamides, tetracyclines used in herd health programs on dairy farms in Victoria, Australia and focused their sampling in different sites covering an irrigation area with drains, creeks and rivers. The authors have found elevated concentrations of sulphasalazine (202 – 321 ng/L) and oxytetracycline (109 – 423 ng/L) in sampling points that were connected to dairy activities, suggesting that runoff from these areas was the main cause. Penicilin, is commonly used for the treatment of mastitis and footrot, was detected in similar concentration range in most of sampling sites [32]. Based on their main findings and the runoff of dairy activities with elevated levels of oxytetracycline and sulphasalazine together with significant amounts of penicilins, the authors have speculated the occurrence of an outbreak of footrot and/or mastitis on the farms that surrounded the drainage area where the samples were taken. Furthermore, the study carried out by [32] reported the detection of erythromycin, although the quantification was not possible due to “matrix suspension” and it was suggested two possible sources: dairy farms or sewage treatment. According to the authors, erythromycin is commonly prescribed for children under 12 years old with persistent infections and it is sometimes administered to curb outbreaks of mastitis.

The occurrence of three ionophore compounds - monensin, salinomycin and narasin - was determined along the Cache La Poudre River in Northern Colorado, USA in a mixed-landscape watershed characterized by urban and agricultural landscapes [33]. Ionophores are used only for veteri-

nary purposes, which makes such pharmaceutical group potential markers in multiple land-use watersheds [33]. Even though ionophores were found in much higher concentrations in solid matrix, monensin and salinomycin were found in sampling sites that were mostly influenced by agricultural activities in concentrations as high as 0.036 and 0.007  $\mu\text{g/L}$ , respectively [33]. The occurrence of naransin in a sampling site that was not much influenced by agriculture in concentrations as high as 0.038  $\mu\text{g/L}$  was explained by the presence of several small chicken farms in this part of the studied watershed. Interestingly, ionophores were found in higher concentrations during periods of snowmelt and consequent high flows in the river, indicating that in this specific case, runoff waters, mainly snow melt, were the main sources of ionophores in the studied area [33].

[16] have also studied the occurrence and temporal variation of tetracyclines, sulfonamides and macrolides in different sites of the same Cache La Poudre River, Colorado, USA being one of them influenced by significant agricultural activity including several CAFOs, dairies and small horses and cattle breeding operations. Reasonably, the authors found significant higher concentrations of animal-used antibiotics such as chlortetracycline in sampling sites that were heavily agricultural- influenced [16]. Furthermore, the investigation show, that antibiotics concentration on environmental matrices varies significantly in different seasons as they have observed with ionophores. The authors observed February as the month of highest concentrations detected which was explained by the low flow of the studied rivers and low temperature waters with consequent inhibition of microbial activity in comparison to warmer months.

The occurrence and transport of compounds from the families of tetracycline, sulfonamides, quinolones and macrolides were studied in a 72-km stretch of the Haihe River, China [34] and sampling points were located in areas that had fishponds, feedlots, dairies, and storage lagoons of feces in swine farms. Sulfonamides were the predominant antibiotics with concentrations ranging between 210-385  $\text{ng/L}$ . High concentrations of sulfachloropyridazine (peak concentration of 385  $\text{ng/L}$ ), which is used only for veterinary purposes, were observed in the water taken from sites influenced by swine farms, fishponds and dairies, make such antibiotic a potential chemical marker for contamination originated from livestock farms in the studied basin of the Haihe River, China. Tetracyclines, sulfonamides, quinolones and macrolides were also detected in swine farms and fishponds in concentrations ranging between 0.12 – 0.47  $\mu\text{g/L}$ , although the study had as main finding the predominant contamination of sulfonamides in the region coming from fishponds and swine farm lagoons as previously mentioned [34].

[35] investigated the presence of anthelmintics in the waters of Llobregat River in Spain, which runs through a part of the country where there are numerous agricultural establishments, mainly pig farms. The authors found that out of ten anthelmintics analyzed, eight were detected in concentrations ranging between 0.32 and 39.43  $\text{ng/L}$  and the most frequently detected one was levamisol with concentrations up to 39.43  $\text{ng/L}$ . The study highlighted the highest cumulative

anthelmintic total concentration in the sampling point corresponding to the discharge of the river to the Mediterranean Sea close to the city of Barcelona, which raises serious concerns due to the use of Barcelona beaches as recreational areas in the summer by many tourists [35].

[36] focused on investigating steroid hormones in surface waters in an area in Central California that was likely to be impacted by dairy farm operations. Among the steroid hormones included in the investigation, the authors detected the synthetic progestin medroxyprogesterone in concentrations as low as  $\leq 1$   $\text{ng/L}$ . The authors affirmed that medroxyprogesterone is used as both human and veterinary medicine as an estrus regulator and has been suggested as means of synchronizing estrus in dairy cattle [36].

[28] investigated the occurrence of veterinary antibiotics in the Mekong Delta, the lowest reach of Mekong River, Vietnam, with focus on macrolides, sulfonamides and trimethoprim. The region of Mekong Delta is characterized by intensive animal husbandry (pig farms, poultry birds and chicken farms, CAFOs) and aquaculture activities and no data has been available on the occurrence and spatial distribution of antibiotics in the Southeast Asia [28]. The concentrations in the Mekong River ranged from 20 to 174  $\text{ng/L}$  (median, 80  $\text{ng/L}$ ) of sulfamethoxazole, 15 to 328  $\text{ng/L}$  (62  $\text{ng/L}$ ) of sulfamethazine, 7 to 44  $\text{ng/L}$  (20  $\text{ng/L}$ ) of trimethoprim, and 9 to 41  $\text{ng/L}$  (32  $\text{ng/L}$ ) of erythromycin-H<sub>2</sub>O [28]. Based on the results, emphasis was given by the authors to the high concentrations of sulfonamides in the Mekong River and its relation to inputs from livestock animals and aquaculture.

[29] studied the occurrence of oxytetracycline, one of the most widely used veterinary pharmaceuticals, in a small drainage basin in Japan influenced by many livestock farms including beef cattle, dairy cattle, swine and chicken farms and concentrations broadly ranging between 2  $\text{ng/L}$  up to 68  $\mu\text{g/L}$  of the studied antibiotic were detected. The authors also found that winter seasons were characterized by higher loads of oxytetracycline, which was related to a very common veterinary practice of using higher dosages as prophylaxis against respiratory infections and diarrhea in the winter when the animals are more vulnerable even though the effect of lower dilution rates in the rivers during the winter was not ruled out [29]. Interestingly no negative effects were observed after rainfall event suggesting that land application of manure in the catchment area was not the main source of oxytetracycline.

[37] reported the quantification of veterinary pharmaceuticals in a rural, central Indiana stream in USA, Sugar Creek, which was highly influenced by CAFO facilities. The authors reported the presence of lincomycin and sulfamethazine in average concentrations of 0.006  $\mu\text{g/L}$ . Furthermore, the authors highlighted distinct spatial trends in the veterinary antimicrobials observed along Sugar creek and concentrations of both lincomycin and sulfamethazine were approximately 30% higher in approximately 10 km downstream of an area that is immediately adjacent to a swine CAFO [37]. However, despite this spatial increase from such upstream point downward 10 km, concentrations rapidly declined downstream.



[21] detected sulfadimidine in 6 of 40 samples collected at different riverbanks in Southern North Rhine – Westphalia, Germany in concentrations up to 7 ng/L. According to the authors, this antibiotic is strictly used for veterinary purposes in Germany, suggesting relatively small input from agricultural sources in the region. Similarly, tylosin that has been used as growth promoter in feed additives was detected in concentration of 90 ng/L, suggesting the input from animal husbandry in the Rhine region [21].

#### 4. OCCURRENCE OF VETERINARY PHARMACEUTICALS IN SOLID MATRIX

The occurrence and fate of veterinary pharmaceuticals in solid matrices have not been studied well, although one can find studies regarding the behavior of such chemicals in solid phase, detected concentrations, analytical methods for detection and quantification and physico-chemical properties. The following sections present studies focused on detection of veterinary pharmaceuticals in 1) animal waste manure and 2) agricultural soils and 3) river bottom sediments. A summary of the veterinary compounds reported in the different studies with focus on solid phase, concentration ranges and respective analytical methods is given in Table 3.

##### 4.1. Animal Waste Manure

The scientific literature in relation to the occurrence of veterinary pharmaceuticals on animal waste manure is still scarce, even though some authors have addressed such issue of concern. [21] investigated the presence of antibiotics in different liquid manure samples collected from different cattle and swine farms in Eastern Westphalia and Lower Rhine region, Germany, and concentrations in the range of 1 to 2 mg/kg of sulfadimidine that often used in pig breeding for the treatment of diarrhea and other intestinal infections were detected in the manures from swine farms [21].

[22] investigated residues of pharmaceutical products in recycled organic manure of different types of solid waste from livestock including manure of cattle, poultry, swine and horse. Whereas the researchers found high concentrations of sulfonamides in both poultry (61 µg/kg of sulfamethoxazole) and swine manure (210 µg/kg of sulfamonomethoxine), high concentrations of chlorotetracycline (280 µg/kg) were only found in swine manure [22]. The samples of horse manure had concentrations of ciprofloxacin as high as 43 µg/kg and according to the authors, veterinary antibiotics have been extensively used in swine and poultry farms with a number of antibiotic classes, specially macrolides, sulfonamides and tetracyclines being commonly detected in liquid waste of swine and poultry feeding operations [22].

[38] studied the presence of tetracyclines, sulfonamides and fluoroquinolones in cattle and poultry manure in the North Marmara region in Turkey, which is characterized by intensive agriculture and animal husbandry such as chicken poultry and intensive animal feeding operation facilities. Sulfonamides were detected in the studied samples with significantly ( $p < 0.05$ ) higher concentrations in comparison to tetracyclines with sulfachloropyridazine (SCP) being detected in fresh poultry manure in concentration as high as 35.53 mg/kg. Although high concentrations of sulfamethox-

azole were detected in fresh poultry manure (3.76 mg/kg), relatively low concentrations were detected in poultry manure that was stored (0.10 mg/kg), suggesting that a considerable amount of this compound could have been transformed or degraded during storage in manure heaps [38]. Among all antimicrobials studied in Turkey, the results have shown that oxytetracycline was the most frequently detected antimicrobial compound in cattle and poultry manure with the highest concentrations in general detected in the poultry manure [38].

[4] monitored the occurrence of tetracyclines, sulfonamides, trimethoprim and fluoroquinolones in manure samples of pig, chicken and turkey. The antibiotic tetracycline was found in 22 of 30 pig manure samples in concentrations ranging from 0.36 to 23 mg/kg and the authors suggest this could have been caused by the use of chlortetracycline or/and oxytetracycline as feeding additives, even though the degradation of these two antibiotics into tetracycline has not been reported in the literature [4]. Oxytetracycline was also detected specially in pig manure in levels ranging between 0.21 and 21 mg/kg and in one of the chicken manure samples in concentration as low as 1.1 mg/kg [4]. Chlortetracycline was the antibiotic found in pig manure with the highest concentrations, up to 46 mg/kg. Furthermore, in eight chicken and turkey manure samples, chlortetracycline was detected with concentrations up to 1.7 mg/kg. The authors detected high concentrations of sulfadimidine (up to 20 mg/kg) in pig manure, whereas sulfadiazine was only found in chicken and turkey dung with concentrations as high as 51 and 91 mg/kg respectively [4]. Differently than the results obtained for tetracyclines in pig manure, only low concentrations of fluoroquinolones were detected (0.13 -0.75 mg/kg) as enrofloxacin and its metabolite ciprofloxacin. On the other hand, chicken and turkey manure samples had concentrations up to 2.8 and 8.3 mg/kg, respectively.

##### 4.2. Agricultural Soils

[21] studied the presence of antibiotics in German soils that were fertilized with seven months in advance with swine liquid manure and have found sulfadimidine in concentrations of 15 µg/kg, suggesting that sulfadimidine is highly stable in soils. [39] investigated the occurrence of veterinary antibiotics in soils that had received swine, cattle and chicken manure as organic fertilizers in China. Whereas the highest detected concentrations in soils that received pig manure were for the sulfonamides sulfamethazine, oxytetracyclines and chlorotetracyclines, only oxytetracycline was found in soils that received cattle manure. On the other hand, soil that received chicken manure was highly contaminated with quinolones and tetracyclines in comparison to sulfonamides, suggesting that such antibiotic groups were used much more frequently in chicken farms [39]. The authors found concentrations of oxytetracyclines and chlorotetracyclines as high as 3212 ng/L and 4331 ng/L respectively in comparison to concentrations in the range of 30 ng/L for cattle and pig farms.

[38] studied the presence of tetracyclines, sulfonamides and fluoroquinolones in soils that were previously fertilized with fresh cattle and poultry manure. Even though the most frequent detection of antimicrobial compounds was

**Table 3.** Summary of the veterinary pharmaceuticals reported in the solid matrix, respective concentration ranges and analytical methods used to detect and quantify

Name	Concentration reported	Analytical Methods	Location	Sources	Reference
<b>Animal Waste Manure</b>					
sulfadimidine	1 – 2 mg/kg	Ultrasonic extraction followed by ELISA test	Manure	Swine farms	[21]
sulfamethoxazole sulfamonomethoxine chlorotetracycline ciprofloxacin	61 µg/kg 210 µg/kg 280 µg/kg 43 µg/kg	LC-MS/MS with ESI positive mode and multiple reaction monitoring (MRM)	Recycled organic manure	Cattle, poultry, swine, horse	[22]
tetracyclines sulfonamides fluoroquinolones	NR 3.76 – 35.53 mg/kg NR	SPE-HPLC	Cattle and poultry manure	Chicken farms and CAFO facilities	[38]
tetracyclines, oxytetracycline chlortetracycline sulfadimidine sulfadiazine, trimethoprim fluoroquinolones	0.36 -23 mg/kg 0.21 -21 mg/kg up to 46 mg/kg up to 20 mg/kg 51 – 91 mg/kg NR 0.13 – 8.3 mg/kg	HPLC-MS/MS	Manure	Pig, chicken and turkey farms	[4]
<b>Agricultural Soils</b>					
sulfadimidine	15 µg/kg	Ultrasonic extraction followed by ELISA test	Fertilized soils	Swine liquid manure	[21]
sulfamethazine oxytetracyclines chlorotetracyclines quinolones	NR	LC-MS/MS	Fertilized soils	Swine, cattle and chicken manure	[39]
tetracyclines sulfachloropyridazine fluoroquinolones (enrofloxacin)	NR NR 0.02-0.05 mg/kg	SPE-HPLC	Fertilized soils	Cattle and poultry manure	[38]
<b>River sediments</b>					
monensin, salinomycin, narasin	31.5 µg/kg 30.1 µg/kg 16.3 µg/kg	SPE-HPLC-MS/MS	River sediments	Chicken, cattle and dairy farms	[33]
tetracyclines sulfonamides	NR	SPE-HPLC-MS/MS	River sediments and soil	Swine manure composting facility	[31]
oxytetracycline chlorotetracycline sulfamethazine, sulfathiazole and sulfamethoxazole	1179- 3106 ng/L 1957 ng/L 89.15 ng/L 0.91 ng/L 0.87 ng/L	LC-MS/MS	River sediments	Cattle, swine and chicken farms	[39]

observed in agricultural soil previously fertilized with poultry manure, no significant differences ( $p > 0.05$ ) in concentrations were found between soils fertilized with manure from

cattle and poultry. Tetracyclines were the most frequently detected compounds in a similar way as the evaluation of the manures, indicating the high transfer rates from manure to

soil. Whereas sulfonamides have been reported as highly mobile in soil, the authors have detected concentrations up to 0.40 mg/kg such concentrations were not significantly different tetracyclines, in manures [38]. Sulfachloropyridazine was detected only in soils fertilized by poultry manure indicating that this can be the main source of soil contamination by such veterinary antimicrobial compound. The fluoroquinolone enrofloxacin was detected in concentrations as low as 0.02 and 0.05 mg/kg in two of the soil samples indicating a high stability of such compounds considering these two soils were fertilized by manure seven months before the sampling [38].

### 4.3. River Sediments

Research in American rivers and the occurrence of veterinary pharmaceuticals in bottom sediments reported by [33]. Sediment samples from the Cache La Poudre River in Northern Colorado, USA, were taken in different periods between May 2003 and February 2005 for an investigation on the occurrence of three ionophore antibiotics, monensin, salinomycin and narasin. Monensin and salinomycin are used for chicken and broilers as feed additives and coccidiosis prevention and in cattle and dairy for increasing the rate of weight gain. Furthermore narasin is used to aid the prevention of coccidiosis in broiler chickens [33]. The three ionophore antibiotics were detected in the sediments with concentrations as high as 31.5 µg/kg, 16.3 µg/kg and 30.1 µg/kg for monensin, narasin and salinomycin respectively. These high concentrations were detected in August and explained by existing interconnection with irrigation ditches that release the antibiotics to the river during runoff period causing the saturation of river sediments [33]. This study highlighted the much higher concentrations of the three studied ionophores in the sediments in comparison to the water phase suggesting the importance of understanding the sediment matrix in order to tackle environmental contamination by ionophores. [31] investigated the seasonal variation of veterinary antibiotics (tetracyclines and sulfonamides) in sediments and soil close to a swine manure composting facility. Antibiotic concentrations in the sediments were also higher in comparison to the water phase and according to the authors, once released into sediments and soil, veterinary antibiotics become persistent rather than in the water due to specific characteristics of both soil and antibiotics such as sorption capacity, distribution coefficient ( $K_d$ ) and hydrophobicity [31]. The authors detected higher amounts of antibiotics in two sites where sandy loam soils had lower pH values and cation exchange capacity (CEC) in comparison to a third site, which can be explained by different cultivation practices [31]. It has been reported in the literature that soil pH is a critical parameter determining sorption capacity of antibiotics in soils and highly acidic clay soils have the right properties to make antibiotics readily sorbed.

[39] investigated the occurrence of a number of different antibiotics in sediments from rivers close to livestock farms in China, including cattle, swine and chicken farms. The investigation has detected concentrations of oxytetracycline and chlorotetracycline as high as 3106 ng/L and 1957 ng/L respectively in sediments close to pig farms. Furthermore, low concentrations of sulfamethazine, sulfathiazole and sulfamethoxazole of 89.15, 0.91 and 0.87 ng/L respectively

were found [39]. According to [39], stringent supervision and inspection of milk has been taking place in Chinese cattle farms suggesting this was the reason of only oxytetracycline was detected in different matrices of cattle farm including sediments (1179 ng/L).

## 5. FINAL THOUGHTS - CURRENT/FUTURE CHALLENGES

It is already recognized by scientists, environmental managers and decision makers that active pharmaceutical ingredients and their metabolites have been contributing to the current contamination of aquatic and terrestrial ecosystems all over the world [40]. It is clear that so far there have been only limited data about these chemicals and there are still considerable gaps to be bridged in order to remediate existing problems and prevent future ones. Still nowadays, the environmental effects posed by these chemicals are largely unknown [41]. Based on this review paper, it was observed that in comparison to other types of contaminants in solid and aqueous matrices, there is clear need to accurately map not only the occurrence of these veterinary compounds in as many regions as possible, but also the main sources, considering that sources of contamination will be included in the design and establishment of further regulatory monitoring programmes and environmental regulations [40]. In the following sections, a brief discussion of some challenges in relation to veterinary pharmaceuticals in the near future is given.

### 5.1. Analytical Challenges and the Detection/Quantification of Parent Compounds and Metabolites

Even though analytical methods for the detection of a number of different pharmaceuticals such as painkillers, fat burners, analgesics, contraceptives and stimulators in domestic wastewater and water recipients has been reported, there are still considerable challenges to be overcome. According to [42], considering the large number of registered pharmaceutical ingredients (>3000) and the large number of corresponding metabolites, analytical methods have only been developed for a very small subset of compounds ( $\approx 150$ ) in environmental matrices. There will be an evident need to address in the near future efforts towards additional methods for the detection and quantification of such chemicals in order to establish adequate strategies to tackle problems caused by veterinary pharmaceuticals in the environment. [17] presented a list of 106 pharmaceuticals that were persistent and bioaccumulative that have not been reported previously in environmental samples due to the lack of analytical methods to determine them at trace concentrations in water (ng/L), which is typically required for environmental impact assessment. According to the author, among the existing challenges the most difficult issue is the determination of metabolites released, which are often in the form of conjugates, as well as transformation products generated in the environment itself by biodegradation, photolysis, or hydrolysis. This highlighted by [43], which states that little attention has been given to the identification and quantification of transformation products mainly when considering water/wastewater treatment plants. As an example, [9] reported that only few methods have been available in the literature for the determi-

nation of these anthelmintics, both in solid and aqueous environmental matrices. Furthermore, the authors also emphasize that analytical methods that are able to detect and quantify anthelmintics mixed with other pharmaceuticals are very limited suggesting that the determination of transformation products and parent compounds in mixtures will be in the near future a crucial research topic [9].

## 5.2. Risks and Toxicity to Human Health/Aquatic Ecosystems

With an increasing awareness to the occurrence of veterinary pharmaceuticals in the environment, the toxic effects and potential risks to environmental health are growing concern. In comparison to studies addressed to pharmaceuticals of human use, the implications of veterinary pharmaceuticals in the environment are still unclear and need to be better investigated [6]. [44] state that according to the World Health Organization (WHO) veterinary pharmaceuticals in the environment have been responsible for the development of antibiotic resistant in water and soil matrices. The author states that there are still great gaps in our understanding of the potential consequences of environmental occurrences of veterinary pharmaceuticals. It is important to highlight that recent advancements have been achieved with the establishment and requirements of environmental risk assessments of veterinary pharmaceuticals in the US and Europe [20]. However, according to [45], test methods that are specifically designed to assess the environmental risks posed by pharmaceuticals have not been developed yet, even though the current guideline on environmental risk assessment in the European Union (EU) states that the risk of veterinary pharmaceuticals has to be assessed.

To emphasize the challenges posed to researchers to deal with toxic effects of veterinary pharmaceuticals, [46] stress the importance of considering as close as possible the real scenario in which organisms are usually exposed to cocktails of chemicals combined with a number of other environmental stressors, which is totally different laboratory conditions where toxicity tests and risk assessments are carried out based on individuals being exposed to single contaminants. Furthermore, contrary to human pharmaceuticals, organisms in aquatic ecosystems are exposed to fluctuating concentrations of veterinary pharmaceuticals since their release occurs usually intermittently and in pulses, which makes the exposure dynamics completely different. Exposure time considered in laboratory nowadays has not been considered realistic also and according to [41], environmental risk assessments based on acute toxicity tests do not adequately reflect the potential for chronic effects following long-term exposure to sub-acute levels. [47] states that although studies addressed to assess the long-term effects of pharmaceuticals in aquatic organisms have been increasing, their number is still very low. Furthermore, there is a need to carry out adequate toxicity tests to evaluate the exposure to metabolites, since pharmaceuticals are only partially excreted in parental form.

According to [48], studies have highlighted the potential effects of metabolites and degradation products and although a wealth of data is available and science continues to advance, much remains to be done. The interaction between

different compounds is also something to be taken into consideration since pharmaceuticals that are routinely used in herd health programs include hormones, antibiotics, udder-cleaning, antiseptics, anthelmintics, ecto-parasitic topicals and others and no knowledge is available whether they react with each other forming other compounds which can either act individually or in combination [32].

According to [41], in order to bridge the gaps in knowledge regarding toxic effects of veterinary compounds and associated risks, a number of studies in different areas are needed: data on used amounts, significance of different exposure routes for spreading veterinary compounds the environment, monitoring of environmental occurrences, species sensitivity distribution, bioaccumulation potential, endocrine disruption potential, and indirect effects on species of higher trophic levels.

As it can be seen, there is a need to overcome existing challenges in terms of detection, quantification, and evaluation of the effects posed by veterinary pharmaceuticals in the environment, not to mention treatment systems. The more research investigations focused on these subjects take place in the near future, more rapidly we will get a better understanding about the behavior of these compounds and the real risks they pose to aquatic and terrestrial organism and also humans. Such data is necessary for evidence-based risk assessment of the effects of veterinary pharmaceuticals in the environment and the subsequent policy making and regulatory measures aiming to monitor and minimize these effects.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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