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Antibiotics Uptake from Soil and Translocation in the Plants – *Meta*-analysis

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Abstract: Antibiotics reach agricultural soils *via* fertilization with manure and biosolids as well as irrigation with wastewater and have the potential to be taken up by growing crops. The fate of antibiotics in terms of uptake from soil to plants, as well as translocation from root to leaves, is determined by a combination of antibiotic's physio-chemical (*e.g.* speciation, lipophilicity), soil (*e.g.* organic carbon content, pH) and plant (*e.g.* transpiration rates) characteristics. In this *meta*-analysis, a literature search was executed to obtain an overview of antibiotic uptake to plants, with an aim to identify uptake and translocation patterns of different antibiotic classes. Overall, we found that higher uptake of tetracyclines to plant leaves was observed compared to sulfonamides. Differences were also observed in translocation within the plants, where tetracyclines were found in roots and leaves with close to equal concentrations, while the sulfonamides represented a tendency to accumulate to the root fraction. The antibiotic's characteristics have a high influence on their fate, for example, the high water-solubility and uncharged speciation in typical agricultural soil pH ranges likely induces tetracycline uptake from soil and translocation in plant. Despite the advances in knowledge over the past decade, our *meta*-analysis indicated that the available research is focused on a limited number of analytes and antibiotic classes. Furthermore, fast-growing plant species (*e.g.* spinach, lettuce, and radish) are overly represented in studies compared to crop species with higher significance for human food sources (*e.g.* corn, wheat, and potato), requiring more attention in future research.

Keywords: Antibiotics · Bioconcentration factor (BCF) · Crop · Plant · Translocation factor (TF) · Uptake

Inna Nybom obtained her PhD (2015) from the University of Eastern Finland from the aquatic ecotoxicology research group led by Dr. Jarkko Akkanen. Afterwards she worked as a postdoctoral researcher in Stockholm University at the Department of Environmental Science, in the research groups of Prof. Dr. Anna Sobek and Prof. Dr. Örjan Gustafsson. Currently she works as a postdoctoral researcher in the Department of Environmental Systems Science at ETH Zurich in the research group of Dr. Gina Garland. Her research investigates sorption, dissipation and accumulation of antibiotics and pharmaceuticals in agricultural soil-plant ecosystems.

1. Introduction

The benefit of antibiotics for human health in modern medicine is undeniable, including treating infectious diseases, enabling surgeries, treating cancer, and consequently lowering mortality.[1] Moreover, the use of antimicrobials in animal husbandry has enabled the growth of intensive animal production, supporting the growing global demand for animal protein.[2] However, the excessive use of antimicrobials has led to widespread environmental contamination with antibiotic residues,[3] raising severe concerns of the loss of antibiotic effectiveness through development of antibiotic resistance.[1] The global antibiotic consumption today, including both human (approximately 20% of the total) and veterinary antibiotics exceeds 200 kilotons,[4] and is expected to increase even further in the future.[2,4,5]

Of the consumed antibiotics, only a fraction is fully processed in the body, up to 60-90% of the remaining parent compound and their metabolites are excreted in feces and urine.[6] Consequently, high loads of antibiotics are discharged into the environment through municipal wastewater, animal manure, and biosolids frequently used for irrigation and fertilization of agricultural soils.[7] Antibiotic residues are generally detected in agricultural soils around the world.[6] Exposure to antibiotics can impact the growth, germination and development of crops,[8] and thus affect yields.[9] Since agricultural crops are often cultivated for food production, the residue concentrations of antibiotics also raise concerns for human health effects, particularly relating to the development and transfer of antibiotic resistance.[10,11] Antibiotic residues have the potential to be taken up by crops, and a number of papers investigating antibiotic concentrations in a variety of plants (*e.g.* lettuce, radish, carrot, peanut and corn), both in experimental exposure settings and under field conditions, have been published, reviewed in refs [12,13]. Crop plant concentrations up to $\mu g kg^{-1}$ level have been reported,[6] sometimes (but rarely) exceeding the maximum allowed residue limits of antibiotics set in the European Union for animal based food products of 100–600 $\mu g kg^{-1}$.[14]

In understanding the environmental behavior of antibiotics in soil-plant systems, simple distribution ratios can provide insight into uptake and translocation patterns, even though such ratios are

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not universally applicable to predict individual cases, influenced by various factors such as crop species, soil characteristics, and physiochemical properties of the antibiotic.[15,16] Bioconcentration factor (BCF) can be used to assess the potential of plants to accumulate antibiotics from soil, calculated as ratio between the concentration determined in the organism (*i.e.* plant) versus concentration in the environment (*i.e.* soil).[17] The translocation factor (TF) describes the plants ability to transport the contaminants taken up *via* root to the above ground plant fractions (leaves, shoots or fruits), and is calculated as a ratio of contaminant concentration in plant leaves (shoot or fruits) versus concentration in the roots.[18]

For an overview of antibiotic uptake in plants, a literature review was conducted. The aim of this *meta*-analysis was to identify uptake and translocation patterns of different antibiotic classes, and to investigate the uptake potential of different plant species. Herewith we then identify knowledge gaps and give recommendations of specific unknowns requiring further attention.

2. Materials and Methods

A literature search for original research articles was performed on 15.12.2023 from ScienceDirect and PubMed. The title, abstract and keywords were screened with search terms: 'antibiotic' AND 'plant' AND 'uptake'. The current review is not exhaustive, and a wider range of keywords and additional search engines might have provided additional useful data not considered in this review. With the selected search terms, 185 and 257 original research articles from ScienceDirect and PubMed were found, respectively. The search demonstrated the exponential increase of antibiotic-related research over time, with 80% of the original research papers published over the past 10 years. Duplicates of the articles found with both search tools were removed, leading to a total of 303 original research articles. These articles were manually screened for the title, abstract and if necessary, materials and methods to select papers discussing antibiotic uptake from soil to plants, eventually narrowing down the number of relevant papers to 65 (Table 1). From the collected and screened relevant literature, a further 27 papers did not provide suitable data for this study, for example reporting relative changes in concentrations, or concentrations in fertilizer amended to the soil, but not soil concentrations, and as such were excluded.[19–21] Additionally, articles discussing plant uptake of antibiotics in hydroponic systems were excluded, although they can be valuable in further understanding the fate and translocation of antibiotics in plants.[22–24]

Table 1. Number of studies including different antibiotic classes; sulfonamides (SAs), tetracyclines (TCs), fluoroquinolones (FQs), macrolides (MCs), aminoglycosides (AGs) and penicillins (PCs), and the number of individual compounds within the classes extracted from the data. Most frequently studied antibiotics in this *meta*-analysis, with number of articles in brackets; sulfamethoxazole (SMZ), sulfamethazine (SM), sulfadiazine (SD), trimethoprim (TMP), oxytetracycline (OCT), tetracycline (TC), chlortetracycline (CTC) doxycycline (DTC), norfloxacin (NOR), ciprofloxacin (CIP), enrofloxacin (ENR), erythromycin (ERY), tylosin (TYL) and streptomycin (STM). Veterinary medicine use data in Switzerland, Europe and globally from refs. [2,37,57].

	SAs	TCs	FQs	MCs	AGs	PCs
Studies including class	27	20	21	9	1	-
Individual compounds	11	8	7	6	1	-
Most frequently studied compounds	SMZ (15) SM (11) SD (5) TMP (5)	OTC (15) TC (11) CTC (7) DTC (5)	NOR (12) CIP (11) ENR (7)	ERY (3) TYL (3)	STM (1)	-
Occurrence (%) from all studies	61%	45%	48%	20%	2.3%	-
Frequency of use in veterinary medicine (mass based)						
Switzerland	28%	21%	0.7%	3%	9%	35%
Europe	11%	24%	3%	9%	7%	33%
Global	7%	30%	2%	9%	5%	13%

Finally, antibiotic soil and plant concentrations, or BCFs, when available, were collected from 38 original research articles. When numerical values of soil and plant concentrations were not provided in the original research article, the data was extracted from figures using WebPlotDigitizer.[25]

The potential of plants to accumulate antibiotics from soil was assessed by calculating BCFs[17] including data from 33 original research articles:

$$BCF = \frac{Concentration\ in\ plant\ tissue\ (ng\ g^{-1})}{Concentration\ in\ soil\ (ng\ g^{-1})} \quad (1)$$

Separate BCFs were calculated for below ground (root) and above ground (leaves) plant fractions. All calculations were done on concentrations per dry weight (dw). If plant concentrations were reported per fresh weight in the original article (6 studies), the concentrations were converted to estimated dw concentrations using literature dw percentages of plants,[26,27] or empirical dw contents from laboratory experiments (data not shown). The BCF calculations with estimated dw contents were tested with a range of dw fractions (4–12%) to assess the uncertainty induced by the transformation. The variation of the BCFs calculated with the range extremes was less than 20% compared to the total variation within the collected data. The measured soil concentrations at harvest were used in the calculations because of the fast degradation of some antibiotics in soil, for example half-lifes as short as a few days have been reported for fluoroquinolones (FQs) and tetracyclines (TCs).[28,29] The plants were exposed to antibiotics throughout their growing period, but the experiment durations sometimes extended over several months depending on the crop species, and the growth of the plants tended to increase towards the end of the experiment. Soil pore-water is an important fraction to consider in plant uptake processes, especially for readily soluble compounds.[30] However, the pore-water to plant BCFs could not be calculated from the collected data, because the pore-water concentrations or the experimental soil-to-water sorption coefficients that would enable proximation of pore-water concentrations, were only reported in the two original research articles.[31,32]

The TFs describes the transport of antibiotics from roots (or bulbs) to leaves (or shoots)[18] and was calculated when both root and leaf concentrations were reported (resulting in data from 24 articles):

$$TF = \frac{Concentration\ in\ leaves\ (ng\ g^{-1}\ dw)}{Concentration\ in\ roots\ (ng\ g^{-1}\ dw)} \quad (2)$$

The graphics and statistical analyses were done with GraphPad Prism 10. A nonparametric Kuskal-Wallis test, followed by Dunn's multiple comparisons test, were used to compare the uptake of different antibiotic classes to plants, and the antibiotic uptake affinity of different plant species. An inclusion criterion, that independent data from minimum of three original research articles was available, was applied for all statistical comparisons and graphs.

3. Results and Discussion

3.1 *Frequency of Reports in Line with Consumption Patterns*

Overall, 39 different antibiotics were reported in the reviewed papers. Sulfonamides (SAs) were the most studied antibiotic class, with 61% of the original research papers including at least one SA, and in total, 11 different SA compounds reported (Table 1). FQs and TCs were included in 48% and 45% of the studies correspondingly, and macrolides (MCs) were studied in 20% of the articles. Few papers discussed antibiotics outside of these classes, for example lincomycin[33–36] and chloramphenicol.[13,32] Despite the apparent diversity, most of the compounds were only found in one or two original research articles and a majority of the studies focused on the same few individual antibiotics (Table 1).

SAs, TCs and MCs are frequently used in veterinary medicine, which might explain the high share of studies focusing on these compound classes. For example, in Switzerland in 2021 the mass-based share of SAs from the total sale of antibiotics was 28%, and TCs 21% (Table 1).[37] Globally, TCs are the most frequently used veterinary antibiotics, followed by MCs and SAs.[2] Compared to the total volume of antibiotic consumption, the share of FQs in veterinary use is low. FQs are listed as critically important antimicrobials for humans by WHO,[38] which might contribute to the scientific interest towards these antibiotic classes. However, some antibiotic classes with relatively high share in veterinary medication, for example penicillins and aminoglycosides (AGs) were poorly represented in this literature search. Data of only one AG (streptomycin) was reported in the literature.[39] Fast degradation rates of penicillins pose difficulties in assessing their uptake or even soil concentrations.[40] Moreover, analytical challenges can skew the focus of the research, potentially leaving antibiotics such as AGs with less attention.[41]

In line with the studied antibiotics, 29 different plants were included in the original research articles, but most of the studies included the same plants in their experimental setups. Lettuce,[13,33–36,42–44] radish,[32,39,43,45–47] pak choi,[46,48–51] and spinach[32,45,52–54] were the most frequently studied plants, included in at least 5 studies. Based on this review, fast-growing plant species tend to be more studied compared to, for example, root vegetables. In addition to the frequently studied and fast growing radish, the only other root vegetables studied were carrots[13,42,55,56] and sweet potatoes,[55] included in four and one original research article, respectively.

3.2 *Uptake of Antibiotics from Soil to Plants*

The BCFs used to assess the potential of plants to accumulate antibiotics were calculated separately for roots and leaves. The comparison of pooled data for all individual antibiotics belonging to the class, as well as data from all plants, demonstrated a statistically significant difference for leaf BCFs between TCs and SAs (Fig. 1). While considerably lower for SA, the median BCF for TCs in leaves was close to 1 (0.95), indicating that the concentration in plant leaves can reach the same level as in soil. In line with this *meta*-analysis, tetracycline (TC) was more frequently detected in the shoot and leaves compared to sulfamethazine (SA) in cabbage, rice and corn,[32] and in carrot, lettuce and tomato.[13] Higher BCFs were also observed for oxytetracycline (TC) compared to sulfamethoxazole (SA) in endive, spinach and cabbage.[53] In contrast, similar BCFs were observed for tetracycline (TC) and sulfamethoxypyridazine (SA) in pak choi[50] and oxytetracycline (TC) and sulfamethoxazole (SA) in lettuce.[33] In peanut leaves, the highest BCFs were observed in doxycycline (TC) followed by sulfamethoxazole (SA), chlortetracycline (TC), tetracycline (TC), sulfamerazine (SA) and sulfamethazine (SA) respectively, whereas oxytetracycline (TC) was not detected.[58] A statistically significant difference was observed between the SA BCFs in roots and leaves, indicating that SAs accumulate in plant roots in higher concentrations compared to the plant leaves. No difference between the root versus leaf accumulation was observed between the other antibiotic classes. When comparing the root and leaf BCFs from the collected data, it should be noted that the majority of the studies report plant concentrations only in the edible plant fraction, which leads to slightly different results compared to TFs calculated from studies where both root and leaf concentrations are determined from the same plant (see Section 3.3).

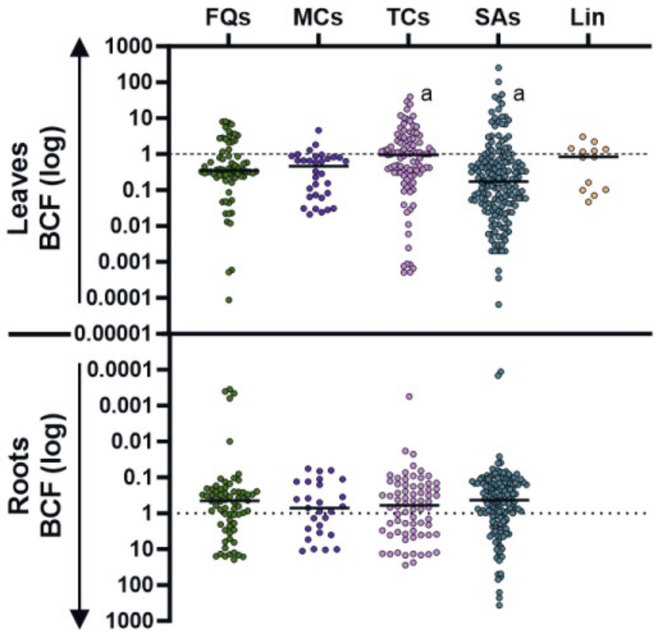

Fig. 1. Potential of plants to accumulate different antibiotics from soil to leaves (top) or roots (bottom) expressed as bioconcentration factors (BCFs). Data from antibiotic classes fluoroquinolones (FQs), macrolides (MCs), tetracyclines (TCs), sulfonamides including trimethoprim (SAs) and the lincosamide antibiotic lincomycin (Lin) (horizontal line = median). BCF observations higher than 1 (dotted line) indicate that the concentration in the plant is higher compared to the soil concentration. A statistically significant difference between TCs and SAs in leaves was observed (a). Data from refs. [13,31–35,39,42–48,50,52–55,58,61–73].

The higher lipophilicity of SAs (octanol-water partition coefficient, log Kow -0.1–1.7) compared to the TCs (-1.3–0.05)[59] contributes to the uptake and translocation of the compounds to the plants, where lipophilic compounds are more likely to fraction to the plant roots generally having higher lipid content compared to leaves.[60] The speciation of the compounds in soil plays a crucial role in the plant uptake processes. The pH difference between the agricultural soils (often 4–7) and neutral to basic pH inside the plant cell (7–7.5) can lead to ion trapping of weak acids, such as SAs, and to the accumulation particularly to the plant roots.[30] In the soil, the weak acids exist at least partially in neutral form with rapid uptake to the plant roots, while inside the plant weak acids dissociate forming anions, with low permeability for reverse diffusion from plant to soil.[30] The translocation of these compounds from roots to shoots and leaves is less effective compared to compounds carried to leaves *via* water mass flow. After uptake by the plants, TCs exist in neutral form,[13] and have higher water solubility compared to SAs (0.2–52 gL^{-1} and 0.008–1.5 gL^{-1} correspondingly).[59] Water-soluble contaminants are rapidly taken up from soil and translocated to plant leaves, and the accumulation rates to different plant species are determined by the plant transpiration rates.[30]

High variation (up to 6 orders of magnitude) was observed within individual antibiotic classes (Fig. 1). The highest BCFs were observed for SAs. The dataset for this study was not sufficient to comprehensively assess the factors causing the variation in BCFs and further research is needed to better understand the factors determining the plant uptake processes, accounting the effects of soil characteristics and the physicochemical properties of the compounds likely inducing variability in the reported data.

Comparison of single antibiotics within the same class (*e.g.* comparing the BCFs for enrofloxacin, ciprofloxacin and norfloxacin) did not explain the variation in leaves, and statistical differences within the classes were not found. However, significant differences in root BCFs were observed within FQ, TC and SA classes (sufficient data was not available for comparison of MCs).

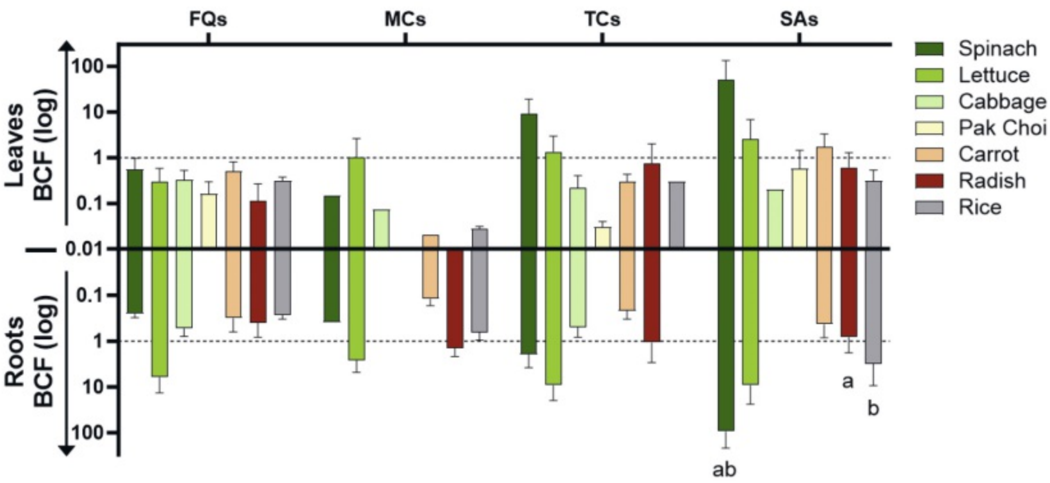

Fig. 2. Accumulation of antibiotics from soil to leaves (top) or roots (bottom) of different plants expressed as bioconcentration factors (BCFs). Data from antibiotic classes fluoroquinolones (FQs), macrolides (MCs), tetracyclines (TCs) and sulfonamides (SAs). Mean and standard deviation (whiskers). BCFs higher than 1 (dotted line) indicate that the concentration in the plant is higher compared to the soil concentration. Statistically significant differences indicated with small letters (a,b). Data from refs. [13,32–35,39,42–48,50,52–55,63,65,70].

The BCF of FQ ciprofloxacin was significantly higher compared to norfloxacin and enrofloxacin (median ± standard deviation 9.2±6.5, 0.3±3.4 and 0.01±1.4, respectively). From SAs, the BCF of trimethoprim was significantly higher compared to sulfamethazine (1.1±3.4 and 0.2±0.4, respectively) and TC oxytetracycline BCF was significantly higher compared to tetracycline, doxycycline and chlortetracycline (3.0±5.8, 0.3±6.4, 0.6±5 and 0.3±5.1, respectively). However, the individual compound comparisons need further studies for verification and should be considered with caution due to the relatively small amount of data available.

Different plant species vary in their potential to accumulate antibiotics, and for a few frequently studied plants data was sufficient to perform a comparison of the BCFs in different species (Fig. 2). Spinach stood out as a plant species expressing higher BCFs, especially in combination with SA exposure. The uptake of SAs to spinach roots was statistically higher compared to carrot and rice roots. Other statistically significant differences were not observed, likely due to the small number of observations per plant. However, indications of the higher accumulation potential of leafy vegetables (spinach and lettuce) over root vegetables can be observed (Fig. 2). Similarly to this *meta*-analysis, the leafy vegetables (lettuce, spinach, cabbage, celery) were found to have higher potential for uptake of compounds of emerging concern (including but not limited to antibiotics) by Christou *et al.*[15]

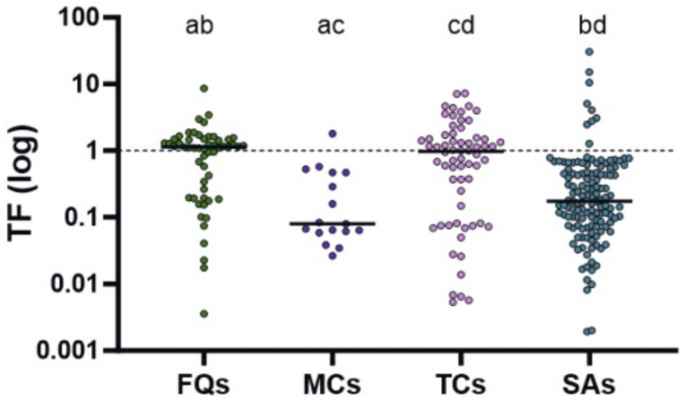

Fig. 3. Translocation factors of different antibiotic classes, fluoroquinolones (FQs), macrolides (MCs), tetracyclines (TCs) and sulfonamides (SAs) from plant roots to leaves (horizontal line = median). TFs higher than 1 (dotted line) indicate that the concentration in the plant leaves is higher compared to the plant roots. Statistically significant difference between antibiotic classes indicated with small letters (a-d). Data from refs. [13,31,32,35,39,45,47,50–52,54–56,58,61,64–66,70–72,76–78].

3.3 *Translocation of Antibiotics in Plants*

The comparison of TFs revealed that FQs and TCs might be translocated in the plant from roots to leaves with higher likelihood compared to the MCs and SAs (Fig. 3). Statistically significant differences between the different antibiotic classes were found between all classes, except FQs *vs* TCs, and MCs *vs* SAs. For FQs and TCs the TFs close to 1 (median 1.1 and 1.0, respectively) indicate that the antibiotics translocated to leaves reach the same concentrations compared to the roots. The data available to calculate TFs was limited since often concentrations only in the edible plant fractions were analyzed and reported. The collected BCF data should be used to assess TF with caution, because of the plant specific uptake patterns. If data only from the edible plant fractions is considered, the results are influenced by the dominance of leafy vegetables in the above ground fraction (*e.g.* spinach, lettuce, and cabbage) and root vegetables in the below ground fraction (*e.g.* radish and carrot). In this *meta*-analysis, the TF data of MCs and SAs, with dominant translocation to the root fractions agrees with the BCF observation. However, the TFs is higher for TCs, and lower for FQs if calculated from the collected BCF data, although in both cases data indicated towards efficient translocation to the leaf fractions. In accordance to this *meta*-analysis, higher translocation potential of norfloxacin (FQ) and tetracycline were observed compared to sulfamethazine (SA) and erythromycin (MC).[13,32] Higher TFs were observed for norfloxacin (FQ) compared to tetracycline (TC) for cabbage, spinach and radish,[32] and for lettuce, carrot and tomato,[13] whereas sulfamethazine and erythromycin were rarely detected in the leaf fraction of the plants.[13,32] In most cases the TFs in lettuce were higher compared to carrot and tomato in a greenhouse trial with soil fertilized with wastewater or animal manure, further the TFs above one for tetracycline and norfloxacin were observed.[13] Accordingly norfloxacin TFs were above one from field samples from China, but TFs for tetracycline were between 0.4-0.7 in spinach, cabbage and radish.[32] Comparison of the individual antibiotics within the classes or comparison of the plant species were not possible in this *meta*-analysis due to the limited data availability. From the perspective of understanding the environmental behavior of antibiotics and plant uptake mechanisms, quantifying different plant fractions is important. Few studies have investigated a range of different antibiotic classes, providing sufficient data for comparisons, and even fewer include multiple crop species, and comprise antibiotic concentrations of the non-edible plant fractions. These fractions may be utilized for soil amendments or cattle feed,[74,75] and thus antibiotic residues may stay in the agricultural soils or cycle back to the livestock. Furthermore, translocation of antibiotics is expected to vary between different plant species, for example higher transpiration rates of the plants can result in higher uptake and translocation potential of water-soluble antibiotics.[30]

4. Conclusions and Future Research Outlook

In this *meta*-analysis, we assessed differences in the plant uptake from soil and within-plant translocation patterns of antibiotics. Our literature search demonstrated that few (fast growing) plant species were frequently studied, and more research is needed on the uptake behavior of slow growing root vegetables and perennial plants (*e.g.* fruit trees). The SAs, FQs, TCs and MCs were the most investigated antibiotic groups, and within the groups the research was focused on limited numbers of individual antibiotics. In terms of use, frequency and expected environmental fate, including additional compounds (*e.g.* aminoglycoside antibiotics) require further attention.

Overall, we found that BCFs of TCs were higher compared to SAs in plant leaves, and TFs showed higher translocation potential from roots to leaves for FQs and TCs compared to MCs and SAs. The root-to-soil BCFs comparison revealed differences in uptake patterns within the antibiotic classes, with ciprofloxacin, trimethoprim and oxytetracycline showing higher uptake potential to plant roots compared to other antibiotics in the same class. Despite these important insights, the available data is limited and did not allow for detailed comparisons of BCFs and TFs in different plant species and for the TFs within antibiotic classes. For understanding the translocation and uptake processes of antibiotics it is important to quantify the antibiotic concentration not only in the edible plant fraction, but also in the fraction not used for human consumption. Simultaneously, for a better risk assessment, further research is needed for commonly cultivated plant species for human food sources (*e.g.* corn and wheat).[79]

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Author Contributions

Nybom I. conceptualization, formal analysis, investigation, visualization, and writing – original draft. Bucheli T.D. conceptualization, resources, supervision, and writing – review and editing. Garland G. conceptualization, resources, supervision, project administration, funding acquisition, and writing – review and editing.

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