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Critical Review

Uptake of Pharmaceuticals by Crops: A Systematic Review and Meta-analysis

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Abstract: Studies on the uptake of pharmaceuticals from soils into crops were first conducted in the 2000s. Since then a wealth of such data has been generated, but to the best of our knowledge, these studies have not been systematically reviewed. We present a quantitative, systematic review of empirical data on the uptake of pharmaceuticals into crops. We developed a custom-made relational database on plant uptake of pharmaceuticals that contained details of the experimental design and associated results from 150 articles, spanning 173 pharmaceuticals, 78 study crops, and 8048 unique measurements. Analysis of the data in the database showed clear trends in experimental design, with lettuce being the most studied crop and carbamazepine and sulfamethoxazole being the most studied pharmaceuticals. Pharmaceutical properties were found to create the greatest range in uptake concentrations of any single variable studied. Uptake concentrations were also found to vary between crops, with relatively high uptake concentrations identified in cress, lettuce, rice, and courgette crops. An understanding of the influence of soil properties on pharmaceutical uptake was limited by a lack of information on key soil properties across the published literature. The data comparisons were inhibited by differences in quality of the different studies. Moving forward, a framework for best practice in this field is needed to maximize the value and further applications of the data produced. *Environ Toxicol Chem* 2023;00:1–14. © 2023 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

Keywords: Soil contamination; Plants; Bioaccumulation; Bioavailability

INTRODUCTION

The issue of pharmaceutical pollution in the environment has received increasing attention in recent decades (Aus Der Beek et al., 2016; Boxall et al., 2012; Halling-Sørensen et al., 1998; Kümmerer, 2009). Factors such as population growth, aging populations, and medical advances are all increasing the number of prescribed pharmaceuticals, thus increasing the load of such drugs that enter the environment (Li, 2014). Whereas early research focused mainly on the presence of pharmaceuticals in aquatic environments, in recent years the occurrence, fate, and risks of pharmaceuticals in terrestrial agricultural environments has received more scrutiny (Carter et al., 2014; Díaz-Cruz et al., 2003; Li et al., 2019; Monteiro & Boxall, 2009).

Human-use pharmaceuticals may be introduced to agricultural environments when wastewater effluent is used for irrigation or sewage sludge is used as a fertilizer (Kinney et al., 2006). Removal efficiencies of pharmaceuticals in wastewater treatment plants vary both spatially, temporally, and also between different pharmaceuticals; however, concentrations of target pharmaceuticals in effluent samples have been identified up to several thousand µg/L (Kibuye et al., 2019). Reported concentrations of pharmaceuticals in raw, primary, secondary, and digested sludge vary over several orders of magnitude but can exceed 10 000 ng/g (Verlicchi & Zambello, 2015). Veterinary pharmaceuticals may be emitted directly onto agricultural land by pasture animals or when slurries and manures from more intensive operations are collected and distributed across fields as fertilizers (Boxall et al., 2003). Pharmaceuticals have now been detected in agricultural environments across the globe (Aus Der Beek et al., 2016), raising concern over their impact on soils, crops, and other organisms (Becerra-Castro et al., 2015; Carter et al., 2021; Liu et al., 2009).

Once introduced to agricultural environments, pharmaceuticals may have wide-ranging effects. Exposure to pharmaceuticals has been shown to induce significant effects on key crop

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quality attributes such as carbohydrate content and fruit firmness (Christou et al., 2019; Dagianta et al., 2014). Agricultural productivity may also be indirectly affected by pharmaceutically induced disruptions to soil microbial communities (Chander et al., 2005; Sallach et al., 2021). The fate of pharmaceuticals in agricultural environments is also an important consideration because an understanding of degradation and transformation products is essential for a full evaluation of environmental exposure. The fate and behavior of pharmaceuticals in plant–soil systems ultimately determines the likelihood of human exposure. Chronic exposure to pharmaceuticals through dietary intake of contaminated crops may have also have important human health implications such as antibiotic resistance, suppressed estrogenic activity, and allergic reactions in children (Ziylan-Yavas et al., 2022). The uptake of pharmaceuticals into crops is central to environmental fate, toxic effects, and implications for human and ecological health. An understanding of the uptake of pharmaceuticals into crops and the factors that affect uptake is essential for the evaluation of toxic effects, effect concentrations, trophic transport of contaminants, and associated implications for human and ecological health.

The pioneering studies on the uptake of pharmaceuticals into plants were published in the early 2000s, notably those by Migliore et al. (1998), Kumar et al. (2005), and Boxall et al. (2006). Since then, this research area has grown rapidly, with 780 papers identified by Web of Science in 2022 (search terms = ((Plant OR Crop) AND Uptake AND Pharmaceuticals). Recent reviews have highlighted the chemical, biological, and environmental factors influencing the uptake and translocation of pharmaceuticals in plants (Gworek et al., 2021; Keerthanan et al., 2021; Miller et al., 2016). Although these reviews have provided an invaluable overview of the field, they have not been systematic, nor have they made quantitative comparisons. To the best of our knowledge, there has been no fully quantitative, systematic review of the literature examining the factors influencing the uptake of pharmaceuticals into plants and the extent to which the published data support theoretical assumptions around uptake. A systematic synthesis of the wealth of evidence surrounding crop uptake of pharmaceuticals would facilitate a better understanding of the relative significance of the factors affecting uptake and would provide a specific framework for the future research needs in this area.

Our study therefore involved a systematic, quantitative literature review examining the available data on the uptake of pharmaceuticals into crops. We had three main objectives: 1) To systematically and quantitatively review the state of the science; 2) To evaluate the relative importance of the chemical, biological, and environmental factors influencing the uptake of pharmaceuticals into crops; and 3) To identify trends and knowledge gaps in experimental design, limitations of current data, and priorities for future research.

METHODS

Our systematic review followed the principles set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The PRISMA diagram is included in the Supporting Information, Figure S1.

Search strategy

Literature searches were conducted on December 3, 2020. Relevant literature was identified from two major scientific literature databases, the Web of Science (search field = topic) and Scopus (search field = article title, abstract, keywords), with the following Boolean search operators: ((Pharmaceutical* OR Medicine* OR *Antibiotic* OR *Antimicrobial*) AND (Uptake* or *Accumulation) AND (Crop* or Plant*) AND (Soil* OR Hydroponic*)), where * denotes a wildcard, which is used in place of any group of characters, including no character.

Selection of studies

A total of 1866 journal articles were identified in the initial database search (Scopus: 991, Web of Science: 875). Duplicate articles ($n = 603$) were subsequently removed. All screening was conducted using Rayyan (Ouzzani et al., 2016), with the following binary primary inclusion criteria being applied to the titles and abstracts of the remaining articles ($n = 1263$):

- studied terrestrial plant(s) or crop(s);
- exposed the crop(s) to one or more pharmaceutical(s) in a field or controlled environment (where controlled environment is defined as a laboratory or greenhouse);
- presented empirical data (i.e. not from a model);
- not a review paper.

To maximize coverage, papers with any ambiguities based on the primary screening criteria were included for full text screening for clarification. Following the primary screening, 217 journal articles were selected for full text screening. The following secondary screening criteria were applied before subsequent data extraction:

- data available for crop studied, pharmaceutical, exposure means and concentration, growth conditions, analytical methodology, uptake concentration or below limit of detection or quantification (LOD/LOQ) when appropriate as a minimum;
- numerical data for uptake concentrations of a pharmaceutical presented in a graph, table, or stated in the text;
- all information required to convert units is given, without making any assumptions about the data;
- sufficient detail to fully interpret data.

Following secondary screening, the experimental methodologies and resultant data from 150 journal articles were systematically extracted into the UTOPIC database. A complete bibliography of publications included in the UTOPIC database is listed in the Supporting Information. The exclusion reasons and frequency count for the studies rejected during the secondary screening stage ($n = 67$) are given in the Supporting Information, Table S1. Any discrepancies or uncertainties encountered during the article selection process were resolved through discussion with a second reviewer.

Data extraction

The data extracted from each article are summarized in Table 1. All data were extracted and recorded with the original units provided. All extracted concentration data were subsequently converted to the chosen standard units of μg/kg (dry plant or soil weight) and μg/L (spiked irrigation water or hydroponic growth solution). Data provided in graphical form were extracted from the literature by digitizing the plot using WebPlotDigitizer (Rohatgi, 2020). When soil textural information was given numerically (%), the soil textural class was calculated according to the classifications defined by the soil survey of England and Wales Land Information Service (Hallett et al., 2017). The following chemical properties of all of the studied pharmaceuticals were retrieved from the US Environmental Protection Agency (USEPA, 2021) CompTox database: log octanol/water partition coefficient (log K_{OW}), molecular mass, acid dissociation constant (pK_a).

Developing the UTOPIC database

A custom-made database was designed in Microsoft Access to systematically compile the extracted data. The data were entered via a purpose-built form. The database links 11 tables with the Experiments table detailing all experimental designs and the Measurements table containing the associated results. The relationships within the database allow the relationships within the data to be preserved, for example, one pharmaceutical may be studied in many experiments from many articles, and thus there is a one-to-many relationship between the Pharmaceuticals table and the Experiments table. A full database description and glossary of terms are included in the Supporting Information, Figure S2 and Table S2).

TABLE 1: Details of data stored within the uptake of pharmaceuticals into crops (UTOPIC) database for all articles meeting the primary and secondary screening criteria[a] and additional details recorded for articles when available and relevant

Data extracted for all articles	Data extracted where available
Article identification details (title, authors, publication year, journal, DOI)	Soil textural classification
Crop(s) studied	Length of exposure in days
Pharmaceutical(s) exposed	No. of pharmaceuticals applied in combination (e.g., single or mixture)
Study conditions (e.g., greenhouse soil, hydroponic, field)	Soil CEC
Method of exposure (e.g., spiked soil, spiked irrigation water, effluent, biosolids)	Soil pH
Exposure concentration and unit	Soil TOC
Analytical methodology (e.g., HPLC, GC–MS)	Concentration of pharmaceutical in soil porewater and unit
Concentration measured in crop (with crop part when available) and unit	Soil concentration at the end of the experiment and unit
Limit of detection/quantification (LOD/LOQ) and unit	

[a]Criteria described in the *Selection of studies* section.
CEC = cation exchange capacity; GC–MS = gas chromatography–mass spectrometry; HPLC = high-performance liquid chromatography; LOD/LOQ = limit of detection/quantification; TOC = total organic carbon.

Data transformation and statistical analysis

Defining comparison metrics. To facilitate comparisons across the different experimental approaches assessed in our review, empirical data were expressed as ratios of chemical concentrations in the plant to the concentrations in the respective exposure medium. Plant soil accumulation factor (PSAF) values and plant water accumulation factor (PWAF) values were generated for all measurements recorded according to Equation (1) and Equation (2), respectively, where C_{crop}, C_{soil}, and C_{water} represent the concentrations of the pharmaceutical in the crop (μg/kg), soil (μg/kg), and hydroponic solutions (μgL), respectively.

$$PSAF = \frac{C_{crop}}{C_{soil}} \tag{1}$$

$$PWAF = \frac{C_{crop}}{C_{water}} \tag{2}$$

Treatment of values less than LOD or less than LOQ. The data set was left-censored due to the proportion of measurements that were less than the analytical LOD/LOQ. When values were less than LOD/LOQ, data were substituted according to Equation 3.

$$\text{Substituted value} = \frac{\text{LOD (or LOQ)}}{\sqrt{2}} \tag{3}$$

The substitution method described in Equation (3) was deemed appropriate because it was found to provide the best reflection of real values in an evaluation of statistical treatments of left-censored data and has been shown to have the smallest overall error rate of the substitution methods (Antweiler, 2015; Croghan & Egeghy, 2003). This method also accommodates multiple different LOD values from different analytical methods in different articles.

Statistical analyses. All statistical analyses were conducted in Jamovi Ver 1.6.23.0 (Jamovi, 2021). Nonparametric tests were utilized to allow comparisons to be drawn accounting for the different sample sizes available for different groups of data. Kruskall–Wallis tests were utilized alongside post hoc Dwass–Steel–Critchlow–Flinger pairwise comparison tests to understand the significance of differences in the PSAF and PWAF values between groups of data when relevant comparisons could be drawn. The range of uptake within individual studies in which only the variable of interest was changed were also compared to understand the relative influence of different variables on pharmaceutical uptake observed. For this comparison the data were "normalized" relative to the smallest measured value in an individual study.

Data quality scoring and assessment. The articles were quality scored according to the inclusion of parameters identified in the priority data list presented by Fantke et al. (2016). This provided an objective baseline with which to quantify the level of detail included in each study. We also introduced some additional parameters: the analytical LOD or LOQ and the associated matrix (e.g., in soil, water, or plant material), the soil and porewater concentrations of the pharmaceutical(s) during the experiment, the soil texture, and the hydroponic solution pH. We considered these parameters to be important for understanding the context of the empirical data presented.

RESULTS

State of the science

The UTOPIC database contains data from 150 articles published between 1998 and 2021 and includes 8048 unique measurements of pharmaceutical concentrations in exposed crops. Uptake data were obtained for 173 individual pharmaceuticals. One-third (31%) of these measurements were below the stated analytical LOD or LOQ. The anticonvulsant medication, carbamazepine and the antibiotic sulfamethoxazole were the most frequently studied pharmaceuticals, having been studied in 47 and 46 individual studies out of the total 150, respectively (Figure 1B). The antibacterial and antifungal agent triclosan and the antibiotics oxytetracycline and trimethoprim were also extensively studied, in 28, 24, and 23 articles, respectively. Overall, 18 pharmaceuticals have been investigated in 10 or more studies, and 74 pharmaceuticals have been investigated in just 1 study. The database contains data for 78 separate crop species, and of these, 30 species have been studied more than once. Lettuce (*Lactuca sativa*) was the most studied crop species ($n = 46$), followed by tomato (*Solanum lycopersicum*; $n = 18$), carrot (*Daucus carota*; $n = 17$), and radish (*Raphanus sativus*; $n = 16$; Figure 1A).

Most of the studies (89%, $n = 138$) were conducted in a controlled environment such as a greenhouse, growth chamber, or laboratory, whereas 11% ($n = 17$) were conducted under field conditions. Of the controlled environment studies, 70% ($n = 97$) were conducted in soil, 28% ($n = 39$) were conducted in hydroponic systems, and 1% ($n = 2$) utilized a synthetic growth medium. The maximum exposure duration in any study was 280 days, and this was conducted in a greenhouse in soil. In general, field studies were associated with the longest exposure times, whereas hydroponic studies, conducted in controlled environments, were associated with the shortest times.

A wide range of different exposure pathways have been investigated (Table 2). For soil studies, the majority of studies used artificially spiked soils or irrigation waters ($n = 47$ and $n = 27$, respectively), but some studies utilized effluent ($n = 16$) and biosolids ($n = 12$) directly from wastewater treatment works. In a handful of studies, biosolids, effluent, manure, and urine were also spiked and utilized as exposure means.

The range of different exposure means described in Table 2 complicated comparisons between studies. To maximize comparability, only the data from spiked soil (for soil studies) and spiked water treatments (for hydroponic studies) were used to generate PSAF and PWAF values, respectively, for our meta-analysis. A total of 1397 PSAF values were generated from spiked soil studies, with measured values ranging from 1.50×10^{-5} for monensin in lettuce grown in a loamy sand soil to 2937 for triclosan in pinto bean roots. Of the 1397 total values, 219 (16%) were estimated using the substitution equation (Equation 3) because data were less than LOD/LOQ; the smallest estimated value was 1.42×10^{-6} for lasalocid in lettuce. In hydroponic studies, 767 PWAF values were generated, and 29 (3.8%) of these were less than the analytical LOD/LOQ. The measured values ranged from 5.38×10^{-6} for ciprofloxacin in Chinese cabbage shoots to 26 040 for carbamazepine in tomato leaves. The smallest estimated value for data less than LOD/LOQ was 3.39×10^{-2} for triclosan in tomato shoots.

Assessment of the quality of articles

Quality assessment of the publications showed that all articles described the study characteristics and the exposure medium. The majority of studies also described key details such as sampling date/time, sampled mass, binomial plant name, and sampled component (e.g., roots/stems/leaves). When the soil properties were relevant (i.e., not including hydroponic studies), 75.9% of studies included measurement(s) of the soil pH, whereas the soil organic carbon and soil cation exchange capacity (CEC) were detailed by 34.8% and 28.6% of studies, respectively. The soil texture was not included in the recommendations of Fantke et al. (2016) but was considered important by the authors and was detailed by 64% of the relevant studies (Figure 2A). Analysis of the contaminant fate and degradation was found to be limited. For soil-based studies, 65.2% of studies analytically determined the soil concentration at one time point during the study. An independent fate study was presented by 14% of relevant articles (Figure 2). Soil porewater concentrations were measured in 9.8% of studies. No article included all of the model parameters presented in Figure 2, with 22 criteria for soil studies and 17 criteria for hydroponic studies (Figure 2B and C). For soil studies, eight articles included 18–20 of the recommended parameters and for hydroponic studies, three articles included 14 of the recommended parameters.

Relative significance of chemical, biological, and environmental drivers of uptake

Clear trends were present in the variables incorporated into the experimental designs (Table 3). The majority of studies ($n = 51$) included data for the uptake of multiple pharmaceuticals in a singular crop type and in the same soil type. Incorporating

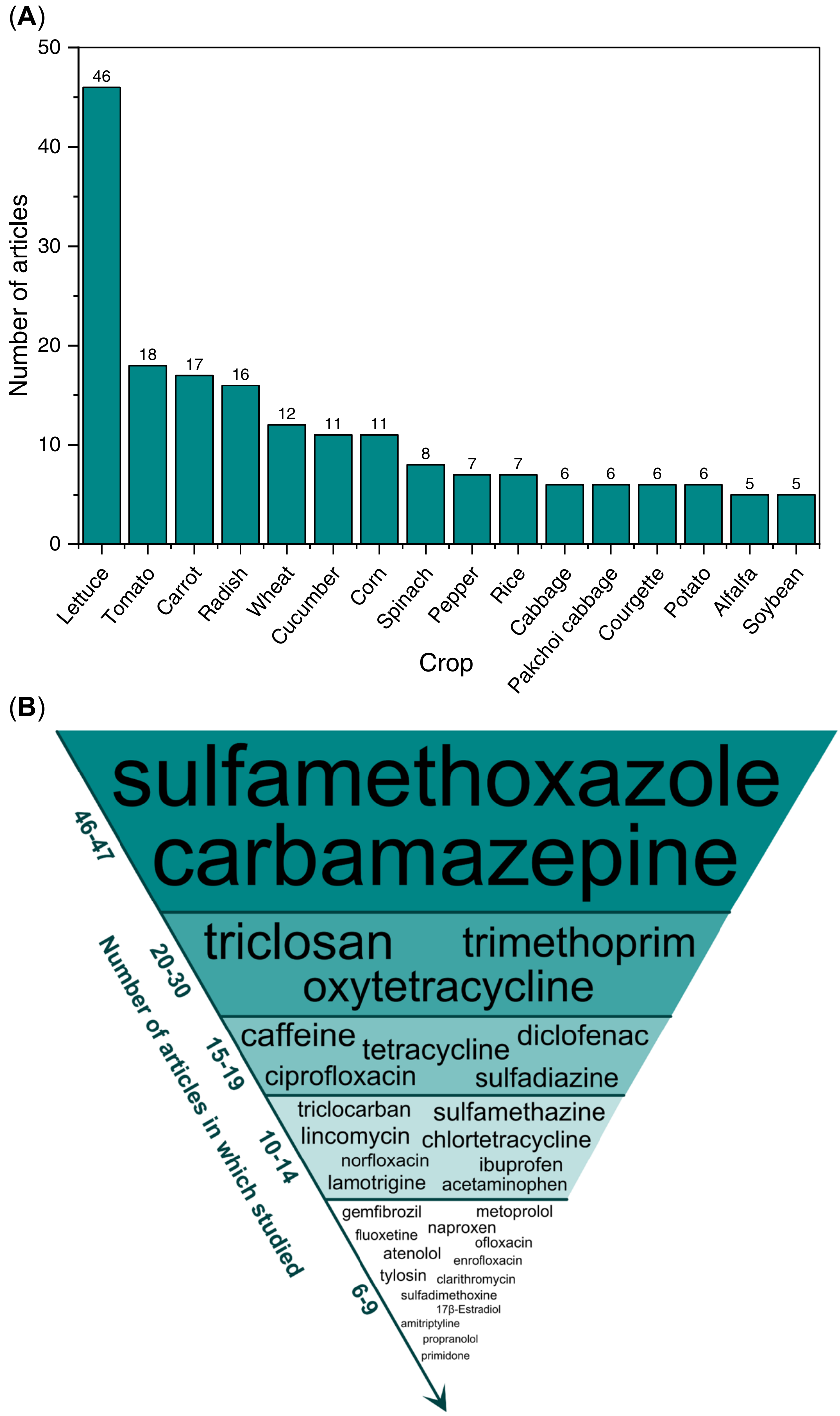

FIGURE 1: The most common crops and pharmaceutical compounds included in studies investigating the uptake of pharmaceuticals into crops as of January 2021 (150 peer-reviewed articles). (**A**) Bars represent the total number of discrete articles published in the peer-reviewed literature for each crop. Data included for crops studied in 5 or more articles. (**B**) A proportional word cloud indicating the 40 most commonly studied pharmaceuticals with the text size proportional to the number of discrete articles in which the compound was studied. Data included for pharmaceuticals studied in more than 5 articles.

multiple crops and multiple pharmaceuticals into the study design was also common ($n = 35$). Thirty-seven articles concerned data on the uptake of one pharmaceutical in one crop in one soil. Variations in soil conditions were less commonly incorporated into experimental designs ($n = 18$). Two articles isolated the soil type as the only variable in the experimental design.

The importance of the variables in Table 3 was systematically quantified through an intrastudy analysis in terms of their relative influence on observed uptake (Figure 3). The range in normalized uptake factors was greatest when multiple pharmaceuticals were tested in the same crop under the same conditions. The range in uptake factors of the same

TABLE 2: Frequency of application of different exposure pathways of pharmaceuticals to crops in soil-based uptake experiments

Treatment	No. of articles
Spiked soil	45
Spiked water	27
Effluent	16
Biosolids	12
Spiked biosolids	9
Spiked effluent	7
Spiked manure	6
Manure	6
Spiked urine	1

TABLE 3: Experimental variables incorporated into the experimental design of studies on crop uptake of pharmaceuticals included in the present review

Experimental variable(s)	No. of articles
Pharmaceuticals	51
None	37
Crops and pharmaceuticals	35
Crops	9
Pharmaceuticals and soils	9
Crops and pharmaceuticals and soils	6
Soils	2
Crops and soils	1

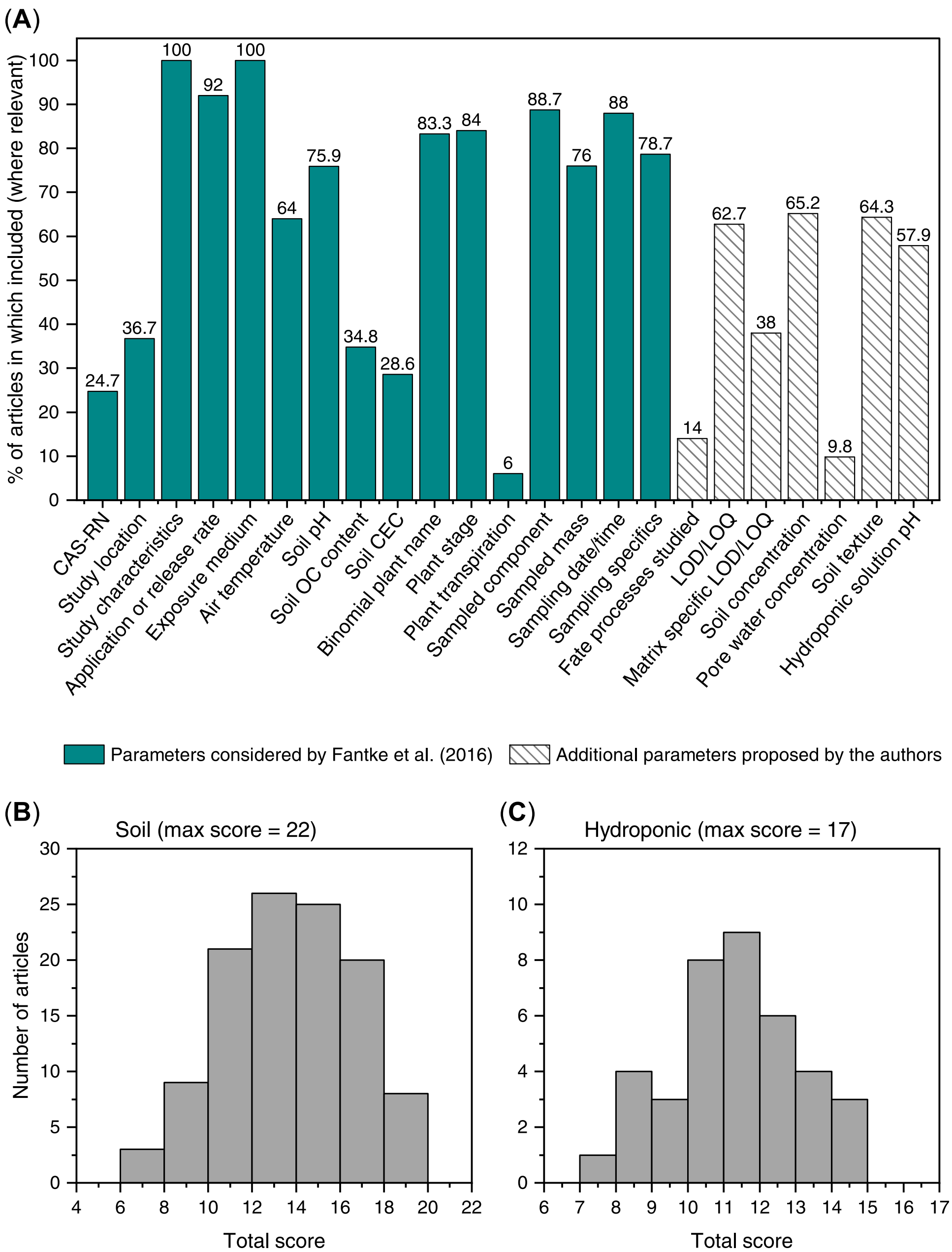

FIGURE 2: Number of studies included in the database (%) that included the priority parameters considered by Fantke et al. (2016), and the additional parameters proposed by the authors of the present study (**A**). Histograms of the distribution of the total criteria score of each article for soil studies (**B**) and hydroponic studies (**C**). CEC = cation exchange capacity; LOD/LOQ = limit of detection/quantification; OC = organic carbon.

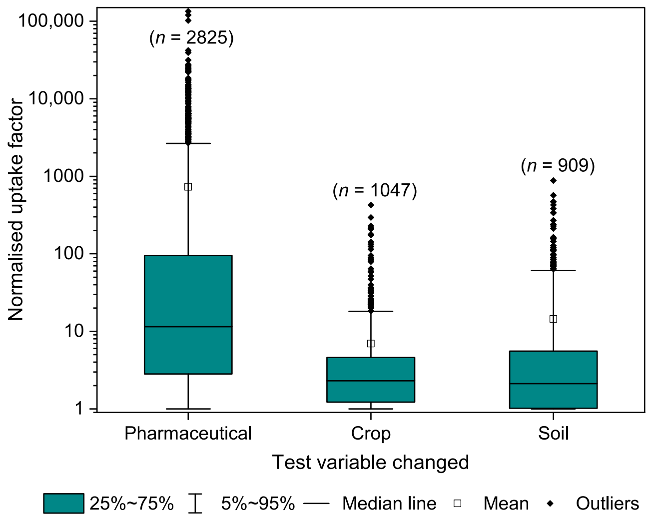

FIGURE 3: Comparison of the range of pharmaceutical uptake concentrations in crops included in studies in which only one test variable (i.e., pharmaceutical compound, crop, or soil type) was changed and the other two were kept constant, indicating the relative significance of each test variable in terms of the overall influence on the resulting concentration of pharmaceuticals measured in the crop. Data were normalized relative to the smallest identified value within the data set for each specific study.

pharmaceutical in different crops was smaller, suggesting that the extent of variation caused by biological properties of different crops is less significant than the extent of variation caused by chemical properties of different pharmaceuticals. The chemical properties of the pharmaceuticals therefore appear to exert a greater influence on uptake observed than differing biological properties of different crops. The range in uptake factors generated by different soil types was slightly greater, but the significance of this result is limited by the number of studies that incorporated different soil types into their experimental design.

Trends between pharmaceuticals

The ranges of PSAF and PWAF values for the most studied pharmaceuticals in soil and hydroponic environments were compared (Figure 4A and B). Observed PSAF and PWAF values varied significantly between different pharmaceuticals, even for pharmaceuticals with similar structures ($H(17) = 290$, $p < 0.001$) for soil environments, and ($H(9) = 262$, $p < 0.001$) for hydroponic environments.

In soil studies, carbamazepine ($\tilde{x}$ = 12.5) was associated with significantly greater PSAF values compared with all other pharmaceuticals ($p < 0.001$), apart from chlortetracycline ($\tilde{x}$ = 13.0), owing to the large range of PSAF values observed for chlortetracycline. Doxycycline ($\tilde{x}$ = 0.004) displayed the lowest median PSAF value, which was significantly lower than all other pharmaceuticals. The range of PSAF values observed for all pharmaceuticals spanned orders of magnitude, but it was noteworthy that large standard deviations were observed for carbamazepine (σ = 28.1), sulfadiazine (σ = 28.0), sulfamethoxazole (σ = 20.0), and chlortetracycline (σ = 15.7).

Experiments conducted in hydroponic environments resulted in greater measured concentrations of pharmaceuticals, and thus PWAF values were generally greater than PSAF values (Figure 4B). Hydroponic studies showed a smaller degree of distinction in PWAF values between different pharmaceuticals. It is worth noting that the most studied pharmaceuticals in hydroponic environments differed from those in soil environments, thus making it difficult to draw direct comparisons between uptake across the two growth media. Ciprofloxacin ($\tilde{x} = 4.5 \times 10^{-5}$) was associated with a significantly lower PWAF value compared with other pharmaceuticals. The PWAF values differed between some pharmaceuticals, but no other significant differences were identified across all pharmaceuticals. Particularly large standard deviations were observed for carbamazepine (σ = 4249), diclofenac (σ = 636), triclocarban (σ = 552), and triclosan (σ = 515).

Overall, carbamazepine, chlortetracycline, trimethoprim, triclocarban, and triclosan showed comparatively high accumulation potentials in crops. However, a range of uptake factors was present in the data for all pharmaceuticals for both soil and hydroponic studies, suggesting that although some pharmaceuticals are more readily accumulated in crops, other chemical, biological, and environmental factors also affect the extent of uptake.

No clear relationship was identified between the pharmaceutical log K_{OW} and the PSAF for crops grown in soil or PWAF for crops grown in hydroponic media (Figure 5C and D). A range of uptake factors was identified across the full range of log K_{OW} values for the pharmaceuticals studied. However, splitting the data by crop part measurements revealed some trends. For data collected in crops grown in soil, the highest uptake values were generally identified in roots and leaves. In hydroponic solutions, the greatest uptake factors were identified primarily in root measurements. This trend was particularly clear for hydrophobic compounds (higher log K_{OW} values).

The majority of the pharmaceuticals studied had molecular masses between 180 and 500 g mol^{-1}, and a range of uptake factors was identified within this range of molecular mass values (Figure 5A and B). Pharmaceuticals with molecular masses in excess of 500 g mol^{-1} such as streptomycin, monensin, iomeprol, iopromide, and tylosin showed lower uptake factors in both soil and hydroponic growth media. However, fewer data points were available for these compounds, introducing a potential for sample size bias.

Trends between study crops

Even though a range of uptake factors was present in all studied crops, some crops showed relatively increased pharmaceutical accumulation potential (Figure 4C and D). In soil studies, lettuce ($\tilde{x}$ = 1.36), pinto beans ($\tilde{x}$ = 0.666), courgette ($\tilde{x}$ = 4.13), and rice ($\tilde{x}$ = 1.38) had PSAF values that were significantly greater than all other crops but were not significantly different from each other ($H(10) = 343$, $p < 0.001$).

A range of PWAF values was recorded for all crops in hydroponic studies except for Chinese cabbage ($\tilde{x} = 4.5 \times 10^{-5}$),

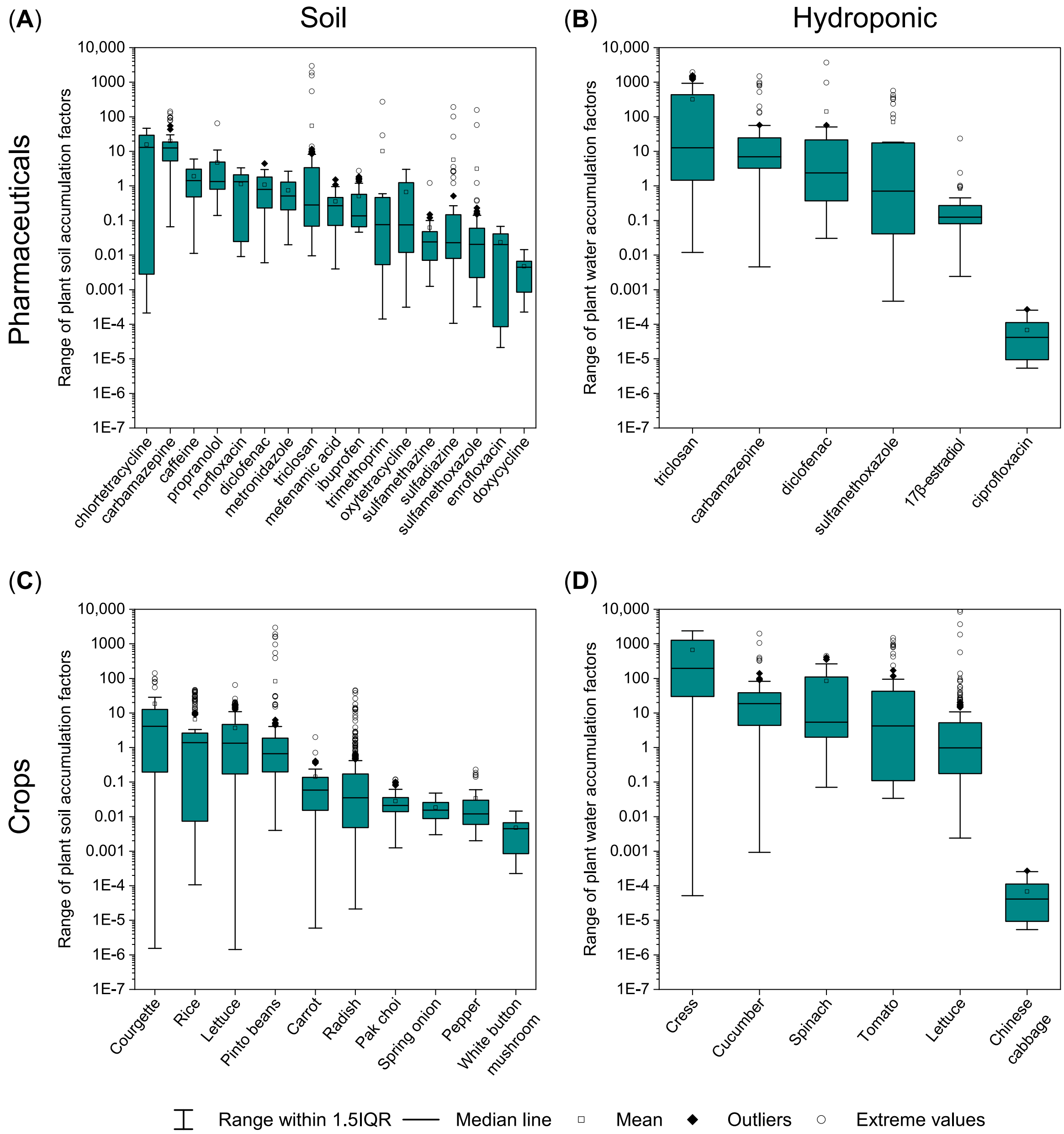

FIGURE 4: Range of plant soil accumulation factors and plant water accumulation factors for the most studied pharmaceuticals (**A** and **B**) and the most studied crops (**C** and **D**). Data were plotted for pharmaceuticals and crops when >30 datapoints were available. For soil studies, data were included only when soil was spiked directly to maximize comparability. IQR = interquartile range.

which displayed a significantly reduced accumulation potential compared with all other crops ($H(5) = 246$, $p < 0.001$).

Overall, lettuce, courgette, and rice showed elevated median uptake factors in soil environments, whereas cress, cucumber, and spinach showed generally greater affinity for uptake in hydroponic solutions. A number of outliers were present across crops in both growth media but most notably for rice, lettuce, and radish grown in soil studies, highlighting the significant variability in uptake data.

The range of data obtained for specific plant components was also compared (Supporting Information, Figure S3). A range of uptake was observed across roots, stems, and leaves in soil studies, and this variation was likely to be both crop and compound specific. However, these data were significantly greater than the uptake observed in fruits. Seeds also showed lower mean uptake, but this plot was limited by data availability (<30 data points). No clear trend was observed in uptake across different crop components in hydroponic environments.

Trends between soil types

The soil textural class significantly influenced the extent of uptake observed in crops ($H(11) = 255$, $p < 0.001$; Figure 6). Significant differences in PSAF values were observed between studies conducted in clay ($\tilde{x}$ = 0.204), sandy clay ($\tilde{x}$ = 0.034), and silty clay loam ($\tilde{x}$ = 0.0032; $p < 0.001$). However, the range of PSAF values across all soil types meant that these were not

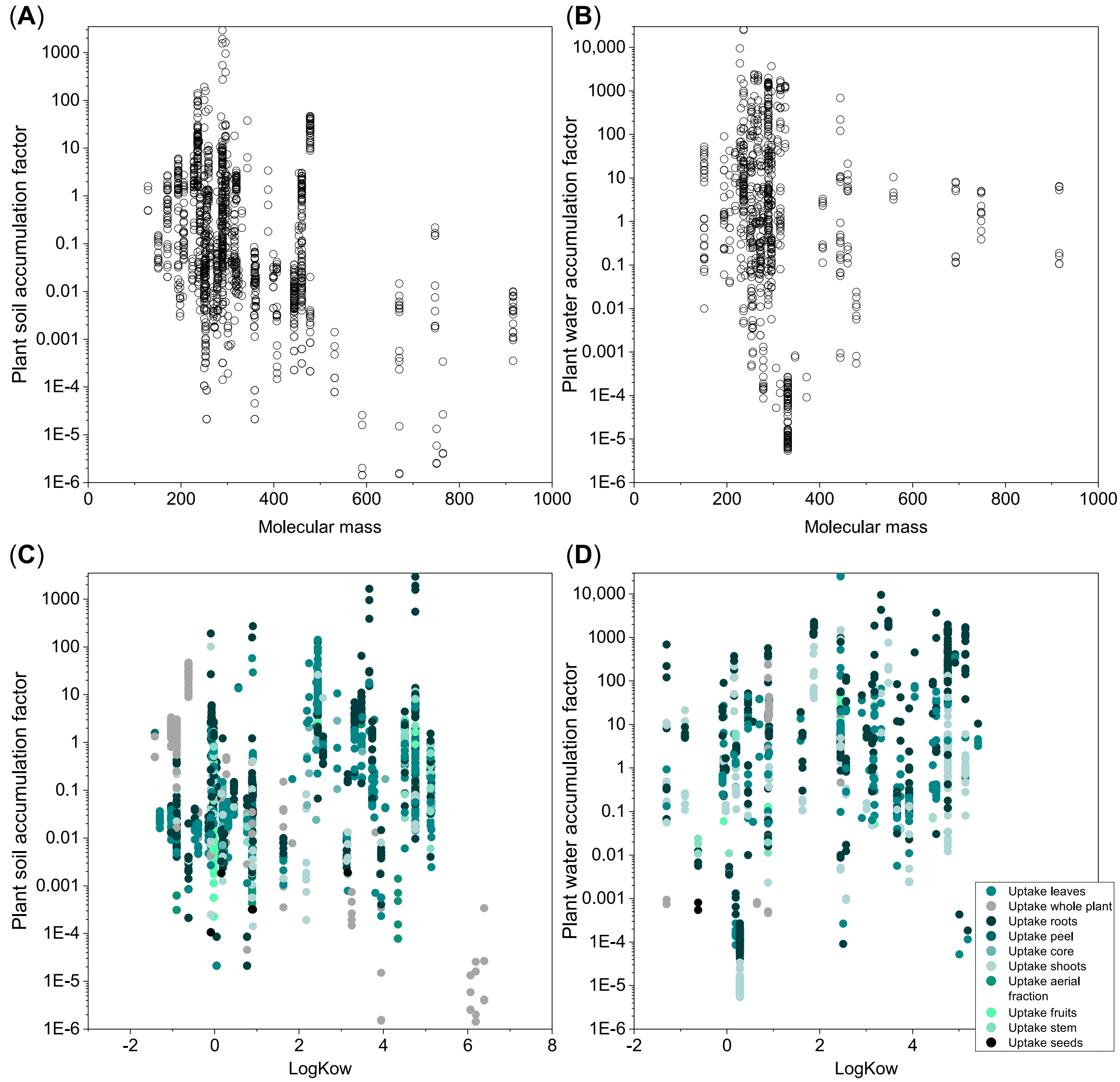

FIGURE 5: Association between plant soil accumulation factor or plant water accumulation factor and respective molecular mass (**A** and **B**) or log octanol–water partition coefficient (log K_{OW}; **C** and **D**) of pharmaceutical compounds investigated in uptake studies into crops.

significant from all other soil types. The greatest ranges in results were observed in sand (σ = 510), sandy silt loam (σ = 48.2), silt loam (σ = 35.2), and loamy sand (σ = 13.4). The soil pH values ranged from 4.0 to 8.7 when pH was measured and reported.

DISCUSSION

State of the science

Emerging evidence about the presence of pharmaceuticals in the environment has led to research efforts to establish the extent of uptake into edible parts of food crops. A wealth of data now exists on the topic. The present review highlights significant variability in this data coverage. A considerable data bias exists toward certain classes of pharmaceuticals, namely, the antibiotics sulfamethoxazole, oxytetracycline, and trimethoprim and the antiepileptic drug carbamazepine. The current focus on these compounds allows for useful comparisons to be drawn between studies of these single compounds in different conditions. However, with >1900 active pharmaceutical ingredients in use worldwide, the potential uptake for the majority of compounds remains unquantified (Burns et al., 2018). A similar data bias is present in the study crops utilized in this field. One-third of the studies included in our review investigated uptake into crops of lettuce (*L. sativa*). Although lettuce is a useful study crop owing to its relatively short growth period, the focus on lettuce may skew future risk assessments because lettuce appears to have a relatively high accumulation potential relative to other study crops. Furthermore, lettuce is not a staple component of global diets. Research attention has also focused on controlled environments, which provide useful insights into the mechanisms of uptake but are unlikely to be representative of field conditions. The majority of studies expose crops to single compounds in isolation, which is not

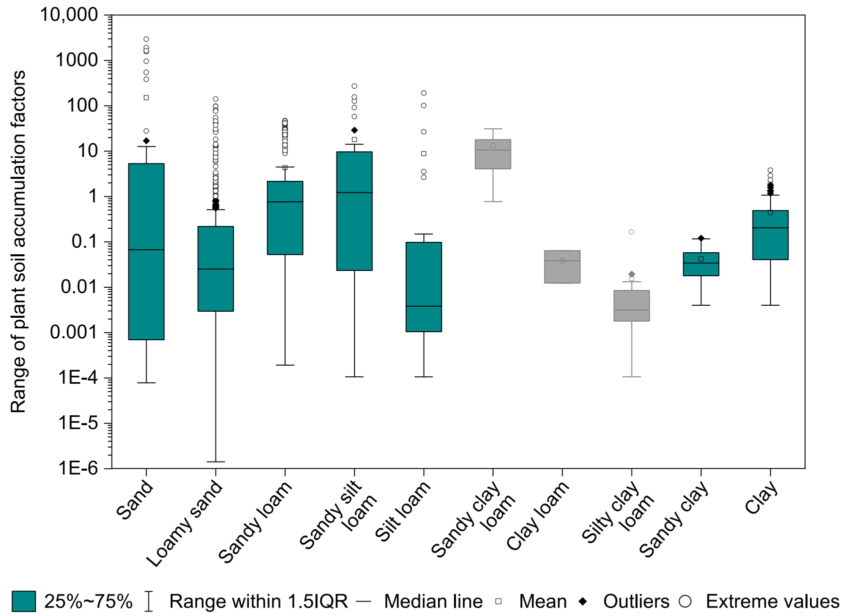

FIGURE 6: Range of uptake factors for all pharmaceuticals and crops expressed across different soil textural classes for studies conducted in controlled environments with spiked soils. Data are presented for soil types with >30 datapoints available across all studies. Boxes indicated in gray denote soil types for which there were <30 values available. IQR = interquartile range.

representative of the pharmaceutical mixtures that crops will be exposed to in real environments. Studies conducted in hydroponic solutions result in greater uptake of pharmaceuticals relative to soils. Previous studies on the uptake of contaminants across soil and hydroponic conditions have identified key differences in plant responses including overall uptake and efficiency of root-to-shoot translocations between soil and hydroponic conditions (Zabłudowska et al., 2009).

Interacting physical, chemical, biological, and environmental drivers of uptake

The concentration of a pharmaceutical taken up into a crop results from a range of interacting physical, chemical, and biological factors that may act in combination to increase or decrease the overall uptake observed. To gain insights into the relative importance of these factors, the present review analyzed the range of data produced in individual studies when data for each variable could be isolated. The uptake concentrations of different pharmaceutical compounds studied in the same crop and under the same conditions spanned more than 3 orders of magnitude, and the pharmaceutical compound studied was therefore identified as the single greatest source of variation in overall uptake observed. Comparisons of different soil types produced the second greatest variability in uptake. Variation in the uptake of single compounds in different crops under the same conditions resulted in the smallest range of data; however, uptake variations across different crops were still more than 1 order of magnitude, thus showing that biological properties still have a significant influence on the overall uptake of pharmaceutical compounds. The experimental design of most studies incorporated multiple pharmaceutical compounds. Differing soil conditions were only investigated in 12% of the studies, and therefore our understanding of the true importance of different soil properties in terms of uptake is limited.

With the specific pharmaceutical compound identified as the greatest single source of variation in uptake data, it is important to consider the individual physical–chemical properties that may contribute to this. Across soil and hydroponic conditions, carbamazepine was found to have the greatest overall accumulation potential.

The K_{OW} describes the hydrophilicity of a chemical compound. It has been identified as an important parameter in determining the fate and behavior of pharmaceuticals in the environment (Briggs et al., 1983; Li et al., 2020; Trapp et al., 1990). The results of hydroponic studies in the present review showed that the greatest uptake was generally found in root measurements. This was clearer for hydrophobic compounds (higher log K_{OW} values) probably because hydrophobic compounds have a greater affinity for crop root surfaces than hydroponic solutions. Overall, our results show no clear relationships between uptake and the log K_{OW} of a pharmaceutical. The log K_{OW} of a pharmaceutical certainly influences the propensity of a pharmaceutical for uptake, but this is not discernible on the scale of our review. On more specific scales, previous studies have suggested a range of theoretical relationships between log K_{OW} of a compound and the expected uptake into a crop. A study of the uptake of nonionized chemicals by barley stems from spiked hydroponic solutions identified a linear relationship, with the greatest uptake observed for compounds with a log K_{OW} of approximately 4.5 (Briggs et al., 1983). A later evaluation of this model found that it was suitable for pharmaceuticals with a log K_{OW} >0.5 but was less applicable to pharmaceuticals with negative log K_{OW} values (Hu et al., 2010).

The molecular mass of a pharmaceutical is another key chemical property that may determine the extent of plant uptake. Most of the pharmaceutical compounds included in our review had masses between 200 and 500 amu. Although a range of uptake factors was observed across the spectrum of molecular mass values, the greatest uptake values were recorded for compounds with molecular mass values between 200 and 300. Previous studies have suggested that the greatest uptake of trace organic compounds will occur when the molecular mass of the compound is <300 (Kumar & Gupta, 2016). The USEPA's ECOSAR package for assessing the ecotoxicity of chemicals assumes that compounds with molecular masses in excess of 1000 are too large to pass through cellular membranes (Sanderson et al., 2004). The findings of our review support this assumption: accumulation factors were significantly reduced for chemicals with molecular mass values >500, particularly in soil environments.

Uptake was found to vary significantly between different crops. In soil studies, courgette, rice, lettuce, and pinto beans exhibited greater uptake potential compared with other crops. In hydroponic studies, cress also showed a high propensity for uptake compared with other study crops. Crops absorb pharmaceutical compounds from the soil or hydroponic solutions through the roots and transport them to the vascular tissues. Plant-specific factors such as transpiration rate, shape and size of leaves, lipid content, and root system characteristics may all affect the extent of uptake of organic contaminants (Colon & Toor, 2016). Passive diffusion across cell membranes is believed to be the dominant mode of transport for organic contaminants into plant roots (Trapp & Legind, 2011). The uptake of organic contaminants into leaves has been positively correlated with transpiration rate for both ionic and neutral compounds, suggesting that transpiration rate is an important factor in the movement of contaminants into plant leaves.

Uptake concentrations were found to vary across different parts of individual crops. A range of accumulation factors was evident for all crop parts, but the highest uptake concentrations were measured in roots across both soil and hydroponic conditions. Measurements from fruits were comparatively reduced in soil environments, and data availability from fruits were limited in hydroponic environments. The general trend for greater accumulation in roots is likely due to proximity to the contaminants in the soil. A range of different models has been proposed for the pattern of accumulation of contaminants across different plant parts. Gworek et al. (2021) concluded that the accumulation coefficients of pharmaceuticals in plants follow the same general order of roots > leaves > stems, with the lowest accumulation being observed in the generative parts such as grains. Overall, our findings loosely follow this suggested pattern, but the trend is particularly clear for data from lettuce crops specifically. Overall, there is no clear trend for accumulation in specific plant parts at the scale of the present review. Accumulation patterns are likely to be both crop and compound specific. For example, roots were identified as the primary plant part for the accumulation of triclosan and 17α-ethynylestradiol as a result of lipophilicity (Karnjanapiboonwong et al., 2011). This is likely because lipophilicity also tends to lead to accumulation in roots and to limit movement out of the roots and into the plant transpiration stream. In a study of uptake and translocation in barley, Inoue et al. (1998) suggest that neutral and cationic species are susceptible to uptake by roots and will therefore translocate to other plant parts. In contrast, anionic compounds are less likely to be transported to aerial plant parts due to their accumulation in root cells by mechanisms such as ion-trapping.

Uptake was also shown to vary across different soil types. A range of soil properties may influence pharmaceutical bioavailability in soils and subsequent uptake into crops. The results of our meta-analysis showed relatively higher crop uptake in sandy and loamy soils and generally lower uptake in soils with higher clay contents. This could be due to the higher CEC of clay soils, with sorption of cations generally increasing with CEC, thus retaining positively charged compounds in the soil matrix and therefore making them less bioavailable for uptake by crops. A study of the sorption behaviors of tetracyclines across a range of soil types found that oxytetracycline, tetracycline, and chlortetracycline exhibited high levels of sorption, but that this was particularly evident in clay soils (Sassman & Lee, 2005). However, the same study suggested that differences in levels of sorption between soil types cannot be fully explained by CEC alone and that soil pH also plays a critical role in the sorption and bioavailability of pharmaceuticals in soils. Our results support this observation because even though sand and loamy soils showed generally higher uptake, there was also a greater range in uptake values within these soil types, suggesting that other factors can act in combination to influence the extent of uptake. These observations indicate the potential importance of soil textural classification in uptake and fate studies but the results are limited by the smaller sample sizes of data sets available for certain soil types; however, the box plots for sand, loamy sand, sandy loam, and clay are all supported by >50 data points, which is considered a significant sample size. Our review highlights a lack of consideration of soil properties in the experimental design of many studies, with only 9.8% of studies including soil textural class information and only 12% of reviewed articles ($n = 18$) incorporating soil type as a variable.

Assessment of the quality of articles and recommendations for future best practice

Our review synthesizes the collective findings of 150 empirical studies concerning the uptake of pharmaceuticals into terrestrial crops. Individual studies highlight trends in data and suggest relationships among key chemical, biological, and environmental properties and the extent of pharmaceutical uptake into crops. These relationships are not evident on the scale of the global literature, and our understanding and interpretations of current data are limited by inconsistencies in data collection and reporting. Experimental approach was considered to be one of the largest sources of uncertainty within the database, and the lack of standardization limited comparisons among studies. Following the recommendations of Fantke et al. (2016), our review found that the study characteristics, exposure medium, sampled component, sampling date or time, and binomial plant name and plant stage were detailed in >80% of the articles studied. Soil pH was reported in 75.9% of the studies, but soil organic carbon content, CEC, and textural classification were only reported in a minority of studies. An understanding of pharmaceutical fate and degradation is also critical to contextualize plant uptake data. Our review found that detailed information on pharmaceutical fate in the study conditions was provided by 14% of studies. We recommend that concentrations of the contaminant in the soil or growth matrix at day 0 and day *n* be measured and reported as a minimum. Measurements of soil concentration at three or more time points during the study would provide a more robust assessment of pharmaceutical fate. Our review also found that soil porewater concentrations were reported for 9.8% of relevant studies. Consideration of soil porewater concentrations is recommended for future studies because the distribution of pharmaceuticals between soil and porewater acts in combination with their fate and biodegradation to determine overall bioavailability for plant uptake (Li et al., 2019).

A range of different exposure mechanisms was recorded (Table 2). These different exposure mechanisms will influence the date and behavior of pharmaceuticals in agricultural environments. Understanding a range of exposure means is important to be representative of realistic environmental conditions; however, there is a need for some standardization to strengthen future data comparisons. Only the data from studies conducted with spiked soils could be easily compared in the present meta-analysis. When spiked irrigation water or spiked biosolids are utilized as the exposure pathway, we recommend additionally measuring the concentration of pharmaceuticals in the soil and porewater to characterize transfer pathways. When spiked irrigation water is utilized, it is important to distinguish between soil surface application and aerial irrigation. Key differences in uptake between these irrigation methods have been highlighted, demonstrating the importance of specific reporting (Bhalsod et al., 2018). Discrepancies were also observed between nominal and empirically measured exposure concentrations. Where exposure concentrations are calculated based on spiking concentrations, the analytically measured concentration should also be determined and reported.

The present review also highlighted a positive results bias in this field, with data below the analytical LODs often being omitted or presented only in the supporting information. When data were less than LOD/LOQ, the numerical values for these parameters were often not stated. These numerical detection limits are invaluable in interpreting the data and may vary significantly between different analytical methodologies and instruments. As shown in the present review, these data may be applied to substitution equations and can allow the data to be utilized in model parameterization. To be fully comprehensive, LOD/LOQ values should be provided for each matrix analyzed, for example, in soil, water, and plant material.

Considering these inconsistencies, a framework for good practice is needed if we are going to fully understand the chemical, biological, and environmental drivers of pharmaceutical uptake into crops. We support the recommendations of Fantke et al. (2016) and propose a number of additional parameters that should be included in future experimental studies in this field to maximize the value of data produced in terms of understanding and future applications (Table 4). Limited availability of measurements of key soil properties and soil porewater concentrations was identified as a constraint in the application of the current literature to predictive assessments of crop root concentrations of contaminants using machine learning models (Gao et al., 2021).

These inconsistencies in data reporting make comparisons of data in this field challenging. Although a range of data is vital to reflect realistic variations in environmental conditions, introducing a degree of standardization into this field by applying the combined guidance of Fantke et al. (2016) and the additional parameters indicated in Table 4 would maximize the value of the results produced, facilitating the construction and calibration of models.

TABLE 4: Data recommended to be included in studies investigating crop uptake of pharmaceuticals alongside the priority parameters identified by Fankte et al. (2016)

Parameter	Description
Fate processes studied	Behavior of the pharmaceuticals in the soil/hydroponic solution over time should be understood
Matrix-specific LOD/LOQ	A value for the analytical limit of detection should be provided for each analyzed compound in each matrix, for example, soil, water, plant material
Single/mixture	Explicit distinction between single exposure and mixed exposure for any study investigating more than one pharmaceutical
Method of pharmaceutical exposure	Spiked water/spiked soil/spiked biosolids/effluent; when spiked irrigation water is applied, the application (e.g., soil surface application or aerial irrigation) should be fully described
Soil concentration	The soil concentration of the pharmaceutical(s) should be measured at intervals throughout the experiment
Porewater concentration	The porewater concentration of the pharmaceutical(s) should be measured at intervals throughout the experiment
Soil textural classification	The soil textural classification should be described when appropriate
pH of hydroponic solution	The pH of the hydroponic solution should be measured when appropriate
Units	All units should be clearly stated with sufficient detail to allow unit conversions when necessary

LOD/LOQ = limit of detection/limit of quantification.

CONCLUSIONS

The present review synthesizes the wealth of evidence surrounding the uptake of pharmaceuticals by terrestrial crops. There are clear trends in the experimental design of existing studies, with a data focus on a limited range of pharmaceuticals and crops. Overall, the biological properties of different crops influence the extent of uptake of pharmaceuticals, but the chemical properties of pharmaceuticals are key in determining the overall uptake. There is a need for some standardization in the reporting of experimental methods and results to maximize the value of the data produced and facilitate future interstudy comparisons. There are limited data available on the influence of different soil properties on uptake, and this is considered to be a priority for future research. Our review has focused on summarizing the state of the science and elucidating the relationships among biological, chemical, and environmental factors and the uptake of pharmaceuticals by crops. In the future, the UTOPIC database could be applied to model validation and to other important and related research questions such as assessment of human exposure from consuming crops in global diets.

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