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A framework to assess pharmaceutical accumulation in crops: from wastewater irrigation to consumption

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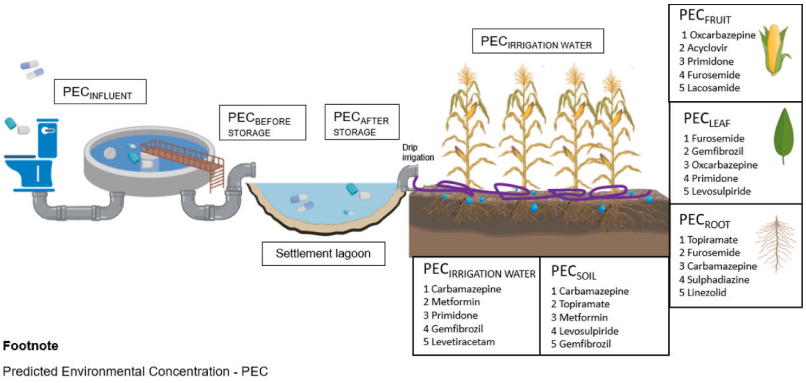
HIGHLIGHTS

- Pharmaceutical uptake can be predicted from a chemical structure and excretion data.
- The framework provides a rapid approach to screen large chemical datasets.
- 56.7 % of the top 30 pharmaceuticals have not been previously reported in literature.
- Consumption of contaminated produce was deemed to be a negligible human health risk.
- Consumption of multiple crops and co-contaminants increased the hazard index > 1.

GRAPHICAL ABSTRACT



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ABSTRACT

The reuse of treated wastewater for irrigation can inadvertently introduce a suite of emerging contaminants such as pharmaceuticals into agri-ecosystems. However, current monitoring efforts to characterise exposure usually focus on a limited range of analytes. A modelling framework was developed that employs a sequence of pre-developed models to predict accumulative potential in a model crop, *Zea mays* (corn), using chemical structure and excretion rate as the only model inputs. *Z. mays* was selected as the model crop as it is a major food source, stands as one of the highest cultivated crops globally, and is characterised as having a medium uptake potential. The framework was used to predict uptake in *Z. mays* in three regions characteristic of high wastewater

Abbreviations: OC, organic carbon; CEC, Cation Exchange Capacity; SPC, Summary of Product Characteristics; PEC, Predicted Environmental Concentration; MEC, Measured Environmental Concentration; RQ, Risk Quotient; HI, Hazard Index; HRMS, High-Resolution Mass Spectrometry; ADI, Acceptable Daily Intake; WW, Wastewater; TWW, Treated Wastewater; WWTP, Wastewater Treatment Plant.

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reuse (Australia, the US and the Middle East). Despite regional and plant specific differences, 72.7 % of the calculated concentrations were within a factor of ten of those reported in the literature. Topiramate, furosemide, and gemfibrozil were observed to accumulate to the greatest extent in *Z. mays*, predicted concentrations ranged between 50.27 and 418.01 ng/g (dw) for the top 10. Acids predominantly accumulated in leaves and fruit whereas a higher proportion of bases were predicted to accumulate in the roots. To the best of our knowledge 56.7 % of the 30 highest-ranked pharmaceuticals have not been previously documented in existing literature or monitoring campaigns. This presented framework demonstrates a method to assess risk posed by pharmaceutical compounds with limited experimental data.

1. Introduction

Agricultural practices are coming under intense pressure from both policy and commercial drivers of change (e.g. UN Sustainable Development Goals (SDGs)) to reduce demand on primary resources (energy, land, water and biomass), contribute towards regenerative approaches and improve soil health [9]. The reuse of wastewater offers a sustainable method to meet these demands whilst providing a suitable means of waste disposal [80,102]. Wastewater reuse for example can improve soil fertility by increasing organic matter/carbon (OM/OC) and nutrient content (N, P, K) and has been shown to increase crop yields (19.7 % when compared to freshwater irrigation) and reduce the need for synthetic fertilizer and freshwater requirements [55]. High wastewater reuse rates are generally associated with regions facing water scarcity. For example, in Mexico wastewater irrigation practices have been utilized for > 100 years in the Mezquital Valley [19,51], and 85 and 90 % of wastewater is reused to support agricultural demand in Israel and Cyprus, respectively [4].

Typically, conventional WWTPs (primary and secondary clarifiers) are designed to treat wastewater for nutrients, OM, and OC, unfortunately these technologies generally neglect emerging contaminants and are generally associated with compound specific removal rates (<0–100 % (n = 28 pharmaceuticals)) [61,73]. Therefore, treated wastewater (TWW) contains a wide array of traditional and emerging contaminants such as heavy metals, pharmaceuticals, biocides, tyre wear products, personal care products and industrial chemicals [60,67]. Regular discharge of contaminated TWW results in the continued addition of emerging contaminants into receiving waterbodies (i.e., rivers or settlement lagoons) [115]. The use of TWW in agriculture therefore presents a means for emerging contaminants (pharmaceuticals), to accumulate in agricultural soils (up to mg/kg levels) [72,83]. Pharmaceuticals are of particular concern owing to their retained biological potency in environmental systems [50]. Carbamazepine, lamotrigine and bezafibrate are frequently detected in TWW-irrigated soils, where concentrations typically range from 0.001 to 0.026 mg/kg, 0.005–3.5 mg/kg, and 0.0006–0.79 mg/kg (dry weight, dw) respectively [20,62,89]. Pharmaceuticals present in soil can be taken up by plants, a process governed by physicochemical properties of the pharmaceutical such as charge, hydrophobicity (log K_{OW} <3.5), aqueous solubility, and molecular weight [114,17], in combination with environmental factors such as temperature and soil pH, and plant parameters (e.g. transpiration) [47].

Monitoring campaigns have detected a suite of pharmaceuticals in crops irrigated with wastewater including carbamazepine, venlafaxine, and lamotrigine which are commonly reported in a number of crops [83, 103], with pharmaceuticals typically accumulating to higher concentrations in leafy crops than roots [93]. Despite the widespread, long-term use of wastewater in agriculture, our understanding of environmental risk is focused on a sub-set of commonly reported pharmaceuticals [103]; a result of their known persistence or the availability of extraction/analytical methodologies [12,45]. Current targeted approaches (~50 chemicals) continue to neglect the majority of the 1900 chemicals that are authorized for therapeutic use, for which we know very little about [12]. This is of particular concern as TWW irrigation results in the repeated exposure to hundreds of pharmaceuticals which have the potential to be taken up and accumulate in crops [49], with recent evidence demonstrating that TWW reuse results in greater bioavailability of pharmaceuticals over that of contaminants present in sludge or animal waste [85]. With current predictions suggesting that irrigated food production will need to increase by 50 % by 2050 to meet global food demands, it is likely TWW will contribute towards a large proportion of this [25,38,101].

There is therefore a clear need to expand research efforts to better understand the fate and effects of pharmaceuticals inadvertently introduced in agricultural systems following wastewater reuse [97,16]. Key to achieving this will be a means of prioritising pharmaceuticals of most concern, as it is not feasible to develop methods and carry out experimental studies for all pharmaceuticals. In this paper, we describe a framework that evaluates the accumulative potential of pharmaceuticals in an arable crop following TWW irrigation; from pharmaceutical consumption to the point of crop consumption. Therein we present a ranking of pharmaceuticals in terms of their accumulation in an example crop, Z. *mays*, from three different regions of high wastewater reuse. Z. *mays* was selected as it is a major food source and a high-yield commodity crop, with an average harvested area of 157 million hectares from 2000 to 2014 [95], and is considered to be at greatest risk in terms of growth in areas with high water stress, the demands of which are expected to be met by increased use of wastewater irrigation [116]. To the best of our knowledge this is the first framework to accurately predict plant uptake following TWW irrigation using chemical structure alone (with the exception of excretion rate); by utilizing this approach we have generated the first comprehensive dataset of prioritised pharmaceuticals predicted to accumulate in crops in areas of high TWW reuse.

2. Methodology

2.1. Modelling framework

With a focus on the use of minimal experimental data input to allow for large scale screening of pharmaceutical datasets our framework links an original model to derive steady-state soil concentrations (PEC_{SOIL}) with previously published models to determine i) wastewater influent concentrations ($PEC_{INFLUENT}$); ii) environmental fate during wastewater treatment ($PEC_{EFFLUENT}$), iii) environmental fate of TWW during settlement periods; and iv) crop uptake (PEC_{PLANT}). Each step of the framework has been described in detail below with a conceptual schematic for the model provided in the Fig. 1.

The framework was used to evaluate crop uptake and prioritse pharmaceuticals previously identified in non-target screening of TWW in three regions characterized by high TWW reuse. The modeling regions were carefully selected to evaluate pharmaceutical accumulation across areas with diverse soil and climatic conditions. The selection criteria were based on the following: High rates of treated wastewater (TWW) reuse (14–86 %), variations in climatic conditions (16–22.7 °C), and regionally distinct soil characteristics (pH, texture, OC, Cation Exchange Capacity (CEC) (SI Table 1). Selected regions were Oman (the Middle East (Israel; 86 % TWW reuse)), Renmark (South Australia; 14 % TWW reuse), and Bakersfield (California, United States (US); 46 % TWW reuse) [69,86]). Representative soil properties were obtained for each

region (SI Table 1) and for simplicity, regions are referred to as the Middle East (ME), Australia, and the US throughout the manuscript.

Pharmaceuticals and their metabolites present in TWW were identified by reviewing available published HRMS datasets, the selected studies were of the highest available quality and met the Level 2 criteria set out via Schymanksi *et al.,* [98]. To achieve this HRMS data must have an accurate mass tolerance of ± 5 ppm, retention time checks, MS/MS spectra comparisons, and isotope checks [46,57,94,100,109]. Selected studies encompassed in-depth sampling regimes from China, Czech Republic, Germany, and Switzerland and utilised solid phase extraction methodologies that would facilitate the collection of pharmaceuticals in varying ionized forms [123]. In total, 946 chemicals were reported, of which 369 were pharmaceuticals or their metabolites, these were reduced to a final number of 171 pharmaceuticals after removing duplicates (66), transformation products (12), illicit origin (10), zwitterionic species (65), and unauthorized chemicals (6) as these chemicals were outside the model applicability domain. Furthermore, zwitterions are typically associated with poor bioavailability (high K_{OC}) and therefore their removal from the ranking is warranted as minimal uptake is expected [24]. Pharmaceuticals, banned substances, and veterinary medicines were also removed to focus on human use prescribed pharmaceuticals.

As many pharmaceutical physicochemical properties are absent from the literature ACD/Percepta was used to predict pK_a, log K_{OW}, molar mass and solubility [1]. Vapor pressure and K_{AW} values were derived from Koawin (Episuite v4.11) [117]. Predictions also removed any potential bias between experimental and predicted model input values, facilitating fair comparisons.

2.1.1. *Pharmaceutical consumption - $PEC_{INFLUENT}$*

Pharmaceuticals were categorised according to their therapeutic class and the average consumption rate for each class was obtained from freely available OECD statistics to derive the $PEC_{INFLUENT}$ values [87]. Consumption rate was calculated using the highest available dosage

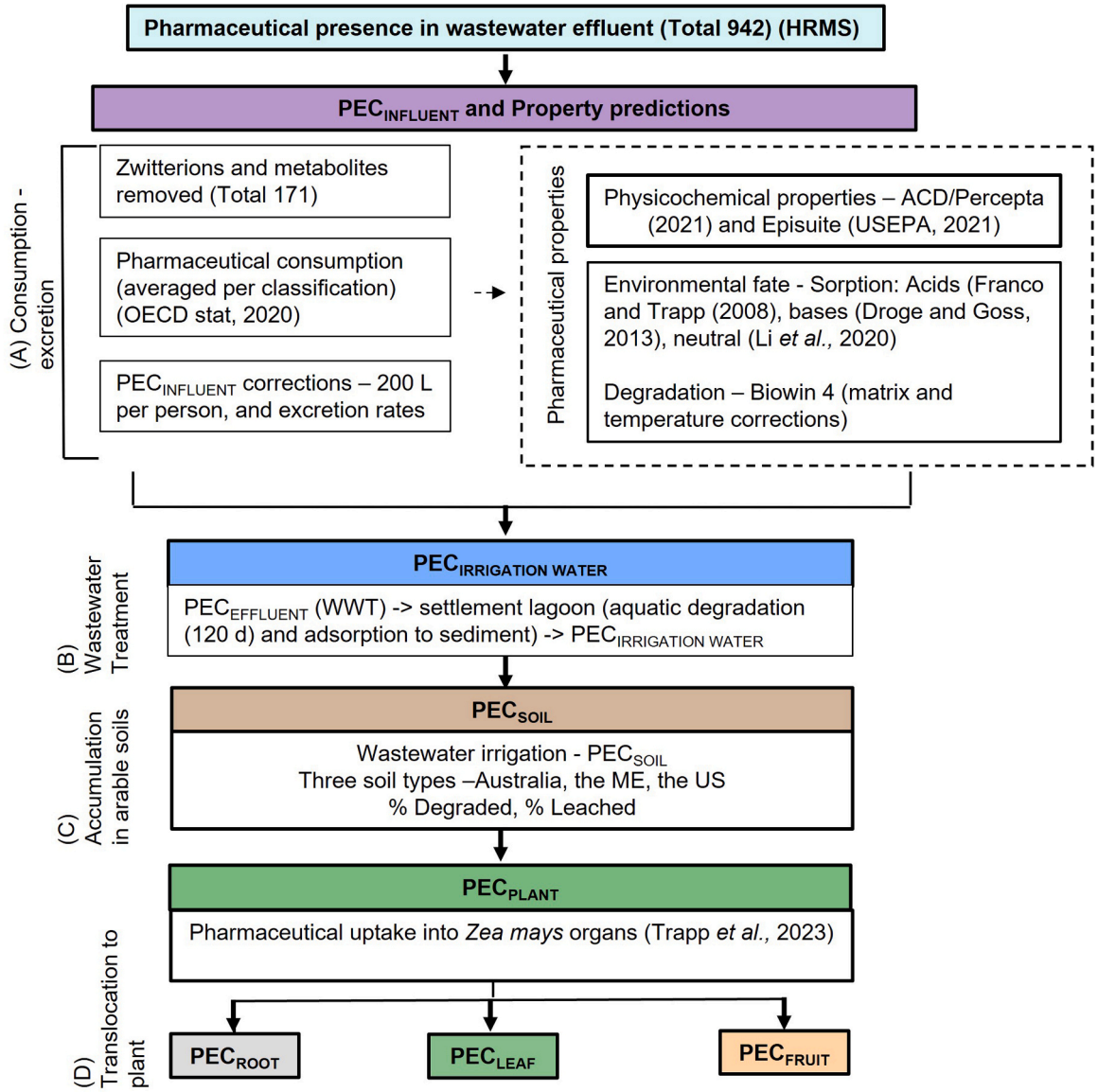

Fig. 1. A schematic diagram detailing the methodological approach to prioritise human pharmaceutical translocation into *Z. mays*. **Legend -** Physicochemical properties were obtained via ACD/Percepta [1] and included molecular weight, pK_a, log K_{OW}, K_{AW}, K_{HSA}, solubility, vapor pressure, whereas degradation was obtained via Biowin 4 (corrected per matrix and temperature), and sorption was achieved using Franco and Trapp, [43] for acids, Li *et al.,* [70] for neutrals, and Droge and Goss, [30] for bases. $PEC_{IRRIGATION\ WATER}$ was calculating via activity SimpleTreat and losses during storage (settlement lagoon) was considered and was comprised of hydrolysis and adsorption to sediment. A steady-state solution was used to predict the accumulation of pharmaceuticals in soil following wastewater reuse and considered degradation and leaching. For explanations of the plant uptake model please refer to Trapp *et al.,* [114].

from the Summary of Products Characteristics (SPC); replicating a worst-case scenario like that of an environmental risk assessment (SI Table 2) [34]. $PEC_{INFLUENT}$ values were then corrected for dilution and excretion (SI Table 1–4), with excretion rate being the only experimental data used in the framework to provide a more realistic $PEC_{INFLUENT}$. SimpleTreat assumes 200 L of wastewater per person which is subsequently corrected for a population of one thousand (SI Table 3) [42].

2.1.2. Environmental fate predictions

The degradability of the pharmaceuticals in environmental matrices was predicted using EPISUITE (v4.10) [117]. Biowin 4 (primary degradation) was employed to predict the half-lives of pharmaceuticals during wastewater treatment processing, assuming first order degradation kinetics and initial transformation (SI Tables 5–6). Biowin 4 was selected over Biowin 3 as it predicts the rate of degradation for initial transformation (not complete), with previous research suggesting that it is more environmentally representative [28,10]. Modelled outputs for aquatic media were converted to soil and sludge DT_{50} values (SI Section A, SI Eq 1–2), temperature corrections were applied to *k*-rate constants using the Arrhenius equation at the average temperature for the defined region of interest during the growth period [106]. The Franco and Trapp [43] (SI Eq. 3 acids), Droge and Goss [30] (SI Eq. 4 bases) and Li *et al.*, [70] (SI Eqs. 5 and 6 neutrals) models were used to predict soil-water and organic carbon-water partition coefficients (K_d and K_{OC}) for each pharmaceutical in the defined soil types (SI Section A Text 1.0).

2.1.3. Wastewater treatment - $PEC_{EFFLUENT}$ and $PEC_{IRRIGATION}$

Activity SimpleTreat was used to predict the fate of pharmaceuticals during wastewater treatment. Please refer to SI section A 2.0 and SI Table 3 for the input parameters and default WWTP parameters. The 9-box system was selected for modelling due to its global representation [91]. The presented framework is designed to approach risk evaluations in a worst-case manner but also to only consider TWW reuse, therefore SimpleTreat biodegradation method 1 was selected (assuming that biodegradation only occurs in the aqueous phase) [42]. Storage in a settlement lagoon for 3 months prior to use as an irrigation source was included, such practices are common in the selected regions [65,99, 122]. During storage in a settlement lagoon the major removal processes were considered (aquatic degradation (hydrolysis), and sorption to riverbed sediment f_{OC} 0.5 %, pH 7) [31].

2.1.4. Wastewater irrigation – PEC_{SOIL}

A single irrigation scenario was employed across all the soil types, including an irrigation rate of 0.5 $L/m^2/d$, soil depth of 0.4 m, bulk density of 1.35 g/cm^3, and an area of 3680,000 m^2 [91]. PEC_{SOIL} following TWW irrigation was modelled using an algebraic steady-state equation which considered agricultural and environmental processes whilst taking a worst-case approach (SI Section A text 1.0, and Eq. 1 and SI Eq 7).

$$PEC_{Soil} = \frac{Input}{k_{loss}}\left(1 - e^{-k_{loss} \quad t}\right) \tag{1}$$

Where: Input is irrigation ($PEC_{IRRIGATION\ WATER}$ (mg/L)), and k_{loss} is the sum of losses (degradation (1/d) and leaching (L/d)).

2.1.5. Plant Uptake – $PEC_{ROOT/LEAF/FRUIT}$

The plant uptake model is an extension of previous versions [113, 112], which includes the outputs for ionizable compounds and accounts for processes such as protein adsorption, xylem/phloem transport and considers transpiration [114]. In brief, the model estimates pharmaceutical concentrations translocated to *Z. mays* roots, leaves and fruits (mg/kg fw) from the bioavailable fraction within the soil profile. Therefore, the modelled scenario for irrigation was via drip irrigation. It is well known that uptake of chemicals can occur from percolation through the stomata, but the process is not relevant for drip irrigation.

2.2. Human health risk – consumption of wastewater derived Z mays (corn)

Acceptable Daily Intake (ADI) values were calculated using the lowest available SPC dosage, converting to mg/kg bw/day (bw is body weight; 72 kg) with a safety factor of 1000 applied (SI Table 7) [91]. Hazard Quotients (HQ) were calculated using a range of realistic consumption rates 17.55 g per day (corn only) [118]. For the higher consumption rate, pharmaceutical concentrations were assumed to be the same across all grains consumed (112.85 g per day) [39]. A Hazard Index (HI) was calculated by summing the HQs for the top ten, twenty, and thirty pharmaceuticals in the Australia, US, and ME soils to provide an indication of risk arising from consumption of a mixture of pharmaceuticals in food crops [91]. For both the HQs and HI assessments, a value > 1 indicates a potential health risk and a value > 0.1 outlines a possible risk [32,72].

2.3. Quality control (QC): Model applicability and domain

In this study, the quality and accuracy of predictions was assessed using QC 1a-b, repeat simulations and comparisons to previous model outputs to predict plant uptake of pharmaceuticals [27], and QC 2 experimental audit simulation (SI Section B text 1.0). QC 1a used previously determined model parameters and simulated an output using the presented framework whilst QC 1 b used the predicted properties and scenarios utilised within this framework. Bioaccumulation factor (BCF) values were calculated and compared to previously published BCF values and outliers identified [27] (SI Section B 1.0: Text, Table 1-3, and Fig. 1). For QC 2 a secondary person used the framework to simulate an output for fifteen pharmaceuticals (randomly selected from each ionised state). Physicochemical properties remained, although consumption and sorption were recalculated. Furthermore, to provide validity and confidence in the dataset calculated PECs for irrigation water, soil, and plant (SI Section B Fig. 2-4), as well as biodegradation rate predictions were compared to the available measured data reported in the literature (SI Tables 5–6) (SI Section B text 2.0–3.0). Although the data for comparisons is often limited and does not replace an experimental validation, performing MEC vs PEC assessments demonstrates the practicality and appropriateness of the framework to accurately predict concentrations in crops receiving TWW.

2.4. Statistical analyses

The majority of statistical analyses were performed using Minitab 18 (v. 21). To assess for statistical differences between pharmaceutical accumulation into *Z. mays* organs as well as soil type, Kruskal Wallace statistical analyses coupled with post hoc (Dunn's) comparisons were employed, statistical significance was reported at the 95 % confidence level. Under the same confidence level, MEC vs PEC comparisons were performed using Mann-Whitney *U* test. To compare between modelled biodegradation rates and experimental, Mean Absolute Errors (AE) were computed. Each model utilised a suite of parameters to determine the environmental fate, linear relationships were assessed using the Pearson's correlation coefficient (Python).

3. Results and discussion

3.1. Effluent and irrigation water concentrations

$PEC_{EFFLUENT}$ values ranged between 1.15×10^{-08} mg/L for phenazone to 1.49 mg/L for carbamazepine, with 10 % of pharmaceuticals predicted at concentrations > 0.07 mg/L (Table 1, SI Tables 7–9). A similar concentration range was calculated for $PEC_{IRRIGATION\ WATER}$ (post storage) indicating limited removal within settlement lagoons, with concentrations observed to range between 7.18×10^{-09} to 0.98 mg/L (SI Table 4). Such a finding is to be expected as hydrolytic

Table 1
Ranked top 10 predictions in various matrices under the three selected modelling regions (Australia, the US, and the ME), please find the top 30 in SI Tables 7–9.

Australia						
Rank	**$PEC_{IRRIGATION\ WATER}$ (mg/L)**	**PEC_{SOIL} µg/kg (dw)**	**PEC_{ROOT} ng/g (dw)**	**PEC_{LEAF} ng/g (dw)**	**PEC_{FRUIT} ng/g (dw)**	**PEC_{TOTAL} ng/g (dw)**
1	Carbamazepine: 0.70	Carbamazepine: 45.10 ± 36.45	Topiramate: 225.29 ± 148.56	Oxcarbazepine: 152.57 ± 120.13	Oxcarbazepine: 55.32 ± 43.56	Topiramate: 248.99 ± 164.19
2	Metformin: 0.63	Metformin: 28.34 ± 22.90	Sulphadiazine: 65.63 ± 39.69	Furosemide: 141.87 ± 91.32	Aciclovir: 30.59 ± 21.40	Oxcarbazepine: 208.90 ± 164.48
3	Primidone: 0.39	Topiramate: 22.37 ± 15.59	Furosemide: 44.31 ± 28.49	Primidone: 53.79 ± 42.59	Primidone: 18.07 ± 14.31	Furosemide: 192.94 ± 124.16
4	Levetiracetam: 0.23	Levosulpiride: 14.26 ± 11.52	Ternidazol: 29.97 ± 22.86	Aciclovir: 48.24 ± 33.74	Lacosamide: 11.69 ± 9.32	Aciclovir: 90.49 ± 63.29
5	Levosulpiride: 0.16	Primidone: 12.08 ± 9.57	Progesterone: 15.52 ± 12.13	Topiramate: 22.53 ± 14.86	Ternidazol: 9.28 ± 7.08	Primidone: 72.13 ± 57.10
6	Ternidazol: 0.09	Lamotrigine: 9.67 ± 7.81	Phenobarbital: 14.45 ± 9.59	Lacosamide: 19.65 ± 15.67	Furosemide: 6.76 ± 4.35	Sulphadiazine: 70.79 ± 42.80
7	Oxcarbazepine: 0.09	Oxcarbazepine: 6.90 ± 5.44	Sulphamethoxazole: 12.01 ± 7.67	Ternidazol: 15.98 ± 12.19	Acetaminophen: 5.92 ± 4.68	Ternidazol: 55.23 ± 42.13
8	Topiramate: 0.08	Sulpiride: 5.85 ± 4.73	Aciclovir: 11.66 ± 8.15	Gemfibrozil: 12.22 ± 8.24	Isopyrin: 1.77 ± 1.42	Lacosamide: 36.74 ± 29.31
9	Sulpiride: 0.06	Furosemide: 5.53 ± 3.76	Linezolid: 9.84 ± 6.44	Acetaminophen: 9.64 ± 7.62	Topiramate: 1.17 ± 0.77	Acetaminophen: 18.24 ± 14.43
10	Isopyrin: 0.06	Ternidazol: 4.67 ± 3.56	Phenytoin: 6.69 ± 4.51	Sulphadiazine: 4.80 ± 2.90	Secnidazole: 1.10 ± 0.84	Phenobarbital: 15.96 ± 10.59
United States						
Rank	**$PEC_{IRRIGATION\ WATER}$ (mg/L)**	**PEC_{SOIL} µg/kg (dw)**	**PEC_{ROOT} ng/g (dw)**	**PEC_{LEAF} ng/g (dw)**	**PEC_{FRUIT} ng/g (dw)**	**PEC_{TOTAL} ng/g (dw)**
1	Carbamazepine: 0.72	Carbamazepine: 52.30 ± 42.23	Topiramate: 508.59 ± 361.14	Furosemide: 369.60 ± 251.97	Oxcarbazepine: 48.80 ± 32.70	Topiramate: 561.87 ± 398.96
2	Metformin: 0.67	Topiramate: 44.26 ± 33.77	Furosemide: 115.43 ± 78.69	Gemfibrozil: 328.13 ± 242.06	Furosemide: 16.02 ± 10.93	Furosemide: 501.06 ± 341.59
3	Primidone: 0.41	Metformin: 33.80 ± 27.32	Gemfibrozil: 52.03 ± 38.43	Oxcarbazepine: 177.35 ± 118.82	Gemfibrozil: 15.55 ± 11.48	Gemfibrozil: 395.72 ± 291.97
4	Gemfibrozil: 0.35	Gemfibrozil: 20.93 ± 16.54	Theophylline: 45.85 ± 31.10	Topiramate: 50.87 ± 36.11	Primidone: 11.34 ± 7.24	Oxcarbazepine: 227.49 ± 152.41
5	Levetiracetam: 0.25	Levosulpiride: 16.53 ± 13.36	Oxaprozin: 44.10 ± 32.95	Primidone: 44.35 ± 28.31	Lacosamide: 9.95 ± 6.72	Primidone: 55.94 ± 35.70
6	Valsartan: 0.24	Furosemide: 15.16 ± 11.15	Phenobarbital: 41.02 ± 29.21	Fenbufen: 37.49 ± 27.68	Lamotrigine: 6.52 ± 5.23	Fenbufen: 50.91 ± 37.60
7	Levosulpiride: 0.16	Lamotrigine: 11.02 ± 8.90	Phenytoin: 40.81 ± 30.15	Ibuprofen: 28.19 ± 20.84	Isopyrin: 5.70 ± 4.60	Lamotrigine: 50.90 ± 41.31
8	Sulphapyridine: 0.13	Sulphadiazine: 10.38 ± 7.61	Sulphadiazine: 33.73 ± 22.93	Lacosamide: 22.16 ± 14.97	Ternidazol: 3.65 ± 2.08	Theophylline: 50.64 ± 34.35
9	Mycophenolic acid: 0.13	Diltiazem: 9.24 ± 7.20	Lamotrigine: 32.34 ± 26.38	Fenoprofen: 17.44 ± 12.93	Aciclovir: 3.59 ± 1.94	Oxaprozin: 48.69 ± 36.37
10	Topiramate: 0.12	Irbesartan: 9.21 ± 7.21	Bemegride: 25.94 ± 18.74	Sitagliptin: 15.19 ± 12.28	Acetaminophen: 3.40 ± 2.15	Phenobarbital: 45.29 ± 32.25
The Middle East						
Rank	**$PEC_{IRRIGATION\ WATER}$ (mg/L)**	**PEC_{SOIL} µg/kg (dw)**	**PEC_{ROOT} ng/g (dw)**	**PEC_{LEAF} ng/g (dw)**	**PEC_{FRUIT} ng/g (dw)**	**PEC_{TOTAL} ng/g (dw)**
1	Carbamazepine: 0.78	Carbamazepine: 66.12 ± 52.94	Topiramate: 401.00 ± 258.61	Furosemide: 357.44 ± 224.90	Oxcarbazepine: 54.27 ± 42.38	Furosemide: 486.14 ± 305.95
2	Metformin: 0.71	Topiramate: 48.59 ± 33.57	Carbamazepine: 191.66 ± 153.45	Gemfibrozil: 290.94 ± 192.18	Aciclovir: 32.29 ± 22.03	Topiramate: 443.19 ± 285.82
3	Primidone: 0.45	Metformin: 42.56 ± 34.22	Furosemide: 111.66 ± 70.35	Oxcarbazepine: 181.64 ± 141.83	Primidone: 19.72 ± 15.53	Gemfibrozil: 352.18 ± 232.54
4	Gemfibrozil: 0.37	Gemfibrozil: 23.25 ± 16.51	Sulphadiazine: 95.28 ± 59.50	Levosulpiride: 123.42 ± 88.15	Furosemide: 17.04 ± 10.70	Oxcarbazepine: 237.22 ± 185.23
5	Levetiracetam: 0.29	Levosulpiride: 20.09 ± 16.14	Theophylline: 61.26 ± 38.14	Primidone: 71.13 ± 56.02	Gemfibrozil: 15.15 ± 10.01	Carbamazepine: 219.43 ± 175.68
6	Valsartan: 0.24	Primidone: 18.90 ± 14.89	Phenobarbital: 59.52 ± 38.56	Aciclovir: 62.38 ± 42.56	Lacosamide: 13.33 ± 10.60	Levosulpiride: 151.86 ± 108.49
7	Levosulpiride: 0.16	Furosemide: 17.43 ± 11.68	Gemfibrozil: 46.09 ± 30.35	Topiramate: 40.10 ± 25.86	Ternidazol: 11.15 ± 8.39	Aciclovir: 110.70 ± 75.52
8	Mycophenolic acid: 0.14	Lamotrigine: 13.20 ± 10.62	Ternidazol: 39.41 ± 29.67	Fenbufen: 35.91 ± 23.78	Carbamazepine: 9.28 ± 7.43	Sulphadiazine: 102.77 ± 64.18
9	Sulphapyridine: 0.13	Sulphadiazine: 12.01 ± 7.97	Oxaprozin: 35.94 ± 23.89	Lacosamide: 27.29 ± 21.69	Acetaminophen: 7.03 ± 5.53	Linezolid: 96.98 ± 62.06
10	Carbamazepine: 0.78	Irbesartan: 10.22 ± 7.20	Phenytoin: 34.31 ± 22.71	Ibuprofen: 26.43 ± 17.48	Levosulpiride: 5.88 ± 4.20	Primidone: 91.23 ± 71.86

rate constants are typically lower than other removal rates across different environmental matrices [108]. Removal in settlement lagoons is typically compound specific, for example, chemicals such as carbamazepine, nalidixic acid, nevirapine have been observed to have increasing loads due to increasing effluent input or deconjugation processes. In contrast removal rates for other chemicals might be underpredicted due to neglection of photolysis [65]. The top 30 pharmaceuticals were mostly comprised of acidic (50 %), 23.3 %

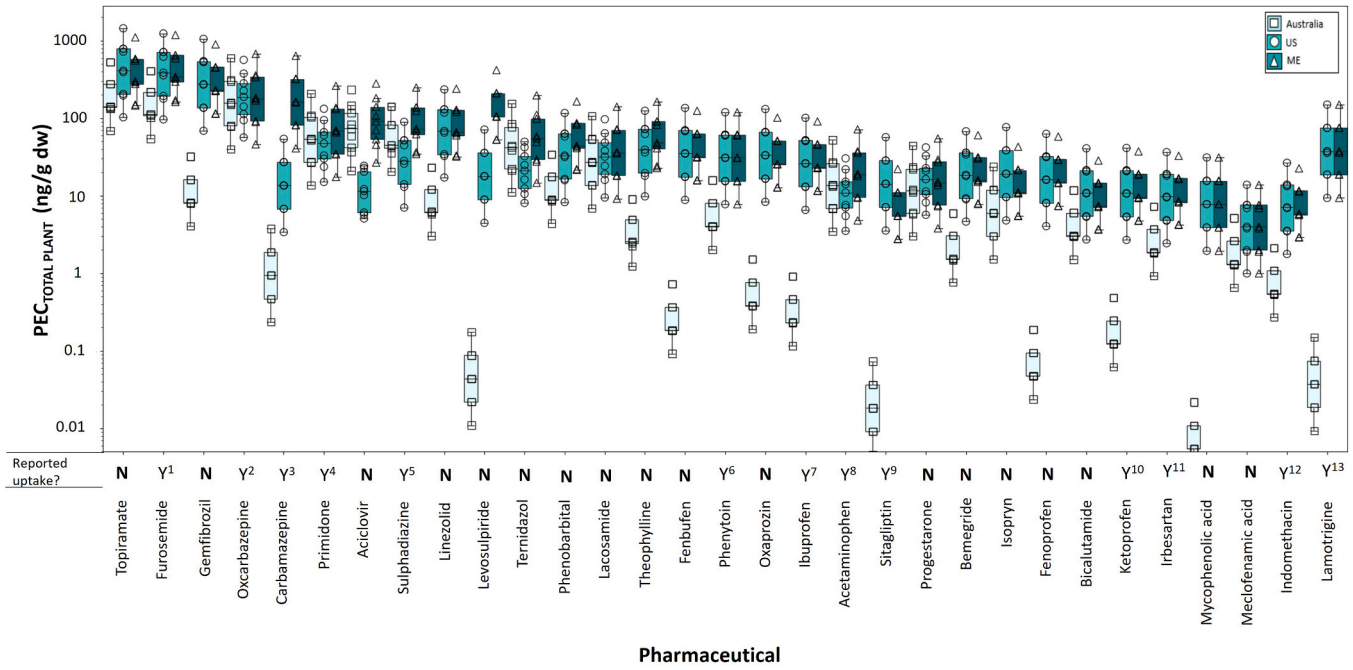

Fig. 2. Top 30 prioritised $PEC_{TOTAL\ PLANT}$ across the three modeling scenarios: Australia, the United States, and ME based on predicted total plant concentrations. Error bars represent the standard deviation (± biodegradation and degradation rates) and previous reported uptake in literature is denoted by Y (yes) or N(no) and represented by squares (Australia), circles (California) and triangles (ME). **Reported uptake citations (Y/N) –** Okihara et al., [88] – 1; Klement et al., [63] – 2; Carter et al., [17] – 3; Christou et al., [23] – 4; Tian et al., [107] – 5; Gorovits et al., [54] – 6; García, and Fernández-López, [48] – 7; Hammad *et al.,* [56] – 8; Gatta et al., [52] - 9; Kovacs et al., [66] – 10; Manasfi et al., [79] – 11; Madikizela et al., [74]-12; Madmon et al., [75] –13.

neutral, and 26.6 % basic. Common therapeutic classes in the top 20 $PEC_{EFFLUENT}$ (≥ 0.06 mg/L) included anti-epileptics (carbamazepine, primidone, levetiracetam), antibiotics (sulphadiazine, linezolid, tinidazole), and cardiovascular agents (valsartan, furosemide). Similar classes were identified within $PEC_{IRRIGATION\ WATER}$ (SI Table 10).

3.2. Soil concentrations

Across the three scenarios considered (Australia, US, ME), 83.3 % of the top 30 pharmaceuticals predicted in effluent were also predicted to be in the top 30 pharmaceuticals to accumulate in soil (Table 1, SI Tables 7–9); including the anti-convulsant carbamazepine and topiramate which were predicted to accumulate to the greatest extent in all three soil types. Maximum PEC_{SOIL} concentrations ranged between 45.1 μg/kg (dw) in Australian soils to 66.1 μg/kg (dw) in the ME soil scenario. In total 97 pharmaceuticals (56.7 %) had PEC_{SOIL} values that ranged between 0.1 – 55.5 μg/kg (dw) which is in line with previously measured soil concentrations in the published literature [26,82].

3.3. Accumulation of pharmaceuticals in Z. mays

3.3.1. $PEC_{TOTAL\ PLANT}$

Prioritisation according to $PEC_{TOTAL\ PLANT}$ (root + leaf + fruit) revealed that across all three scenarios evaluated (Australia, ME, and US), the anticonvulsant topiramate accumulated to the greatest extent in *Z. mays* with average concentrations predicted to range between 249.9 – 561.9 ng/g (dw) (Table 1, SI Tables 7–9). $PEC_{TOTAL\ PLANT}$ revealed similar regional rankings, with topiramate (neutral, log K_{OW} 2.15), furosemide (pK_a acid 3.0, log K_{OW} 2.35), and oxcarbazepine (strong acid, pK_a acid −0.5, log K_{OW} 1.7) being present (top 5) across all three scenarios (Fig. 2). In total plant the top 30 pharmaceuticals were dominated by acids representing 53.3 %, followed by neutral and bases at 23.3 %. The predominant therapeutic classes in the top 20 PEC_{FRUIT} (≥ 0.4 ng/g dw) were similar to that of PEC_{LEAF}, and PEC_{ROOT} and included nervous system (oxcarbazepine, lamotrigine, carbamazepine), NSAIDs (isopryn, fenbufen, ibuprofen), and anti-infectives (acyclovir, ternidazol) (SI Table 10).

Comparatively large differences in uptake between exposure scenarios were observed for some chemicals, for example differences in $PEC_{TOTAL\ PLANT}$ values for furosemide and lamotrigine were up to a factor of 2.6 and 1003 between the US and Australia scenarios respectively, highlighting the role that soil properties play in the uptake of pharmaceuticals and value of regional specific assessments when considering risk (SI Tables 7–9). Pharmaceutical uptake into plants depends on a combination of the physicochemical properties of the chemical and the soil and plant properties [83,111]. For example, Christou *et al.,* [23] found that soils with higher sand contents or that were low in OM, or clay content typically present higher pharmaceutical accumulation compared clay or organic matter rich soils where the chemicals are less bioavailable to plants due to strong sorption interactions. Our results show that soils with a lower organic content had 13.1 and 61.6 % lower accumulation in total. In previously published research, Kodešová *et al.,* [64] found that bioaccumulation factors for carbamazepine in spinach were negatively correlated with CEC. This negative correlation between bioaccumulation factors and CEC was also observed for tramadol (roots and leaves), citalopram (roots), and telmisartan (roots). For citalopram, our results also suggest a weak negative relationship between CEC and PEC_{ROOT}. Furthermore bioaccumulation factors for venlafaxine in spinach roots were negatively correlated for CEC, however, this disagreed with our findings which found weak positive correlations for venlafaxine in *Z. mays* root [64].

Overall, our results show that soil pH is a fundamental parameter in determining pharmaceutical fate, governing ionization and sorption mechanisms which can then influence plant uptake (SI Figure 1). Previous studies have also shown this, such as Kodešová *et al.,* [64], where the uptake of select pharmaceuticals (e.g. sertraline, amitriptyline, mirtazapine, metoprolol) in soils with a higher pH and base cation saturation significantly differed from soils with a lower pH and base cation saturation. Our findings revealed that for $PEC_{TOTAL\ PLANT}$ the

uptake of these chemicals was not significantly different between soils with higher pH or at base cation saturation. However, significant differences were observed for amitriptyline and sertraline in root ($P \leq 0.05$) where uptake was elevated here for two cationic and ionized chemicals at a pH of 7.2. Gemfibrozil provides further evidence of this as it was ranked outside the top 10 in the Australian scenario yet was ranked third for the US and ME scenarios which highlights the role that soil properties play in influencing the uptake of pharmaceuticals by plants (Table 1). Combined, our results, and alignment to previous published findings show strong compound dependent influences of soil conditions on pharmaceutical uptake by plants. However, it is important to note that many variables contribute to the final ranked position of the pharmaceutical, as Spearman's rank correlation analysis revealed that $PEC_{EFFLUENT}$ (0.82) and leaching rate (0.54) played a significant role (SI Figure 1).

Despite the fact that many pharmaceuticals are classed as weak bases, with pK_a-values ranging between 6.5 and 10.5 [77,78] the majority of pharmaceuticals identified in the top 10 were weakly acidic (40–70 %) or polar neutral (30–60 %). This finding can in part be explained by the fact that weak bases with pK_a above 7 are retained in the acidic (pH 4–5) vacuoles of root cells [58] and little translocation and thus uptake to higher parts of the plant (leaf and fruit) is to be expected. Furthermore, basic pharmaceuticals are largely cationic at the given soil pH-range 5.4–7.68 and are accompanied by higher K_{OC}/K_d--values than neutral chemicals or anions with comparable lipophilicity [30,43]. Reduced bioavailability owing to higher sorption therefore plays an important role in determining which pharmaceuticals are likely to accumulate in the plant and supports the findings of our model output. This is further supported by results from Spearman's rank correlations which revealed a moderate negative correlation for K_{OC} and uptake into Z. *mays* across all assessed soil types (-0.51 to −0.55) (SI Figure 1). Further investigations suggested that uptake was negligible for pharmaceuticals with a $K_{OC} > 1000$ L/kg in all plant organs (SI Figure 2). In general, a lower affinity of a pharmaceutical for soil (K_{OC}) does not correlate to high plant uptake, but a high affinity does indicate low uptake. Such correlations are to be expected, as they underpin the mechanisms of the model; however, this correlation also highlights that K_{OC} could be used as a potential threshold to inform future risk assessment where minimal uptake would be expected to occur for pharmaceuticals with $K_{OC} > 1000$ L/kg.

Contrarily, neutral acid molecules typically have a higher K_{OC} than their anionic counterparts (except for very polar chemicals, with log $K_{OW} < 1$) (SI Eqs 3, 5 and 6) [41]. This coupled with temperature corrected rate constants likely explains why predicted concentrations were generally higher for neutral acidic pharmaceuticals but lower in the Australian scenario (23 °C) over that of ME (19.5 °C) or US (18 °C). To the best of our knowledge, research has yet to identify pharmaceuticals with the greatest tendency for uptake into arable crop, yet this information is crucial to ensure future efforts are directed towards understanding the potential human and environmental health concerns associated with pharmaceuticals predicted to most likely accumulate in the crops.

The lowest 10 % of $PEC_{TOTAL\ PLANT}$ values were predicted to accumulate below 0.000103 ng/g (dw) and included almost exclusively weak to strong bases: roxithromycin < azithromycin < atazanavir < paliperidone < phenazone < aliskiren < atenolol < haloperidol < verapmil < quetiapine < celiprolol < amisulpride < bupvicaine < benzamidine < procaine < gilbenclamide < isoetharine. As expected, published wastewater irrigation monitoring studies report little to no existing in-plant concentrations for these pharmaceuticals. However, the low ranking of alprazolam (rank 133) was unexpected given its known environmental persistence/presence as well as the demonstrated accumulation of benzodiazepines in crops [18].

In comparison to other pharmaceuticals, the low emission of alprazolam, moderate biodegradability (half-lives two to three weeks), K_{OC} in the range 280–580 L/kg and rather high adsorption to proteins ($> 10^4$ L/mol) provide some explanation as to the predicted low accumulative potential of this compound. Similarly, despite the documented environmental persistence of 17β-estradiol (rank 141), it is suggested the low ranking in our framework can be attributed to use of the SPC dosage concentration (10 μg) which overlooked human production, combined with Biowin degradation half-life around one week (SI Table 5) [21]. Interestingly, despite the reported accumulation of fluoxetine in soils following TWW irrigation (0.5 – 2.78 ng/g) [104,8], and uptake into soybean [121], the low uptake observed in the study is suspected to be attributed to fluoxetine's high log K_{OW} (= 4.23) and high K_{OC}-values. Limited uptake potential has also been observed for other pharmaceuticals (phenazone, and acetaminophen), although poor translocation in these cases is hypothesized to be related to rapid metabolism and formation of bound residues, which was neglected here [59,71].

3.3.2. PEC_{ROOT}

PEC_{ROOT} presented a differing ranking to that of total plant, here topiramate > furosemide > sulphadiazine > linezolid were predicted to rank in the top 10 across all scenarios in Z. *mays* roots (60.41–378.29 ng/g dw) (Table 1). For the ME and the US scenarios, PEC_{ROOT} results were similar to leaf for the top 10 prioritised pharmaceuticals ($p > 0.05$) (SI Table 11). However, for the Australia prioritisation, ternidazole (rank 4, neutral and polar with log K_{OW} 0.17), sulphamethoxazole (rank 7, polar weak acid, pK_a acid 5.81, log K_{OW} 0.65), aciclovir (rank 8, neutral and polar with log K_{OW} −1.45) were outside the top 10 for the ME and US scenarios. As a whole (across all regions) most of the pharmaceuticals predicted to accumulate in the roots were still polar neutral or acidic compounds. The top 30 pharmaceuticals in root were mostly comprised of acidic (53.3 %), 23.3 % neutral, and 23.3 % basic. Common therapeutic classes in the top 20 PEC_{ROOT} (≥ 6.7 ng/g dw) included anti-epileptics (topiramate, furosemide, carbamazepine), NSAIDs (oxaprozin, fenbufen, isopryn), and cardiovascular agents (mycophenolic acid, and mephentermine) (SI Table 10). Root accumulation of strong-weak bases (pKa > 5) can be expected to be low as they will be retained in the soil, and this phenomenon is exacerbated at low soil pH (< pH 7) because weak bases will then be charged in soil but more neutral inside of the roots (cytosol pH 7.4, vacuole pH 5). As evidenced by results for lamotrigine (pK_a base at 5.39) in this study, where PEC_{ROOT} values for this chemical was in the top 30 at soil pH 7 (ME) and pH 7.68 (US) but not at soil pH 5.4 (Australia).

For acidic and neutral pharmaceuticals, sorption to the selected soils will be less than for basic pharmaceuticals and accumulation in the leaf will occur following translocation [114]. Modelled scenarios confirm this to be true with only 16.7 % of the top 30 PEC_{LEAF} values being basic pharmaceuticals. This phenomenon is likely explained via the fact that polar/neutral species are capable of moving freely to higher parts of the plant, once they cross into the xylem, pharmaceuticals will be translocated to the leaves (in the early developmental years) [16,53]. Weak acids are neither retained in soil nor in root vacuoles and can also enter the xylem (pH 5.5) for translocation to higher organs. Thus, likely explaining why furosemide (weak acid), gemfibrozil (weak acid), and lacosamide (neutral, polar) feature within the top ten across all the assessed scenarios (SI Tables 7–9).

3.3.3. PEC_{LEAF} and PEC_{FRUIT}

The ranking revealed a different prioritisation for PEC_{LEAF} values in comparison to PEC_{ROOT}, which is suspected to be a result of in-plant mechanisms (ion trapping and in-plant absorption). For example, carbamazepine (neutral, medium polar, log K_{OW} 2.28) ranked in position 12 and 27 (ME and the US) and 37 at a pH of 5.5 and pharmaceuticals such as fenbufen (weak acid, pK_a 4.56, log K_{OW} 3.10), aciclovir (neutral, very polar, log K_{OW} −1.45) and lacosamide (neutral, polar, log K_{OW} 0.83) featured in the PEC_{LEAF} top 10 which were not observed in the PEC_{ROOT} top 10 prioritisation. Similarly to that of roots, the Australian scenario had comparably lower PEC_{LEAF} values (≤ 152.57 ng/g dw)

with the greatest accumulation in the leaf observed in the slightly alkaline and cooler soil in the US scenario ($\leq$ 369.60 ng/g (dw)) where weak acids would behave as anions ($p < 0.05$) (SI Table 10). The top 30 pharmaceuticals in leaf were mostly comprised of acidic (56.7 %), 23.3 % neutral, and 20 % basic. The predominant therapeutic classes in PEC_{LEAF} ($\geq$ 4.7 ng/g dw) were similar to that of PEC_{ROOT} and included nervous system (oxcarbazepine, primidone, topiramate), NSAIDs (fenbufen, ibuprofen, fenoprofen), and anti-infectives (acyclovir, and ternidazol) (SI Table 10). In some instances, PEC_{LEAF} values were observed to be greater than that of PEC_{ROOT} values, examples of this include, gemfibrozil (10.45 < 210.43 ng/g (dw)), and levosulpride (2.44 < 41.41 ng/g (dw)) (Table 1, SI Tables 7–9).

Among the plant organs considered, *Z. mays* fruit had the lowest PEC values ($\leq$ 52.8 ng/g (dw) on average), with oxcarbazepine (a strong acid) being predicted to accumulate to the greatest extent. Despite a slightly different rank order across the three scenarios, oxcarbazepine, aciclovir, primidone, furosemide, lacosamide, and gemfibrozil, all featured in the top 10 for PEC_{FRUIT} and were similar to those ranked in the top 10 for PEC_{LEAF}. All these have in common that their adsorption to plant tissue is minimal, allowing transport in both xylem and phloem to fruits. As a regional average 43.3 % of the top pharmaceuticals in PEC_{FRUIT} were acids and neutral, with 13.3 % being basic. At pH 5.5 this changed to 53.3 % neutral, 40 % acidic, and 6.7 % basic. The predominant therapeutic classes in the top 20 PEC_{FRUIT} ($\geq$ 0.37 ng/g (dw)) was similar to PEC_{LEAF} and included nervous system drugs (oxcarbazepine, lamotrigine, carbamazepine), NSAIDs (isopryn, fenbufen, ibuprofen), and anti-infectives (acyclovir, ternidazol) (SI Table 10). This finding aligns to the leaf results but also to previous findings that show the translocation of neutral polar chemicals to above ground plant material [110,114]. Once the plant reaches maturity, pharmaceuticals that have entered the xylem/phloem and are present in the leaf can move into the fruit [53]. The presented results demonstrate that nervous system, NSAIDs, and anti-infectives are key therapeutic classes of concern in all plants organs.

3.4. Human health risks arising from consumption

A negligible risk to consumers was identified for the assessed pharmaceuticals (top 30) when considering daily typical (17.55 – 122.9 g) corn and grain consumption rates under any of the specified regions (HQ < 0.76) (SI Tables 11–14). Hazard quotients were shown to vary in the modelling regions supporting previous findings by Burns *et al.,* [12] that risk is region specific (SI Tables 12–14). This finding also aligns with previous monitoring and modelling studies which suggest minimal risk following the ingestion of contaminated crops [76,84,91]. However, it is important to acknowledge that these assessments do not incorporate toxicological data, but instead rely on the lowest medical dosage per 1000 individuals. Additionally, these assessments often overlook risks arising from co-contaminants, antimicrobial resistance, chronic repeated exposure, and the presence of metabolites [6,23,33,101].

Despite the limitations of current models, there is pressing need to evaluate the environmental fate and risks associated with pharmaceutical metabolites and transformation products. Transformation of pharmaceuticals starts within the gastrointestinal system and continues across various environmental compartments, from WWTP to plants. Transformation products in soils have demonstrated translocation potential into crops [29,64,81]. Predicting transformation and metabolism is a complex challenge and further complexity is added when predicting concentration. Quantified data is improving and will provide a baseline for future modelling efforts, for example, Kodešova *et. al.,* [64] found 37.8–75.6 ng/g (dw) of 10,11-epoxide carbamazepine and O-desmethylvenlafaxine in spring onion and carrot. Hydroponic studies offer a unique insight into in-plant metabolism of pharmaceuticals by excluding soil transformation processes. For example, a range of in plant metabolites have been reported for atenolol (atenolic acid), carbamazepine (e.g. 3-OH carbamazepine), and diclofenac (e.g. 4-OH diclofenac), in *Canna indica* and *Chrysopogon zizanioides* [96]. In plant phase I and II enzymes are closely aligned to that of the human biome which could aid modelling efforts in predicting changes in mass and structure but neglects differences in rate constants and secondary transformation of metabolites [120]. Furthermore, Meffe *et al.,* [81] suggested that future research should investigate the potential for increased toxicity and fate of 4-acetamidoantipyrin (a metamizole metabolite), underlining that additional risk may stem from metabolites of originally administered pharmaceuticals.

There is a clear need to use a more comprehensive procedure to evaluate the risks towards human health, currently risk assessment approaches could potentially overlook toxicological concerns such as those pointed out via Bauer *et al.,* [6] for chronic and low exposure paracetamol in pregnant women. Similarly, assuming a 72 kg body mass potentially overlooks the risk in those below this weight, such as children where the concern for toxicity is heightened. Furthermore, the risk evaluations performed here assume that uptake into *Z. mays* is similar to that of other crops, whereas recent research has demonstrated crop type to have a fundamental role in determining uptake [103,23]. For example, Christou *et al.,* [23] found that celery and spinach exhibited the highest potential for uptake, whilst almonds and grapes showed the lowest. Nevertheless, our findings clearly indicate that the current evaluation of risk should be broadened to consider the consumption of more than a single contaminated crop to reflect typical varied diets consisting of leafy greens, fruits and roots.

Despite published literature supporting the presence of co-contaminants in crops (e.g. pharmaceuticals, personal care products and pesticides) [83], very few studies have implemented a HI evaluation to consider the combined risk. Our results demonstrate that if the top ten, twenty, and-thirty ranked pharmaceuticals existed in produce at the predicted concentration as a mixture, there would be a risk (HI > 1) when consuming 112.9 g of contaminated grains under the US and ME scenarios (SI Table 15). It is interesting to note that chemicals ranked 11–20 add 3.24 % of the total risk, while chemicals ranked 21–30 contribute to 2.9 % of the total HI. Thus, prioritising future efforts to focus on the top 30 chemicals is expected to assess most of the human health risk originating from the consumption of pharmaceutical contaminated produce. However, for this purpose, the top 30 chemicals must be identified first.

4. Comparison to measured data, applicability domain, and shortcomings

4.1. Comparison of predicted and measured concentrations in Z. mays

Comparisons of the $PEC_{IRRIGATION\ WATER}$ and PEC_{SOIL} values to MECs revealed good comparability (SI Section B 1.0), however, these were compound specific and driven by the availability of suitable data, degradation predictions, and emission calculations (SI Section B 2.0). As a whole, 57.1 % of irrigation water were found to be within the minimum to maximum range (SI Section B 3.0, and SI Section B Figs. 1–3), PEC_{SOIL} predictions were also found to be comparable with 87.5 % of the assessed predictions being within a factor of ten of those measured (SI Section B 3.0, and Fig. 3A). Monitoring data for Z. *mays* following TWW irrigation is lacking, and therefore prevented a true comparison of predicted and measured concentrations. Nevertheless 72.7 % of the calculated PECs were within the reported range of published literature values for other fruit crops (Fig. 3B). Differences between PEC_{PLANT} and MECs are likely driven via regional differences but also for plant physiology (evapotranspiration rate, water content, in plant metabolism, and dilution), soil type, effluent concentrations, and growth cycles [114,23]. By incorporating the recent plant uptake model extension into the framework, predicted crop concentrations account for processes relevant for ionisable pharmaceuticals, such as sorption to proteins, ion trapping mechanics, and downward phloem flow movement [114].

Discrepancies between measured and predicted values in plant could

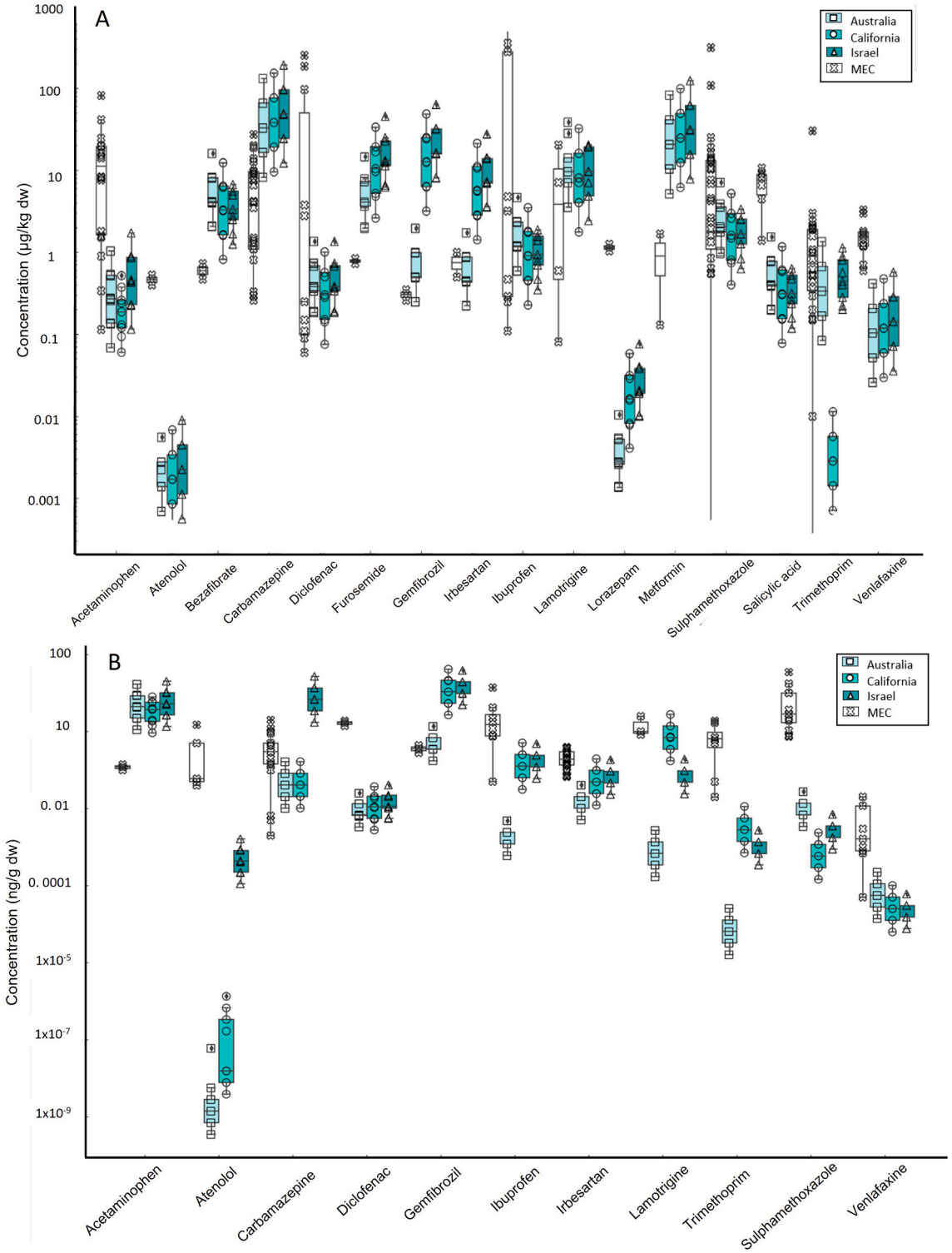

Fig. 3. *Comparison between Predicted Environmental Concentrations in soils receiving TWW (A) and Z mays fruit and Measured Environmental Concentrations (B).* ***Foot note*** *- Replicated simulations (markers) represent the predicted range of soil concentrations under ± 50 % sludge and soil biodegradation rates.* ***Plant fruits -*** *Z. mays for acetaminophen [81], cabbage, maize, radish, z. mays for atenolol; [81,7,90], cucumber, pepper, wheat, tomato, and Z. mays for carbamazepine [22,23,49,81,82,85,89,11], tomato for diclofenac [22,11], cucumber, eggplant, long bean, and wheat for ibuprofen [72], tomato for irbesartan [49], cucumber, pepper, and tomato for lamotrigine [49], cucumber, pepper, wheat, tomato, zucchini, eggplant, long bean, and wheat for trimethoprim [22,72,44], tomato, wheat, eggplant, long bean, and cucumber for sulphamethoxazole [14,22,72], cucumber, pepper, tomato, pepper, and Z. mays for venlafaxine [49,81,82,85].* ***Soil*** *– acetaminophen [62] (fw); [82,119,81], bezafibrate [26], carbamazepine [119,26,5,40,62,81,82], diclofenac [22,26,5,81], furosemide [81], gemfibrozil [81], ibuprofen [5,26,81], lamotrigine [49,82], lorazepam [81], salicylic acid [21], sulphamethoxazole [14,26,62,81,82], trimethoprim [119,22,26,49,62], venlafaxine [49].*

be related to the general overprediction of biodegradation rates (SI Tables 5–6 and SI section A 2.0 Biodegradation Predictions), or due to degradation rates all assuming 1st order kinetics . Specifically, increased degradation rate predictions resulted in lower in-plant concentrations than previously reported in the published literature. However, it is important to highlight that many pharmaceuticals are not always present in the environment above analytical detection limits, due to poor extractability and sensitivity and are therefore not reported. This may result in a potential bias in the reported concentrations. The complexities of the framework and the environment resulted in a compound/organ specific effect when direct comparisons were made to the available literature. Nevertheless, predicted in plant concentrations for sulphamethoxazole ranged between 2.59 and 12.01 ng/g (fw) for ME and Australia, which was comparable to concentrations reported in tomato roots (9.8 ng/g (fw)) in a similar soil type (1.54 % (estimated from OC) < 3.37 %) [14]. Apposing this trend lamotrigine was found to be underpredicted, measured values have been reported between 30 and 50 ng/g (dw) which is a factor of 8.66–14.33 greater than regional average for PEC_{LEAF} [83]. However, this finding is supported by the absence of lamotrigine in tomato fruits, as well as the minimal uptake reported in wheat [89]. Differences are likely driven by differences in emission levels (consumption 0.31 <1.66 moles/d/1000 habitants) [68], irrigation practices, plant physiology (tomato vs Z. *mays*), overlooking biosolid applications, or the under/over prediction of K_d values.

A comparison of PEC_{LEAF} to concentrations previously reported in tomato leaves (0.001–0.02 mg/kg (dw)) [83], revealed the framework under predicted concentrations for some bases and acids whilst for neutral species predictions were comparable. For example, carbamazepine predictions were within a range of those reported by Mordechay *et al.,* [82] (0.2–100 ng/g), whilst atenolol and venlafaxine were under predicted by a factor of 14952 and 148 in tomato leaves. The cation atenolol was underpredicted in leaf, a result of the rapid Biowin-estimated degradation rate (i.e., soil rate constant ranged from 0.16 to 0.21 d^{-1}, temperature-corrected). Despite sparse literature values, carbamazepine, and irbesartan were within a factor of 10 of the average MEC, whilst lamotrigine, trimethoprim, and venlafaxine maximum predictions were within the minimum maximum of measured (Fig. 3B). For example, reported carbamazepine (tomato) and trimethoprim (wheat) concentrations are up to 2 ng/g (dw) and 0.05 ng/g (dw) respectively, whilst predictions ranged from 0.03 to 9.78 ng/g (dw) and 0.001–0.08 ng/g (dw) [72,83,82].

The comprehensive study of Meffe *et al.,* [81] provides measured concentration data of 20 PPCP and 5 transformation products in *Z. mays* following irrigation using TWW (river water). The results from this real-world study can be compared to our priority setting. Of the assessed (20 pharmaceuticals), ten were identified within the top 30 prioritised ranking (metformin, furosemide, valsartan, gemfibrozil, sulphamethoxazole, metronidazole, ibuprofen, diclofenac, acetaminophen, carbamazepine). Fruit concentrations were found to be comparable for acetaminophen (fruit 0.12 ng/g dw), gemfibrozil (fruit 0.36 ng/g dw), atenolol (fruit 0.05 ng/g dw), venlafaxine (fruit 0.4 ng/g dw), and carbamazepine (SI Table 7–9, Fig. 3 b). The absence of other chemicals in the ranking can be attributed to the following: not medicinal (caffeine, nicotine), low excretion data (atorvastatin, venlafaxine) (SI Table 4) or predicted rapid degradation (atenolol, naproxen). Comparisons to other plant species also revealed comparability to predicted concentrations. Specifically, concentrations of ibuprofen in eggplant, wheat, cucumber, and bean fruit (0.78–13.82 ng/g (dw)) were found to be comparable in the US (0.43–1.69 ng/g (dw)) and the ME (0.41–1.65 ng/g (dw)) scenario but under predicted for Australia (0.008–0.03 ng/g (dw)). The discrepancies associated with the Australian scenario are most likely related to the acidic pH, whereas the authors reported a pH value of 8.17 in their rhizosphere. In contrast predicted concentrations for warfarin in *Z. mays* fruits were 2009 fold lower as a regional average than those measured in bell peppers (0.000044 ng/g (fw) < 0.03–0.09 ng/g (fw)) [83]. Such differences are likely attributed towards the vast over prediction of degradation rate (1.7 d vs 150 d (AE 147.3–149.1)) [37]. In summary, about half of the chemicals that were identified by the field study of Meffe *et al.,* [81] at an irrigation site in Spain were also identified by our framework as high priority for occurrence in effluents, soil and plants. Given the efforts and costs associated with a field study, this finding not only provides further evidence of the reliability of our predictions but highlights a suitable lower cost method of prioritisation.

4.2. Priority setting

The presented framework demonstrates a means to screen the environmental fate of pharmaceuticals in agri-ecosystems following TWW reuse. The model requires minimal experimental input (excretion), indicating the methods could be utilised for example, within the early stages of drug development as a screening tool. This framework would also be valuable as a screening tool for regulators to prioritise where future experimental and monitoring efforts should focus given that an estimated 1900 pharmaceuticals are available on the market, and only 11 % have data suitable for an environmental risk assessment [12]. It is also unlikely that products authorised for use prior to 2006 will be further assessed for risk [35]. Therefore, a framework which supports the prioritisation of pharmaceuticals is required, specifically within the terrestrial environment where data is lacking the most.

The lack of existing data to support terrestrial risk assessments is exemplified by the presented results which show that in just the top 30 prioritised pharmaceuticals, 56.7% were absent from existing monitoring campaigns and uptake studies (Fig. 2). In terms of total plant some of the pharmaceuticals that are absent include, topiramate (rank 1), gemfibrozil (rank 3), primidone (rank 6), aciclovir (rank 7), levosulpiride (rank 10), ternidazol (rank 11), phenobarbital (rank 12), lacosamide (rank 13), theophylline (rank 14), fenbufen (rank 15), oxaprozin (rank 16), progesterone (rank 21), bemigide (rank 23), isopryn (rank 23), fenoprofen (rank 24), bicalutamide (rank 25), isopryn (rank 26) mycophenolic acid (rank 27). This finding is surprising given the toxicological concern of aciclovir and its metabolites within the aquatic environment [3]. Whilst these contaminants have been revealed to have little toxicological concern to plants, sublethal effects are often overlooked, as are the impacts towards pollinators [15]. Further research is needed to understand the potential sub-lethal impacts of pharmaceuticals at these environmental concentrations on forager health owing to previous research which has shown that small organic molecules with biological potency can impair the ability of pollinators to function [105].

4.3. Future perspectives

The clear absence of experimentally derived data to inform an assessment of exposure and potential risk of pharmaceuticals in agricultural systems necessitates the utilization of novel approaches to prioritise future research efforts. The framework supports the determination of predicted environmental concentrations in soil and plants, enabling us to tackle thousands of pharmaceuticals from numerous classes.

Comparative analysis revealed that modelled predictions of plant uptake were within a factor of ten of measured concentrations for carbamazepine, ibuprofen, irbsesartan, and venlafaxine demonstrating good reliability of the modelled outputs. Nevertheless, the framework should only be used as a screening tool rather than a replacement for traditional quantification techniques, as further model development is needed to integrate country specific consumption rates, improved degradation predictions, zwitterions, differing agricultural practices, and a wider range of plant species [112]. Further development of the framework could also integrate more environmental complexity by accounting for differences in irrigation technique (drip vs. sprinkler), in-plant metabolism, volatilization and uptake via stomata which are acknowledged to play a key role in the uptake and accumulation of

pharmaceuticals [27,36,92]. Moreover, the framework relies on estimated 1st order biodegradation rates and on K_d-regressions which were derived for other classes of chemicals (e.g. primary, secondary, and tertiary amines and quaternary ammonium compounds for the K_d of bases [30]). Zwitterions were excluded from this evaluation as they are generally considered less mobile in the environment, although, evidence suggests some can be taken up into crops (e.g. gabapentin) [83].

Droge and Goss, [30] was selected for the estimation of K_d for cations because the regressions of Franco and Trapp [43] for bases did not perform well in a recent study [70]. However, we observed that the Droge and Goss method gives often much higher K_d-values for the polar cations, compared to Franco and Trapp, [43]. As high K_d-values in soil generally result in low uptake capacity in plants, our selection of the Droge and Goss [30] model therefore may have contributed to low occurrence of bases among the top 30 PEC_{Root} and $PEC_{TOTAL\ PLANT}$ in our wastewater irrigation scenarios. Limited experimental data necessitates further experimental data to confirm the validity of the K_{OC} or K_d regressions for cationic pharmaceuticals in our dataset specifically. Additional next steps for modelling the fate of pharmaceuticals in the environment warrant the inclusion of the complex fate processes associated with zwitterions. In addition, pharmaceuticals that are authorised for use but are not commonly prescribed were removed (e.g. vigabatrin) as calculating their potential for plant uptake using the current methodology to determine consumption rate (i.e. based on the highest available dosage from the SPC) would result in bias and an over-predicted concentration. To include these pharmaceuticals further work is needed to identify a method for determining consumption rates of pharmaceuticals infrequent usage. Future work in this space should also include transformation products/metabolites, as this was out of the scope of the current framework.

Future modelling efforts should focus on prioritising metabolites to determine the associated environmental and human health risks. Furthermore, it is anticipated that soil and plant predictions are likely to be improved using site-specific data and matched experimentally derived physicochemical properties and fate parameters. In summary it is important to highlight that despite these shortcomings the framework could also be easily adapted to predict the risk associated with numerous of chemical groups and other matrices (groundwater or surface water), to enable prioritisation beyond pharmaceuticals specifically. Additional chemical groups could include veterinary medicines, pesticides, poly- and perfluoroalkyl substances, biocides, controlled substances, flame retardants, plasticizers, and even tyre wear products, for which we have very few currently available options for chemical prioritisation and ranking. As emerging contaminants in the environment become more diverse, we must leverage frameworks like this to effectively prioritise and predict exposure risks. Furthermore, presence at trace levels means that experimental approaches often fail (i.e. low extraction recoveries, matrix effects, analytical sensitivity) [2,13], therefore methodologies that can predict concentrations lower than that of experimental means are required. Moreover, analytical challenges such as isomers, separation, column retention/selection (polar vs non-polar) can be tackled appropriately with improved knowledge of contaminant fate in environmental systems.

5. Conclusion

The presented modelling predictions showed good comparability to experimental findings. Some discrepancies existed but were attributed towards poor emission predictions, uncertain biodegradation predictions and differences in plant and soil properties. Such parameters can be modified or parameterised within future research or risk evaluations. The prioritised ranking identified that 56.7 % of the top 30 pharmaceuticals predicted to accumulate ($PEC_{TOTAL\ PLANT}$) were absent from previously published literature, thus demonstrating the value of this framework as a screening tool to identify pharmaceuticals of concern where future research efforts need to focus. Some compounds requiring urgent attention include: topiramate, gemfibrozil, aciclovir and levosulpride. The presented framework highlights that the acidic, neutral/polar pharmaceuticals pose the greatest potential for uptake into crops following TWW reuse. In addition, nervous system, NSAIDs, and anti-infective pharmaceuticals were the dominant pharmaceutical classes accumulated in *Z. mays* fruit. Soil type was found to significantly affect PECs and the prioritised ranking, thus demonstrating risk evaluations and prioritisation efforts need to consider regional differences such as soil type and temperature. With the exception of furosemide, minimal risks to human health were identified when exposure scenarios considered the consumption of a single pharmaceutical. Human health concerns however were identified when exposure estimates accounted for the co-occurrence of pharmaceuticals in the environment and following the consumption of multiple contaminated produces. Overall, the presented framework has the capability to screen pharmaceutical risk within agri-environments with minimal experimental input required, demonstrating a novel means to evaluate risk for pre-authorised chemicals or new compounds.

Model availability

The model framework is available upon request. Please contact the corresponding author.

SI contents

The SI contains a range of contents that contribute and compliment the manuscript itself. Section A contains details regarding modelling aspects, such as, environmental fate (degradation predictions and SimpleTreat). Section B details comparisons to measured data, model validity, and applicability domain. Moreover, it contains text to compare biodegradation predictions to that of measured concentrations in irrigation water and soil. The tables contain a wide array of experimental detail such as, model setting (soil properties, SimpleTreat), emission calculations, SimpleTreat default parameters, excretion rates (influent to irrigation water predictions), results (priority rankings, pharmaceutical classifications, risk evaluations), statistics, and quality controls.

Environmental implications

The presented manuscript predicts the fate of 171 human pharmaceuticals in three agricultural regions following treated wastewater reuse and ranks them according to their accumulation in *Zea mays*. The top 30 priority ranking identified 56.7 % to have no existing literature or monitoring campaigns regarding uptake. The framework and presented ranking has reasonable comparability to measured data for soil and plant, demonstrating its appropriateness as a screening tool. The present work aids to focus future research and monitoring efforts towards key knowledge gaps, ultimately improving pharmaceutical environmental risk evaluation.

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CRediT authorship contribution statement

Garduño-Jiménez Andrea: Writing – review & editing, Validation, Data curation. **Trapp Stefan:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Data curation, Conceptualization. **Carter Laura:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Nightingale John:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data

curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Laura Carter reports financial support was provided by UK Research and Innovation. John Nightingale reports financial support was provided by UK Research and Innovation. Andrea Garduno Jiminez reports financial support was provided by UK Research and Innovation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.138297.

Data availability

Data will be made available on request.

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