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Pharmaceutical and Personal Care Products: From Wastewater Treatment into Agro-food Systems

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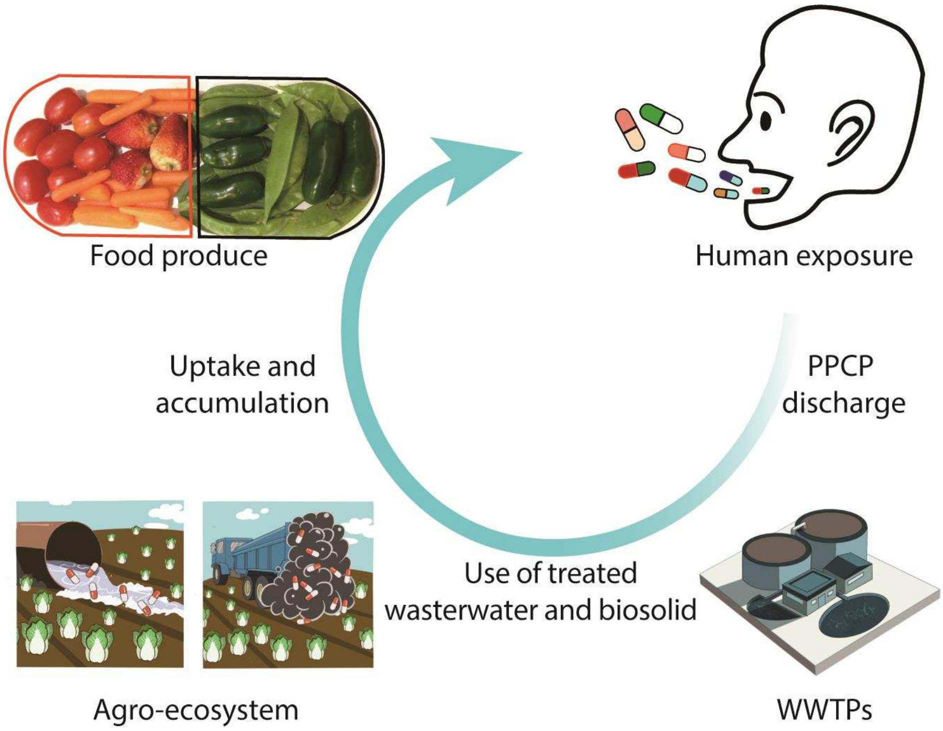

Abstract

Irrigation with treated wastewater (TWW) and application of biosolids introduce numerous pharmaceutical and personal care products (PPCPs) into agro-food systems. While the use of TWW and biosolids has many societal benefits, introduction of PPCPs in production agriculture poses potential food safety and human health risks. A comprehensive risk assessment and management scheme of PPCPs in agro-food systems is limited by multiple factors, not least the sheer number of investigated compounds and their diverse structures. Here we follow the fate of PPCPs in the water-soil-produce continuum by considering processes and variables that influence PPCP transfer and accumulation. By analyzing the steps in the soil-plant-human diet nexus, we propose a tiered framework as a path forward to prioritize PPCPs that could have a high potential for plant accumulation and thus pose greatest risk. This article examines research progress to date and current research challenges, highlighting the potential value of leveraging existing knowledge from decades of research on other chemicals such as pesticides. A process-driven scheme is outlined to derive a short list that may be used to refocus our future research efforts on PPCPs and other analogous emerging contaminants in agro-food systems.

Introduction

Many regions in the world are experiencing unprecedented water stress due to growing populations, increasing urbanization, higher living standards and a greater demand for food. In addition, climate change-induced variations in precipitation patterns are further exacerbating the water crisis. Water scarcity is especially acute in many arid and semi-arid regions, such as the Middle East, East Africa and the U.S. Southwest.[1,2] California, an important agricultural state relying heavily on irrigation, has experienced a perennial drought in recent years, with nearly the entire state designated as under "severe drought" as recent as 2017.[3] To combat water shortage and meet increasing water demand in agricultural production, treated wastewater (TWW) is accepted as a reliable alternative to augment irrigation. In Israel, TWW has been used for crop irrigation since the early 1980s, with TWW accounting for over 50% of water used in agricultural production (**Figure 1A**).[4] Comparatively, the amount of TWW used for agricultural irrigation in California is less than 10%, but has been increasing steadily.[5] Likewise, agricultural irrigation with TWW is a common practice in many other areas, including Greece, Italy, Spain, France, and China.[6–8]

Wastewater treatment also produces large quantities of biosolids. Biosolids are a source of organic matter and nutrients, and have been widely used to improve soil structures and soil fertility.[7–12] A U.S. national survey in 2007 suggested that about 6.5 million tons of biosolids (dry weight) were produced and about 55% was recycled to soils.[13] With increasing populations worldwide, biosolid production increased to 8.2 million metric tons in 2010[14] and is likely to continue to increase in the future. Traditional biosolid disposal approaches (e.g., ocean-dumping, landfills, incineration) are limited by regulation or are becoming prohibitively expensive. Therefore, land application of biosolids is considered an optimal solution, and is expected to be extended more widely when concerns such as pathogens, heavy metals, and trace organic contaminants have been sufficiently addressed. [15]

The reuse of TWW and biosolids in agriculture brings many societal and economic benefits and contributes to agricultural and environmental sustainability. However, irrigation with TWW and land application of biosolids introduce numerous PPCPs to agro-food systems.[16–22] Painkillers, antibacterial agents, antidiabetics, beta-blockers, contraceptives, lipid regulators, antidepressants, and many other classes of PPCPs, as well as their metabolites, have been found in TWW and biosolids.[23–25] Use of TWW and biosolids in agriculture leads to soil contamination with PPCPs and their metabolites, providing a route for accumulation in food produce, [12,18–28] which poses potential risks to environmental and human health.

Since about 2009, an increasing number of studies have documented the uptake and accumulation of PPCPs by plants (**Figure 1B**). However, so far data have been generated only for a small subset of PPCPs using different experimental setups, e.g., cell culture, hydroponics, soil cultivation in a growth chamber or greenhouse, and field experiments (**Figure 1B-D**).[21,30–33] At present, the evaluation of PPCPs in agro-food systems is rather disjointed and lacks a coordinated approach. One way forward would be a prevalence study to understand what is known and what is still yet unknown about PPCPs in the agricultural environment. Identification of knowns and unknowns can advance our community's understanding of knowledge gaps and address future research needs, as emphasized in a recent review by Carter et al..[24] The greatest challenge to understanding plant accumulation of PPCPs is the sheer number of the compounds,their different physicochemical properties, as well as their metabolites. Given the large number of PPCPs, it is infeasible to evaluate all PPCPs through experimentation. Thus, there is an urgent need to develop a framework to identify "high-risk" PPCPs on the basis of uptake and accumulation in food production and potential harm to human health. Future research efforts could target the short-listed PPCPs, and the value of our research efforts could therefore be maximized.

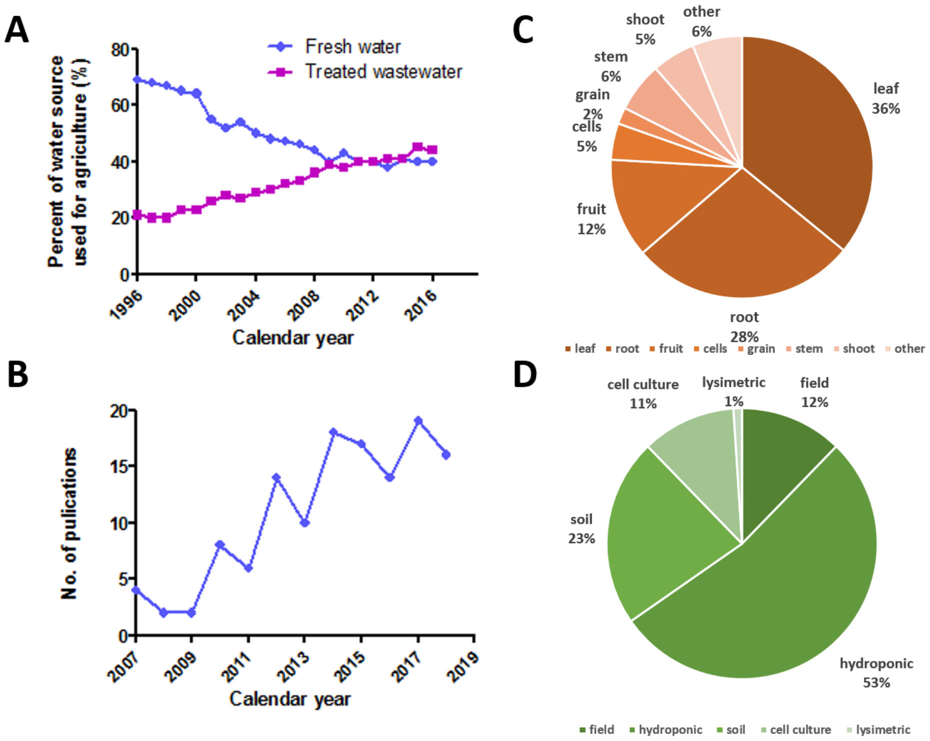

Figure 1. (A) Proportions of water sources used in agricultural irrigation in Israel from 1996-2016 (data from Israeli Central Bureau of Statistics); (B) Number of publications on uptake and accumulation of PPCPs by plants (retrieval from PubMed from 2007-2019 in March 2019); (C) Studies of plant uptake and accumulation on different plant organs; and (D) Studies using different experimental setups (i.e., field, hydroponic, soil cultivation in greenhouse or laboratory, cell culture, and lysimeter).

Here we first briefly discuss the flux processes of PPCPs in the water-soil-plant continuum by highlighting key research advances and identifying fundamental knowledge gaps. We then outline a conceptual framework as a path forward by prioritizing PPCPs that may have an elevated probability of accumulation in food produce.

Soil Processes

Soil serves as the initial recipient of PPCPs when agricultural fields are irrigated with TWW or amended with biosolids.[16,34,35] Sorption to soil ($K_{d\ soil}$) and degradation in soil (k_{deg}) play an important role in controlling the concentration of PPCPs in soil porewater ($C_{porewater}$)

and hence the availability of PPCPs for plant uptake (**Figure 2**). Soil can therefore act as both a source and a sink for PPCPs, regulating the amount of PPCPs available for plant uptake.

Sorption of PPCPs by soil generally reduces their uptake by plants, especially for those chemicals with strong hydrophobicity or positive charge.[25,26,36–38] For these PPCPs, the soil may act as a source after irrigation or rain events, as a fraction of the adsorbed chemicals may be released to the soil porewater to maintain apparent chemical equilibrium. Indeed, Mordechay et al. [22] detected carbamazepine in wheat that was only rain-fed and in the same soils previously irrigated with TWW. Comparatively, PPCPs with a low sorption capacity typically remain in the aqueous phase, and are readily available for plant uptake but have high susceptibility to off-site transport via runoff or leaching. The physicochemical properties of PPCPs and soil collectively govern PPCP sorption.[36,39–42] It has been noted that irrigation with TWW and soil amendment with biosolids can change soil composition and chemistry, e.g., increasing soil organic matter content.[25,31,36] Batch methods have been used to derive $K_{d\ soil}$ values for a small number of PPCPs in select soil types. Molecular descriptors, combined with artificial neural network, has also been used to predict $K_{d\ soil}$ values of organic compounds including PPCPs.[43–45] However, such predictive models have not been fully tested or refined for different chemical classes of PPCPs. It must be noted that substantial knowledge has been accumulated from decades of research on sorption of other organic compounds including pesticides.[46–49] The fact that pesticides are also extremely diverse in structures and physicochemical properties underscores the value to use some of the established models for predicting $K_{d\ soil}$ of PPCPs and further $C_{porewater.}$[46,50,51].

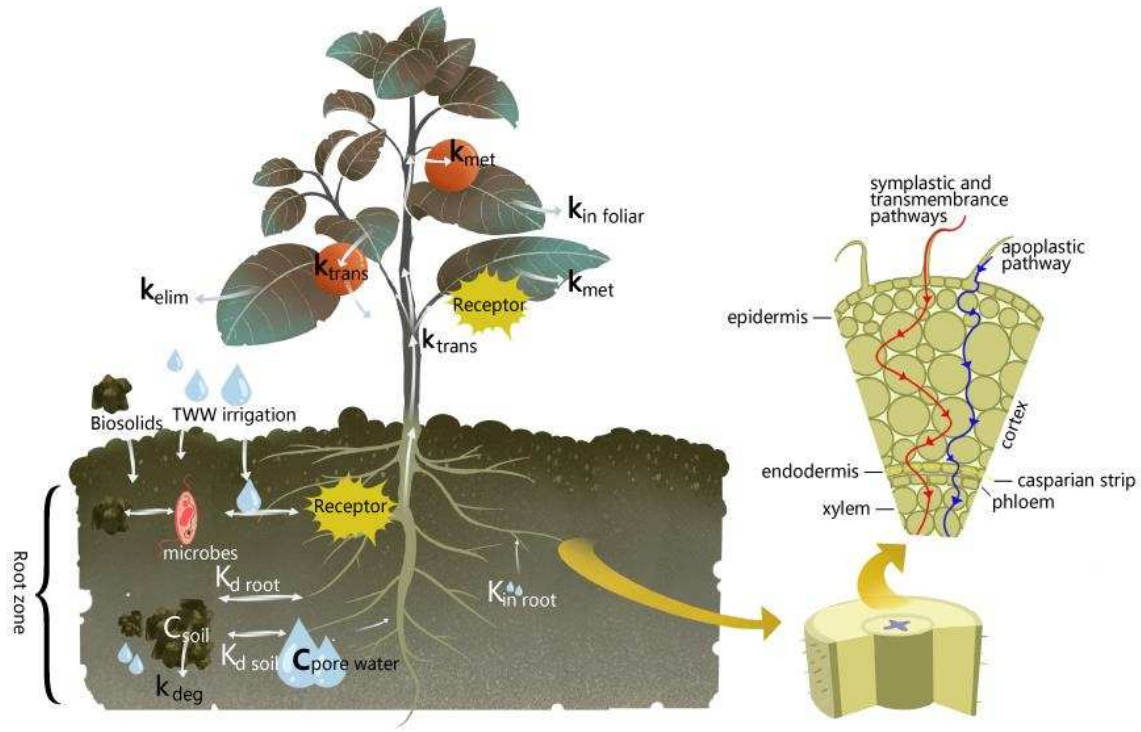

Figure 2. Fate and transport processes of PPCPs in the soil-plant system. Note: C_{soil}, concentration in soil; $C_{porewater}$, porewater concentration; $K_{d\ soil}$, soil/water partition; $K_{d\ root}$, root/water partition; k_{deg}, degradation in soil; $k_{in\ root}$, uptake into root, $k_{in\ folia}$, foliar uptake; k_{trans}, translocation in plant; k_{met}, in-plant metabolism; k_{elim}, potential loss from plant.

Abiotic and biotic degradation (k_{deg}) also influences PPCP availability for plant uptake. Like pesticides, k_{deg} values are wide-ranging among different PPCPs, and also vary in different soils for a given PPC[25,36,52]. Many factors affect PPCP degradation in soil, including soil microbial communities, pH, moisture, and the physicochemical properties of the PPCP itself. [25,39,40,53] Microbial degradation is a major process governing the dissipation of many PPCPs in soil, especially in the rhizosphere where plant root exudates often contribute to enhanced biodegradation by increasing microbial activity and altering the sorption dynamics and bioavailability.[53–59] On the other hand, wastewater irrigation and biosolid amendment may introduce antimicrobial agents (e.g., triclosan, triclocarban) and microplastics, which have the potential to alter soil microbial communities or phase distribution of PPCPs.[25,36,60]

Additionally, PPCPs with short half-lives should not be ignored as these chemicals can become pseudo-persistent through continual application of TWW or biosolids. In addition, metabolites from PPCPs could retain the bioactive moiety of the parent compound, and be taken up by plants.[40,41] Therefore, an improved understanding of the fate and biological activity of metabolites in soil is needed for a comprehensive evaluation of PPCP plant uptake. It must be again stressed that biosolid application and TWW irrigation have the potential to alter biotic and abiotic characteristics of a soil. It is important to understand the subsequent effects on PPCP degradation and also the long-term consequences resulting from repeated applications of TWW and biosolids.

To date, soil processes have been evaluated for only a small number of PPCPs, often using a single chemical while ignoring the effects of chemical mixtures or the influence from the components of wastewater or biosolids.[61] In addition, research efforts have typically focused on short-term TWW and biosolid application scenarios. Therefore, we need to improve our predictive capability on sorption and transformation of PPCPs in soils under various application scenarios in the field, e.g., long-term, repeated applications of TWW or biosolids. The movement of PPCPs in the water-soil-plant continuum is a dynamic process, and a better understanding on water flow in soil and plant systems and PPCP chemical fluxes is essential to elucidating the transport and accumulation of PPCPs under certain scenarios, for example, between irrigation events. Again, leveraging information from other man-made chemicals such as pesticides offers a logical and cost-effective means to fill some of these knowledge gaps.

Root Uptake and Accumulation

Roots are the primary entry point for PPCPs into plants from the soil via soil porewater (**Figure 2**). To date, more than 100 PPCPs have been shown to be taken up into roots of agricultural plants from studies using a hydroponic or soil setup.[21,26,30,31,62,63] PPCPs enter a plant vascular system with water flow via apoplastic, symplastic and transmembrane pathways (**Figure 2**).[64–67] Root uptake of PPCPs is determined by a combination of PPCP physicochemical properties (e.g., molecular size, charged speciation, lipophilicity), the bioavailable fraction in soil, and plant species of interest.[26,30,38,66] Many non-ionic compounds such as carbamazepine and caffeine have been shown to be more favorable for root uptake than ionic compounds (e.g., diclofenac) in crops irrigated with TWW.[30] Currently, PPCPs are believed to be passively transported into plant roots through cell membranes; however, the diffusion rate and magnitude to penetrate cell membranes or Casparian strip domains remain largely unknown. Nevertheless, some transporter proteins such as organic cation transporters are substrate versatile, and have been suggested to facilitate active transport of metformin, an anti-diabetic drug, into plant roots.[68]

The accumulation of PPCPs in root is governed by the combination of intake flux ($k_{in\ root}$), metabolism (k_{met}) in roots and translocation out of the root (k_{trans}) with transpiration flow (**Figure 2**). These kinetic parameters are intrinsically influenced by plant physiological properties such as root lipid content or the dynamics of root and plant growth.[30] In addition, the metabolism of PPCPs in roots can alter the chemical structure and hydrophobicity and hence accumulation in roots and transport from roots to leaf/fruits. Information on these individual processes is currently limited, but is needed to develop better predictive models to estimate root uptake and accumulation potential for PPCPs. As active transport may be involved in the translocation of PPCPs out of the root, it is also important to consider the role of active transporters in the distribution and redistribution of PPCPs within plants.[68]

Translocation and Accumulation in Plants

Once PPCPs enter plant roots, these chemicals can potentially translocate to different organs. The extent of the translocation of PPCPs depends primarily on the transpiration stream where a compound moves with water flow through the xylem to the sites of greatest transpiration.[22,69] As the rate of transpiration (k_{trans}) is influenced by ambient temperature and humidity,[70] environmental conditions can exert significant influences on the accumulation of a compound. Higher temperature, lower humidity, greater wind speed, and higher soil water content may result in greater transpiration rate and thus increased accumulation of PPCPs in the upper portions of plants.

Passive diffusion, xylem transport, and phloem transport are the main processes governing the translocation of PPCPs within plants (**Figure 2**). The major factor determining PPCP translocation is, however, the physicochemical properties of the chemical including for example lipophilicity. As reported for pharmaceuticals and pesticides, moderately lipophilic neutral compounds (log K_{ow} 2 to 5) such as carbamazepine, diazepam and phenytoin can cross membranes through passive diffusion[64] and enter the symplast pathway, which enables translocation via the xylem.[26,30,31,38] Additional physiochemical properties such as hydrogen bonding, molecular size, and ionization properties may also influence the translocation of PPCPs. For example, ionized and polar PPCPs passively diffuse across the plasma membrane at a much slower rate.[26,38] In addition, xylem transport has the potential to introduce PPCPs to developing fruits that transpire water, via similar principles to the translocation to leaves. The movement of PPCPs to fruits can also occur via phloem transport. The Münch theory derived from other xenobiotics such as pesticides suggests that substances move from source organs to sink organs driven by the osmotic gradient.[71,72] This translocation mechanism is less reported for PPCPs. Further studies are needed to evaluate whether the similar mechanism is applied for the translocation of PPCPs in plant.

Predictive models have been proposed and tested for pesticide translocation in plants. These models demonstrate a bell-shaped curve of transpiration stream concentration factor with respect to hydrophobicity (i.e., logK_{ow}) for compounds of a similar chemical class.[73,74] A sigmoidal relationship between translocation concentration factor and logK_{ow} was found for a wide range of compounds that differ greatly in physicochemical properties.[75] A recent article by Bagheri et al.[76] showed two different curves (i.e., bell-shape and sigmoidal) for compounds with log K_{ow} >1 and K_{ow}<1. As the translocation of PPCPs is not expected to solely depend on hydrophobicity, future model development or refinement needs to incorporate additional parameters, such as pK_a, charged species, and molecular size, to understand if relationships and models can account for the different physicochemical properties of PPCPs. Furthermore, models in pharmacodynamics and pharmacokinetics should be explored and utilized if possible, as rich data in mammalian systems are available for many PPCPs. Indeed, Limmer and Burken[45] applied molecular descriptors initially used in drug discovery and found that similar descriptors, including K_{ow}, molecular weight and H-bond donors that control translocation across the blood-brain barrier also influence the uptake into plant roots for selected pharmaceuticals. More recently, the same group applied machine learning (i.e., fuzzy logic) to predict the translocation of emerging contaminants into plants with a neural network-based model and achieved higher accuracy predictions.[76]

Plant Metabolism

Metabolism in plants (k_{met}) plays an important role in determining the ultimate fate and accumulation of PPCPs in plant organs (**Figure 2**). Thus, plants may be considered as a “green liver” for metabolizing PPCPs. Once in plants, many PPCPs are metabolized primarily via phase I metabolism, phase II conjugation, and phase III compartmentation.[77] Research to date on plant metabolism of PPCPs has only focused on a small number of compounds, such as nonsteroidal anti-inflammatory drugs,[78–82] lipid-lowering drugs,[83] antibiotics,[84–86] antibacterials,[87–89] psychoactive drugs,[90,91] and anti-epileptic drugs.[30,31,33,92] Transformation products, in-plant processes, and metabolic reactions of PPCPs are largely unknown. While some biotransformation reactions are shared across species for the same PPCPs, others are likely also planted species-specific.[78,80,82] For example, diclofenac was transformed mainly to

4’OH-diclofenac and diclofenac-glucose conjugate in barley,[78] but to diclofenac-glutamate conjugate in Arabidopsis cells and whole plant.[82]

Screening and identification of unknown metabolites from PPCPs in plants are particularly challenging, because of little prior structural information of the metabolites and interference from complex plant matrices (e.g., pigments, sugars, secondary metabolites). Research is needed to use cutting-edge high-resolution mass spectrometry, along with chemoinformatic algorithms, metabolomic software, and improved mass spectra databases and knowledge rooted in the study of pharmacokinetics to establish target, suspect, or non-target workflows in order to obtain a more comprehensive picture of PPCP metabolism in plants. Fu et al.[83] developed a stable isotope labeling assisted method to probe structural information of metabolites in plant matrices, which allows tentative identification of unknown metabolites in the absence of authentic standards.

In most cases, conjugation with biomolecules is a modulator to detoxify PPCPs in plants; however, recent studies have shown that metabolites could be more toxic than the parent compound, such as the genotoxic metabolite of carbamazepine, i.e., 10,11-epoxycarbamazepine.[22,30,31] In addition, plant metabolism via conjugation can ‘mask’ the parent compound or its metabolites;[81,82,87,93] after ingestion, such conjugates may be de-conjugated in human gastrointestinal tract.[94] Furthermore, a recent study showed that a metabolite of triclosan, methyl triclosan, was converted back to the parent compound in plants.[95] These studies suggest potential preservation of biological activity in plant metabolism; neglecting to account for metabolites may lead to an underestimation of human exposure. Therefore, further studies are needed to explore the formation of biologically active metabolites, including conjugates, in food plants and to evaluate their contribution to human exposure.

Phytotoxicity

PPCPs are bioactive chemicals, and therefore the uptake of these chemicals into plants has the potential to alter plant physiology and key biochemical pathways.[96,97] Early studies with a primary focus on antibiotics have demonstrated adverse effects on root growth and development,[98] seed germination, and photosynthesis,[62,99] in a concentration-dependent and compound-specific manner. However, it is largely unknown if such deleterious effects occur across different groups of PPCPs or different plant species, or under environmentally relevant conditions. Again, PPCPs from TWW irrigation and biosolid application introduced to the agricultural environment as a mixture, and yet there have been only a few studies that have considered the mixture effects of PPCPs to plant.[100–102] Indeed, it was found that mixtures of PPCPs could exacerbate cytotoxicity to alfalfa compared with that exposed individually.[100] Therefore, further research should consider phenotypic differences of PPCP-induced phytotoxicity, effects at the subcellular and molecular level, such as changes in phytohormones, cellular metabolism, nutrient uptake and signaling[63,100,102–104] that may be considered as the underlying mechanisms for the long-term visual phytotoxic responses, and the influence of plant health (e.g., plant physiological and biochemical processes) on the fate of PPCPs and their phytotoxicity potential.

Human Exposure

Uptake and accumulation of PPCPs in edible crops present a potential route for human exposure via dietary ingestion.[105] Based on observations to date, PPCPs are accumulated in the edible fruits, leaves or roots, typically within the ng/g range. Under field conditions, the estimated dietary consumption would be several orders of magnitude less than a prescribed daily dose for a given pharmaceutical. However, there is little knowledge pertaining to short- or long-term human health effects of chronic exposure to a mixture of PPCPs, including metabolites.[22,30,31,105] This is especially true for PPCPs that have known additive effects, or contraindications and metabolites that are potentially more toxic than the parent compound. The potential risk may be also significantly greater for sensitive populations such as children and individuals with genetic, metabolic and immunological disorders.

While there is little doubt that PPCPs are present in food products under current agricultural production (e.g., irrigated with TWW or amended with biosolids), to date, field-scale data are scarce. Recently, Paltiel et al.[105] reported concentration of carbamazepine and its metabolites in human urine for individuals who consumed vegetables and fruits produced with TWW irrigation. The study showed that consumption of the contaminated food increased urinary carbamazepine and metabolite concentration. However, the peak urinary concentration of carbamazepine was 4 orders of magnitude lower than the urinary concentration after a single medical dose of 400 mg of carbamazepine; this exposure was deemed unlikely to have clinical effects for most adults.[105] Similar field-oriented studies are needed to provide a better understanding of the exposure to humans and the potential health risk of PPCPs. Further research is needed to develop threshold or trigger values for accumulation of PPCPs in food products with human exposure. Research should also consider mixture effects (e.g., additive, synergistic) of PPCPs on human exposure through the dietary intake of food produce impacted by TWW and biosolids.

Prioritization Scheme of PPCPs in Agro-Food Systems

The primary challenge in evaluating PPCPs in agro-food systems is a large number of PPCPs, which makes the experimentation-based approach infeasible. This is evident in the fact that research so far has touched upon only a very small subset of PPCPs and mostly in artificial experimental settings. Therefore, a strategic approach to developing a short list of potential "high risk" PPCPs is urgently needed so that we can better focus our next-step research and maximize the use of our resources and research capacity. Here we outline a tiered framework to accomplish the above objectives by considering each of the threshold processes and by tracing the flow of a chemical from TTW/biosolids to soil to the edible organ of a plant (**Figure 3**).

Specifically, future efforts should focus on: 1) developing databases of occurrence of PPCPs in TWW and biosolids, and estimating their input flux into agroecosystems, 2) evaluating persistence ($T_{1/2,\ soil}$) and sorption ($K_{d\ soil}$) of PPCPs entering agroecosystems using empirical, descriptor-based and deep learning models, 3) refining quantitative structure-activity relationship (QSAR) based models and/or deep learning models to prioritize compounds that are capable of entering plant roots and translocating within plants, 4) determining metabolism rates and identifying metabolites including conjugates for those PPCPs with appreciable uptake and translocation, and 5) predicting human exposure to such "high risk" PPCPs and their biologically active metabolites.

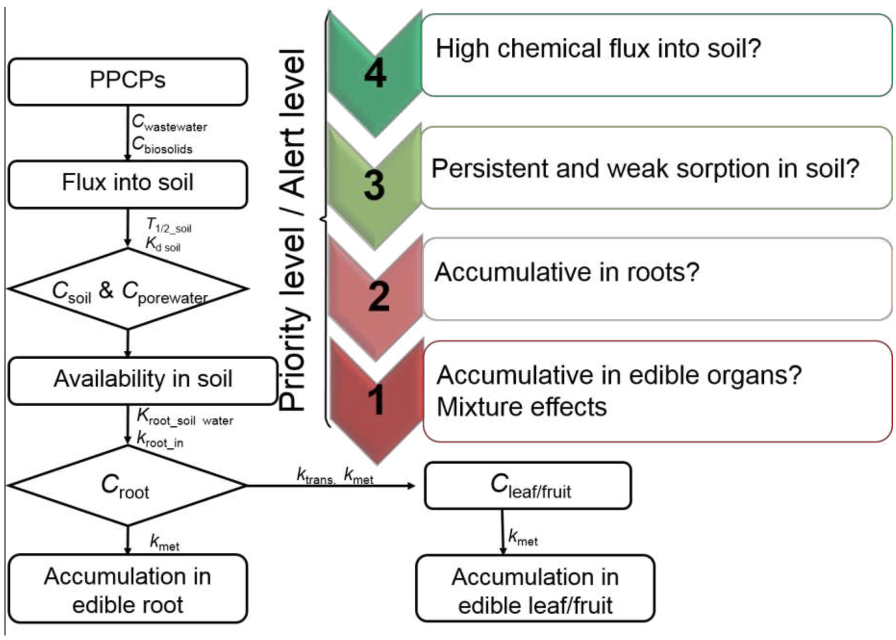

Figure 3. Prioritization of PPCPs in agro-food systems

While the prioritization scheme outlined above provides a necessary direction going forward, it is critical that we make use of knowledge gleaned from many decades of research on other man-made chemicals, especially pesticides. Likewise, information on pharmacokinetics and toxicokinetics of PPCPs in humans and animals should be mined and used wherever possible. While this article highlights mainly PPCPs, this prioritization approach should be also suitable for other emerging contaminants, such as corrosion inhibitors, microplastics, flame retardants, perfluorinated compounds, among others.

Conclusions and Future Prospects

The extensive use of TWW and biosolids in agriculture introduces PPCPs and other contaminants of emerging concern to arable soil and has the potential to contaminate food produce, constituting a route for human exposure. In order to provide sufficient food for the growing populations, the global agricultural sectors have to continue or even enhance the use of TWW for irrigation and biosolids as a soil amendment and fertilizer. Here we have discussed the potential transfer of PPCPs to food products under the premise that TWW and biosolids are used in production agriculture.

When circumstances allow, TWW and biosolids may be used on non-food crops such as fiber-producing plants (e.g., cotton) or in landscape settings, which would prevent PPCPs from coming into contact with agro-food systems in the first place. The use of TWW and biosolids on landscape plants may also offer the advantage of lower energy cost and infrastructure investment, as residential homes and parks are generally located in closer vicinity of municipal wastewater treatment plants than agricultural fields. In addition, the emission of PPCPs into the environment, including agro-food systems, may be reduced by improving wastewater treatment capacities via advanced technologies, so that trace contaminants such as PPCPs are removed at the source. In regions or countries where advanced treatment is economically or technically infeasible, TWW effluents of different quality may be used on different crops. For example, TWW that has not undergone advanced treatments may be used on certain perennial stonefruit trees (e.g., walnut, apple), while only rigorously treated water is allowed for use on vegetables. These and other management practices (e.g., allowing TWW to be used for irrigation based on soil properties) may help minimize the unintended human exposure to PPCPs by averting or decreasing the accumulation of PPCPs in food produce. While more research is needed to validate the merits of these alternative practices, the potential risk of PPCPs as a result of agricultural use of TWW and biosolids should be addressed holistically by weighing the cost and benefits as well as the need against other uses.

What we know about PPCPs in agro-food systems is rather limited at present; there are still many unknowns. More research is urgently needed to fill these knowledge gaps to better elucidate the fate of trace-level PPCPs in the TWW/biosolids-soil-plant-human continuum, and ultimately the exposure to humans via dietary intakes of the impacted agricultural products. While our discussion outlines some of the most relevant questions needing answers on PPCPs in agro-food systems, it cannot be overstated that we could and should leverage our existing knowledge, including that derived for pesticides and other man-made chemicals. By doing so, we not only avoid “reinventing the wheel”, but also maximize the use of our limited research resources by addressing only questions of the greatest relevance and significance. Parallel to the above prioritization scheme, below we propose some research needs meriting immediate attention:

1) Synthesize occurrence data of PPCPs in TWW and biosolids, and consumption and other information where necessary, and develop a database of PPCPs with a high probability to enter agro-food systems;
2) Use experimental data and apply modeling approaches to identify PPCPs that are persistent in soil and with an elevated likelihood for plant uptake and accumulation;
3) Employ non-target screening and other analytical tools to better understand plant metabolism of PPCPs, with a focus on biologically active metabolites, including conjugates;

4) Consider chemical mixtures in plants and their implications in human exposure through the dietary intake of food produce impacted by TWW and biosolids;

5) Understand the behavior and fate of PPCPs following chronic or repeated applications of TWW and biosolids in agro-food systems;

6) Relate accumulation of PPCPs and their metabolites in food products with human exposure and develop threshold or trigger values; and

7) Last but not least, standardize experimental protocols so that data may be compared across studies and be related to common agricultural practices.

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