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Can the pharmaceutically active compounds released in agroecosystems be considered as emerging plant stressors?

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ABSTRACT

Pharmaceutically active compounds (PhACs) entering agroecosystems as a result of various human activities may be taken up by and accumulated within crop plants, with potential human health implications. Despite their extensive metabolism by a sophisticated enzyme-based detoxification system in plant cells, PhACs and their transformation products (TPs) may result in adverse effects on plants' physiology. PhACs–mediated phytotoxic effects, as well as plants' defense responses have been depicted on plants exposed to individual or low number of PhACs under controlled conditions. We highlight the need to consider the cocktails effects and synergistic interactions of PhACs present in mixtures in actual agroecosystems, towards phytotoxicity and agricultural sustainability in general. Considering PhACs as emerging plant stressors will better facilitate the understanding of their phytotoxic effects.

1. Pharmaceutically active compounds are ubiquitous in agroecosystems

Farmers worldwide are struggling to meet increasing global demand for food, feed and fiber, which is forecasted to be further increased due to increasing world population, demand and prosperity (Godfray et al., 2010). Several challenges faced by the agricultural sector, such as the growing competition for land, water and energy, the overall degradation of soil and water resources, and climate change and global warming effects are expected to substantially affect farmers' ability to produce adequate volumes of food in an environmentally sustainable way (Hanjra and Qureshi, 2010). Among others, chemical pesticides and fertilizers in agriculture, and antibiotics and growth promoting agents in livestock and aquaculture are being employed with the aim to boost the primary production of foods (Tilman et al., 2002). In addition, non-conventional water resources such as reclaimed wastewater (RWW) and aquaculture effluent are being used for crop irrigation, attributing to the alleviation of increasing scarcity of good quality agricultural water (Hamilton et al., 2007). Besides promoting food production, these technological advances are accompanied with potential negative implications to agroecosystems and public health. The use of animal manure and biosolids as soil conditioners and amendments, and the use of RWW and intensive aquaculture effluent for crop irrigation, constitute significant pathways for the introduction of pharmaceutically active compounds (PhACs) in agroecosystems (Christou et al., 2017a) (Fig. 1). This is attributed to the fact that most PhACs (antibiotics, analgesics, anti-inflammatory, cardiovascular, antidiabetics, estrogens, antiepileptic, psychiatric drugs, etc.) are poorly absorbed and not completely metabolized in human and animal bodies and therefore a high percentage of the intake dosage (30–90%) is excreted via urine and feces within hours after application either in the form of the parent compound or as metabolites (Zhang et al., 2014). Moreover, conventional biological wastewater treatment processes are only moderately effective at removing PhACs from the RWW and biosolids (Michael et al., 2013). Therefore, PhACs are routinely detected in RWW and in biosolids and manure, and in RWW-irrigated and biosolids- and manure-amended agricultural sites, soils receiving raw wastewater, and surface and groundwater systems and sediments receiving runoff from these sites (Fatta-Kassinos et al., 2011; Gottschall et al., 2012; Kinney et al., 2006) (Fig. 1). Accumulating evidence highlight the ubiquity of PhACs in a number of environmental matrices, with concentrations ranging from low ng L^{-1} (groundwater) to high μg L^{-1} (wastewater) in water sources, and ng kg^{-1} to low mg kg^{-1} in soil, depending on the type and physico-chemical properties of PhACs (Li,

Abbreviations: CytcOx, cytochrome *c* oxidase; D_{ow}, pH-dependent speciation of ionic compounds; GSTs, glutathione S-transferases; H^+-ATPase, proton pump; K_{oc}, organic carbon-normalized sorption coefficient; RWW, reclaimed wastewater; TPs, transformation products

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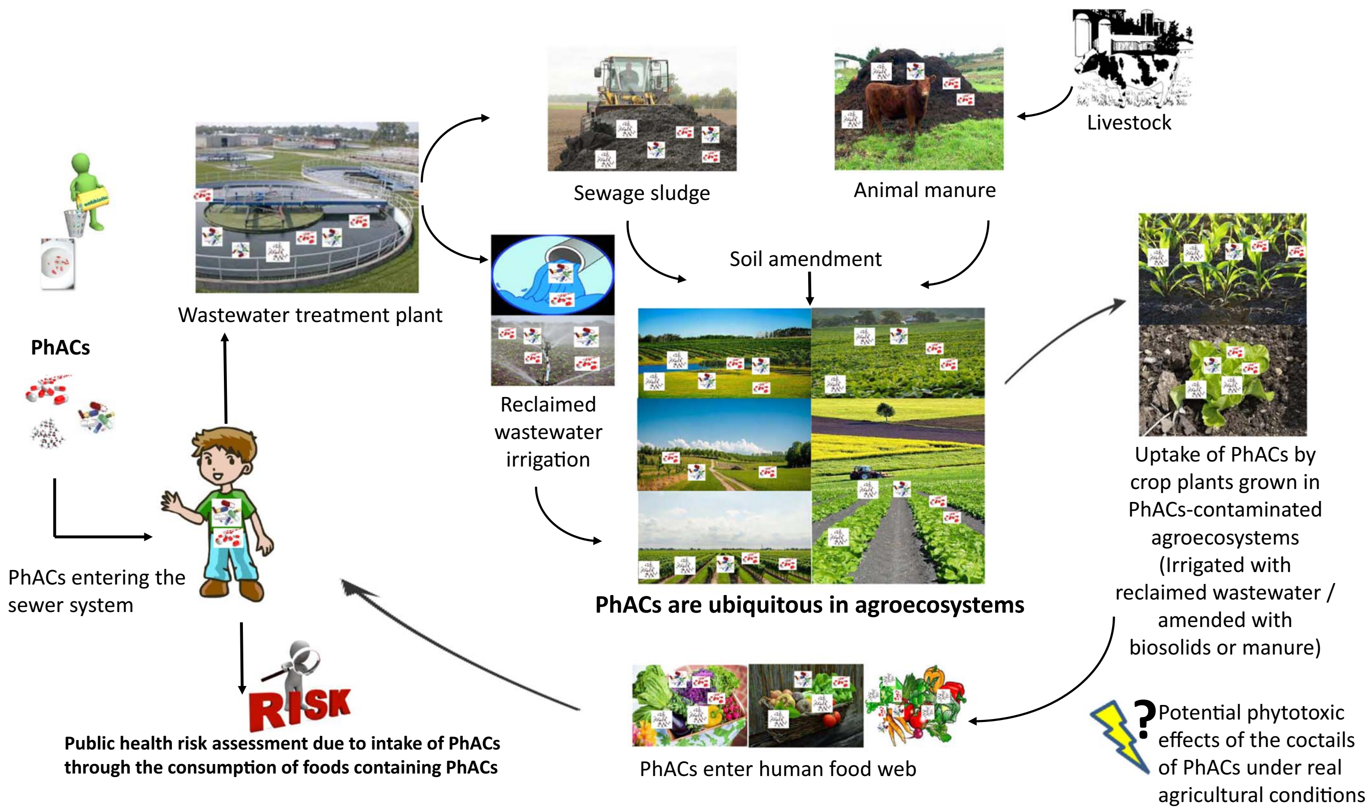

Fig. 1. Main sources and fates of PhACs in agroecosystems. The use of RWW for irrigation, as well as the use of biosolids and animal manure as soil conditioners and amendments constitute the most important pathways for the introduction of PhACs in agroecosystems. Due to their ubiquitous presence and continuous introduction, PhACs exert significant side effects to aquatic and terrestrial organisms. PhACs are taken up by, and bioaccumulated in the edible tissues of crop plants grown in PhACs-contaminated agroecosystems, thus entering the food web with potential negative implications to public health. Moreover, PhACs have been found to exert phytotoxic affects to crop plants.

2014; Pan and Chu, 2017). Importantly, PhACs are present in mixtures of dozen or even hundreds of individual active ingredients and their transformation products (TPs) in the majority of environmental matrices. These mixtures are continuously varying (intra- and inter-daily, seasonally and inter-annually) in composition and concentrations, depending on their introduction and degradation-removal rates (Christou et al., 2017a; Paíga et al., 2017). Despite their short environmental half-lives, PhACs are regarded as pseudo-persistent contaminants of emerging concern (CECs) due to their continual introduction into the environment and permanent presence (Michael et al., 2013). PhACs residues and/or their TPs detected in the environment at trace levels can induce toxic or other kinds of effects on terrestrial or aquatic organisms, while their uptake by crop plants and aquatic organisms and their subsequent entry into human food web warrants special concern and further investigation due to possible public health effects (Fatta-Kassinos et al., 2011) (Fig. 1). Antibiotics residues in agroecosystems and generally in the environment can cause the development of resistance in natural bacterial populations (including human commensals or pathogens of clinical relevance), while steroids residues can cause endocrine disruption effects (Bondarczuk et al., 2016; Hernando et al., 2006), posing major risks to human health and ecological sustainability in the 21st century (Berendonk et al., 2015).

2. Uptake and bioaccumulation of pharmaceutically active compounds by plants

The uptake of PhACs by crop plants was initially verified by studies conducted under environmentally irrelevant conditions (i.e. in laboratory or greenhouses, with plants growing in nutrient solutions or inert materials), employing single or mixture of small number of PhACs spiked in the growing medium at environmentally relevant or mostly higher concentrations (Migliore et al., 2000, 2003; Shenker et al., 2011; Tanoue et al., 2012). Such studies were proven to be useful in elucidating the mechanism of PhACs' uptake by plants, which was found to be simply driven by the transpiration derived mass flow (energy independent) or facilitated by transporters and channels through a symplastic, energy dependent route (Dodgen et al., 2015; Malchi et al., 2014). Most importantly, however, they highlighted the need for exploring the uptake of PhACs by plants under real field conditions, as hydroponic and greenhouse experiments though, even if conducted at environmentally relevant PhACs concentrations, are unable to manifest the complexity of an actual agricultural environment (Malchi et al., 2014).

Several studies revealed the abundance of PhACs in agroecosystems receiving RWW or biosolids or manure worldwide (Calderón-Preciado et al., 2011; Chen et al., 2014; Du and Liu, 2012) (Fig. 1). Furthermore, field surveys (Pan et al., 2014; Prosser and Sibley, 2015; Riemenschneider et al., 2016) and studies conducted under field conditions where real RWW for irrigation and biosolids or manure as soil amendments were employed (where a continuously varying cocktail of PhACs prevails) (Christou et al., 2017b; Sabourin et al., 2012; Wu et al., 2014), showed that crop plants grown in PhACs-contaminated agroecosystems uptake and accumulate these active compounds in their tissues (Fig. 1). Such studies allowed, although not fully, to understand how the environmental parameters and the physicochemical properties of the PhACs, as well as those of the soil and the soil pore water affect the uptake of PhACs by plants. These studies also provided data for assessing the PhACs-mediated risks to public health (Christou et al., 2017b). It is now widely accepted that the lipophilicity and speciation of PhACs strongly affect their uptake by the roots and their translocation within the plants. The octanol-water partition coefficient (K_{ow}) has been suggested as a predictor of the uptake behavior of non ionizable