1 # **Pharmaceuticals and personal-care products in plants**

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Pharmaceuticals and personal-care products (PPCPs) derived from agricultural and urban areas accumulate in plants at concentrations (ng to µg kg^{-1}) that can be toxic for plants. Importantly, the dietary intake of these PPCP-contaminated plants may also pose a risk to human health, but currently little is known about the fate of PPCPs in plants and their effect or risk to the ecosystem. In this opinion article we propose that in-depth research on the use of plants as a monitoring device for assessing the use and environmental presence of PPCPs is warranted. The toxicity of PPCPs to plants and their microbiota needs to be established, as well as any toxifying effect to plant herbivores, humans included..

Pharmaceuticals and personal-care products in plants and food webs

Plants act as excellent tracers of global pollution [1], because they are present in almost all areas of the planet and accumulate chemical compounds present in the atmosphere, the water with which they are irrigated, and the soil on which they grow. Thousands of new chemical compounds have been continuously produced every year since the industrial revolution to facilitate our lives. Some of these substances, such as heavy metals and persistent organic pollutants (POPs), are toxic and widely distributed, and their synthesis and use have been substantially regulated [2]. Several have been documented by using plants as natural biomonitors of environmental pollution [2]. Technical development in the field of environmental chemistry has recently led to a new and increasing concern over the environmental risks of a new group of chemicals—'contaminants of emerging concern' [3].

'Contaminants of emerging concern' mostly include pharmaceuticals and personal-care products (PPCPs), such as analgesics and anti-inflammatories, anti-diabetics, anti-epileptics, anti-estrogenics, anti-protozoals, antiseptics, lipid regulators, diuretics, medications for treating erectile dysfunction and pulmonary arterial hypertension, psychiatric drugs and antidepressants,

38 psycho-stimulants, veterinary and human antibiotics, β-blockers, X-ray and contrast media,

39 cosmetics and personal-care products, surfactants and phytosanitary products (Table 1).

40 Assessing the risks of all these compounds within a reasonable time frame is very difficult, due

41 to the large number of new substances developed every year [4]. More than 4000

42 pharmaceuticals are currently in use; the total global consumption of antibiotics is estimated at

43 100000–200000 tons, approximately 15000 tons y^{-1} of antibiotics are released into the

44 European environment alone [5]. The great advances in the detection and analysis of trace

45 pollutants during recent decades indicate that PPCPs are very frequently detected anthropogenic

46 contaminants in the environment [6]. Not all PPCPs are newly designed compounds. Some have

47 been dispersed into the environment over a long period of time, but their presence, toxicity and

48 regulation have not currently been recognized and established. In fact, PPCP emission to the

49 environment is mostly associated with human activities and the discharge of wastewater (Figure

50 1). These PPCPs are taken up, accumulated and metabolized by plants, which may affect the

51 plants, their microbiota and the organisms feeding on them, including humans. We here present

52 the current limited knowledge on the life cycle of PPCPs and their effect on the environment

53 and call for further research on the use of plants as a monitoring device for assessing the fate

54 and environmental presence of PPCPs. Research is needed into the toxicity of these compounds

55 to herbivores, humans included, as well as any toxic effect to plants and their microbiota.

56

57 **Environmental sources and pathways of transport to plants**

58 PPCPs in the environment are mainly associated with municipal, agricultural and industrial

59 wastewater sources and pathways [7–9]. Point-source contamination with 'contaminants of

60 emerging concern' includes discharges or leaks of domestic, hospital or industrial wastewater

61 (conventional secondary processes such as the use of activated sludge and trickling filters are

62 not designed to remove PPCPs from influent water); application of sewage sludge to land;

63 pharmaceuticals and pesticides voided by treated animals in manure or applied to agricultural

64   land or water (aquaculture facilities); leaching from disposed solid waste; pesticide applications

65   and disposal of carcasses of treated animals. Diffuse pollution includes agricultural runoff from

66   biosolids (treated sewage sludge intended for agricultural use as a soil conditioner) and manure,

67   storm-water and urban runoff, leakage from reticulated urban sewage systems and diffuse aerial

68   deposition.

69   The pathways of transport for PPCPs through air, water or soil are difficult to characterize due

70   to the little information on the fate and behavior in the environment for most of these

71   compounds but will depend on their physicochemical properties, such as solubility in water,

72   coefficient of octanol-water partition Kow (surrogate of a chemical partition between an organic

73   and aqueous phase) or persistence and on the properties of the surrounding matrices (such as

74   water or soil) [10]. Dust [11] or microplastics [12] may also play an important role in the entry

75   of non-volatile PPCPs to the environment.

76   PPCPs reach plants mainly from the use of reclaimed wastewater for irrigation, the application

77   of biosolids (treated sewage sludge) and manure for the fertilization of agricultural soils and

78   from deposition from volatilized compounds. PPCPs tend to dissolve relatively easily in water

79   and do not evaporate at normal temperatures, so they often end up in soil and water bodies.

80   The use of treated wastewater for agricultural irrigation is becoming common, especially in arid

81   and semi-arid regions. For example, more than 85, 71 and 46% of treated wastewater is used for

82   agricultural irrigation in Israel, Spain and California, respectively [13]. With the current climatic

83   projections, these percentages may dramatically increase in these and other countries. The

84   concentrations of PPCPs in irrigated agro-ecosystems will accordingly increase due to the

85   occurrence and accumulation of PPCPs in reused water, also increasing the potential for plant

86   uptake and subsequent human exposure by ingestion [14].

87   Biosolids are rich in minerals and organic compounds and are therefore added to soils to

88   improve soil fertility, restore organic matter, improve the physicochemical and biological

89   features of soils, facilitate the resettlement of plants and restore altered communities [15]. This

practice will become crucial for the sustainability of agriculture due to the growing population and lack of nutrients (mostly phosphorus) [16]. In the U.S., for example, 55% of biosolids are applied to soils and 45% are landfilled or incinerated [17]. The safety of this practice is, however, constantly discussed due to the amounts of antibiotics, non-steroidal anti-inflammatories, anti-convulsants and other PPCPs that biosolids may transfer to soils.

Veterinary antibiotics are the most abundant PPCPs in manure. The detected concentrations of these compounds are very variable among source species and type of operation but range from 0.1–46.0, 0.1–24.4 and <0.5 mg kg^{-1} in Germany, Denmark and Turkey, respectively [18]. Antibiotics are persistent, with long half-lives in soils.

Knowing the amounts of PPCPs in wastewater, biosolids and manure before they are applied to agro-system soils is thus crucial to avoid possible problems of toxicity for plants, their microbiota and animals, including humans, feeding on them. PPCPs from wastewater, biosolids and manure, though, are not regularly monitored and therefore are not considered in the decision to irrigate soils with wastewater, amend them with biosolids or fertilize them with manure.

Plant uptake, bioaccumulation and metabolization

The uptake of PPCPs by plants is receiving increased attention. Large amounts of PPCPs have been found in various species and tissues [3,19–23], with highly variable concentrations, ranging from no detection to 487 µg kg^{-1} (Table 2). Antibiotics are usually the most abundant PPCPs in plants due to their high concentrations in the biosolids and animal manure applied to agricultural fields [19]. The physicochemical properties of the compounds (such as hydrophobicity and ionization behavior) greatly influence the uptake, accumulation, translocation and transformation of PPCPs in plants. The physiological nature of the plant and its tissues, soil properties (such as pH and organic matter content), water quality and exposure concentration and duration also affect the uptake and accumulation of PPCPs.

115   The pathways of the uptake and bioaccumulation of PPCPs in plants, however, are not well

116   understood [22]. Plants take up PPCPs through roots and aerial tissues (Figure 2). Roots take up

117   PPCPs by mass flow or the diffusion of dissolved compounds into roots [24]: neutral

118   compounds diffuse across the root-cell membrane with a partition very similar to the partition to

119   octanol, and ionizable compounds enter roots by a combination of diffusion of the neutral

120   fraction and electrostatic interactions of the ionic fraction. Aerial tissues take up PPCPs via

121   deposition from volatilized compounds and aerosols, direct contact (diffusion or ionic fraction

122   uptake) with irrigation or amendment materials and translocation from root tissues [25].

123   Hydrophobic compounds may partition to lipids and will be predominantly retained by roots,

124   while most hydrophilic compounds will move to the xylem (in equilibrium with the water),

125   from which nonionic PPCPs accumulate in leaves, transported predominantly in the direction of

126   the transpiration stream, and ionic PPCPs, repelled by the negatively charged cell walls and

127   cytosol, may be trapped in the phloem and can accumulate more in the fruit [26]. Metabolic

128   enzymes, such as hydrolases or cytochrome p450, transform the PPCPs once they are in the

129   plant cells, creating a variety of transformation products, which are eventually mineralized or

130   incorporated into the plant tissue [27]. PPCP metabolites are also produced in plants for treating

131   wastewater or in soils, and their concentrations and biological activities are similar or even

132   higher than those of the PPCP parental compounds [28], but less is known about their uptake by

133   plants.

134

135   **Toxicity**

136   Exposure to PPCPs may affect plant development, either as a result of direct damage to the

137   plant (decreased photosynthetic pigments, reduced number and size of mature leaves, inhibition

138   of root elongation or negative effects on growth and development) (Table 2) or as a result of the

139   antimicrobial action of pharmaceuticals on plant microbiota [29,30] and on soil microorganisms

140   that affect plant–microorganism symbiosis and nutrient cycling in soils [31]. The specific

141   effects on each plant species obviously depend on the compound, compound concentration, and

142   plant species. A recent review shows that most studies only tested the effects of individual

143   compounds and frequently at concentrations much higher than are environmentally relevant

144   [31]. Some recent studies, however, report adverse effects of PPCPs on natural populations of

145   plants at environmental concentrations, for example decreased plant growth and crop production

146   (Table 2). Other studies have found no phytotoxic effects at environmental PPCP levels [32,33].

147   The toxic effects of most compounds of emerging concern on plants, their microbiota and entire

148   ecosystems are thus still far from clear, but the few data available and the likely effects of many

149   PPCPs such as antibiotics warrant further research.

150   Most assessments of the risks of PPCPs on both environmental end-points and human receptors

151   indicate that the risk of adverse effects in the various trophic levels of food webs or in human

152   health could be low [e.g. ,34]. The assessments are based on the low concentrations of PPCPs in

153   plants and the low toxicity of most compounds (exposure levels are usually below human

154   therapeutic dose levels or acceptable daily intakes). The potential toxic effects of PPCPs on

155   organisms, however, are an increasing concern, with particular emphasis on the microbiomes

156   (bacteria, fungi and archaea that live on and in organisms' bodies) of humans and other animals,

157   due to (a) the long-term exposure to these compounds (even at low levels), (b) the little

158   comprehensive information on the fate and effects in the environment and the lack of

159   pharmacovigilance programs examining the environmental effects [35], (c) the effects of the

160   transformation products with potentially greater health concerns than their parental compounds,

161   (d) the possible synergistic effects between PPCPs and other micropollutants or medicines taken

162   by a patient for an existing condition, (e) the multiple routes of exposure of PPCPs (most studies

163   of risk assessment have only considered one route of exposure) and (f) the increasing selection

164   of antibiotic-resistant microorganisms in the environment, including pathogens.

165   In fact, some PPCPs may have dramatic adverse effects on wildlife such as tadpoles, aquatic

166   invertebrates, fish, earthworms and birds and on soil microbial communities, even at very low

167   levels of exposure [7,36,37]. Some of the first and most famous cases of PPCP toxicity for

168 example were observed after the extremely rapid massive decline (>95%) of the population of

169 oriental white-backed vultures caused by the residues of veterinary diclofenac in scavenged

170 cattle carcasses [38], or after the collapse of the population of fathead minnows caused by the

171 exposure to low concentrations (5–6 ng L^{-1}) of the synthetic estrogen vitellogenin [39]. Further

172 attention has recently been given to the effects of human and veterinary antibiotics. They

173 dramatically affect the structure and function of soil microbial communities and promote the

174 emergence of multi-drug resistant human pathogens that increasingly threaten the successful

175 antibiotic treatment of bacterial infections [40]. The variability of the effects of PPCPs and their

176 metabolites on humans and the entire biosphere, even at low concentrations, indicates that more

177 research is needed to clarify the ecotoxicology of PPCPs. Most of these compounds are quite

178 persistent, and tonnes are emitted every year into the environment, contaminating groundwater,

179 supplies of drinking water, streams and agricultural land to an unprecedented degree.

180

181 **Regulation, plant monitoring and decontamination methods**

182 Due to the lack of data on the fate of PPCSs in the environment and the toxicity to plants and

183 humans, no regulations exist for most PPCPs in irrigation water, biosolids or manure before

184 being reused for agriculture or in supplies of drinking water, vegetables and other food to be

185 commercialized. Some of these compounds will likely soon be included in the list of priority

186 organic pollutants of updated versions of the Water Framework Directive. Less is done for

187 unknown chemicals, which should also be evaluated using effect-based trigger values that

188 account for multiple chemical mixtures [41], and then accordingly regulated.

189 In addition to the required regulations and the innovation of treatment techniques, large-scale

190 monitoring of the fate of PPCPs in the global environment should be prioritized, with special

191 attention to vegetables cultivated with biosolids, manure or re-used irrigation water, in addition

192 to drinking water. The analysis of PPCPs in plants as natural passive samplers of PPCPs in the

193 global environment would be an excellent and relatively cheap tool to assess both the historical

194 and spatial fate of PPCPs in various ecosystems and to identify their sources. The use of plants

195 as biomonitors of pollution (e.g. persistent organic pollutants and heavy metals), due to the

196 widespread distribution of plants and to their ability to absorb a diverse range of chemicals from

197 the air, water and soil, has indeed gained increased attention in recent years [1,2]. In fact, some

198 studies are starting to develop pilot pan-European monitoring of current priority and emergent

199 compounds, but using sentinel raptors, not plants [42]. We reinforce the need to track the

200 environmental fate of PPCPs by also using plants. Plants are sessile and often in direct contact

201 with wastewater from irrigation or the application of biosolids and manure to soils, so they are

202 key for tracing point-source contamination. Plants occupy the first trophic positions in food

203 webs and so are the principal route for the exposure of ruminants and humans to PPCPs.

204 Improving the methods of wastewater decontamination to remove and remediate PPCPs from

205 plants for treating wastewater is also crucial [43]. Some of these methods of purification include

206 sludge activation, nitrification, sand-filtering, aeration of sludge with ferrous chloride, oxygen

207 activation, biological contractors and chlorination. Even the most efficient of these methods

208 (two-step sludge activation), however, require up to 49 days of processing and cannot

209 completely remove PPCPs. This processing is too slow, considering the extremely high daily

210 emission of PPCPs to the environment, including agro-systems, groundwater and drinking

211 water.

212

213 **Concluding remarks**

214 PPCPs facilitate everyday life in our society. Thousands of new substances are developed every

215 year, and thousands of tons are consumed and emitted to the sewage system, mostly in large

216 urban centers. PPCP removal from plants for wastewater treatment is incomplete, and the

217 dispersal of these compounds into the environment and accumulation in plants mostly occurs

218 from irrigating with reused water and the application of biosolids and manure to land. Plants

219 thus become a monitoring device for assessing the use and environmental presence of PPCPs.

220 They could also be considered for phytoremediation [31]. Plants accumulate PPCPs at levels

221 from ng to µg kg^{-1}. At these concentrations, PPCPs can be toxic to plants, plant microbiota and

222 soil microorganisms that affect plant-microorganism symbiosis and nutrient cycling. An in-

223 depth understanding of the behavior and fate of PPCPs in plants is unfortunately lacking. The

224 health risk to ecosystems and humans that the dietary intake of these PPCP-contaminated plants

225 (mostly crops) pose is even more uncertain (see also outstanding questions). For example, the

226 influences of PPCPs on the human microbiome are increasing the threat of multi-drug resistant

227 human pathogens. Improved toxicological studies of the short- and long-term impacts of

228 relatively low doses of the many PPCPs in the environment, the regulation of PPCPs, the

229 development of extensive spatiotemporal protocols for monitoring water, soils, plants and

230 humans and the innovation of treatment techniques are key for the future safety of drinking

231 water and the fertilization of agro-systems with reused irrigation water, manure and biosolids.

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366

367 **Table 1. Examples of pharmaceuticals and personal-care products (PPCPs) in the influent**
368 **and effluent of plants for treating wastewater**

Family of contaminant of emergent concern	Examples
Analgesics and anti-inflammatory	Codein, diclofenac, fenoprofen, ibuprofen, indomethacine, ketoprofen, ketorolac, paracetamol, phenylbutazone, naproxen, clofibric acid
Anti-diabetics	Metformin
Anti-epileptics	Carbamazepine, 4-aminoantipyrine, antipyrin, codein, diclofenac
Anti-estrogenics	Tamoxifen
Anti-histaminics	Dephenhyldramine
Anti-protozoals	Quinacrine dihydrochloride
Antiseptics	Triclosan, chlorophene
Lipid regulators	Acebutolol, atenolol, atorvastatin, bezafibrate, fenofibric acid, gemfibrozil
Diuretics	Furosemide, hydrochlorothiazide, amidotrizoic acid, diatrizoate, iotalamic acid
Medication used to treat erectile dysfunction and pulmonary arterial hypertension	Sildenafil
Psychiatric drugs and antidepressants	Diazepan, fluoxetin
Psycho-stimulants	Caffeine, paraxanthin
Veterinary and human antibiotics	Azithromycin, chlortetracycline, clarithromycin, ciprofloxacin, doxycyclin, enrofloxacin erythromycin, erythromycin–H_2O, levofloxacin, lincomycin, methronidazole, norfloxacin, ofloxacin, oxytetracycline roxithromycin, salinomycin, sulfamethazine, sulfamethoxazole, sulphadimethoxine, sulfapyridin, tetracyclin, trimethoprim, tylosin
β-blockers	Celiprolol, metoprolol, propanolol, sotalol, timolol
X-ray and contrast media	Iopromide, iopamidol, iohexol, diatrizoate
Cosmetics and personal-care products	Benzophenone, galaxolide, N,N-diethyltoluamide, tonalide, triclosan, triclocarban
Surfactants	PFOA, tergitol
Phytosanitary products	Clofibric acid

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Table 2. Minimum and maximum concentration of pharmaceuticals and personal-care products (PPCPs) in microalgae and crops from agricultural fields, and the subsequent phytoxicicity effect of each compound under realistic field conditions[a]

Compound		Concentration			Phytotoxicity			
		Plants	Min-max[b]	Ref.	Plants and algae	Effect	Conc.[c]	Ref.
Analgesics and anti-inflammatory	Diclofenac	Lettuce (*Lactuca sativa*), carrot (*Daucus carota*)	nd-19 µg kg^{-1} dry weight	[20]	Microalga (*Pseudokirchneriella subcapitata*)	Growth reduction	10 mg L^{-1}	[44]
	Ibuprofen	Lettuce (*Lactuca sativa*), carrot (*Daucus carota*)	nd-30 µg kg^{-1} dry weight	[20]	Great millet (*Sorghum bicolor*)	Decreased quantum efficiency of photosystem II & photochemical quenching coefficient	83 mg kg^{-1} dry weight, spiked soil	[45]
Anti-diabetics	Metformin	Barley sedes (*Hordeum vulgare*)	nd-440 µg kg^{-1} dry weight	[46]	Carrot (*Dacus carota*)	Growth and development reduction	10 mg kg^{-1} dry weight, spiked soil	[46]
Veterinary and human antibiotics	Amoxicillin	Chinese white cabbage (*Brassica rapa*), water spinach (*Ipomoea aquatica*), rice (*Oryza sativa*), Chinese radish (*Raphanus sativus*), corn (*Zea mays*)	2.6-22.4 µg kg^{-1} dry weight	[47]	Alfalfa (*Medicago sativa*), Carrot (*Dacus carota*), Lettuce (*Lactuca sativa*)	Growth and germination reduction	0.001–10 mg L^{-1}	[48]
	Chlortetracycline	Corn (*Zea mays*), green onion (*Allium cepa*), and cabbage (*Brassica oleracea*)	2–17 µg kg^{-1} fresh weight	[49]	Alfalfa (*Medicago sativa*), Carrot (*Dacus carota*), Lettuce (*Lactuca sativa*)	Growth and germination reduction	0.001–10 mg L^{-1}	[48]
	Sulfadiazine	Winter wheat (*Triticum aestivum*)	nd-487 µg kg^{-1} dry weight	[50]	Maize (*Zea mays*)	Death	10 and 200 mg kg^{-1} dry weight, spiked soil	[51]
	Tetracycline	Chinese white cabbage (*Brassica rapa*), water spinach (*Ipomoea aquatica*), rice (*Oryza sativa*), Chinese radish (*Raphanus sativus*), corn (*Zea mays*)	4.0-10.1 µg kg^{-1} dry weight	[47]	Alfalfa (*Medicago sativa*), carrot (*Dacus carota*), Lettuce (*Lactuca sativa*)	Growth and germination reduction	0.001–10 mg L^{-1}	[48]
	Tetracycline	Radish (*Raphanus sativus*), rape (*Brassica napus*), celery (*Apium graveolens*) and coriander (Coriandrum sativum)	nd-330 µg kg^{-1} dry weight	[52]	Cucumber (*Cucumis sativus*), Rice (*Oryza sativa*), Sweet oat (*Cichaorium endivia*)	Growth and germination reduction	0–500 mg L^{-1}	[53]
Cosmetics and personal-care products	Triclosan (antimicrobial in liqued soaps, underarm deodorants, and toothpastes)	Soybean (*Glycine max*), lettuce (*Lactuca sativa*), carrot (*Daucus carota*) , radish (*Raphanus sativus*), pepper (*Capsicum*), tomato (*Solanum lycopersicum*), lettuce (*Lactuca sativa*), cucumber (*Cucumis sativus*)	24.2-80.1 µg kg^{-1} dry weight	[20,54–56]	Freshwater alga	Lower algal richness and biomass	0.012-1.2 µg L^{-1}	[57]
Phytosanitary products	Clofibric acid	Lettuce (*Lactuca sativa*), carrot (*Daucus carota*)	nd-18 µg kg^{-1} dry weight	[20]	Microalga (*Pseudokirchneriella subcapitata*)	Growth reduction	75 mg L^{-1}	[44]

Abbreviations: Conc, concentration; max, maximum; min, minimum; nd, not detected
[a]For the phytotoxicity assays, the concentration or range of concentrations indicate the concentrations of each compound in irrigation water applied to each soil (or directly the concentrations in soil) under which the plant showed a toxicological effect. Soils can achieve those PPCPs concentrations through the application of irrigation water, biosolids and animal manure to agricultural fields, or through experimental spikes of particular concentrations of PPCPs (spiked soil). Only compounds with available information on environmental and plant concentrations and phytotoxicities are presented.
[b] Min-max concentration in plants.
[c]Concentration studied in irrigation water (mg L^{-1}) or in soil (mg kg^{-1})

371 **Figure captions**

372 **Figure 1. Main sources and fates of pharmaceuticals and personal-care products in plants**

373 **and the environment.** Human activities are the main source of PPCPs in the environment,

374 which are concentrated in municipal, agricultural and industrial plants for treating wastewater.

375 PPCPs in reused irrigation water, biosolids and manure are applied to soils where they can

376 affect soil microbiota and can be taken up, accumulated and metabolized by plants. Aerial

377 uptake of PPCPs can also occur via deposition from volatilized compounds and aerosols and by

378 direct contact with irrigation water or amendment materials. PPCPs affect plants, their

379 microbiota and the subsequent food-web organisms feeding on them, including humans.

380 Abbreviations: PPCPs, pharmaceuticals and personal-care products.

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382 **Figure 2. Principal pathways of PPCP uptake in vegetation.** The main parameters affecting

383 each pathway are annotated: f (function of), K_{OA} (coefficient of octanol-air partition), V/P

384 (vapor-particle partitioning), SA (plant surface area), lipid (plant lipid concentration), K_{OW}

385 (coefficient of octanol-water partition), sol_W (water solubility) and Org_s (organic content of the

386 soil). Abbreviations: PPCP, pharmaceuticals and personal-care product.

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