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White paper on the uptake and translocation of organic microcontaminants and ARB&ARGs in crops

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ACRONYMS

AR	Antibiotic Resistant
ARB	Antibiotic-Resistant Bacteria
ARGs	Antibiotic Resistance Genes
CECs	Contaminants of Emerging Concern
K_{ow}	Octanol-water partition coefficient
TWW	Treated Wastewater

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1. Introduction

Climate change and global warming effects are widely recognized during the recent decades, and therefore water availability, and management issues are of special significance in all arid and semi-arid regions worldwide. Water scarcity already affects every continent, and it is among the main problems to be faced by many societies and the world in the twenty-first century (March et al., 2012). Therefore, water resources are facing huge challenges due to both climatic and anthropogenic changes (Milano et al., 2012). Agriculture is likely to encounter the most serious threats due to water scarcity, as it is the major consumer of water. Therefore, treated wastewater (TWW) reuse, mainly for irrigation purposes, is already an established practice as it represents an advantageous alternative for the mitigation of the ever increasing irrigation water scarcity and demand (Angelakis and Durham, 2008). TWW of high quality represents a potentially valuable, nutrient-rich source of water for the agricultural sector, available all year round. Although TWW reuse for irrigation has gained an acceptance as an economic alternative that could substitute nutrient needs and water requirement of crop plants, and major advances have been made with respect to producing safe treated effluents for reuse (e.g. successful removal of metals, chemical oxygen demand down to low levels), TWW may contain undesirable chemicals, organic constituents and pathogens that may pose negative environmental and health impacts (Fatta-Kassinos et al., 2011). Consequently, several important questions concerning the presence of chemical and organic contaminants, the so-called contaminants of emerging concern (CECs) in treated effluents and their subsequent release to the environment through TWW irrigation, are still unanswered and barriers exist regarding the safe/sustainable reuse practices. Available/applied technologies fail to completely remove such contaminants, while no consolidated information exists concerning a) the efficacy of the conventional activated sludge process (which is the most widely applied process) to remove antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARGs), and b) the fate of ARB&ARGs within the biomass of activated sludge, in the TWW and in the agricultural environment (i.e. soil, ground/surface waters, plants/crops) in the framework of reuse applications (i.e. irrigation, groundwater replenishment, storage in surface waters for subsequent reuse) (Fatta-Kassinos et al., 2011).

The contamination of the environment, possibly the food chain and the drinking water with antibiotics, ARB&ARGs is presently considered as a *serious public health problem*. For this reason, the World Health Organization (WHO) (World Health Organization, 2014)

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identified the development of antibiotic resistance (AR) as one of the *major global threats to society* and recommends intensive monitoring for the identification/surveillance of critical hot spots (i.e. urban wastewater treatment plants; UWTPs), aiming at reducing its propagation. Moreover, TWW reuse has been placed as a top priority by various European Initiatives such as the Joint Programming Initiative of Water Challenges, the European Blueprint of Water, and the Strategic Implementation Plan of the European Innovation Partnership on Water, aiming at tackling all the associated derived challenges.

Although the role of aquatic environments as reservoirs and routes for CECs and ARB&ARGs dissemination is now recognized, knowledge on the fate of the contaminants during TWW reuse in agriculture and on the actual effects in relation to the evolution/release of AR in the environment is currently not consolidated. In addition, scientific data are still scarce regarding (1) the potential uptake of CECs and ARB&ARGs by crop plants under actual farming conditions, (2) the fate and adverse effects of the CECs in the environment, (3) the development of innovative technologies and solutions able to remove such contaminants from TWW and decontaminate the agricultural environment, and (4) the identification of methodologies/strategies to overcome these problems, and promote safe reuse practices. To avoid negative impacts on environment and human health due to TWW reuse, regulatory frameworks are required based on validated scientific information. The associated risks are in general unknown, since the vast majority of studies have focused on human pathogen indicators (e.g. coliforms) or soil properties (e.g. heavy metals). Knowledge gaps also exist with regard to public health risk assessment, since solid data regarding the actual uptake of these CECs by crop plants under actual farming conditions are largely missing. Given the increasing interest in reusing TWW, there is a clear need to include TWW as an additional exposure route for CECs and ARB&ARGs in impacted ecosystems, in order to assess the potential risks derived, in both the agricultural ecosystem (soil, water resources, plants, etc.) and the public health.

Besides the reuse of TWW for irrigation, the use of biosolids and manure as soil conditioner constitute other significant pathways for the introduction of CECs to the environment (Pan and Chu, 2016). Thus, CECs and ARB&ARGs are now commonly detected at relevant concentrations in both the aquatic and the terrestrial environments as a consequence of their continuous introduction in the environment through the disposal of TWW, biosolids and manure (Fatta-Kassinos et al., 2011; Meffe and de Bustamante, 2014). The scientific interest on the uptake and bioaccumulation of CECs

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in the edible parts of food crops and fodders and their subsequent entry into the human food chain has gained prominence over the last several years. Numerous studies, however, have been mainly conducted under hydroponic or greenhouse conditions, highlighting the uptake and bioaccumulation of CECs in plants exposed to known concentrations of individual or cocktails of such contaminants (Christou et al., 2017a). Such studies were proven to be useful in elucidating the uptake mechanisms of CECs by plants. Uptake was found to be driven by the transpiration derived mass flow and largely to be depended on the chemical properties of the compounds, especially their hydrophobicity and charge. Hydroponic and greenhouse experiments though, even if conducted at environmentally relevant CECs concentrations, are unable to represent the complexity of an actual agricultural environment, highlighting the imperative need for conducting studies under real agricultural conditions where actual farming practices will take place and real TWW will be applied for irrigation (Malchi et al., 2014).

2. Existing EU legislation on the quality of TWW reuse for irrigation

The existing body of legislation, in the EU, which covers the discharges of the treated urban wastewater (TWW) is Directive 91/271/EEC, as amended by Directive 98/15/EC. This Directive sets some quality requirements that the TWW should fulfill in order to be accepted for disposal in the environment in general, as well as for disposal in sensitive areas (e.g. to eutrophication). These requirements concern the levels of the BOD, COD and TSS in the TWW and in addition, if the discharges are to be made in sensitive areas, the levels of total nitrogen and total phosphorous. The Directive (a) does not define the fate of the discharges at the end of the pipe: i.e. whether the TWW would be used for irrigation, for aquifer recharge or just disposed in surface water bodies, although in Article 12(1) it is stated that TWW shall be reused "whenever appropriate", and (b) does not consider the presence of CECs, which are present in the TWW, and most often escaping from the conventional biological treatment. However, as far as point (a) is concerned, a number of EU countries (i.e. Cyprus, France, Greece, Italy, Portugal and Spain) have issued regulations, although with lot of variations, for reuse, in particular for irrigation. But again the presence of CECs is not addressed. Mostly microbiological parameters are included along with the conventional physico-chemical parameters (BOD, COD, TSS, pH, N, P, chlorides etc.). All the information concerning these regulations can be found in the synoptic overview on water reuse in Europe of the JRC (Sanz and Gawlik, 2014).

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With the EU Commission Decision 2015/495, amending the Water Framework Directive 2000/60/EC, a watch list of ten substances and group of substances was established aiming at collecting data on their levels in the EU aquatic environment for future inclusion in the priority substances list. This list, among other compounds, includes EE2, E1 and E2, diclofenac, three macrolide antibiotics namely erythromycin, clarithromycin and azithromycin and two compounds used in the personal care products i.e. 2,6-Ditert-butyl-4-methylphenol (antioxidant, BHT) and 2-Ethylhexyl-4-methoxycinnamate (sunscreen substance). Obviously, these substances mostly originate from the discharges of TWW. The collected data will open also the discussion for possible inclusion in the requirements for maximum permissible levels in TWW discharges of some pharmaceutical and personal care products compounds.

In February 2017, an effort was undertaken by the JRC to develop minimum quality requirements for water reuse in agriculture irrigation and aquifer recharge (Sanz and Gawlik, 2017), but failed to address specific requirements for the chemical contaminants that are present in the TWW even in the new version of the document, in June 2017. This flaw has been also identified by the EFSA's expert opinion issued in May 2017 (Allende et al., 2017) and the Scientific Committee on Health, Environment and Emerging Risks (SCHEER) (Rizzo et al., 2018).

In May 2018, a proposal for a regulation of the European Parliament and of the Council "On the minimum requirements for water reuse" has been launched (COM(2018) 337 final). However, the two important annexes of this regulation: Annex I on the uses of reclaimed water and the minimum requirements and Annex II on the risk management tasks are still blank. It is also stated that "*given the expected evolution both in knowledge and in the policy framework as regards contaminants of emerging concern, the proposal includes a clause to adapt annexes to technical and scientific progress, as well as a requirement for evaluation*".

3. The uptake of CECs by crops and the potential entrance to human food chain

Below, an effort is made to present the current knowledge with regard to the introduction of CECs to the agricultural environment through the reuse of TWW for irrigation and the use of biosolids and animal manures as soil amendments, and the consequent entrance of CECs to human food chain as a result of their uptake and accumulation by crop plants grown in such contaminated sites.

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3.1 TWW irrigation as a pathway for the introduction of CECs to the agricultural environment

Several classes of CECs have been proven to be taken up through roots and translocated to the aerial parts of TWW-irrigated crop plants grown under hydroponic or greenhouse control conditions, as well as TWW-irrigated soils, in real agricultural systems (Boxall et al., 2012; Tanoue et al., 2012; Goldstein et al., 2014; Wu et al., 2015; Miller et al., 2016; Christou et al., 2017b). However, despite the relatively large number of predominantly descriptive studies undertaken, the mechanistic understanding of CECs uptake by the roots of crop plants remains rather limited (Miller et al., 2016). It has been previously shown that the uptake of CECs by crop plants is largely dependent on their bioavailability/bioaccessibility in soil pore water near the rhizosphere (sorption to soil constituents and transformation by soil organisms reduce bioavailability), and thus on their physicochemical properties and the properties of the soil environment (Goldstein et al., 2014). Once taken up, the transport of CECs within the plant vascular translocation system (xylem and phloem) largely depends on their physicochemical properties (i.e. lipophilicity and electrical charge), as well as on the physiology and transpiration rate of crop plants (Goldstein et al., 2014; Dodgen et al., 2015) and environmental conditions (i.e. drought stress) (Zhang et al., 2016). In particular, preferential accumulation of charged CECs in specific plant tissues may occur as a result of ion trapping, due to differences in pH among plant tissues and plant cell compartments (Goldstein et al., 2014; Hofstetter et al., 2018). The movement of CECs from the soil pore water to the vascular tissues of plants may be distinguished to transmembrane, symplastic and apoplastic, depending on the ability of CECs to cross the membranes of plant cells (Miller et al., 2016).

The uptake and translocation of CECs within TWW-irrigated crop plants grown in real agricultural systems, where a cocktail of CECs can occur in TWW and the complexity of soil-plant-environment interactions prevails, have not been widely studied. Only few studies followed experimental setups where real TWW was applied for the irrigation of crop plants in field, representing actual farming practices, or genuine soil, or ecological conditions typical for commercial agriculture farming, simultaneously allowing for the assessment of the actual potential uptake of CECs by crops (Malchi et al., 2014; Prosser and Sibley, 2015).

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Wu et al. (2014) detected CECs (including caffeine, meprobamate, primidone, DEET, carbamazepine, dilantin, naproxen, and triclosan) in 64% of all collected samples from eight vegetable species irrigated with TWW under field conditions. The total concentration of the studied CECs detected in the edible tissues of TWW-irrigated vegetables were in the range of 0.01–3.87 ng g^{-1} of dry weight (d.w.), revealing that the accumulation of CECs in TWW-irrigated vegetables is likely limited under field conditions. Moreover, the uptake of 28 CECs, including carbamazepine metabolites in 10 different field-grown vegetable species (among them carrot, lettuce, potato, and zucchini) was studied in Jordan (Riemenschneider et al., 2016). Results revealed that a total of 18 CECs (including six carbamazepine metabolites) could be detected in all samples in concentrations ranging from 1.7 to 216 ng g^{-1} d.w., with the total concentration of CECs in the edible tissues decreasing in the order of leafy (247–533) > root (73–126) > fruit-bearing (5–76 ng g^{-1} d.w.) vegetables. A preliminary health-risk assessment for nine CECs according to the threshold of toxicological concern (TTC) approach showed no risk for seven of the CECs; however, more-specific toxicity data are required for a refined risk assessment for ciprofloxacin and 10,11-epoxycarbamazepine (Riemenschneider et al., 2016). In addition, Malchi et al. (2014) studied the uptake of CECs by TWW-irrigated root crops (carrots and sweet potatoes) grown in lysimeters in fields and evaluated the potential risks. In both crops, the nonionic CECs (carbamazepine, caffeine, and lamotrigine) were detected at significantly higher concentrations than ionic CECs (metoprolol, bezafibrate, clofibric acid, diclofenac, gemfibrozil, ibuprofen, ketoprofen, naproxen, sulfamethoxazole, and sildenafil), while the concentration of studied CECs in leaves was higher compared to that in roots. The health risk associated with the consumption of these TWW-irrigated root vegetables was estimated using the TTC approach, revealing that the TTC value of lamotrigine can be reached for a child at a daily consumption of half a carrot (~60 g). This study highlighted that certain CECs could be accumulated in edible tissues at concentrations above the TTC value, thus caution should be given to the consumption of TWW-irrigated root crops with regard to certain CECs. By conducting a field study, Christou et al. (2017b) explored the long-term (three years) effects of two distinctly tertiary-treated effluents (effluent from WWTP applying activated sludge, slow sand filtration and chlorination, and effluent derived from an MBR treatment) applied for the irrigation of tomato plants under commercial agricultural farming on the fate of specific CECs (diclofenac, sulfamethoxazole, trimethoprim) in soil and their uptake and bioaccumulation in tomato fruits. Results revealed that the concentration of the studied

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CECs in both the soil and tomato fruits varied depending on the qualitative characteristics of the TWW applied for irrigation and the duration of irrigation. The concentration of CECs in fruits increased with the increasing duration of TWW irrigation, reaching the highest concentration values during the last harvest of the third year of the study (5.26 μg kg^{-1} for sulfamethoxazole and 3.40 μg kg^{-1} for trimethoprim; in d.w. basis), though the consumption of tomato fruits represented a *de minimis* risk to human health, as estimated by both the TTC and the hazard quotient approach.

The above low volume of literature indicates that CECs uptake, translocation and accumulation in the edible parts of crop plants irrigated with TWW under real agricultural systems is feasible and likely dependent on crop species, soil type and soil pore water chemistry, the physicochemical properties of CECs, the concentration of CECs in TWW applied for irrigation and the duration that TWW irrigation is being practiced. Nonetheless, plenty of knowledge gaps still exist, requiring further studies utilizing TWW irrigation under real field conditions. Such studies should incorporate a wider spectrum of plant species, while the concentration of CECs in TWW applied for irrigation, the soil and the edible parts of plants should be quantified, allowing for more accurate estimations of the bioconcentration factors and the estimation of potential public health risk associated with the consumption of such produce. The metabolites of CECs in plant tissues should also be quantified in studies evaluating the uptake of CECs by TWW-irrigated plants, since metabolites may occur in concentrations similar or even higher compared with the ones of parent compounds, while also being more toxic (Malchi et al., 2014; Miller et al., 2016; Paltiel et al., 2016).

3.2 Manure as a source of veterinary pharmaceuticals in agricultural soil

A variety of manure and slurries with different treatment are used in agriculture as a source of nutrients, to increase the field capacity (water soil retention) and to improve the soil texture especially in organic farming. However, veterinary medicinal products (VMPs) are administered to domestic animals to treat diseases, to prevent infections, to increase weight, or to improve feed efficiency. Common VMPs include antibiotics, anti-parasitics, anti-inflammatory, anesthetics, pain relievers and specialized products to manage animal reproductive or metabolic conditions. These VMPs are excreted either metabolized or as parent compounds in the manure. The excretion rate of VMPs is largely variable, ranging from 5% (i.e. erythromycin) to up to 90% (i.e. amoxicillin, difloxacin and sulfamethazine) (Kuppusamy et al., 2018).

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Among the VMPs mentioned above, antibiotics is a relevant class of contaminants in terms of environmental impact. They can be mobilized depending on their physico-chemical properties by surface runoff, thus contaminate surface watercourses or groundwater (Elena et al., 2014). Furthermore, some antibiotics can be taken up by crops and fodder, and as a consequence, they can be introduced into the food chain and food products leading to unintentional human or animal exposure (Dolliver et al., 2007; Hu et al., 2010; Bassil et al., 2013; Chung et al., 2017).

The widespread use of VMPs in confined animal-feeding operations (CAFOs) has led to an annual discharge from 3,000 to 27,000 tons of VPMs via livestock manure into the environment, worldwide (Song and Guo, 2014). More than 40 antibiotics and 11 metabolites and transformation products from sulfonamides, tetracyclines and fluoroquinolones have been detected in poultry, swine, cattle and horse manure at concentrations ranging from 0.001 to 765 mg kg^{-1} d.w.. Sulfadimidine, tetracycline, oxytetracycline and chlortetracycline are among the most frequently detected antibiotics in manure (Wohde et al., 2016). In a number of cases, uptake of CECs by plants after manure application has been observed (Hu et al., 2010; Fussell et al., 2014; Li et al., 2014). In order to predict the environmental concentrations (PEC) of CECs in manure, the European Medicine Agency has developed a guideline based on several parameters (EMA, 2008), but due to several reasons, the agreement between PECs and experimental values is not completely achieved in the case of some antibiotics (Wohde et al., 2016).

Steroid endogenous hormones (beta-estradiol and testosterone) and their associated estrogenic activity have also been detected in manure amended soils and runoff from manure-amended silty-clay soils (Combalbert et al., 2012; Qi and Zhang, 2016). Ivermectin used to treat antiparasitic infections in livestock has been shown to affect the growth of aquatic invertebrates at extremely low concentrations (Garric et al., 2007).

Once VMPs are added to soil via manure amendment, a fraction is incorporated into the humic fraction or clays leading to the formation of non-extractable residues which are not bioavailable to microbiota and plants and slowly desorbed (Jechalke et al., 2014). However, several manure management practices such as digestion or composting have been evaluated aiming at reducing the VMPs content in the manure used as soil amendment. Anaerobic digestion and aerobic composting can reduce the content of CECs in manure (Arikan et al., 2018; Liu et al., 2018; Wallace et al., 2018) and diminish the spread of antibiotic resistome in agricultural soils (Gou et al., 2018). The addition of

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zero valent iron and natural zeolites during the anaerobic digestion (termophilic>mesophilic) can enhance the reduction of ARGs (Zhang et al., 2018).

3.3 Biosolids as a source of CECs in agricultural soil

Due to the extremely large amounts of biosolids produced worldwide from UWTPs, several managing practices of biosolids have been developed including landfilling, incineration and land application depending on the biosolids' contamination levels and the regional regulations. If biosolids fulfill the quality standards (heavy metals and pathogens), land application of biosolids is the most common practice worldwide since it is the cheapest management option and allows for recycling of nutrients. In the EU, UK and Germany are leading the biosolids utilization for land application amounting the 85% and 60%, respectively, while the average value in the EU and USA ranges from 40% and 55% respectively (Sharma et al., 2017).

Biosolids are applied up to 3 times per year to agricultural soil (U.S. EPA, 2000) and concentrations of CECs in soil amended with biosolids can be lower than original biosolids due to dilution and biodegradation (Wu et al., 2015). For instance, it was found that the long-term application of biosolids to soil does not build up the concentration of triclosan, triclorcarban and nonylphenol suggesting that biodegradation takes place in the arable soil (Xia et al., 2010). Nevertheless, a large variety of pharmaceuticals and personal care products have been identified in biosolids, namely pharmaceuticals, benzothiazoles, bisphenol A, organotins, phthalate acid esters (PAEs), polybrominated diphenyl ethers (PBDEs), polychlorinated alkanes (PCAs), polychlorinated naphthalenes (PCNs), polydimethylsiloxanes (PDMSs), perfluorochemicals (PFCs), quaternary ammonium compounds (QACs), steroids, synthetic musks, triclosan and triclocarban (Clarke and Smith, 2011). Although pharmaceuticals are considered as not very stable in soil conditions, in a mesocom outdoor study conducted during 3 years with 72 pharmaceuticals in Baltimore (MA, USA) with biosolids and soil mixtures, chemical half-lives exceeded those determined empirically from laboratory studies or fate models, and some compounds did not show any loss during the experimental period (3 years) (diphenhydramine, fluoxetine, thiabendazole and triclocarban) (Walters et al., 2010). As in the case of manure and related products, biosolids are usually subjected to stabilization via aerobic, anaerobic or thermal treatment, before field application, but transformation processes of CECs are less understood than in manure samples. However, several studies have shown that phytoaccumlation of CECs from soils amended with biosolids can take place (Aryal and Reinhold, 2011).

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4. Uptake of ARB&ARGs by crops

4.1. Dynamics of antibiotics*, ARB&ARGs in the agri-environment*

Results from the developments on DNA sequencing showed that the presence of plant complex microbiomes associated to the skin of the aerial parts and even inside the plant itself are more or less loosely related to the root- and rhizospheric- (the soil adjacent to the roots) microbiomes (Berg et al., 2014). The relationship between these compartments is presently unclear but it is known that bacteria can enter into the plant vascular system and can be translocated to the aerial parts, through either root hairs or micro-wounds (Hallmann et al., 1997; Compant et al., 2010; Prieto et al., 2011), reaching the various plant organs through either the vascular system (Hallmann et al., 1997; Compant et al., 2010) or the apoplast (Reinhold-Hurek and Hurek, 2011). This internal colonization occurs without any apparent adverse effects on the host (Hallmann et al., 1997; Gaiero et al., 2013; Berg et al., 2014). In fact, endophytic bacteria can be partly considered as symbionts, promoting plant growth and helping the plant against pests and pathogens and alleviating abiotic stress (Compant et al., 2005; Ryan et al., 2008). While bacterial endophytes were earlier considered to be present in relatively small numbers (Hallmann et al., 1997), recent molecular studies demonstrated the existence of sizeable bacterial populations, largely in a non-cultivable form (Lundberg et al., 2012). ARB are abundant in soil microbiomes. In fact, there is little doubt that most, if not all, known ARB, including those of clinical concern, originate in soil communities, in which the harsh competition between microorganisms (bacteria and fungi) results in a delicate balance between antibiotic producers and degraders (Forsberg et al., 2012). There are many reports that demonstrate that contaminated waters alter soil microbiomes, reducing their population complexity and favoring the appearance of ARB&ARGs (Bengtsson-Palme and Larsson, 2016). While the direct connection between these observations and water-reuse strategies is not yet clear, the presence of antibiotics in these waters is a potential hazard that needs to be addressed. Although not so solidly tested, ARB&ARGs generated by antibiotic treatments of animal husbandry and humans could conceivably reach soils through TWW irrigation. Their capacity to compete with the resident soil microbiome is still to be determined.

There are numerous reports on the detection of ARGs in endophytic bacteria from roots, leaves, and fruits (Abriouel et al., 2008; Zhu et al., 2017). It is generally believed that endophytic ARGs are originated in the soil microbiome. For example, there are

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evidences that the composition and abundance of endophytic ARGs seem to depend on the farming procedure, mainly when comparing conventionally and organically-produced vegetables (Ruimy et al., 2010; Raphael et al., 2011; Wang et al., 2015). From all ARGs, the extended-spectrum beta-lactamase (ESBL) genes seem to be ubiquitous in soils and plants (Jones-Dias et al., 2016), although it is not clear whether or not this abundance is related to the decades-long use of penicillin. As in the case of endophytic populations, the use of culture-independent molecular methods, like qRT-PCR and massive sequencing methods has changed our vision of the resistome present in these populations and of their relationship with farming conditions, including the use of TWW.

4.2. ARGs mobilization between water, soil, plants, animals and humans

One of the main questions concerning the reuse of TWW (and of the associated biosolids) for irrigation and/or fertilization (ferti-irrigation) is that TWW may conceivably constitute a source of ARB&ARGs that could ultimate result in antibiotic resistance-infections of clinical relevance (Martins et al., 2014; van Overbeek et al., 2014; Becerra-Castro et al., 2015). Antibiotic resistance infections originate when pathogenic bacteria acquire resistance to clinically relevant antibiotics, making it difficult, or even impossible to find an adequate treatment of the patient. In general, AR and non-resistant bacteria coexist in many environments (including the human gut), and it is the presence of antibiotics (either natural or artificially produced ones) that favors ARB rather than non-resistant bacteria in a given population, a classic case of selective pressure (Perry and Wright, 2014). This also applies to pathogenic bacteria, so the emergence of AR is intimately linked to the massive use of antibiotics in the last 50 to 70 years. The last term of this equation is the ability of bacteria to acquire ARGs (and therefore, become ARB) from other bacterial cells even from different taxonomic groups, and do so in genetic elements conferring resistance to many antibiotics at once.

A crucial point on assessing the risks derived from the propagation of potentially pathogenic ARB&ARGs through food and the influence of TWW reuse is the characterization of the routes of ARB&ARGs transmission to the plants, the mechanisms of ARGs formation in the environment, and the factors controlling the ARB&ARGs prevalence and persistence in the plants, particularly in edible parts. Biological systems are subjected to selective pressures from the environment, being antibiotics one of these potential pressures. The continuous presence of antibiotics in the environment would favour resistant genetic setups and reduce the fitness of sensitive species and strains.

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While the general effect of selective pressure on microbiomes is relatively well studied by population genetics, the particular problem of AR, and specifically in soils, plants, and fruits, is still poorly understood.

Population genetics studies on AR have been mainly focused on optimizing medical treatments to make them more efficient, cheaper, and safer (Levin et al., 1997; Stewart et al., 1998; Laxminarayan and Brown, 2001; MacLean et al., 2010). While similar approaches could in principle be applied to predict the presence and evolution of AR in soils, plants, and food, they need to introduce the particular characteristics of the soil microbiomes, such as the likelihood of horizontal gene transfer or the presence of many ARGs in a single genetic element (Engelstadter et al., 2016). These models should include not only the selective advantage given by a certain ARG or combination of ARGs, but also the physiological cost of maintaining the genetic elements required to codify and to propagate the resistant phenotype, like integrons, integrase and the burden of the added mutation rate these elements produce.

Figure 1 outlines the complex interrelations that connect ARB&ARGs in soil to AR infections. One can define at least three main types of compartments in which ARB&ARGs may originate or propagate (Fig 1): a) the human body and, more specifically, the human gut (orange boxes); b) food, either animal or vegetal (blue boxes); and c) the environment, including water bodies and soils (green boxes). These compartments are interconnected by both direct contamination by ARB or ARGs, including phages and other isolated DNA/RNA elements (purple arrows), and by water and soil pollution by antibiotics (blue arrows). The presence of antibiotics in a particular compartment may confer a selective advantage to ARB against the other resident microorganisms, facilitating ARGs transfer between non-pathogenic and pathogenic bacteria. This ultimately increases their potential to contaminate other compartments and their likeliness to develop into AR infections (red box).

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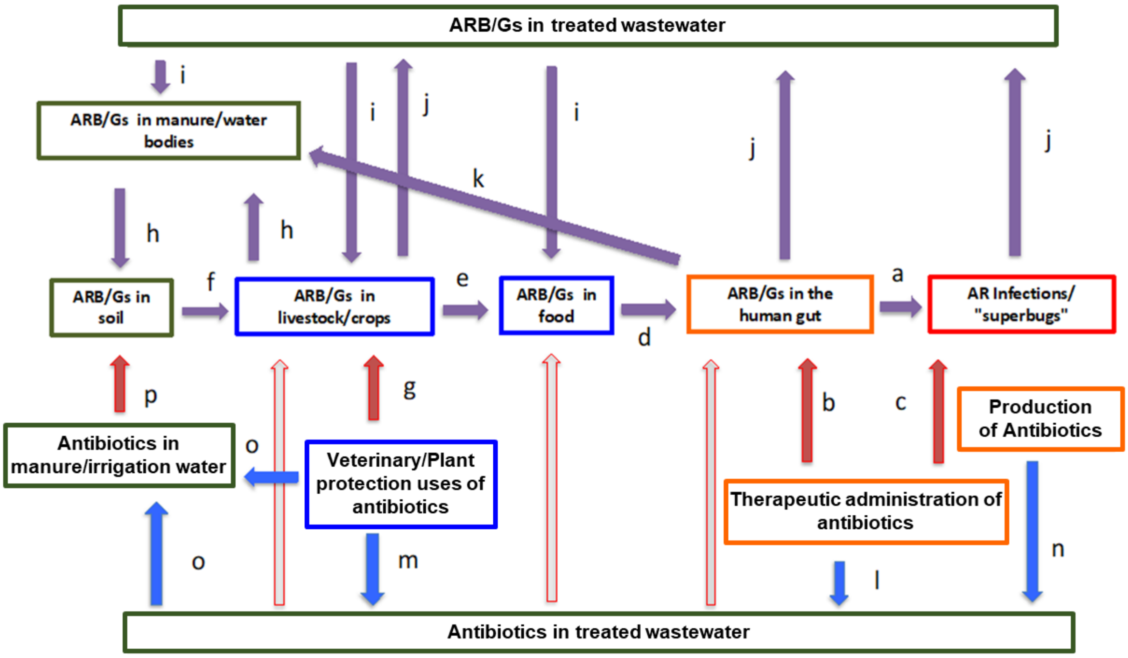

Figure 1 - Schematic depiction of antibiotics and ARB&ARGs interactions in the human environment.

Pathogens can acquire ARGs from other bacteria in the gut (Moubareck et al., 2003) (**a**), likely the human gut is the environment with the highest density of both endogenous and exogenous bacteria. In this environment, like in many others, the prevalence of AR is linked to the therapeutic use of antibiotic, either domestic for treatment of mild illnesses (Caucci et al., 2016) (**b**) or during hospital treatments (Forslund et al., 2013; Timraz et al., 2017) (**c**) (Figure 1). Note that selective pressure effects are labeled in red. It is important to separate these two types of treatment, since the later tend to involve stronger and more sophisticated antibiotics; this is the likeliest origin of "superbugs", bacteria with multiple AR mechanisms that are essentially impossible to treat.

While the origin of the human gut microbiome is surely diverse, there are few doubts that the main source is food (Smith et al., 2002; Ahrens and Bundschuh, 2014; Hu et al., 2016) (**d**), so this is also the probable main source of human bacteria ARGs. In turn, food ARB&ARGs probably originate in the bacterial populations in livestock or crops (Hu et al., 2016) (**e**), although some of them may come from the direct contamination from TWW. As in the case of the human ARB, the prevalence of AR in livestock or crop bacterial communities is determined by their exposure to soil (both) and food (livestock)

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bacterial communities (**f**) plus the selective pressure originated by the use of antibiotics as veterinary remedies, growth enhancers or plant protection products (Looft et al., 2012; Stockwell and Duffy, 2012) (**g**). ARGs are natural elements from soil bacteria, but the use of manure as fertilizer or of TWW, or even untreated wastewaters for irrigation may contribute to the overall loads, and the nature ARB&ARGs loads present in the soil (Ghosh and LaPara, 2007; Nesme and Simonet, 2015; Kang et al., 2016) (**h**). Poorly TWW, particularly when not bacteriologically inert, may constitute an additional direct or indirect source of ARB&ARGs for soil and food (Chen et al., 2016) (**i**). Water bodies receive ARB&ARGs from TWW originated from human (including hospital residues) and livestock excreta (Johnning et al., 2013; Berglund et al., 2015) (**j**); in addition, sludge from urban sewage treatment plants (STPs) may also represent a significant source of ARB&ARGs, especially in soils (Chen et al., 2017) (**k**).

In parallel to the contamination by potentially bioactive ARB&ARGs, antibiotics polluting water bodies may add extra selective pressure in favor of AR microorganisms. Antibiotics in waters may come from discharges of TWW or sewage to water bodies (**l**) or from runoffs from farms and crop fields (**m**). Less widespread, but much higher antibiotic pollution loads may come from antibiotic- producing factories (Johnning et al., 2013) (**n**). With some exceptions, antibiotics concentrations in polluted waters should not be high enough to represent a selective pressure for ARB&ARGs in humans, livestock, and crops (light red arrows), although their continuous presence in irrigation waters (particularly if they are reclaimed), together with their presence in livestock manure, may represent a substantial contribution to the presence of clinically-relevant antibiotics in the soil (Graham et al., 2016) (**o**) and, hence, to increase the prevalence of potentially dangerous ARB&ARGs (**p**) that eventually could end affecting humans (**a-f**).

ARB&ARGs risk analysis should characterize i) the minimum loads of ARB&ARGs in manure/irrigation waters able to displace the soil bacteriome towards a higher prevalence of ARB&ARGs, ii) at which extend this enrichment results in a parallel increase of ARB&ARGs in food, iii) the susceptibility of different crops to become ARB&ARGs vectors to the humans, and iv) which is the proportion of ARB&ARGs in the human gut microbiome that can be linked to the food microbiome. In short, we need to evaluate the importance of the ARB&ARGs transfers (**d**, **e**, **f**, and **h)**, and then use this information to characterize safe loads for antibiotics in irrigation waters and manure (**o**). Other aspects, as the direct contamination of soil by livestock manure (**h**) or biosolids (**k**) need also to be addressed. The function of UWTPs appears as a crucial factor in the whole scheme, as they control the inputs both for ARB&ARGs and antibiotics (**j**, **l**, **n**, and

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k). Needless to say, the selective pressures associated to **b**, **c,** and **g** (excessive use of antibiotics in humans, livestock and crops) probably should be reduced to the minimum, which is at the key action of any comprehensive program for reducing the prevalence of ARB in all the compartments outlined in Fig. 1.

5. Modelling plant uptake of contaminants of emerging concern

In the past three decades, models have been developed to describe the uptake of organic and/or inorganic contaminants in plants. Traditionally used to assess the uptake of priority pollutants (e.g., PAHs, PCBs) and pesticides (Briggs et al., 1982; Topp et al., 1986; Trapp et al., 1990; Dettenmaier et al., 2008; Juraske et al., 2009; Collins and Finnegan, 2010; Fantke et al., 2011), models have recently found application to CECs such as pharmaceuticals and personal care products (Prosser et al., 2014; Polesel et al., 2015; Hurtado et al., 2016).

In the context of TWW reuse for irrigation, predicting CECs uptake in crops can prove highly beneficial (i) in the consideration of the high number of contaminants, often requiring major analytical efforts; (ii) for long-term predictions, which cannot be appreciated in short-term laboratory-scale and field-scale studies; and (iii) for risk assessment, with estimation of human exposure to CECs through food.

The rationale behind the development of models is the possibility of predicting plant uptake of chemicals as a function of their physico-chemical properties. In this context, an overall distinction can be made between (i) empirical models, which are based on correlations between physico-chemical properties of contaminants and bioconcentration (or translocation) factors, and (ii) mechanistic models, which additionally incorporate explicit description of plant physiology. In the latter case¸ a further distinction can be made between steady state models and dynamic models, assuming constant and varying contaminant input over time, respectively.

Several examples of empirical models exist (e.g., Briggs et al., 1982; Topp et al., 1986; Dettenmaier et al., 2008) and typically rely on empirical correlations with hydrophobicity indicators (K_{OW}, molecular weight) to describe contaminant mobility, hence the possibility for plant uptake with transpiration. These models have been generally tested for neutral molecules, hence their applicability may be limited for major CECs categories such as pharmaceuticals, for which many substances are ionized at environmental and plant pH conditions.

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Mechanistic approaches typically rely on multi-compartment approaches (i.e., definition of different soil and plant compartments) and are based on explicit mass balances of contaminants in these compartments. Differential and/or analytical equations include a description of processes (partitioning, diffusion, degradation) that determine the accumulation of contaminants in a specific compartment and the exchange among adjacent compartments. Model parameters include (i) contaminant properties; (ii) environmental conditions; and (iii) plant properties. While parameters in the first two categories can be easily accessed (through database, predictors, etc.), plant properties (size, mass and volume of all compartments, growth rates, transpiration rates, flow rates in xylem and phloem, tissue composition, etc.) are neither easily accessible, nor always reported in plant uptake studies. Examples of mechanistic models include the steady-state one-compartment model (Trapp and Matthies, 1995), the dynamic cascade model for ionizable compounds (Trapp, 2004; Rein et al., 2011), and the dynamic model Multicrop (Fantke et al., 2011). Such models have found application to describe the plant uptake of CECs (pharmaceuticals and biocides) in real and simulated sludge application and irrigation scenarios (Prosser et al., 2014; Polesel et al., 2015), also with incorporation of in-plant biodegradation only (Hurtado et al., 2016b).

While providing for wider flexibility and higher level of detail, the use of mechanistic models has been often limited by the comparably high number of parameters. In particular, model predictions have been found to be highly sensitive to plant properties and environmental conditions, highlighting the need of using site- and plant-specific data (Trapp, 2015). Minimum data reporting a list for plant uptake experiments have been accordingly developed to improve the availability of measured parameters from plant uptake studies (Fantke et al., 2016; Trapp et al., 2016).

To date, plant uptake models have found limited application due to inherent challenges of validating simulation results with empirical data. This challenge has been associated to the high variability in measurements for the same compound, even within the same study (Dettenmaier et al., 2008). Probabilistic modelling approaches (i.e. consideration of parameter uncertainty and its propagation to model predictions) have been partly successful in describing measurement variability (Polesel et al., 2015).

6. Risk mitigation strategies / Recommendations and suggestions

The obvious first strategy to minimize the contamination of soils and crops by partially TWW is to limit the amount of contaminants in the source. The consumption rate of

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antibiotics is difficult to be tackled in human populations, but there are many good reasons for limiting it at maximum -if not, to prevent the onset of ARB in human guts. Sensitive facilities (hospitals, antibiotic-producing factories) should have separated water treatment systems in order to prevent massive contamination of the public sewerage (Verlicchi and Zambello, 2014). Nevertheless, the contribution of sensitive facilities to loads entering UWTPs may vary across catchments (pharmaceuticals manufacturing) and countries (due to different hospitalization practices), and upgrade of existing treatments technologies may require case-specific evaluation (Scott et al., 2018). And finally, the use of VMPs in animal farming has to be reduced and controlled, in line with the modern tendencies in different countries. Management decisions should also consider the benefits of the use of VMPs (including antibiotics) in animals, such as improved animal welfare, reduction in losses due to morbidity and mortality, and any production efficiencies or food safety benefits that may arise from the use of VMPs.

However, the contamination of TWW from urban effluents by antibiotics, ARB&ARGs is inevitable. Different tertiary and quaternary wastewater treatments have been developed to potentially eliminate these contaminants at economically-feasible cost. Another mitigation strategy is the soil amendment with biochar which has been shown to diminish the bioavailability of CECs and ARGs (Ye et al., 2016; Hurtado et al., 2017). However, long-term effects on the microbiome and ultimate degradation of adsorbed contaminants are unknown.

In conclusion, we consider that the use of TWW for irrigation of edible crops represents potential hazard associated to their content in antibiotics, ARB&ARGs, the magnitude of which needs to be evaluated. We propose first to limit the contamination in the sources, promoting a rational use of antibiotics and of their disposal both for human and veterinarian treatments. A second preventing strategy would be to reduce or prohibit the use of TWW in crops which are consumed raw, particularly leafy vegetables (e.g., lettuce). Finally, advanced water treatment methodologies able to remove CECs from TWW would be advisable if TWW became a general commodity to irrigate edible crops.

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