

HESS Opinions: Agricultural irrigation with effluent – Pharmaceutical residues that we should worried about

Dror Avisar¹, Gefen Ronen-Eliraz¹

¹ The Water Research Center, Hydrochemistry Research Group, Porter School of Environment and Earth Sciences, Faculty of
5 Exact Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Correspondence to: Dror Avisar (droravi@post.tau.ac.il)

Abstract. Policy regarding effluent water and reclamation aims to prevent environmental pollution while proposing an alternative water resource. Water makes up 99–99.9% of raw wastewater. Thus extracting organic and inorganic matter from water is a must. Worldwide, but especially in developed countries, great effort has been made to reuse wastewater, and it is
10 becoming a reliable alternative source. Israel is the world leader in water reuse, allocating 85% of effluent water for agricultural irrigation. As such, it constitutes a “living laboratory” in which to study the implications of the intensive use of treated wastewater for agricultural irrigation, leading to research and legislation regarding effluent quality and regulation. Effluent produced in Israel is subject to severe regulations and standards and is considered suitable for every use except drinking water. It is mostly allocated for agricultural irrigation with no restrictions. The irrigated lands are close to natural water sources, and
15 therefore water leaching from the fields infiltrate those sources, becoming part of the water cycle. A group of persistent and toxic nano- and micro-organic contaminants, including pharmaceutical residues, flows to water-treatment plants from hospitals, industry, agriculture and especially the domestic sector. These contaminants' chemical structure, characterized by a couple of aromatic rings and double bonds, makes them especially persistent; they are resistant to conventional biological treatment, used as a secondary treatment. As a result, the effluent that leaves the treatment plants, which is considered to be of
20 high quality, actually contains pharmaceutical residues. After secondary and tertiary treatment, these persistent chemical residues can still be found in surface water, groundwater and agricultural products. Pharmaceutical residues in effluent allocated for agricultural irrigation are undesirable. Expansion of the monitoring system for those contaminants, improvement of the tertiary treatment, and implementation of advanced technologies for decomposition and removal of pharmaceutical contaminants are thus needed.

25 1. Background

Water scarcity is a global problem caused by increasing demand from one hand and dwindling resources, triggered both naturally and artificially (humanmade), on the other hand. The alert of “water scarcity” reflected in the World Health Organization (WHO) reports. According to WHO data, over 800,000 deaths worldwide were caused by contaminated drinking water, inadequate handwashing facilities, and inappropriate sanitation services, in 2012, and more than 30% of the world’s
30 population had no access to safely managed water (Ghebreyesus and Lake, 2017; Grojec, 2017; UN-Water, 2017). Therefore, alternative water resources are essential.

On the contrary, wastewater production keeps increasing, since most activities that use water produce wastewater in even higher quantities. Wastewater composed of roughly 99% water and 1% suspended, colloidal and dissolved solids. Untreated wastewater or wastewater without adequate treatment is a source of chemical, physical and biological pollution, threatening on the environment and human health. (UN-Water, 2017). Therefore, opportunities offered by improved wastewater management and reuse is of a good water alternative resolving water scarcity and eliminate the threat of contamination that might be caused by untreated wastewater.

2. Global water reuse

On comprehensive worldwide assessments, 20% of wastewater going under some treatment (UN-Water, 2017). 85% of secondary effluent is reuse, allocated mainly for agricultural irrigation. Europe countries reuse about 2.4% of the treated wastewater, Mediterranean countries in Europe reuse 5%-12% of the treated wastewater except for Spain, which reuse about 25% of the treated wastewater. (Saliba et al., 2018; Sato et al., 2013). In this context, Israel is a leading country with 85% reuse of the treated wastewater (Cohen et al., 2016).

3. The complications of wastewater reuse

The quality of the treated wastewater is variable. It is composed of many different compounds depending on its source (municipal, industrial or agricultural) and wastewater-treatment plant operation and technology (Salgot & Folch, 2018). In contrast to fresh water, wastewater contained organic and inorganic contaminants, e.g., pharmaceutical or toxic metals, as dissolved and suspended particles (Grossman and Rurman, 2007; Strauch, 2011; WHO, 2006; Yeh et al., 2015; Zhang et al., 2013). Recycling of treated wastewater can lead to secondary contamination of soil and vegetation, surface water and adjacent groundwater because of these additional chemical compounds (Becerra-Castro, 2015; Christou et al., 2017; Desbiolles et al., 2018; WHO, 2006). On the last decades, contamination from pharmaceutical residues is noticed all over the world and therefore considered as emerging environmental pollution (Bagheri et al., 2016; Ortiz de Garcia et al., 2013; Strauch, 2011). Although pharmaceutical residues found in many aqueous environments worldwide, Israel, as a leading leading country in allocating treated wastewater for agricultural irrigation, which is in essence as a "living laboratory", and committed to carefully examining the various issues and implications that are tightly bound to unlimited wastewater reuse (Cohen et al., 2016). In this paper, we examine the complexity of the implications arising **from recycling wastewater**, which contains discrete amounts of pharmaceutical residues and their metabolites, that should treated cautiously. To clarify these implications, we will answer the following questions: What other components are present in effluents? At what concentrations? What are their degradation products? How chemically stable, and how toxic are these degradation products? How do these components and degradation products affect the irrigated environment? What are the regulated parameters in water regulation? Do they provide any parameters in the context of recycled water? Do the regulated parameters indeed define high-quality effluents?

3.1 What components are present in high-grade effluents? At what concentrations?

The wastewater flowing into wastewater plants carries pharmaceutical residues, including antibiotics, anti-inflammatory drugs, anti-depressants, sex hormones, lipid regulators and beta-blockers (Desbiolles et al., 2018). Depending on the specific circumstances, studies have shown that about 30–90% of all medications consumed, excreted via the urine and feces, as the parent compound or its metabolites, are introduced to wastewater (Adamczak et al., 2012; Christou et al., 2017).

The conventional treatment procedure for wastewater includes pretreatment, which is filtration and sedimentation, a secondary treatment that is based on biological degradation, and a tertiary treatment that consists of filtration and disinfection. The secondary treatment is the main stage designed to remove dissolved organic compounds. Apparently, it may remove -20% - +80% of the degraded organic compounds, as measured by biological oxygen demand (BOD) (Grandclément et al., 2017). In practice, at the end of the treatment procedure, the treated wastewater is considered “high-quality effluent” as it meets the standards for the main tested parameters, including BOD, COD, TSS, Soluble sodium percentage, Turbidity, N Total, NO₃⁻, NH₄⁺, Oil and Grease, etc. (Shakir et al., 2016). Studies have shown that during the biological treatment of wastewater, resistant pharmaceutical, for example ATZ, diazinon (DZN), diclofenac (DCF), carbamazepine (CBZ), metoprolol (METOP), do not degrade easily (Grandclément et al., 2017) and practically, different pharmaceutical residues have been detected in the aquatic environment around the world (Comber et al., 2018; Yang et al., 2017). The concentration of pharmaceutical residues in wastewater range from 100 to 100000 ng/L or even microgram/L in treated wastewater (Desbiolles et al., 2018; Lamm et al., 2009; Shafrir and Avisar, 2012; Souza et al., 2018; Zhang et al., 2008).

3.2 Degradation products – Are they chemically stable? Are they toxic?

Despite their chemical stability, some of the pharmaceutical residues might be degraded while flowing with the wastewater (Kosjak & Heath, 2011; Wang and Wang, 2016). In addition, natural degradation can be caused by solar radiation, wastewater acidity (pH), or integration of additional organic compounds such as humic acid (Gozlan et al., 2010, 2014). Variation in wastewater composition influences degradation processes differently, although the parent compound will degrade preferentially to different specific degradation products under different conditions. This further complicates the monitoring and analysis of degradation products (Gozlan et al., 2013, 2016). The following example with the degradation of Amoxicillin (AMX) emphasizes part of the complications. AMX is the active ingredient in commonly consumed antibiotics worldwide. Surprisingly, it has never been detected in wastewater or effluent. It was found that AMX degrades easily due to opening of its strained β -lactam ring during its hydrolysis. As a result, its chemical identity changes, and its degradation product diketopiperazine-2', 5' (ADP), which is neither stable nor toxic, is produced (Gozlan et al., 2013, 2016; Lamm et al., 2009). This product continues to degrade into a few unstable and nontoxic degradation products, and one stable and toxic product, ADP3 (Gozlan et al., 2016; Lamm et al., 2009).

ADP3 is the major degradation product of AMX and is defined as a stable, biologically active compound. It has been detected in surface water as well as in groundwater and represents its parent molecule's distribution. The case of AMX exemplifies the essence of degradation processes that might affect the parent compound and its degradation products while in the environment. It emphasizes the difficulty in detecting compounds and their degradation products in their stable form, which might lead to the development of resistant bacteria and even cause other possible health hazards to human, wild and domestic animals (Gozlan et al., 2010).

As already noted, there are many types of degradation products that might be more chemically stable than their parent compound (Gozlan et al., 2013). This stability is alarming since such products might form a chemically active structure that is toxic and threatens human and animal health. Another alarming outcome of these degradation products' chemical stability might be the development of resistant bacteria when the parent product is an antibiotic (Gozlan et al., 2010; Lamm et al., 2009). Active degradation products might form during treatment by advanced oxidation processes (AOPs), although this is the suggested treatment type for the degradation of drug residues. Therefore, learning and investigating degradation processes under a variety of conditions, in addition to developing monitoring and measurement methods to detect them, is of great importance (Gozlan et al., 2010).

Effluent that has been allocated for agricultural irrigation might be rich in chemically stable drug residues and their degradation products. These compounds then flow and drain into the environment, infiltrating with the water and mixing with surface and groundwater, especially next to cultivated areas (Avisar et al., 2009; Zhang et al., 2008). Measuring and detecting all degradation products in the environment is difficult since many have not yet been identified (by name or by chemical definition). Our knowledge is restricted and there are literally hundreds of unknown compounds in the aquatic environment that cannot be detected or measured (Lamm et al., 2009; Yin et al., 2017), and therefore cannot know whether these unknown compounds are toxic or how their presence in the environment influences human health and the environment (Grossman and Rurman, 2007). On the other hand, we do know that pharmaceutical residues in the influent flowing into wastewater treatment plants may exert toxic or inhibitory effects on activated sludge bacteria (Yang et al., 2017). There are also studies that showed that long-term exposure to very-low concentration of pharmaceutical residues in the aquatic environment pose risk on the aquatic ecosystem (Strauch, 2011), and mixture of pharmaceutical residues and accumulation in soils, can threaten the environmental and human health (Beccera-Castro et al., 2015). Awareness to these dissolved and suspended organic compounds and their degradation products in water, and their stable structure which is not mineralized to water and CO₂ during dedicated treatment (secondary, tertiary or AOPs), emphasize the importance of exploring the toxicity of these products in water.

30 **3.3 How do residual drugs and their degradation products affect the irrigated environment?**

By the time the pharmaceutical residues reach the agroecosystem, via either irrigation or fertilizers using effluent or wastewater sludge, respectively, they may have gone through different processes that will seal their fate. Degradation (Grossberger et al., 2014), sorption and desorption to and from solid matter, infiltration into the groundwater (Paz et al., 2016) and plant uptake

(Ben-Mordechay et al., 2017; Christou et al., 2017; Goldstein et al., 2014; Malchi et al., 2014) are examples of some of those processes. The processes are likely to rely upon the physicochemical properties of the pharmaceutical compounds—their molecular charge, which depends on the pKa, the water partition coefficient (Kow), and the soil properties—pH and total organic compounds (Goldstein et al., 2014).

5 Irrigation with effluent known to affect the soil properties, including physical, chemical and biological qualities of the soil (Becerra-Castro et al., 2015; Dvorkin et al., 2012; Fernández-Gálvez et al., 2012; Ye et al., 2015). Especially concern is with their organic carbon (OC) content, that has been demonstrated to influence the processes or adsorption and desorption of the soils, and changes in the soil's microbial community and its attendant activities (Rodríguez-Liévana et al., 2018).

In plant uptake, the pharmaceutical residues and their degradation products are translocated to the leaves and fruit where they
10 accumulate. They subsequently enter the food chain, as the agricultural products (leaves, fruit, and roots) are sold on the free market with no restrictions (Ben-Mordechay et al., 2017; Goldstein et al., 2014; Malchi et al., 2014).

In a different process, due to lipophilic sorption to the soil matrix resulting in high bioavailability, electrochemical interactions and an ion-trap effect, pharmaceutical residues and their degradation products with changed chemical properties can be transported through the phloem. Therefore, not only do the degradation process and products need to be carefully elucidated,
15 but also phloem transport and translocation need to be well deciphered (Ben-Mordechay et al., 2017; Christou et al., 2017; Trapp, 2000). A high concentration of drug residues ($\mu\text{g}/\text{kg}$), from hormones and antibiotics, among others, was found in wastewater sludge designated for agricultural field composting. These products are characterized by a high partition coefficient (Kow), meaning that they prefer the solid phase to the liquid phase. Therefore, when they leach and flow into the cultivated land, they absorb to the soil. Sometime later, when the conditions change, they desorb into the soil water, and are transported
20 to the phloem or percolate into the groundwater (Shafrir and Avisar, 2012; Tenenbaum et al., 2014).

Drugs residues that have not been translocated to the vegetation may infiltrate from the agricultural fields into the saturated layer, and be pumped into production wells with the groundwater (Avisar et al., 2009; Lamm et al., 2009). Indirect, unknowing and uncontrolled consumption of drugs through drinking water and food can cause allergic reactions and health problems, thus constituting a serious human health threat (Christou et al., 2017).

25 **3.4 What are the regulated parameters in water regulation? Do these parameters define high-quality effluent?**

To date, discharge guidelines and standards regarding pharmaceutical residues in effluent for irrigation is not exist, although there is some consideration for general framework (Grandclément et al., 2018). The worldwide approach for effluent use in agriculture is to combine risk assessment with the control of water-released diseases. This provides a framework for the development of health-based guidelines and standards. Three types of risk assessments are performed: microbial and chemical
30 laboratory analyses, epidemiological studies, and quantitative microbial and chemical risk assessment (Carr et al., 2004; Saliba et al., 2018; Shakir et al., 2017). Much information is available from epidemiological studies of infectious disease transmission, as opposed to health risks from chemicals that are mostly based on quantitative risk assessment and depend on the types of chemicals and the physical and chemical properties of the soil (Becerra-Castro et al., 2015; Carr et al., 2004).

A variety of health-protective measures, including all customary chemical and microbial analyses, are carried out on a regular basis in all big treatment plants in Israel as well in most developed countries. In addition, measurements that attest to treatment quality in the treatment plants, such as BOD, total suspended solids (TSS), etc., are also tested on the products (Becerra-Castro et al., 2015; Bower, 2000; Carr et al., 2004; Grossman and Rurman, 2007).

5 In most of the world, pharmaceutical residues and their degradation products found in treated wastewater and has no regulation restricting them (Blair et al., 2015; Grandclément et al., 2017; Yang et al., 2017). It is particularly because of their low concentration, their large variety of chemical structures and the unknown degradation products, that posing a challenge on the analytical methods and though leave them out of regulation (Beccera-Castro et al., 2015; Blair et al., 2015). On the last decades, with analytical development and increasingly frequent medical prescriptions, and medication consumption, many studies
10 detected pharmaceutical residues and their metabolite, in contaminating soils (Blair et al., 2015), agricultural products (Becerra-Castro et al., 2015; Christou et al., 2017) and water resources (Ortiz de Garcia et al., 2013; Strauch 2011). It is already clear that some pharmaceutical residues cause health implications and hazards and the research must deepen the understanding of this context. Pharmaceutical residues mixing can synergistically enhance their toxicity, similarly to the phenomena happened with patients who taken mix of medications, although the residues are on order of magnitude lower than
15 administrated pharmaceutical (Comber et al., 2018; Ebele et al., 2017). It is also clear that the possible implications need to be consider for future regulation although there is much more we do not know than what we know (Desbiolles et al., 2018). The consideration of pharmaceutical residues in wastewater effluent got expression recently, while some pharmaceutical residues start to be monitored by European counties in the field of water policies. In the national level of Switzerland and England, monitoring and treatment efforts to remove or dilute antibiotics from the treatment-plant effluent, has already held (Comber et
20 al., 2018; Swiss Federal Concl, 2016).

4. Where do we go from here?

It is obvious that in the coming years, additional regulatory requirements will be needed to monitor and treat pharmaceutical residues. The required treatment will be applied at the treatment plants, or at the wastewater source in the case of industries or
25 hospitals (Gerrity and Snyder, 2011). Treatment at the wastewater source will need to be performed on smaller volumes and with specific contaminants to degrade specific pharmaceutical, to make the process more efficient and less expensive.

The main difficulty in degrading pharmaceutical is their physico-chemical properties. As mention earlier, these compounds are only partially degraded by the common biological degradation process and the effluent leaving the plant designated for agricultural irrigation with no restrictions, is actually contains a mixture of pharmaceutical residues. Many studies promoting
30 researches to prevent or eliminate pharmaceutical residues to get to the effluent water. In the last few years, research groups worldwide have been developing combined methods to degrade and remove pharmaceutical residues at the treatment plant as well as at the wastewater sources (industry and hospitals. Biological treatments such as activated sludge, membrane bioreactor

treatment (MBR) are examples of biological degradation in treatment plants, in which operating conditions effect removal efficiency (Ejhed et al., 2018; Grandclément et al., 2017). Membrane filtration such as reverse osmosis reactor is also one of the solution under research (Cerro-Lopez et al., 2019). On the nanomaterials techniques there are metal nanoparticles, carbon nanotubes and nano filters which all of them found to be efficient removal for some of the contaminants (Bagheri et al., 2016).

5 One of the solutions stem from examinations of different technological aspects, focus on the development and improvement of Advanced Oxidation Process (AOPs). Some of AOPs techniques, can effectively treat the problem and degrade pharmaceutical residues, although not all of them (Lester et al., 2013; Siedlecka et al., 2018), Anyway, it comes up from different studies, that almost all of the treatment possibilities describe above, are often not sufficient ensure high removal of the pharmaceutical and therefore much of the technique improves by combining two or more treatment processes to one hybrid

10 treatment procedure (Grandclemente et al., 2017; Zucker et al., 2015).

5. Awareness

The most important task from the above manuscript is to raise awareness of the possible risks folds in using secondary effluent for agriculture irrigation. Arguments that pharmaceutical residues concentrations are too small to influence human health are

15 easy to make, but have never been proven. There have not yet been enough studies to confirm or reject this argument. It is therefore important to emphasize that even though pharmaceutical residues and their degradation products, are not supposed to be in the drinking water at all, they do exist there, as a mixture. However, awareness to the possible danger impose by this unknown mixture must be carefully consider, before it can be ignored.. The authors think that "conducting business as usual", i.e., persisting with a regulatory attitude that ignores OMPs in effluent, is tantamount to "turning a blind eye" and allowing the

20 overwhelming neglect to worsen.

Globally, renewed legislation and the establishment of concentration permits for pharmaceutical residues contaminants in water resources and effluent are essential (Gozlan et al., 2014). Preparation for this essential stage includes comprehensive studies of the different chemical groups of the widespread drugs and their degradation products, method development to identify and measure them, awareness of the analytical restrictions, and testing the possible influence of different

25 pharmaceutical residues mixtures on human health. Similar source treatment of hospital and industrial wastewater is a must, and obliging the drug industry to treat their waste and establish specific permits for pharmaceutical residues concentrations in wastewater are critical to successfully implementing treatment methods to remove it. This will enable the production of high-quality effluent that is readily available for any use.

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