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Research article

# A critical evaluation of comparative regulatory strategies for monitoring pharmaceuticals in recycled wastewater

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## ABSTRACT

Pharmaceuticals are a subset of micropollutants, present in the environment in trace concentrations. Because of their persistent nature, these chemicals are of particular concern. Little is known about how mixtures of pharmaceutical residues, found in WWTP effluents, affect the environment or public health. Yet, numerous studies show negative outcomes for both aquatic and terrestrial organisms, suggesting that they are given both to bioaccumulation and uptake in plants. Israel leads the world in effluent reuse (86%), almost exclusively utilized for purposes of agricultural irrigation. Pharmaceuticals, however, are not included in Israel's water regulatory oversight or management, essentially creating an epidemiological experiment among its citizens and environment. Globally, these compounds also are not commonly subject to monitoring or regulation. This study reviews and analyzes water policies and regulation worldwide that address the presence of pharmaceuticals in water resources, with a particular focus on Australia, Singapore, Switzerland, and the USA. Furthermore, the study investigates the reasons why these chemicals are not yet regulated in Israel. Based on a comprehensive evaluation of the data and analysis of the regulatory rationale in other countries, a list of recommended pharmaceutical standards that should be measured and monitored in Israel's wastewater treatment system is proposed. The suggested prioritization criteria should be at the heart of a new regulatory agenda for controlling pharmaceutical contamination in wastewater.

## 1. Introduction

Micropollutants are compounds (e.g. pesticides, pharmaceutical products and endocrine disruptors, detergents, cosmetics etc.) which are found in the environment in small concentrations in water, wastewater, crops and soil. Concerns about pharmaceuticals in the environment are increasing (Virkutyte et al., 2010), primarily due to uncertainty about the fate and impact of the resulting mixture of compounds in the water cycle. Pharmaceuticals typically are complex molecules with different physicochemical and biological properties and functions.

Up to 95% of administered pharmaceutical doses can be excreted unchanged in urine or stool and discharged into domestic wastewater (Calamari et al., 2003; Zuccato et al., 2000). After their therapeutic use and excretion, pharmaceuticals are released into raw wastewater. When wastewater treatment is inefficient or nonexistent, these residuals are discharged into rivers, streams, and lakes. Removal rate of pharmaceuticals in wastewater treatment plants (WWTPs) vary, depending on factors such as their chemical properties, the treatment process, age of

the activated sludge and associated environmental conditions (e.g., temperature and the light intensity), and the biochemical characteristics of the influent (Carballa et al., 2004; O'Brien and Dietrich, 2004). Myriad pharmaceutical compounds are detected in treated wastewater, contributing to water contamination (Hughes et al., 2012; IWW, 2014).

Once pharmaceutical compounds reach the environment several processes determine their fate: degradation and transformation (Grossberger et al., 2014); adsorption and flow towards groundwater (Paz et al., 2016); or plant uptake (Mordechay et al., 2018; Malchi et al., 2014). These processes depend on the chemical-physical properties of the pharmaceutical substances; the molecule's charge (depending on the pKa-pH based acid dissociation constant), octanol/water partition coefficient (Kow), and soil characteristics (Avisar and Ronen-Eliraz, 2017).

Given the volume of prescriptions, toxicity, and their presence in the environment, antibiotics, hormones, non-steroidal anti-inflammatory drugs (NSAIDs),  $\beta$ -blockers, blood lipid regulators, antiepileptics, analgesics, anti-inflammatories, and antidepressants are the most studied pharmaceutical groups (Jelić et al., 2012; Miega et al., 2009). A large

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variety of pharmaceuticals has been detected in Israel's effluents and natural water bodies during the past decades. Iopromide (Contrast media), Primidone (Anti-epileptic), Bezafibrate (Lipid regulator), Metoprolol (b-blocker), Venlafaxine (Anti-depressant), Carbamazepine (Anti-epileptic), Diclofenac (Anti-inflammatory), and Sulfamethoxazole (Antibiotic) have all been measured in wastewater, secondary effluent, groundwater, and surface water at various concentrations (Avisar et al., 2009a, 2009b, 2010; Lakretz et al., 2017; Lamm et al., 2009; Lester et al., 2013; Shafir and Avisar, 2012; Zucker et al., 2015).

Consuming water or food containing antibiotic residues may lead to various adverse effects on human health, such as allergic hypersensitivity reactions, toxic effects, hepatotoxicity, nephropathy, mutagenicity, carcinogenicity, and antibiotic resistance (Mensah et al., 2014). Estrogens in contaminated water have been linked to breast cancer in women (Moore et al., 2016) and prostate cancer in men (Nelles et al., 2011). Estrogens also disrupt fish physiology and can affect reproductive development in both domestic and wild animals (Rose et al., 2013; Van Donk et al., 2016).

Treatment of plants with steroid estrogen hormones or their precursors can affect root and shoot development, flowering, and germination (Adeel et al., 2016; Janeczko and Skoczowski, 2011). Studies evaluating the adverse effects of antihistamines in aquatic organisms have tested soil bacteria, worms, fish, invertebrates, biofilm and many more media, confirming several adverse effects (Kristofco et al., 2016; Kristofco and Brooks, 2017). Residuals from anticancer drugs interfere directly or indirectly with the structure and functions of DNA, which also affect non-target cells and tissues of exposed organisms (Heath et al., 2016). Several studies indicate that psychiatric pharmaceuticals can affect physiological systems at very low concentrations. Van Der Ven et al. (2006) demonstrated that 'Mianserin', a tetracyclic antidepressant, has estrogenic activity and produces endocrine disruption in zebrafish. A number of other studies on Fluoxetine, Diazepam, Prozac, Sertraline, Paroxetine, along with other pharmacologically active compounds clearly showed significant adverse effects of antidepressants and anxiolytics on living organisms of aquatic matrices (Fong and Molnar, 2008; Ford et al., 2016; Gust et al., 2009; Melvin et al., 2017; Pascoe et al., 2003; Peter et al., 2017; Silva et al., 2017).

A range of health effects recently identified in Israel suggest there may be meaningful local environmental exposures to micropollutants. Evidence includes a steady decline in the age of puberty among the general population of Israeli girls (Flashe-Luzzatti et al., 2014), an increase in the prevalence of male factor infertility (Sella et al., 2011), an increase in various cancer rates such as colon cancer (IMH, 2017a), prostate cancer (IMH, 2017b), and testicular cancer (IMH, 2016). Environmental exposure to pharmaceutical residues should be considered as a potentially contributing factor to Israel's health issues.

It is difficult to assess the number of pharmaceuticals used globally. Nonetheless, Rand-Weaver reported over 3000 human pharmaceuticals in general use (Rand-Weaver et al., 2013). Boxall et al. reported over 4000 pharmaceutical products available worldwide for medicinal and veterinary purposes, resulting in annual production exceeding 100,000 tons of pharmacologically active compounds (Boxall et al., 2012; Hird et al., 2016). Moreover, pharmaceutical consumption continues to increase. The rise in pharmaceutical consumption can be attributed to the growing demand for drugs to treat aging-related and chronic diseases and by changes in clinical practice (OECD, 2015). Modern medicine is unimaginable today without pharmaceuticals and this dependence promises to only increase with time. A growing world population, increasing investment in the health-care sector, advances in research, global market availability, along with aging societies contribute to significant increases in pharmaceutical demand during past decades (Van Boeckel et al., 2014; Weber et al., 2016). Moreover, new pharmaceuticals are being developed and produced each year. For instance, a total of 43 New Active Substances (NASs) were launched in 2015 in the United States alone (IMS Health, 2015).

Concentrations of many micropollutants in drinking water are

limited under existing legislation. But pharmaceuticals are not yet commonly subject to environmental monitoring or regulation, even though they have potential adverse effects on human and ecosystem health. Given the growing global concern about pharmaceuticals, questions about this problem in the Israeli context are particularly relevant. Israel's situation is unique because the country recycles 86% of its wastewater (Tal, 2018). Despite the advanced treatment, effluents containing drug residues are utilized as a primary source for unlimited irrigation. Given the country's small dimensions and the ubiquitous wastewater recycling, regulating and monitoring for pharmaceutical residues is imperative.

This article compares different strategies that have emerged in several countries who have begun to regulate pharmaceutical residues. It reviews the associated legislative and regulatory challenges involved in establishing criteria for prioritizing pharmaceutical residues that need to be monitored. Finally, the article offers a list recommended pharmaceutical compounds that should be measured and monitored. It concludes with regulatory recommendations and the associated tasks for policy makers in Israel, where the challenge of pharmaceutical residues in wastewater can no longer be ignored.

## 2. Environmental pharmaceutical regulation: A comparative analysis

Monitoring or treating pharmaceutical substances after their release into the environment is not a common practice internationally. There are, however, several regulatory initiatives that emerged to address this challenge. These interventions can be classified according to the intensity of the measures taken to regulate pharmaceutical pollutants in the environment:

- Level 1- comprehensive interventions, where the country/state has taken systematic legal measures to regulate pharmaceutical residues in order to reduce their volume in the environment (e.g., Switzerland and California).
- Level 2- moderate interventions, where monitoring of pharmaceuticals is conducted on a regular basis, without a formal statutory requirement. Usually these efforts are based on global or local guidelines (e.g., Australia, and Singapore).
- Level 3- limited interventions, where pharmaceutical residues are monitored intermittently, with little or no formal statutory foundation.

We review existing regulatory efforts in order to identify the costs and benefits of different alternatives and solutions designed to reduce the health risks associated with exposure to pharmaceutical residuals in water resources.

### 2.1. Level 1 – California (USA) and Switzerland – advanced regulatory framework

California's State Water Boards do not require pharmaceuticals to be routinely monitored for irrigation projects using recycled water (SWRCB, 2013). Nonetheless, potable water reuse projects do require monitoring of many chemical substances associated with pharmaceutical use in accordance with the state's Title 22 regulations. California's *Recycled Water Policy* requires treatment plants which discharge recycled water for the purposes of groundwater recharge to monitor groundwater recharge reuse (surface or subsurface application) for 17 $\beta$ -estradiol (steroid hormones), Gemfibrozil, and Iopromide. One such facility, subject to these regulations, is the Orange County Water District (OCWD) Groundwater Replenishment System (GWRS) in California which has been operating since January 2008. The GWRS takes highly treated wastewater that would otherwise be discharged into the Pacific Ocean, and purifies it using a three-step, advanced treatment process consisting of microfiltration (MF), reverse osmosis (RO), and UV light

with hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) before groundwater recharge for potable reuse.

California's advanced wastewater treatment and monitoring program is not without associated costs. The first phase of the plant cost US \$480 million. The GWRS underwent a \$142.7 million expansion, which was completed in 2013. It costs approximately \$40 million a year to operate the GWRS. Although only two pharmaceuticals and one hormone are recommended to be monitored in recycled water used for groundwater artificial recharge reuse in California, in practice, the GWRS voluntarily monitors a wider range of pharmaceutical substances on a quarterly basis in the purified recycled water: 17a-Estradiol, 17a-Ethynylestradiol, 17b-Estradiol, Atenolol, Diclofenac, Diethylstilbestrol, Dilantin, Epitestosterone, Equilin, Estriol, Estrone, Fluoxetine, Iohexol, Iopromide, Meprobamate, Naproxen, Progesterone, Testosterone, Trimethoprim, Acetaminophen (Paracetamol), Azithromycin, Carbamazepine, Erythromycin, Gemfibrozil, Ibuprofen, Sulfamethoxazole, and Triclosan. Monitoring reports suggest that California's GWRS effectively eliminates these pharmaceutical contaminants from water supply. In 2016, analyses of purified recycled water for aforementioned substances largely measured non-detectable levels or if detectable, below levels thought to pose any significant public health risk (OCWD, 2017a; OCWD, 2017b).

Beyond groundwater recharge or surface water augmentation projects where recycled water is indirectly reused, California intends to develop criteria to enable direct potable reuse in the state, in which advanced treated recycled water is supplied to drinking water treatment plant headworks or distribution systems. Given the current California requirements for pharmaceutical monitoring in potable reuse for recharge, such requirements are highly likely to be integrated in the state's future regulation and standards for direct reuse (Olivieri et al., 2016).

In contrast to the California approach which is limited to pharmaceuticals monitoring in potable reuse, Switzerland has a more comprehensive environmental program that includes monitoring pharmaceuticals in several media of the aquatic environment. During the country's first pilot study in 2013, the National Surface Water Quality Monitoring Program (NAWA) only measured a small group of pharmaceuticals (EAWAG, 2013). As of 2018, the original NAWA testing program was supplemented with regular measurements of additional micropollutants including pharmaceuticals (Atenolol, Azithromycin, Bezafibrate, Carbamazepine, Clarithromycin, Diclofenac, Mefenamic acid, Metoprolol, Naproxen, Sotalol, Sulfamethazine, Sulfamethoxazole, and Trimethoprim). Results of the expanded Swiss micropollutant monitoring program will become available in November 2019 (FOEN, 2019). An additional program which is designed to generate relevant data about pharmaceutical residuals is the Swiss National Groundwater Monitoring (NAQUA) that regularly measures Carbamazepine and Sulfamethoxazole (FOEN, 2019).

Switzerland was dissatisfied with merely monitoring micropollutants, and began to act to reduce them. It launched a 20-year commitment to invest in reducing micropollutant release into the aquatic environment from wastewater treatment plants. The Swiss federal water protection legislation seeks to ensure that groundwater, the country's primary drinking-water resource, is kept clean and free from persistent, artificial substances, even if these are not deemed acutely toxic to humans (FOEN, 2015). This approach has recently been formally codified in legislation. At the start of 2016, new regulations came into effect in Switzerland requiring roughly one hundred of the country's municipal WWTPs to be upgraded over the next 20 years to remove micropollutants, such as pharmaceuticals (SR 814.201.231., 2016).

The Swiss program targets dissolved compounds. The new regulations require upgrading to advanced treatment (ozone based: Advanced Oxidation Process- AOP), as a fourth step, after tertiary treatment is completed, with the aim of achieving an overall reduction of 80% in the micropollutants discharged.

The Swiss micropollutants strategy establishes a set of indicator compounds by which to regulate micropollutants. The indicator selected compounds are easy to analyze, so that they can be detected regularly and compared with influents and effluents in treatment plants. The aim of the Swiss regulations is to achieve 80% removal across the plant as a whole. The regulation focuses on dissolved compounds. Accordingly, indicator compounds involve compounds that have not yet been substantially degraded at the biological treatment stage.

It is important to note that the 10 pharmaceutical indicator compounds can be assessed in a single laboratory test, using a combination of HPLC and MS/MS, offering a relatively efficient monitoring option. Typically, chemical analysis of a water sample costs around 350 CHF (350 US \$), with larger plants required to test influents and effluents twelve times annually. (FOEN, 2015; EAWAG, 2016). The estimated marginal increase in wastewater treatment expenses is 12%, involving an additional cost of 9 US dollars per person per year, for the next 25 years (FOEN, 2015).

Switzerland offers an example where high awareness about micropollutant contamination has led to a significant intervention. NAWA and NAQUA monitoring programs, alongside the Swiss plan to upgrade its major WWTPs, represents an ambitious and comprehensive approach to monitoring, reducing, and eliminating micropollutants prior to release into the environment.

## 2.2. Level 2 – Australia and Singapore – basic monitoring guidelines

Second level projects, such as those operating in Australia and Singapore, regulate pharmaceutical residues in water without a binding legal framework. The associated interventions rely on general guidelines, using pharmaceuticals as indicators for the effectiveness of the water purification process.

In Australia, monitoring and reporting contaminants associated with production of recycled effluents is the responsibility of the state or territorial government. At present, there are no Australian states or territories that recycle water for potable use. For the most part, recycled water in Australia is used for irrigation (in direct use). The main environmental concerns, therefore, involve metals, salinity, nutrient, and pH that might impact the crops being irrigated (DAWR, 2009).

Officially, the Australian Department of Health has downplayed the significance of regulating pharmaceuticals in effluents, explaining that it is not a common practice internationally. Nonetheless, the *Australian National Guidelines for Water Recycling (Phase 2)* reflect a pro-active approach that provides guidelines about concentrations (and an approach for further developing guidelines) that are applicable to potable water supplies intentionally augmented by recycled municipal effluents. Use of Australian guideline values must be considered when risk assessment identifies "significant contributions by municipal effluent, whether intentional or unintentional" (AGDH, 2017; NRMCC EPHC & NHMRC, 2008).

The Guidelines' general recommendation holds that with the exception of programs designed to augment drinking water supplies, the chemical quality of recycled water is unlikely to represent a public health concern due to the relatively low levels of human exposure (less than 1 L per person, per year) (DAWR, 2009). As a result, monitoring for pharmaceuticals and other trace organics, in particular, have been limited under most recycled water schemes.

Drinking water guideline for pharmaceutical chemical values were derived by dividing the lowest daily therapeutic dose by a safety factor of 1000. Presumably, this margin provides reasonable assurance that any adverse health effects, either pharmacological or toxic, are unlikely. The guideline provides a recommended drinking water concentration for a total of 86 human pharmaceuticals and pharmaceuticals, with agricultural and veterinary applications (DAWR, 2009).

Two Australian pharmaceutical programs have begun – in Western Australia and in Queensland (Western Corridor scheme). They include involvement in the treatment stages that remove chemical



contaminations as well as pharmaceutical monitoring. *The Western Australian Scheme* focuses on groundwater recharge while the *Queensland-Western Corridor Scheme* is designed to augment surface water. Pharmaceutical concentrations will also be monitored in the Queensland reservoir when it becomes operational (AGDH, 2017; Seqwater, 2019a; Seqwater, 2019b).

Technologically, the treatment process at the Advanced Water Recycling Plant in Western Australia includes numerous stages: Ultra-Filtration, Reverse Osmosis (RO), UV Disinfection and, following water recharge into the Yarragadee and Leederville aquifer, recharge bores at depths of between 120 and 300 m. Based on the aforementioned guidelines, the three pharmaceutical indicators monitored regularly in this project are Carbamazepine, Estrone and Diclofenac. Carbamazepine and Diclofenac are monitored monthly and Estrone quarterly, with testing frequency determined by the Department of Health based on estimated risk levels. A full suite of hormones (13) and pharmaceuticals is measured once a year in line with the standard water quality testing. Substances includes: Estriol, 17 alpha estradiol, 17 beta estradiol, Testosterone, Androstenedione, Etiocholanolone, Equilenin, Ethinyl estradiol, Estrone, Equilin, Mestranol, Norethindrone, and Progesterone (GWADH, 2010a; Water Corporation, 2017a; Water Corporation, 2017b; Water Corporation, 2017c).

In a similar program, Public Utilities Board (PUB), Singapore's national water agency, has a comprehensive water monitoring program which includes a range of pharmaceuticals in the treated wastewater effluent. This involves high-grade reclaimed water, referred to as "NEWater" which are a part of Singapore's water sustainability strategy. (PUB, 2019a; PUB, 2019b). In this program raw wastewater is treated in a WWTP, effluents undergo additional treatment, including MF, RO, and UV disinfection. During dry periods, NEWater is channeled into reservoirs where it is mixed with rainwater and undergoes further treatment at a water works before being supplied to households. This serves as an environmental buffer, providing meaningful retention time and natural attenuation. NEWater (non-potable application) effluents are used primarily for industrial and air-conditioning cooling purposes at wafer fabrication plants, industrial estates, and commercial buildings. NEWater is delivered to industrial customers via a dedicated pipe network (PUB, 2019b).

Thus far over 330 physical, microbial, chemical, and radiological parameters have been monitored pursuant to Singapore's new initiative, including several pharmaceuticals. The pharmaceuticals were selected according to Global Water Research Coalition (GWRC) priority listing (GWRC, 2008) and from information provided by Singapore's ministry of health on local drug consumption. As of 2007, 6 pharmaceuticals (Ibuprofen, Naproxen, Ketoprofen, Triclocarban, Gemfibrozil and Diclofenac) are regularly monitored (PUB, 2019a). Capacity for monitoring has steadily expanded and now includes Carbamazepine, Trimethoprim, Salicylic Acid, and Paracetamol. Initial results suggest that these compounds are not found in drinking water (PUB, 2019a).

Although successfully identifying and removing many pharmaceutical residues, these projects remain local in their scope. They lack a holistic orientation, and are not part of a comprehensive, long-term plan that addresses pharmaceuticals in the environment, leaving many potential hazards unaddressed.

### 2.3. Level 3 – sporadic monitoring and other small-scale mechanisms

The U.S. EPA uses the Unregulated Contaminant Monitoring Rule (UCMR) to collect data for contaminants suspected of being present in drinking water for which health-based standards are not yet established under the Safe Drinking Water Act (SDWA). Occurrence data are collected through UCMR to support the Administrator's determination of whether to regulate particular contaminants in the interest of protecting public health. EPA's selection of contaminants for a particular UCMR cycle is largely based on a review of the Contaminant Candidate List (CCL). The drinking water CCL is a list of contaminants, known or

anticipated to occur in public water systems, that are currently unregulated under national primary drinking water regulations.

Contaminants listed on the CCL may require future regulation under the SDWA. For instance, in New York City, as well as other selected states, pharmaceutical residues were monitored in drinking water supply under the UCMR3 between 2013 and 2015 for seven hormones: 17- $\beta$ -estradiol, Ethinyl estradiol, Estriol, Equilin, Estrone, Testosterone and 4-androstene-3,17-dione (EPA, 2012). According to the 'New York City 2016 Drinking Water Supply and Quality Report' (NYC-DEP, 2016; NYC-DEP, 2019) these substances were not detected in drinking water samples. Unfortunately, the new UCMR4 (expected between 2017 and 2021) does not include pharmaceutical substances (EPA, 2017). Nonetheless, several pharmaceuticals and hormones are part of the CCL4 list, such as 17 $\alpha$ -Estradiol, 17- $\beta$ -estradiol, Equilenin, Equilin, Erythromycin, Estriol, Estrone, Ethinyl Estradiol, Norethindrone, and Quinoline (EPA, 2016).

An additional regulatory mechanism to control pharmaceutical residues in the environment involves business permits. In the United Kingdom (UK) businesses that produce clinical/pharmaceutical waste or conduct activities where they may discharge such wastes into water-courses, in liquid form, are typically required to receive a permit from the UK Environmental Agency (UK-EA, 2011). The agency regularly monitors and tests such discharges. Facilities are expected to treat any effluent that may contain clinical wastes prior to discharges into the environment. This demand is made on a case by case basis (UK-EA, 2011; UK-EA, 2019). Hospitals, in particular may need an Environment Agency permit if they are treating wastes on-site or releasing them into waterways or groundwater. (UK-EA, 2019).

Denmark also has a decentralized orientation towards regulation of pharmaceuticals in water. According to the Danish Environmental Protection Act No. 1189 of 2016 (DEPA, 2016; DMEF, 2019) hospitals are to apply to local municipalities for a wastewater permit, which will include terms for discharge of wastewater containing dissolved pharmaceuticals. (DMEF, 2019). Moreover, recently, the Indian government published its National Action Plan on Antimicrobial Resistance (Government of India, 2017) declaring its intention to monitor and regulate antibiotic discharges from manufacturing sites within three years.

### 2.4. Levels 1-2-3 discussion

As summarized in Table 1, some countries, like Australia or Singapore have developed long-term water strategies that rely on highly treated effluents as a substitute for potable water in case of severe drought. Even though pharmaceuticals can effectively be removed by advanced treatment plants, pharmaceutical residues are not regulated systematically. In the absence of a normative framework for pharmaceutical control, countries lack a comprehensive policy to address these environmental pollutants.

While still in the early stage of implementation, the Swiss strategy involves a large-scale national wastewater treatment plant upgrade project. Associated regulations are designed to verify the effectiveness of measures to eliminate trace organic substances in wastewater treatment plants. Switzerland is the first country to openly decide that pharmaceuticals constitute a potential environmental insult sufficient to justify application of the precautionary principal. It is too early to determine whether this "Level 1" intervention will generate meaningful benefits for public health. But Swiss regulators implicitly preferred possible critiques about inefficiency in use of public funds over the risk of negative health impacts because of government inaction. Table 1 also reflects California's decision to require residual pharmaceutical monitoring in potable reuse groundwater recharge projects. Unlike Switzerland and California, in other jurisdictions pharmaceutical residues monitoring is not mandatory, but driven by formal or informal guidelines.

Regarding the pharmaceuticals being monitored, there are several recurring substances which are prioritized; Gemfibrozil (lipid

**Table 1**  
Regulatory strategies for monitoring pharmaceuticals in recycled wastewater.

Country	Region/Project	Purpose	Status	Treatment	Monitored substances	Water resource type tested	Regulatory framework
Australia	Western0020Australian (Perth) Project	Drinking water augmentation - groundwater recharge	Trial 2010–2014 Full operation: 2018	* WWTP * UF (ultra-filtration) * RO * UV * aquifer recharge	Carbamazepine Diclofenac Estrone	Monitoring points throughout the process	Australian Guidelines for Water Recycling 2006–2009 not mandatory
	Queensland (Western Corridor) Project	Drinking water augmentation - surface water reservoir	Constructed. Not active	* WWTP * MF (Micro-filtration) * RO * AOP * Surface water augmentation	ND	ND	
USA	Orange Country California	Groundwater replenishment (8 projects)	Active	* WWTP * MF/UF * RO * AOP * Groundwater replenishment	17 $\beta$ -estradiol Gemfibrozil Iopromide	Potable water recharge	Title 22 Regulations, CA Water Boards-Recycled Water Policy
	EPA UCMR	Data collection	Active	ND	Estradiol Estrinol Estrone Ethinylestradiol Testosterone	Drinking water	UCMR3
Switzerland	National Waste water treatment plant upgrade	Micropollutants treatment	Active	* WWTP * Ozonation * SSF (slow sand filtration) * Released into surface waters	Amisulpride Carbamazepine Citalopram Clarithromycin Diclofenac Hydrochlorothiazide Metoprolol Venlafaxine Candesartan	Influent and Effluents	DETEC Swiss Regulation SR 814.201.231.
Singapore	NEWater Project	Industrial/Drought reservoir	Active	* WWTP * MF * RO * AOP * Supplied to industries	Irbesartan Ibuprofen Naproxen Ketoprofen Triclocarban Gemfibrozil Diclofenac Carbamazepine Trimethoprim Salicylic Acid Paracetamol Carbamazepine	Drinking water Reclaimed water	None
Israel	Tel Aviv Region	Identifying sewage leakage into the water supply system	Active	No treatment	Carbamazepine	Drinking water	None

regulator), Iopromide (Iodinate contrast media), Carbamazepine (anti-epileptic), Diclofenac (anti-inflammatory) and steroid hormones. Our analysis suggests that particular groups of compounds increasingly constitute a common source of concern in drinking water treatment processes around the world. Should regulators be concerned about pharmaceutical residues in effluents utilized for irrigation and if so, what form should such regulation take? Because wastewater reuse is so ubiquitous in Israel, this question is particularly germane in the Israeli context.

### 3. Present and proposed pharmaceutical residual monitoring in Israel

As Israel's population grows, so does the consumption of pharmaceuticals. Like most Western societies, increasing investment in the health-care sector, advances in research and development, pervasive global market availability of pharmaceuticals, and aging populations in industrialized countries have led to a significant increase in the consumption of pharmaceuticals over the last few decades (Van Boeckel et al., 2014). According to 'Maccabi Health Services', one of the four

leading health maintenance organizations operating in Israel, 72% of pharmaceutical categories showed an increase in consumption between 2014 and 2016, while only 28% of categories showed a decrease. For example, estrogen consumption (ATC code: G03C) increased by 7.1%, from 9,146,251 DDD in 2014 to 9,800,019 DDD in 2016. Define Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO world health organization, 2017). Moreover, at 2%, Israel's annual demographic growth rate is more than three times faster than the OECD average (OECD, 2017). The expanding population accelerates pharmaceutical consumption, which is already increasing on a per capita basis. Because WWTPs do not always eliminate pharmaceutical residues, the extensive use of effluents for irrigation poses a potential risk to the local environment and public health.

#### 3.1. Present pharmaceutical residual monitoring in Israel

Like most parts of the world, in Israel, pharmaceuticals are neither treated nor monitored in wastewater, agricultural produce, or the environment within a systematic regulatory framework. The country's

*Water Law, 1959* establishes a framework for the control and protection of Israel's water resources, but its extensive regulations are silent on the regulation of pharmaceuticals (*Water Law, 1959*). *The Public Health Regulations (Purification of sewage intended for irrigation), 1981*, prohibits irrigation of crops with wastewater unless they are effluents treated in accordance with the regulations' provisions. While there are strict limits on parameters such as BOD, COD, TSS, E-coli, metals, NO<sub>3</sub>, Cl, Ca, Mg, Na, and several other conventional contaminants, there is no mention of pharmaceutical monitoring in effluents or in agricultural produce (*Public Health Standards, 2010*).

Any strategy for upgrading water quality is complicated by bureaucratic unruliness: Oversight of water resources regulation is divided between several government agencies – Ministries of Environment, Health and Energy/Water – who frequently disagree about appropriate regulatory strategies. Nonetheless, in interviews with a range of authorities, there is a rare consensus that financial dynamics make standards for monitoring or treating pharmaceuticals in wastewater a significant challenge.

About 530 million cubic meters of wastewater are produced annually in Israel. To address the country's water shortage, 93% of the total wastewater is treated and 86% of treated wastewater under secondary and/or tertiary level treatment is later reused for agriculture, streams rehabilitation, groundwater recharge (SAT), industry and gardening, replacing conventional fresh water sources for these purposes (Israel Water Authority – IWA, 2017a). By way of contrast, Spain recycles some 17% of its sewage, Australia-10% and the USA only 1%. Within 5–7 years Israel is expected to increase the use of the total national effluent produced each year from 86% to 90% (IWA, 2017a).

Treated wastewater in Israel is regarded as a valuable financial resource for agricultural irrigation which utilizes 56% of Israel's 2 billion cubic meter total water supply (CBS, Israeli Central Bureau of Statistics, 2017). Effluents constitute a critical substitute for freshwater and a reliable water source, providing Israeli farmers with over of 50% of their irrigation needs (IWA, 2017a). The price for one cubic meter of potable water (desalinated or fresh water) for agricultural use is 2 shekels/m<sup>3</sup> (0.57 US dollar/m<sup>3</sup>), while the price for treated effluents for irrigation is (on average) less than 1.20 shekels/m<sup>3</sup> (0.34 US dollar/m<sup>3</sup>) (IWA, 2017b). This constitutes a significant financial difference for Israeli farmers given required water consumption levels on agricultural lands that are largely arid.

Israel has 89 wastewater treatment plants, which are not designed to produce effluents that meet Israel's 'Drinking Water Regulations' (*Public Health Standards, 2013*). Some (63) large WWTPs in Israel utilize intensive treatment methods, typically involving activated sludge secondary treatment, and frequently including tertiary processes as well.

Although pharmaceutical residues are not included among the country's drinking water standards, there is rising concern in the Israeli Ministry of Health (IMH) about the associated risks. For instance, Carbamazepine has been sampled by IMH laboratories in many drinking water wells and several WWTPs on a regular basis as an indicator of wastewater influence (IMH Israeli Ministry of Health, 2017c). Because of its conservative (non-biodegradable) and hydrophobic nature, Carbamazepine is an excellent indicator that wastewater is contaminating a drinking water source (Clara et al., 2004; Fenz et al., 2005; Gasser et al., 2010).

In total, about 1000 groundwater wells provide drinking water in Israel. Yet, only 187 of them have ever been tested for Carbamazepine as an indicator for wastewater influence. A nascent monitoring survey implemented between 2012 and 2017 revealed that 34 (18%) of drinking water wells tested positive (IMH Israeli Ministry of Health, 2017c). *Caffeine* and *Acesulfame* – a common sweetener – are also used as indicators of anthropogenic water pollution. Thus far, there has been no significant effort to characterize the magnitude of the contamination nationwide or the associated risks (Hen, 2019).

Israel is unique in the multiple routes through which its population is exposed to pharmaceutical residues. Human exposure occurs through

drinking water pathway, but exposure also takes place through consumption of fruits and vegetables irrigated with reclaimed water. For almost a decade, researchers have been studying the process of pharmaceutical uptake by plants in Israel (Golan-Rozen et al., 2015; Goldstein et al., 2014; Malchi et al., 2014; Mordechay et al., 2018) as well as the biodegradability of pharmaceutical compounds in agricultural soils (Grossberger et al., 2014). Carbamazepine and its metabolites have also been detected in urine samples from individuals exposed to carbamazepine (in a controlled study) via dietary consumption of fruits and vegetables irrigated with reclaimed wastewater (Fedorova et al., 2016; Paltiel et al., 2016).

As the world leader in utilization of treated effluents for agricultural irrigation, by default, the country's environment and public health have become an epidemiology experiment. There is strong justification for upgrading the monitoring, research, and regulation of pharmaceutical residuals in the water cycle. The results will have significance not only for local decision making, but for the design of waste water reuse strategies worldwide (Avisar and Ronen-Eliraz., 2017).

Ministry of Health officials in Israel are forthright about the learning process which takes place prior to regulation. Two main reasons cited for the absence of pharmaceutical residue regulation involve uncertainty about the potential health effects of such residues and the limited available resources for regulating them. Rather than adopting a "precautionary" approach, they prefer to wait until proven negative health effects from irrigation with effluents emerges. For instance, if industrial pretreatment failure or poor performance at a WWTP is not discovered in time, it is deemed a higher institutional priority than any hypothetical health impacts associated with small residual concentrations of Carbamazepine. To date, the Ministry of Health is working with the Ministry of Environmental Protection to initiate a program that would limit pharmaceutical waste in the pharmaceutical industry effluents (Weinberg, 2019).

Wastewater reuse is not the only area where exposure from pharmaceutical residuals is ignored. Although the IMEP states that industrial pharmaceutical wastewater is currently monitored in a pilot survey, the data are not made public, and no information is provided about the rationale according to which pharmaceutical industries are monitored. In the rare cases where mandatory sampling is required, the public is not informed about which pharmaceutical substance is monitored, how standards and concentrations are chosen or enforced. The lack of transparency undermines public engagement and oversight.

Of even greater concern, hospitals are not even included in regulation under Israel's *Licensing of Businesses Law (1968)* and their wastewater is not defined as "industrial wastewater". Hospital wastewater is directly discharged into nearby municipal wastewater system without any *in-situ* pre-treatment required. The wastewater streams from hospitals frequently contain assorted concentrations of microbial pollutants, clinical emissions (such as blood, tissue), toxic metals, highly concentrated pharmaceutical residues as well as radioactive materials. Government estimates suggest that the average hospital in Israel contributes between 5% and 30% of the medical substances found in municipal wastewater (IMEP Israel Ministry of Environmental Protection, 2017).

If the environment and public health are to be protected from potentially harmful exposures, pharmaceutical residues should be monitored in effluents on a regular basis, with regulatory intervention triggered when high concentrations are measured. This is most efficiently done through reliance on pharmaceutical tracers that are chemically stable and not biologically degradable. Tracers must be easily detectable by commonly available analytical technology (IWW, 2014). Yet, before these can be selected, it is critical to prioritize the pharmaceutical residues that need to be monitored.

### 3.2. Proposed pharmaceutical residual monitoring in Israel

Different methods for prioritization of monitoring pharmaceuticals

in wastewater have been suggested in Western Europe, North America, and Asia in order to focus attention on the residues that are most hazardous for the environment (Besse et al., 2008; Guo et al., 2016; Roos et al., 2012; Wu et al., 2017). Typically, these approaches use information about pharmaceutical consumption to assess likely exposure scenarios (also referred to as PEC: Predicted Environmental Consumption) and compare them for potential risk. At the same time, there have been only limited efforts to prioritize pharmaceutical monitoring in water throughout less developed regions of the world, including Eastern Europe, Africa, and South America (Al-Khazrajy and Boxall, 2016; Aubakirova et al., 2017). Characterizing pharmaceutical exposures in these regions is more challenging because information about pharmaceutical consumption is either limited or nonexistent.

This is not the case with Israel, however, which collects broad data on pharmaceutical consumption but whose healthcare organizations are unwilling to disclose them in meaningful detail, to the public (Clalit Health Services, 2017; Maccabi Health Services, 2017). Accordingly, designing a prioritization process for Israeli pharmaceutical residue monitoring, ultimately relies on many assumptions and extrapolations, using methods which may also be applicable in economically less-developed regions.

A list of recommended pharmaceutical standards to be monitored in Israel effluents is proposed, based on an analysis of common pharmaceutical residues detected in surveys in Israel's effluents in 2012 (IWAIsrael Water authority, 2012), the international literature, the results of monitored pharmaceutical programs internationally and the changes in local pharmaceutical consumption by pharmaceutical category (Maccabi Health Services, 2017). The following are suggested as relevant criteria for selecting pharmaceutical residue concentrations that need to be monitored in Israeli effluents and drinking water:

- o Presence in meaningful concentrations in effluents and other water resources;
- o Percentage of positive findings in Israeli effluents in IWA survey, 2012;
- o Prioritized in water monitoring program abroad;
- o Availability of analytical laboratory infrastructure that can complete tests at a reasonable cost.
- o Positive trends in local consumption levels;
- o Negative impact on human health and/or the environment;

This final criterion is given greater weight in the selection process than the first five, as it constitutes a "bottom-line" justification for any resulting regulatory intervention.

Ideally, prioritizing pharmaceutical residuals for monitoring would enjoy the benefit of precise sales data for specific pharmaceuticals, choosing the most consumed, toxic, and persistent, (resistant to wastewater treatment) chemicals. Unfortunately, such data are not yet available in Israel, and the proposed prioritization framework relies on consumption according to pharmaceutical categories making the most plausible conclusions possible given limited data. The evaluation did, however have the advantage of access to a 2012 comprehensive study conducted by the IWA regarding the pharmaceuticals it detected in secondary effluents: Diclofenac, Ibuprofen, Naproxen, Gemfibrozil, Bezafibrate, Carbamazepine, Atenolol, Metoprolol, and Sulfamethoxazole (IWAIsrael Water authority, 2012).

Over a decade ago, the Global Water Research Coalition (GWRC) prepared one of the first manuals in the field: 'Development of an International Priority List of Pharmaceuticals Relevant for the Water Cycle' (GWRC, 2008). The list identifies compounds that are most likely found in water supplies and that may have significant impacts on human and environmental health. Ten high priority pharmaceuticals are identified. According to this study, these compounds represent the minimum number of substances that should be considered in any study on pharmaceuticals in water management, as the rest of the list represent secondary targets (GWRCGlobal Water Research Coalition, 2008).

Although the list is ten years old, it still offers a helpful foundation for pharmaceutical prioritization today, because it is based on criteria that include: regulation, consumption, physicochemical properties, degradability, resistance to treatment, human toxicity and ecotoxicity.

Based on these considerations and the above criteria for prioritizing pharmaceutical residues that need to be monitored, Table 2 presents the following:

- o Pharmaceutical standard name and use;
- o Pharmaceutical WHO ATC class code;
- o Average concentration and percentage of positive findings in effluents, conducted in the 2012 survey (IWA, 2012); (over 50% positive findings - 2 points; meaningful concentration- 1 point)
- o Whether the pharmaceutical is monitored in overseas projects reviewed in this study (1 point for each country);
- o Negative impact on human health and the environment (1–5 points): the pharmaceutical groups' eco-toxicity ranking is based on a few scientific publications and reports, selected for their high quality which report the effects of pharmaceuticals on live organisms. The aggregate score is based on the following criteria:
  - a. Acute toxicity (Mortality) – 5 points
  - b. Carcinogenic effects or Developmental disorders – 4 points
  - c. Behavioral disorders – 3 points
  - d. Low level physical impacts (allergies, rashes, etc.) – 2 points
  - e. No known effects yet - 1 point
- o Pharmaceutical rank based on the number of citations in prioritization documents, analyzed by GWRC, 2008 (if included in the top 10 on list- 1 point);
- o The changes in the consumption levels of the given pharmaceutical category (2014–2016) (increase- 1 point);
- o The total score for examined criteria; and
- o A recommendation to be monitored in Israel's effluents as a pharmaceutical group indicator.

All pharmaceuticals receive a score according to each criterion, with each dot in the table representing a single point. The highest score in each pharmaceutical group (e.g. Anti-inflammatory, beta-blocker etc.) is recommended to be monitored as a *pharmaceutical residue with a relatively high-environmental risk*.

Creating lists of compounds that should be monitored is a relatively easy task. The challenge of course involves implementation – applying these general decision rules to the specific, management dilemmas facing monitoring programs. For instance, how can we determine if a 0.395 µg/L concentration of Diclofenac in effluents has more potential to cause negative health effects than Naproxen, in an identical concentration? And how can such a ranking system be dynamic, reflecting the steady expansion of knowledge in the fields of toxicology and epidemiology? To be sure it is a blunt instrument, but surely better than the intuition which seems to drive most pharmaceutical waste monitoring programs to date, given only limited data as in Israel.

The key advantage of the proposed system involves its simplicity. As mentioned, the eco-toxicity ranking proposed in this section is based on several recent scientific publications and reports and can easily be updated as new studies are published, showing more (or less) adverse effects on live organisms. While not a tool for precise risk assessments, this ranking system can help determine which pharmaceutical residue has greater potential to cause harm to public health, compared to other groups of pharmaceuticals (for instance: EDCs vs antibiotics) or within the same group (Diclofenac vs Naproxen for the Anti-inflammatory group).

Generally, adoption of the suggested ranking system and intervening when concentrations above de minimis trace levels are identified, can help contract the antibiotics group, that without abatement may lead to resistant bacteria and gene development, allergies, and cancer (thus ranked with 4 points), to the antiepileptic group of drugs, that may initiate developmental and behavioral changes in live organisms (thus,



**Table 2**  
Recommended pharmaceutical standers to be monitored in Israel's environment.

Pharmaceutical	Use	ATC class code	Israel-average conc. In effluents 2012 ug/L	Percentage of positive findings in effluents 2012	Monitored in projects abroad	Negative impact on the environment and/or live organisms	Groups' ecotoxicity rank (1-5)	Priority pharmaceutical (GWRC, 2008)	2014-2016 % change (Maccabi) for pharmaceutical class (not the specific drug)	Current study total score	Recommended for monitoring in Israel
Diclofenac	Anti-inflammatory	M01A	0.395	86%	Australia, Switzerland, Singapore	Oaks et al., 2004; Mcrae et al., 2017; Guiloski et al., 2017;	Death, Genotoxicity 5 *	3	+3.1%	11	Diclofenac Recommended
Ibuprofen			0.727	75%	Singapore	Ragugnetti et al., 2011;		4		9	-
Naproxen			0.361	100%	Singapore	Lucero et al., 2015;		5		9	-
Gemfibrozil	Lipid regulator	C10A	17.3	25%	California, Singapore	Ruhi et al., 2016; Teles et al., 2016; Barreto et al., 2017; Salesa et al., 2017;	Genotoxicity 4 *	10	+9.4%	9	Gemfibrozil Recommended
Bezafibrate			1.1	75%				6		6	-
Carbamazepine	Antiepileptic	N03A	1.31	100%	Australia, Switzerland, Singapore	Jarvis et al., 2014; Oropesa et al., 2016; Qiang et al., 2016; Kohl et al., 2019;	Developmental and behavioral changes 4 *	1	+15.8%	10	Carbamazepine Recommended
Atenolol	Beta blocker	C07A	0.878	100%		Ings, J. S. et al., 2012;	Developmental Disorders 4 *	7	+0.8%	6	-
Metoprolol			0.161	75%	Switzerland	Godoy et al., 2015;		22		7	Metoprolol Recommended
Sulfamethoxazole	Antibiotic (Sulfonamides)	J01E	0.280	100%		Gothwal & Shashidhar, 2015; Carvalho & Santos, 2016; Kwon et al., 2016; Straub, 2016;	Resistant bacteria and genes, allergies, cancer 4*	2	ND	6	Insufficient data
Estrogens (Estradiol, Estrone)	EDCs	G03C	ND	ND	California, Australia	Orlando and Guillette, 2007; Mejjide et al., 2016	Carcinogenic 4 *	ND	+7.1%	7	Estrogens Recommended

\*ND=No Data



also ranked with 4 points). Moreover, the proposed rules for prioritizing allows for ranking within a given pharmaceutical group. For example, although both belong to the anti-inflammatory group of pharmaceuticals, Diclofenac and Naproxen are two different drugs, that almost certainly have different effects on live organisms, and the natural environment: Diclofenac has been shown to have adverse effect on several aquatic animals and vultures (Oaks et al., 2004), as recently reviewed by Lonappan et al. (2016). Subsequent studies show toxicologically-relevant adverse outcomes and bioconcentration of diclofenac at environmentally-relevant levels in galaxiid fish (Mcrae et al., 2018), and histological (tissues), hematological, immunotoxic effects in fish exposed to treated sewage effluents containing Diclofenac (Guiloski et al., 2017; Näslund et al., 2017; Ribas et al., 2016).

Thus, according to the suggested ranking system, Diclofenac would receive 5 points, as it is associated with mortality in vultures. On the other hand, the rank given to Naproxen is based on its ability to induce oxidative stress (increased lipid and protein oxidation) and genotoxicity in amphipods (Lucero et al., 2015) and gene alternations (Stancová et al., 2015). Thus, Naproxen would be ranked as a “4” according to the suggested method, allowing for a relatively transparent, comprehensible and highly convenient comparison between two pharmaceuticals for the anti-inflammatory group.

This basic model can be developed in the future, as more data accrue. The suggested ranking model should evolve as available knowledge about the various adverse effects of pharmaceutical residues expands. Moreover, it needs to be applied beyond individual chemicals, to include the effect of mixtures of compounds on live organisms or the environment.

#### 4. Conclusions: regulatory recommendations and expected challenges

Wildavsky (1979) argued that people wrestle with policy problems only when they sense that feasible solutions exists. Several countries have already demonstrated proof of concept with regards to the potential for monitoring and treating pharmaceutical residues at different levels. Programs in Australia, Singapore, California (USA) and Switzerland suggest that there are alternatives for measuring and treating pharmaceutical residues, which can be successfully eliminated from water, using advanced treatments, thus protecting the environment and public health.

On the other hand, there are challenges and risks associated with such projects: financial obstacles, unknown degradation products, and difficulties in establishing new regulations. Given the alternatives proposed in this document, Israel should consider monitoring the suggested pharmaceuticals (Diclofenac, Gemfibrozil, Carbamazepine, Metoprolol and various hormones) currently as health indicators, or as WWTP performance indicators after treatment plants are upgraded. (as did Switzerland).

Several regulatory approaches come to mind when considering an effective strategy for monitoring or treating environmental pharmaceutical residues. In analyzing the current global regulation for pharmaceutical residual substances detected in water and the environment, it is impossible not to mention two standard regulatory principals which are particularly appropriate: the *precautionary principle* and the *polluter pays principle*.

In the past two decades, the *precautionary principle* has been at the forefront of the management and assessment of risks in the fields of environmental protection and human health. In environmental policy and regulation, where the scientific knowledge about risks can be persuasive, but not conclusive and unequivocal, it is important to be cautious in adopting a management approach and as a strategic principle for policy making (Karassin, 2017). The precautionary principle offers a particularly appropriate paradigm for addressing the environmental pharmaceutical residues problem. Though direct linkages have yet to be established between human health and environmental

exposure to lipid regulators, antibiotics, NSAIDs, and other pharmaceuticals in various water resources, enough preliminary evidence has emerged to make caution a necessity in this matter.

The assumption by most policy makers is that unrestricted effluent irrigation is limited and involves implicit risks, whose severity needs to be characterized prior to any regulatory intervention. But as water scarcity drives countries to expand the scope of wastewater recycling to levels currently found in Israel, the potential impact is too significant to ignore. A precautionary approach seems prudent, given the exposure scenarios associated with ever-expanding wastewater utilization.

A second environmental principle that should inform regulatory strategies is the *polluter pays principle*. Adopted by OECD in 1972 as an economic principle for allocating the costs of pollution control (OECD, 1992), the Polluter-Pays Principle holds polluters should bear the “costs of pollution prevention and control measures required to ensure that the environment remain in an acceptable state” (OECD, 1992). The pharmaceutical industries, hospitals and individuals utilizing medication can be expected to internalize any associated externalities (Muthukrishnan, 2015), and taxed to cover the additional expenses associated with new monitoring and analytical requirements.

Relying on these two approaches, several general and specific regulatory recommendations emerge from this study:

The lack of basic data about pharmaceutical consumption constitutes an obstacle to cost effective monitoring and control programs. A database listing all yearly pharmaceutical sales should be created and made accessible to the public. Health providers should be required to provide relevant information in real time so that pharmaceutical release can be more precisely estimated.

Legislation needs to be enacted creating a simple system for household medical waste collection and disposal. In Israel more than 85% of the public with medications, eventually throws them into the garbage or flushes them down the toilet or sink (CBS, 2016). Less than 14% of the Israelis return unused medications to pharmacies (CBS, 2016). This is not unusual. It is estimated that the annual medical collection of unused pharmaceutical products rate ranges from 0.01 kg/capita (USA, Canada, Hungary) to 0.03 kg/capita in Australia (Barnett-Itzhaki et al., 2016). Disposal instructions on medication containers are not enough. Incentives for responsible return should be created, public awareness expanded, and collections programs in retirement communities and hospitals established (Barnett-Itzhaki et al., 2016).

If implemented, such measures will under lately reduce moderately the release of pharmaceuticals into the environment. Nonetheless, most pharmaceutical discharges to the environment will continue to be the result of human excretions (Keil, 2008). As populations and drug production/consumption grow, pharmaceuticals will find their way to the environment in greater volumes.

While there is evidence that pharmaceuticals reach the environment, including the food supply, the precise risk to public health from low level exposure to pharmaceuticals in the environment is currently unknown. More information about whether or how human health is affected by environmental pharmaceutical pollutants is required. Under conditions of such significant uncertainty, information gathering is an essential tool for managing informed policy.

One approach to addressing these dynamics involves a Human Bio-Monitoring initiative (HBM). Such programs have emerged as a tool for assessing cumulative exposure to complex mixtures of chemicals, and for monitoring chemical exposures in general population (Sexton et al., 2004). Many countries, including the US, Canada, Germany, France, and Belgium, have developed National Biomonitoring Programs (Choi et al., 2015). But frequently, pharmaceuticals are not included in current HBM programs (Berman, 2017a). Regular urine samples from children and adults can not only provide ongoing surveillance of population exposures to a range of contaminants (e.g., pesticides and environmental tobacco smoke), but also offer critical information about pharmaceutical release into wastewater.

As presented in previous sections, hospital effluents throughout the

world are released into municipal WWTPs without pre-treatment. These effluents contain a variety of pharmaceuticals, potentially reaching drinking water or serving as irrigation sources with likely risks to the environment and public health. Regulatory oversight of wastewater releases and enforcement of pretreatment standards – along with cooperative efforts with the pharmaceutical industries – are an important part of any regulatory strategy for countries that are home to such facilities.

While programs exist which can be emulated, many associated challenges can be anticipated. When the possibility of monitoring or treating pharmaceuticals in effluents is raised, officials and experts invariably cite the economic implications as one of the main concerns (Berman, 2019; Caspi-Oron Sarit, 2017; Groisman, 2017; Inbar, 2017; Karassin, 2017; Weinberg, 2019). Analytical laboratories need to be established for effluent testing that are separate from facilities used to monitor drinking water. New regulatory requirements can be phased in, allowing local and national monitoring programs the time to expand their capacity to address this new challenge.

Another problem involves the constant development of new pharmaceutical products, a process that creates a moving regulatory target. Furthermore, enhanced scientific capabilities and analytical devices make it easier to detect small concentrations of many chemical substances. And even so, not all pharmaceutical compounds can be detected. Innumerable, unidentified pharmaceutical degradation products are present in the environment, that have yet been identified by the scientific community (Bueno et al., 2016; Daouk et al., 2016; Yin et al., 2017).

Pharmaceutical degradation products are abundant, varied, and may be even more chemically stable than the original molecule (Gozlan et al., 2013). This is of particular concern when they form an active chemical structure that can be toxic, and pose a risk to organisms, or in the case of antibiotic degradation products, lead to the development of resistant bacteria (Gozlan et al., 2010; Lamm et al., 2009). Such pharmaceutical substances can no longer be considered “transparent”. Investigating the processes of decomposition under different conditions, monitoring and measuring these compounds is of great importance. This is especially true in countries where agricultural irrigation increasingly relies on treated effluents and their cocktails of pharmaceutical residues (Avisar and Ronen-Eliraz, 2017; Tal, 2016).

Pharmaceutical residues, like pesticides, do not belong in the human diet, and ideally should not be present in drinking water, fruits, and vegetables. The time has come for countries, like Israel, that rely on effluent reuse for agricultural irrigation and other purposes, to develop programs for monitoring pharmaceutical residues. Resources should be found for studying their effect on the environment, live organisms, and regulating them when concentrations go beyond the minimized levels. We suggest a monitoring program that is informed by the *precautionary* and *polluter pays* principles, prioritizing those substances that have the greatest likelihood of harming human health and the environment.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jenvman.2019.109794>.

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