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TREND EDITORIAL

Pharmacopollution and Household Waste Medicine (HWM): how reverse logistics is environmentally important to Brazil

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Abstract Pharmacopollution is a public health and environmental outcome of some active pharmaceutical ingredients (API) and endocrine-disrupting compounds (EDC) dispersed through water and/or soil. Its most important sources are the pharmaceutical industry, healthcare facilities (e.g., hospitals), livestock, aquaculture, and households (patients' excretion and littering). The last source is the focus of this article. Research questions are "What is the Household Waste Medicine (HWM) phenomenon?", "How HWM and pharmacopollution are related?", and "Why is a reverse logistic system necessary for HWM in Brazil?" This article followed the seven steps proposed by Rother (2007) for a systematic review based on the Cochrane Handbook and the National Health Service (NHS) Center for Reviews Dissemination (CDR) Report. The HWM phenomenon brings many environmental, public health, and, social challenges. The insufficient data is a real challenge to assessing potential human health risks and API concentrations. Therefore, the hazard of long-term exposure to low concentrations of pharmacopollutants and the combined effects of API mixtures is still uncertain. HWM are strongly related to pharmacopollution, as this review shows. The Brazilian HWM case is remarkable because it is the fourth pharmaceutical market (US$ 65,971 billion), with a wide number of private pharmacies and drugstores (3.3: 10,000 pharmacy/inhabitants), self-medication habits, and no national take-back program. The HWM generation is estimated in 56.6 g/per capita, or 10,800 t/year. The absence of a reverse logistics for HWM can lead to serious environmental and public health challenges. The sector agreement for HWM is currently under public consultation.

Keywords Active pharmaceutical ingredients (API) · Reverse logistics · Household waste medicine · Discard

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Introduction

This article addresses the household waste medicine (HWM) phenomenon, how it is generated, and what are its consequences to the environment and public health. According to Macedo (2015, p. 2), HWM is a disused/leftover medicine generated by a household patient. HWM does not include home care services leftovers, considering healthcare waste (HCW, also known as medical waste). HWM have two household-related source pathways (Macedo 2015): (1) active pharmaceutical ingredients (API) and endocrine-disrupting compounds (EDC) (Kostopoulou and Nikolau 2008) excreted (primary pathway) and (2) HWM directly discarded in sewage treatment plants (STP) (Luo et al. 2014) or littered (secondary). The secondary pathway is a result of HWM discard in (1) toilet and sinks (solid or liquid contents) (Jones et al. 2003) and (2) household waste (without further treatment, recycling, or sanitary landfilling) (Rodrigues 2009), representing an important household

micropollutant contamination source (Rodrigues 2009). The API dispersion through sewage is continuous, a result of the excretion (related to the prolonged and wide drug use) and inappropriate HWM disposal in sink and toilet (Jones et al. 2003, 2005).

HCW and HWM (pharmaceuticals) are part of the emerging contaminants, such as steroid hormones, pharmaceuticals and personal care products (PPCP), industrial chemicals, and pesticides.[1] Some studies analyze the household micropollutants as part of expanded analytical groups: other contaminants of organic effluents (Barnes et al. 2008), PPCP,[2] metabolites and EDCs,[3] illicit drugs,[4] and trace organic contaminants (TrOCs) (Yang et al. 2013). HWM research fields encompass (ABDI 2013; Touraud et al. 2011): (i) API dispersion through environment and removal treatments; (ii) pharmacopollution effects on the environment and on non-human life forms (e.g., algae, birds, crustaceans, cnidarian, and fish); and (iii) the wide use of medicines, accidental ingestion and self-medication habits, abusive use, and other public health matters. There are many legal challenges about HWM. In Europe, there are no guides and disposal standards for the most part of micropollutants and Directive 2008/105/EC mentions only a few of them, such as nonylphenol, bisphenol A, and others (Luo et al. 2014). The HWM relationship among information, regulation, pharmacopollution, excretion, reverse logistics, and other destinations is synthesized in Fig. 1[5]:

Methods

This article followed the seven steps proposed by Rother (2007) for a systematic review based on the Cochrane Handbook and the National Health Service (NHS) Center for Reviews Dissemination (CDR) Report. (i) Research questions are: "What is the Household Waste Medicine (HWM) phenomenon?", "How HWM and pharmacopollution are related?", and "Why is a reverse logistic system necessary for HWM in Brazil?" (ii) The bases for literature review were: EBSCO HOST, "Portal de Periódicos CAPES/MEC," and SciELO. (iii) The article assessment criteria were (Marconi and Lakatos 2003): feasibility, novelty, timeliness, relevance, and viability. Among the 205 selected articles, 60 were out of scope, including pharmacopollution originated exclusively or predominantly by farming, HCW, home care services or health facilities, divergent conclusions from data, and description only of waste treatment technologies. The remaining publications were also again assessed according to the relevance; to establish the most cited articles, relevant cross-reference studies were reconsidered. (iv) December 2015 was the deadline cut-off. At the end, authors got one remaining/selected article from EBSCO HOST, 208 articles from Portal de Periódicos CAPES/MEC (148 selected), and four articles from SciELO (all selected). (v) Main interdependent research areas were sanitation, environment, health, and socioeconomics (reverse logistics is implicit in the last area). (vi) The frequently cited articles adopted as main references were: Bound et al. (2006); Braund et al. (2009); Persson et al. (2009); Slack et al. (2007); Tong et al. (2011); and Vellinga et al. (2014). (vii) Reviewers' suggestions were incorporated. Removal rates, concentration, and environmental data presented in this review aim to build a broad pharmacopollution panorama and stimulate further studies, but are not part of the focus.

Pharmacopollution and HWM

Pharmacopollution is a health and environmental outcome of some active pharmaceutical ingredients (API) and endocrine-disrupting compounds (EDC) dispersed through water and/or soil. Its most important sources are the pharmaceutical industry, healthcare facilities (e.g., hospitals), livestock, aquaculture, and households (patients' excretion and littering) (Fig. 1). The veterinary APIs (whether for animal use only or not) are not part of this review, but they may be considered when analyzing household-related environmental pharmacopollution. Information about veterinary API dispersion is available in Brambilla and Testa (2014). Pharmacopollution is a mixture of drugs and its source is the wide use of many medicines concomitantly (Jones et al. 2003, 2005; Vajda et al. 2011). There are more than 4000 medical and veterinary APIs (Mompelat et al. 2009; Arnold et al. 2014). The studies about pharmacopollution risks to environment, life, and water resources became more prominent in the last 10 or 15 years (Arnold et al. 2014; Halling-Sørensen et al. 1998, Kostopoulou and Nikolau 2008; Ternes 1998, Ternes et al. 1999a, b, Xu et al. 2009).

[1] Farré et al. 2008; Gavrilescu et al. 2015; Jelic et al. 2011; Valcárcel et al. 2011a; Joss et al. 2006; Kümmerer 2009; Luo et al. 2014, Muñoz et al. 2008; Rodríguez-rodríguez et al. 2014.

[2] Behera et al. 2011; Blair et al. 2013; Boyd et al. 2003; Boyd et al. 2004; Bu et al. 2013; Carballa et al. 2007; Edwards et al. 2009; Ellis 2006; Esplugas et al. 2007; Ferguson et al. 2013; Gagné et al. 2006; García et al. 2013; Kasprzyk-Hordern et al. 2008; Hedgespeth et al. 2012; Hijosa-valsero et al. 2010; Kasprzyk-Hordern et al. 2007; Kim et al. 2007; Kumar and Xagoraraki 2010; Kosma et al. 2014; Lapen et al. 2008; Li 2014; Li et al. 2013; Lishman et al. 2006; Liu and Wong 2013; Mcclellan and Halden 2010; Muñoz et al. 2008; Peng et al. 2008; Richardson et al. 2005; Topp et al. 2008; Walters et al. 2010; Xu et al. 2009.

[3] ABDI 2013; Auriol et al. 2006; Belgiorno et al. 2015; Bila and Dezotti 2007; Boyd et al. 2004; Chang et al. 2009; Esplugas et al. 2007; García et al. 2013; Jackson and Sutton 2008; Kumar and Xagoraraki 2010; Liu et al. 2010; Liu et al. 2009; Nakada et al. 2006; Pothitou and Voutsa 2008; Spongberg and Witter 2008; Stasinakis et al. 2008; Zhao et al. 2009.

[4] Kasprzyk-Hordern et al. 2007, 2008, 2009a, b.

[5] Ternes (1998); Jones et al. (2003); Ministry of Health (2006); Stuart et al. (2012); Ruhoy and Daughton (2007, 2008); Baquero et al. (2008); Kostopoulou and Nikolau (2008); Yiruhan et al. (2010); Valcárcel et al. (2011a); Pereira et al. (2012); WHO (2012); Garcia et al. (2013); Xie and Breen (2014); Acúrcio (2013); Arnold et al. (2014); RDC 306/2004; CONAMA Resolution 358/08.

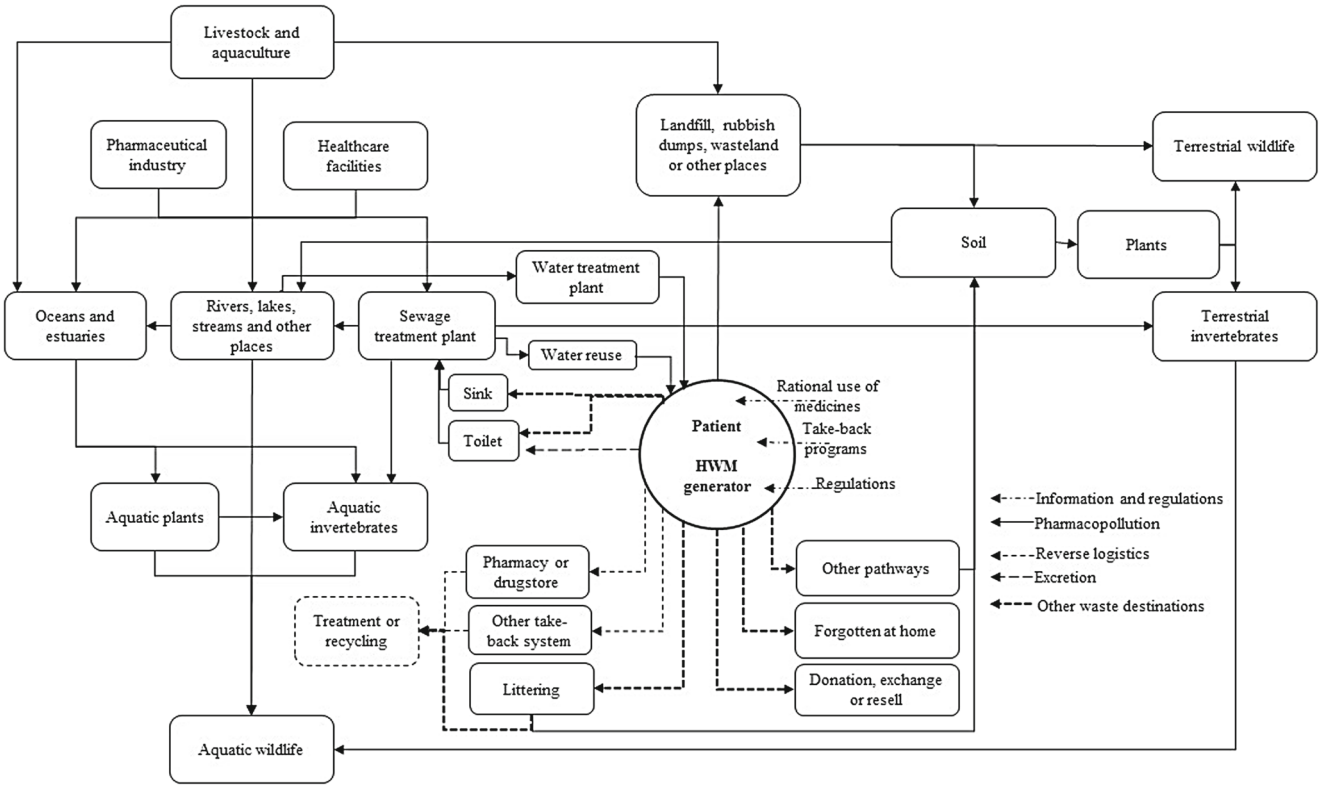

Figure 1 Household waste medicine coalescence pathways (HWM)

Many APIs are degradable by human metabolism, except for those of higher liposolubility, which tends to be adsorbed by organic matter and thus remain immobilized (in low bioavailability) (Acurcio 2013). EDC, API, and/or other micropollutants are present in many sewage treatment plants (STP), water treatment plants (WTP), water bodies (receiving discharges), and groundwater (Deblonde et al. 2011; Furuichi et al. 2004; Joss et al. 2006; Lapworth et al. 2012; Luo et al. 2014; Liu et al. 2010; Zhang et al. 2011). Synthetic steroids 17α-ethynyl estradiol (EE2), 4-nonylphenol (NP), and natural steroids such as estrone (E1), 17-B-estradiol (E2), and estriol have been found in many aquatic environments (Stasinakis et al. 2010). As strong endocrine disruptors, a medium/long-term toxicity and endocrine disruption caused by their occurrence in the aquatic environment is expected (Fent et al. 2006; Pruden et al. 2006; Jones et al. 2003). The API selection criteria in environmental studies suggest a "Matthew effect" (Daughton 2014b). Researchers tend to select the same API identified in previous studies rather than considering different ones and/or other API not investigated so far that may have an important connection to pharmacopollution (Daughton 2014b).

Some authors argue that there are no environmental or human health risks about API. To Cunningham et al. (2009) (GlaxoSmithKline laboratory), API potential environmental exposure on drinking water and fish consumption does not appear to pose an appreciable risk to human health. Environmental exposure to carbamazepine does not pose any significant risk to human health according to Cunningham et al. (2010) (Novartis laboratory). Taylor and Senac (2014) (Sanofi laboratory) argue that focused API generally poses no risk to the environment and human health. Schwab et al. (2005) (Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Merck and Schering-Plow laboratories) conclude that the focused API in surface and drinking water does not pose appreciable risks to human health.

Seasonality (Fernández et al. 2010) influences API and other micropollutants concentrations, as clearly evidenced by Yiruhan et al. (2010). The long-term effects of API dispersion to human health are not well known yet (Stackelberg et al. 2004). Some authors define preventive methodologies and approaches about API potential ecotoxicity and environmental impact. Jones et al. (2002, p.5021) compile the toxicity of seven main human medicine groups to aquatic organisms:

- Extremely toxic (EC_{50} < 0.1 mg l^{-1}): antibiotic (for microorganisms);
- Very toxic compounds (EC_{50} 0.1–1 mg l^{-1}): antibiotic (algae), antidepressant (crustaceans), cardiovascular drugs (crustaceans), and cytostatic (microorganisms);
- Toxic compounds (EC_{50} 1–10 mg l^{-1}): analgesic (crustaceans) and antiepileptic (cnidarian);
- Harmful compounds (EC_{50} 10–100 mg l^{-1}): analgesic and cytostatic (crustaceans and fish); and

- Non-toxic compounds (EC_{50} > 100 mg l^{-1}): antiepileptic (crustaceans and fish) and X-ray contrast (microorganisms, algae, cnidarian, crustaceans, and fish).

Fent et al. (2006) systematize API risk assessment in occurrence and concentration in aquatic environment, surface waters, human health interaction, acute and chronic ecotoxicological effects, and concentration effects and how they relate to different environmental levels. Crane et al. (2006, p. 26–33) reviewed the chronic toxicity of some APIs to aquatic organisms, classifying them by therapeutic class, action mode on humans, pathogen target, taxonomic group, specie, results from long-term exposure, and acute to chronic ratio.

Daughton (2014a) suggests an eco-directed sustainable prescription as a method to mitigate the API environmental consequences to reduce the use of medicines, and therefore decreasing excretion (prioritizing more extensively metabolizable medicines) and its littering. Dosage optimization is corroborated by Daughton and Ruhoy (2013). Cooper et al. (2008) environmental impact reduction strategy frames a preliminary risk assessment database about common pharmaceutical products. Five different combinations of toxicological and physicochemical data and its different risks are presented to support prescription (Cooper et al. 2008). As concluded by Roos et al. (2012) on their environmental risk assessment, the availability of input data may vary significantly, as well as information about environmental concentrations and bioconcentration (still scarce). Muñoz et al. (2008) highlight the low data availability challenge in their life cycle analysis for API.

Pharmacopollution contamination traces at Liuxi and Zhujiang rivers do not represent potability problems, but Shijing is pharmacopolluted by nearby cities' sewage (Zhao et al. 2009). In the USA, 81% of 47 groundwater samples from 18 states had organic effluent contaminants (Barnes et al. 2008, p.194). The maximum concentrations of prescription ingredients detected in USA samples are:

a) Antianginal: dehydronifedipine (0.022 μg/l);
b) Human and animal antibiotics: lincomycin (0.32 μg/l), sulfamethazine (0.36 μg/l), and sulfamethoxazole (1.11 μg/l);
c) Antidepressant: fluoxetine (0.056 μg/l); and
d) Antihypertensive: diltiazem (0.028 μg/l).

Maximum concentrations of non-prescription detected in USA samples are:

a) Anti-inflammatory: ibuprofen (3.11 μg/l);
b) Antipyretic and analgesic: acetaminophen (0.38 μg/l);
c) Stimulant: caffeine (0.13 μg/l); and
d) Caffeine metabolite: 1,7-dimethylxanthine (0.057 μg/l).

API concentrations of non-prescription ingredients tend to be higher than prescript ones. Another effluent-related ingredient detected was the insect repellent N,N-diethyltoluamide (concentration 13.5 μg/l). Fram and Belitz (2011) detected seven API in 2.3% of 1231 groundwater samples from California (USA). The mean concentration for API was like volatile organic compounds and higher than pesticides (Fram and Belitz 2011). Several mood stabilizers, analgesic, antibiotic, anticonvulsant, anti-inflammatory, antimicrobial, analgesic, and other API are detected in water from USA, Spain, and Germany (Table 1).

API is present in STP, soil, and even in tap water (Acurcio 2013; Verlicchi et al. 2012b). Water and sewage treatment plants are not specifically designed to eliminate micropollutants, so API can remain in tap water (Luo et al. 2014, p. 620). Usually, STP does not incorporate technologies to API monitoring or removal (Bolong et al. 2009). API removal technologies are not universally adopted and they increase the water treatment costs (Jones et al. 2003, 2005). Therefore, the incomplete API removal at STP results in dispersion through the environment (Joss et al. 2006; Valcárcel et al. 2011a, 2011b). In Rio de Janeiro city (Brazil), Stumpf et al. (1999) detected API removal rates in STP ranging from 12 to 90%. An STP in Louisiana (USA) reduced almost all API concentrations, perhaps due to the higher hydraulic retention time (HRT) of approximately 30 days (Conkle et al. 2008). API removal percentage in Mandeville system is higher than in conventional STPs, possibly related to the treatment time, too (30 days) (Conkle et al. 2008). In a northern Greece STP, the treatment process removes 86 to 99% EDCs, mainly by biodegradation (Pothitou and Voutsa 2008). The mefenamic acid and lincomycin concentrations level increased at Ulsan treatment station (26.3 and 11.2%, respectively) (Behera et al. 2011).

The 17β-estradiol, estrone, galaxolide, ibuprofen, iopromide, naproxen, sulfamethoxazole, and tonalide behaviors in an STP in Galicia (Spain) is (Carballa et al. 2004):

a) 17β-estradiol lipophilic characteristics and adsorption to the solid surface facilitate its removal along lipids during the primary treatment;
b) All detected compounds are partially removed in the second phase of effluent treatment, except for iopromide; and
c) The removal rates are 70–90% for fragrances, 60% for sulfamethoxazole, 65% for 17ß-estradiol, and 40–65% for anti-inflammatories.

Among the various technologies available for API removal, the wetlands and lagoons seem promising. They are cost-effective for API removal and their biological process is the most significant (Hijosa-valsero et al. 2010, Joss et al. 2005, Matamoros et al. 2007, Matamoros et al. 2008, Matamoros et al. 2009). As an example of how wetland may remove micropollutants, Matamoros et al. (2007) studied the behavior of phenoxy carboxylic acid (herbicide), organochlorines (insecticide), chloroacetanilide (herbicide), phenols (anti bactericide), phenylurea (fungicide), organophosphates (insecticide),

Table 1 Micropollutants concentrations in the USA, Spain, and Germany

Micropollutant	Location/reference	Common use	Mean individual concentrations/higher and lower concentration limits
Acetaminophen	Groundwater used for public drinking water supply in California Fram and Belitz (2011)	Antipyretic	1.89 μg/l
Carbamazepine		Mood stabilizer	0.42 μg/l
Codeine		Analgesic	0.214 μg/l
P-xanthine		Caffeine metabolite	0.12 μg/l
Sulfamethoxazole		Antibiotic	0.17 μg/l
Trimethoprim		Antibiotic	0.018 μg/l
Acetaminophen	Near-shore habitats of southern Lake Michigan (USA) Ferguson et al. (2013)	Antipyretic	5.36 ng/l
Caffeine		Stimulant	31.0 ng/l
Carbamazepine		Anticonvulsant	2.23 ng/l
Cotinine		Nicotine metabolite	4.03 ng/l
Gemfibrozil		Lipid regulator	7.03 ng/l
Ibuprofen		Anti-inflammatory	7.88 ng/l
Lincomycin		Antibiotic	4.28 ng/l
Naproxen		Anti-inflammatory	6.32 ng/l
Paraxanthine		Caffeine metabolite	46.2 ng/l
Sulfadimethoxine		Antibiotic	0.94 ng/l
Sulfamerazine		Antibiotic	0.92 ng/l
Sulfamethazine		Antibiotic	0.92 ng/l
Sulfamethoxazole		Antibiotic	0.92 ng/l
Triclocarban		Antimicrobial	5.72 ng/l
Trimethoprim		Antibiotic	5.15 ng/l
Tylosin		Antibiotic	3.75 ng/l
Antipyrine	River and drinking water of the Madrid region in Spain Valcárcel et al. (2011a)	Antipyretic	0.053–0.752 μg/l
Atenolol		Antihypertensive	0.318–6.167 μg/l
Bezafibrate		Antilipemic	0.234.000–2315 μg/l
Codeine		Analgesic	0.025–0.751 μg/l
Diclofenac		Anti-inflammatory	0.313–3.363 μg/l
Furosemide		Diuretic	0.262–3.222 μg/l
Gemfibrozil		Antilipemic	1288–5192 μg/l
Hydrochlorothiazide		Diuretic	1261–17,589 μg/l
Ibuprofen		Anti-inflammatory	2234–16,886 μg/l
Indomethacin		Anti-inflammatory	0.066–0.267 μg/l
Ketoprofen		Anti-inflammatory	0.043–1.567 μg/l
Mefenamic acid		Anti-inflammatory	0.026–0.104 μg/l
Metoprolol tartrate		Antihypertensive	0.025–0.076 μg/l
Nadolol		Antihypertensive	0.016–0.062 μg/l
Naproxen		Anti-inflammatory	0.387–3.140 μg/l
Paracetamol		Analgesic	0.188–2.813 μg/l
Pravastatin sodium		Antilipemic	0.042–0.378 μg/l
Propifenazone		Analgesic	0.002–0.056 μg/l
Propranolol		Antihypertensive	0.015–0.178 μg/l
Salicylic acid		Analgesic	0.027–0.083 μg/l
Simvastatin		Antilipemic	0.42–0.378 μg/l
Sotalol hydrochloride		Antiarrhythmic	0.123–0.864 μg/l
Antipyrine	Wassmannsdorf, Weir Diedersdorf, Pumping Station Genshagen Weir Thyrow, Estuary of Nuthegraben into the Nuthe River (South of Berlin, Germany) Müller et al. (2012)	Herbicide	0.23–0.06 μg/l
Atenolol		Antilipemic	1.1–0.17 μg/l
Bezafibrate		Anticonvulsant	2.35–1.14 μg/l
Codeine		Analgesic	4.60–0.5 μg/l
Diclofenac		Antilipemic	0.39–0.42 μg/l

Source: Ferguson et al. (2013), Valcárcel et al. (2011a), and Müller et al. (2012)

and triazine (herbicide) in northeastern Spain. The results are (Matamoros et al. 2007):

a) Highly efficiently removed micropollutants (> 90%): lindane (pesticide), pentachlorophenol (bactericide), endosulfan (insecticide), and pentachlorobenzene (disinfectant and other uses);
b) Efficiently removed micropollutants (80–90%): alachlor (herbicide) and chlorpyrifos (insecticide); and
c) Poorly removed micropollutants (20%): mecoprop (herbicide) and simazine (herbicide).

Biodegradation and plant absorption are the most likely micropollutants' removal mechanism in Spain STP, with a

low accumulation of contaminants injected into the gravel bed (0–20%) (Matamoros et al. 2007). *Trametes versicolor* fungus (reinoculated) increased the micropollutants degradation rate up to 86% of APIs, 81% of brominated flame retardants (BFR), and 80% of ultraviolet filters (UV) (Rodríguez-rodríguez et al. 2014). Some interesting technologies to remove API are reviewed by Auriol et al. (2006); Belgiorno et al. (2015); Carballa et al. (2007); Carballa et al. (2005); Hijosa-Valsero et al. (2010); Clara et al. (2005); Klavarioti et al. (2009); Liu et al. (2009); Murugesan et al. (2014); Qiang et al. (2013); Xu et al. (2009); Yang et al. (2013); Zhang et al. (2013); and Zhou et al. (2011). HWM/HCW incineration and plasma pyrolysis are treatment technologies that may reduce the mass and volume collected by 90%, but they present high initial costs for implantation, maintenance, operation, and specialized labor (Torres-filho et al. 2014). Ribera et al. (2014) propose a combination of API life cycle analysis and human health risk assessment as data to support decision about which percentage of effluent should be nanofiltered to remove the micropollutants. A full review of treatment technologies for removal of API from drinking water can be found in WHO (2012).

To Zenker et al. (2014), API bioaccumulation, biomagnification, and bioconcentration are important elements to environmental impact assessment of pharmacopollution. These authors define bioaccumulation as the compound absorption or retention over time. Biomagnification is the xenobiotic compounds transfer (from food), so higher-level organisms present higher concentrations than lower-level ones (Zenker et al. 2014). Bioconcentration is the accumulation of a substance dissolved in water by aquatic organisms. The highest bioconcentration factors for fish reviewed by Zenker et al. (2014, p.380) are diclofenac (liver: 12–2732), fluoxetine (185–900), gemfibrozil (113), and norfluoxetine (body: 80–650). Other animals are affected by pharmacopollution, too. The white-rumped vulture (*Gyps bengalensis*) was the most common raptor bird in India until the 1990s, when its population decreased 95% (OAKS et al. 2004). Visceral gout and renal failure related to diclofenac (anti-inflammatory) were the cause of death, as discovered by a 2000–2003 study (Oaks et al. 2004). The antidepressant fluoxetine decreases goldfish (*Carassius auratus)* feed intake and weight gain (Mennigen et al. 2009) and inhibits ova production of zebrafish (*Danio rerio*) (Lister et al. 2009). From July 2005 to August 2006, in a controlled experiment, fathead minnow (*Pimephales promelas*) exposed to household effluents in Boulder (Colorado) presented a demasculinization process (Vajda et al. 2011). After 14 days of exposure, fish's sperm abundance changed, as well as its nuptial tubercles and dorsal fat pads (100% of specimens). Estrogen 17ß-estradiol, estrone, estriol, 17α-ethinyl estradiol, estrogenic alkylphenols, and bisphenol A were detected in Boulder effluent (VAJDA et al. 2011). Fathead minnows (*Pimephales promelas*) exposed during 21 days to 305 and 1104 μg/l of venlafaxine and 0.0052 μg/l of sertraline (both antidepressant) presented mortality and anatomical modification in their testicles (Schultz et al. 2011). Brook trouts (*Salvelinus fontinalis*) exposed to household effluent, under laboratory conditions, presented biologically active compounds (antidepressant) in their livers, brains, and muscle tissues (Lajeunesse et al. 2011). Ciprofloxacin, enoxacin, and sulfamethoxazole (antibiotics) in Laizhou Bay and salt water (China) aquatic environments raised potential ecological damages to bacteria *Vibrio fischeri*, *Microcystis aeruginosa*, and *Synechococcus leopoliensis* (Zhang et al. 2012), higher than pesticide effects. Some articles frame data references to pharmacopollution environment risk assessment. Fick et al. (2010) focus the predicted critical environmental concentrations of 500 API to fish. Calisto and Esteves (2009) focus the acute and chronic toxicity values for psychoactive drugs to invertebrates, algae, fish, and crustaceans. The relative API susceptibility order for Sanderson et al. (2004) is dafinidae > fish > algae, contrasting with Gros et al. (2010) for whom the order is algae > dafinidae > fish.

Antibiotics

Some authors highlight a potential microbial resistance result of antibiotics in surface water, groundwater, and sewage and it may be relevant because contamination is not fully removed by conventional STP (Jones et al. 2003; Martinez 2009). Other authors suggest a parallel between the antibiotics in sewage effluents from STP and a potential increase in the natural resistance of bacteria (Jones et al. 2003; Martinez 2009).

The four major genetic agents involved in the antibiotic resistance process are presented by Baquero et al. (2008): (i) the primary agent is the human and animal microbiota, involving more than 500 bacteria species; (ii) the secondary agents are hospitals, home care services, farms, and other places with large numbers of individuals susceptible and exposed to the exchange with bacteria; (iii) the tertiary agent is the sewage and biological wastes from (ii), e.g., STP, lakes, or toilets of common use, where different individuals' bacteria may interact; and (iv) the fourth and last agent is soil, surface water, or groundwater, where bacteria from previous processes mix and interact with others from environment.

Tap water analysis in Guangzhou (77.5% samples) and Macao (100% samples) detected four antibiotics (norfloxacin, ciprofloxacin, lomefloxacin, and enrofloxacin) (Yiruhan et al. 2010) and their concentration ranged from 0.001 to 0.6797 μg/l in Guangzhou and from 0.002 to 0.037 μg/l in Macao. The antibiotics concentration in Guangzhou's tap water tends to reduce in the beginning of rainy season (Yiruhan

et al. 2010). Antibiotics such as sulfonamides are present in Huangpu River (Shanghai) with 34–859 ng/l^{-1} concentration (Chen and Zhou 2014). Animal farming and effluents downstream the Yuanxie River are the main pharmacopollution sources (Chen and Zhou 2014). Ternes et al. (1999a) detected estrogen in STP from Brazil, Germany, and Canada. The mean concentration in Rio de Janeiro/Brazil of 17β-estradiol was 0.021 μg/l and estrone 0.040 μg/l, close to the values of Frankfurt/Germany, 0.015 μg/l and 0.027 μg/l, respectively. São Paulo's water samples analyzed by Leal et al. (2012) also present farming-related antibiotics.

Frédéric and Yves (2014), Lin and Tsai (2009), Lin et al. (2010), Sim et al. (2010), and Verlicchi et al. (2012a) present a broad environmental impact assessment of API from hospitals. However, hospitals and other healthcare facilities are not the main antibiotics source for municipal sewage contamination, but instead the population is. The population is responsible for 75% antibiotics discharges in Germany and USA, as well as 70% in the UK (Kümmerer 2008, Schuster et al. 2008). In France, hospitals consume 22% of anticancer drugs but represent 13.8% of its sewage discharge (Besse et al. 2012, p. 82). The reasons above explain why it is so relevant to focus the household generation, due to their large coalescent pharmacopollution volume.

HWM generation and destinations

The API physical-chemical properties determine its capability to reach the aquatic and/or terrestrial environments (Luo et al. 2014; Vajda et al. 2011). The main reasons for HWM generation are the non-adherence and non-compliance to prescribed treatment (Ruhoy and Daughton 2008), therapeutic obsolescence, improvement in the clinical state, suspension, interruption, intolerance, packages with greater quantities than prescription, and free sampling (Acurcio 2013). Some HWM are out of date, but not all of them.

Sometimes, HWM is forgotten at home, as prevalent among Swedish (55%) (Tong et al. 2011), or it can be donated, exchanged, or resold. There is no easy way to guarantee the identification, purity, or proper storage conditions of HWM; therefore, donation, exchange, or resell is not commonly recommended (Glassmeyer et al. 2009). Donation, exchange, or resell can also be related to self-medicine and abusive use (Glassmeyer et al. 2009). English INTERCARE (2015) promotes awareness-raising campaigns about HWM, sending the returns to developing countries. Donation is recommended by Pomerantz (2004) as a strategy for reusing expensive HWM that is not out of date.

The reverse logistics system is an adequate destination for HWM, followed by the sanitary landfill (Xie and Breen 2014). However, the most common destination for HWM is the littering (Tong et al. 2011): 45% in the USA, 63.2% in the UK, 80% in New Zealand, 89% in Lithuania, and 97% in Kuwait. Discard in the sink or toilet is often adopted in New Zealand (liquids: 55%) and UK (11.5%) (Tong et al. 2011). In variable frequencies, 55% Germans prefer to return the HWM to pharmacy (Tong et al. 2011). In Brazil, 62% prefer the littering and 19% prefer the sink or toilet disposal, according to a study in Paulínia city (São Paulo state) (Pinto et al. 2014). In another Brazilian city, Belo Horizonte (Minas Gerais state), 52% prefer the littering and 32% prefer the sink or toilet disposal (Ferreira et al. 2015). In Brazil, 50.8% of littering is sent to rubbish dumps (IBGE 2008); so HWM is in direct contact with the soil. Landfilling the HWM is based on its lower "relative direct cost" (Aduan et al. 2015) and it is an important obstacle to consolidation of reverse logistics systems/practices (Xie and Breen 2014).

According to the IMS Health Global report 2012, the Brazilian pharmaceutical industry trade was US$ 28.5 million (sixth largest market, US$ 144.40 per capita) (IMS Health 2013). Projections to 2017 indicate that Brazil will be the fourth largest market in sales volume (US$ 38–48 billion). Surprisingly, in 2014, the pharmaceutical trade was US$ 65.971 billion, higher than the projection for 2017, representing a volume of 3,154,252,382 drugs (IMS Health do Brasil 2015). Meanwhile, WHO recommends the ratio of 1:10,000 pharmacy/inhabitants; in Brazil, there is 3.3 (Domingues et al. 2015). At least 35.0% (CI95% 29.0; 40.0, I^2 = 83.9%) adopt self-medication, a value higher than Colombia (27.3%), Hong Kong (32.5%), Sudan (28.3%), and close to Ethiopia (39.2%) (Domingues et al. 2015). The access to health treatments and medicines is a constitutional right ("Article 196: 'Health is the right of all persons and the duty of the state […]"). The judicialization of health is growing and many taxes are used to afford expensive treatments (Pepe et al. 2010). Pepe et al. (2010) synthesize the following challenges of judicialization of health in Brazil: most part of the lawsuits is individual and judges' sentences are based mainly on common prescriptions; the prescription contains both drugs recognized and not recognized by the pharmaceutical assistance (Public Health System-SUS) and many of them do not have the national registration or sanitary registry of their therapeutic indications; and there is an exponential growth of lawsuits and drug spending.

ABDI (2013) estimates the Brazilian HWM generation in 56.6 g/per capita/year (10,800 t/year), similar to Danmark (55) and Spain (57) (Vollmer 2010). The Brazilian HWM generation (g/per capita/year) is higher than Italy (54), Belgium (46), Liechtenstein (39), Czech Republic (36), Nederland (30), Iceland (19), Finland (11), Lithuania (10), Slovenia (4.5), Estonia (3.4), and Croatia (0.4) (Vollmer 2010). The Brazilian HWM generation is a very conservative estimative.

Table 2 Definitions of reverse logistics

Author	Definition
Stock (1998)	The role of logistics in product returns, source reduction, recycling, material substitution, reuse of materials, waste disposal, and refurbishing, repair, and remanufacturing
Rogers and Tibben-Lembke (1999)	The process of planning, implementing, and controlling the efficient, cost-effective flow of raw materials, in-process inventory, finished goods, and related information from the point of consumption to the point of origin for the purpose of recapturing value or proper disposal
Fleischmann (2001)	Reverse logistics is the process of planning, implementing, and controlling the efficient, effective inbound flow and storage of secondary goods and related information opposite to the traditional supply chain direction for the purpose of recovering value or proper disposal
Dowlatshahi (2000)	A process in which a manufacturer accepts previously shipped products or parts from the point of consumption for possible recycling, remanufacturing, or disposal
Steven (2004)	Reverse logistics comprises all activities involved in managing, processing, reducing, and disposing of hazardous or non-hazardous waste from production, packaging, and use of products, including the processes of reverse distribution

Source: Stock (1998), Rogers and Tibben-Lembke (1999), Fleischmann (2001), Dowlatshahi (2000), and Steven (2004)

HWM reverse logistics

Table 2 summarizes important definitions of reverse logistics and highlights its connection to HWM.

HWM reverse logistics is "the collection activity, from the final consumption point to its origin" and "can lead to reuse and to return raw materials to the productive cycle, as well as provide an environmentally (and adequate) destination" (Acurcio 2013, p. 57). According to Acurcio (2013), reverse HWM logistics mainly focuses the returns. Xie and Breen (2014) understand that HWM reverse logistics also encompasses the measures taken to increase the safety of drug use, protect the environment, and to reduce the littering generation. Xie and Breen (2014) present two major reverse logistics groups: (1) end of life and (2) end of use. The first one is the returns collected to avoid environmental and commercial damages. The second is the products collected after the end of their use, trade-in, or replacement.

Cook et al. (2012) compared the life cycle methodology to HWM and the environmental impact of three waste treatments in the USA: pharmacy returns and incineration, sewage treatment after discharge, and landfill or incineration. In American HWM scenario, returning 50% HWM to the pharmacy and discarding 50% to littering would reduce the API dispersion by 93%. The authors conclude that the best destination for HWM is the littering (domestic trash), followed by landfill or incineration disposal (in opposite to Xie and Breen 2014).

Some countries are potential benchmarking for HWM reverse logistics programs (take-back), such as France, Germany, Portugal, USA, and Sweden (Falqueto and Kligerman 2013). In Europe, a reverse logistics system with pharmacy recoil is the main HWM strategy (ABDI 2013, Persson et al. 2009). HWM reverse logistics is the prevalent strategy in 19 members of 27 European Union members (ABDI 2013). In 2008, the White House Office of National Drug Control Policy (ONDCP) recommended toilet disposal for 13 drugs of high potential to self-medication, abuse, and toxicity (Glassmeyer et al. 2009). The reverse management can help to reduce capital costs and medical risk and increases the finance available for frontline medical treatment (Xie et al. 2016). Some relevant reverse logistics programs worldwide are:

a) Australia: Return Unwanted Medicines (RUM) Project;
b) Belgium: Bonusage;
c) Brazil: Programa Destino Certo; Programa Descarte Consciente; Programa Descarte Correto de Medicamentos.
d) Canadá: Post-Consumer Pharmaceutical Association (PCPSA), EnviRX, Post-consumer Residual Stewardship Program Regulation;
e) Colombia: Plano de Gestão de Devolução de Produtos Pós-Consumo de Fármacos ou Medicamentos (PGDM), Punto Azul;
f) Europe: Medsposal;
g) France: Programa Cyclamed;
h) Hungary: Recyclomed;
i) Mexico: Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), Sistema Nacional de Gestión de Residuos de Envases y Medicamentos (SINGREM);
j) Portugal: Programa VALORMED;
k) Spain: SIGRE;

l) Sweden: APOTEKET AB; and
m) USA: SMARxT Disposal™ program, Secure Medicine Return, National Prescription Drug Take-Back Day, Great Lakes Earth Day Challenge.

Information and regulations

The presence of API, EDC (Stasinakis et al. 2010; Vajda et al. 2011), and other micropollutants in water and STP, surface and groundwater resources are relevant to public health studies (Deblonde et al. 2011; Furuichi et al. 2004; Lapworth et al. 2012; Liu et al. 2010; Luo et al. 2014; Zhang et al. 2011). Medicines (and consequently, HWM) are part of a medical dilemma about their inherent social role (Lèfevre 1983). Medicines can be considered a "special merchandise" and their commerce must be guided by market rules. Others see medicines and HWM as a "healthcare input" that must be strictly oriented by public health interests. Each interpretation leads to serious challenges about the access of low-incomers (reflecting in how patients generate HWM), market share, interests of shareholders, and pharmaceutical companies' investment and innovation (see Lèfevre 1983).

>Figure 1 shows information and regulations split into three variables: (1) the rational use of medicines, (2) take-back programs (compiled in the reverse logistics item), and (3) regulations. The rational use of drugs, in right amount as prescript, is the best way to avoid HWM generation (Xie and Breen 2014). HWM is related to domestic incidents such as self-medication, abusive use, and children's accidental ingestion. From 1997 to 2002, abusive use of opioids increased in the USA from 5.75 to 9.85% (Højsted and Sjøgren 2007). Accidental and intentional (suicide) ingestions, self-medication, and abusive use of medicines are serious medicine/HWM matters (Persson et al. 2009). In Brazil, Mota et al. (2012) carried out an extensive study of medicine and HWM health hazards, analyzing Mortality Information System (SIM/MS) data. From 1996 to 2005, 4.6 per 10,000 records/year died as a result of medicine and HWM intoxication. About 57.2% cases are suicide, 34.7% are ignored cause, and 19.2% are accidental ingestion. The death rate (household drug intoxication) increased by 17.8% and children under 4 years old (51%) and elderly (27%) are the main victims of HWM intoxications in Brazil. HWM in Brazil got some governmental focus, even without a specific regulation. The Brazilian Solid Waste National Policy (PNRS) (BRAZIL 2015a) and the National Medicine Policy-ordinance GM/MS n ° 3.916/1998 (Brazil 2015b) do not formalize an HWM reverse logistics system. Nonetheless, the Brazilian Ministry of Health and the National Health Surveillance Agency (ANVISA) created a thematic working group for medicine reverse logistics (GTT Medicamentos), a member of the Advisory Committee for Reverse Logistics Systems Implementation-CORI. Reverse logistics for HWM is not a legal obligation according to PNRS, but there is a specific working group (GTT Medicamentos) to settle a HWM sector agreement. PNRS establishes three models of contracts for national reverse logistics: the sectoral agreement, the regulation, and the term of commitment. The sector agreement is a contract among governing manufacturers, importers, distributors, and traders, an aim to a shared responsibility about the product life cycle. So far, three HWM sectoral agreement proposals were assessed and one is in public consultation. When running, the sector agreement will provide HWM recoil station to 54.75% Brazilians. The main target is to increase returns rather than trash or toilet/sink. Luetge's (2005) idea of mutual advantages, going beyond the traditional idea of a fundamental contradiction between ethics and economics, can be a useful framework to improve the Brazilian regulation about HWM. Understanding which advantage(s) is (are) efficient to make Brazilians cooperate with the HWM reverse logistics system is fundamental to a successful system.

The health, environmental, and sociocultural values influence the generator's behavior about reverse logistics system effectiveness (Kotchen et al. 2009). Home generators tend to be less engaged if they are not required to participate or do not perceive sufficient "apparent benefit" in cooperating (Xie and Breen 2014). In a reverse logistics system, the volume of returns is a consequence of generators' awareness and how much they are willing to cooperate (Pereira et al. 2012). If generators present low awareness about how it is important to cooperate and see an insufficient apparent benefit to return, the volume collected tends to be irregular (Pereira et al. 2012, Xie and Breen 2014). Strategies to stimulate the awareness about environmental protection may increase or significantly influence the HWM return rate (Xie and Breen 2014). The return rate is a real challenge to the secondary raw material market (economic cost recovery) (Pereira et al. 2012). HWM is far from being economically recoverable if compared to other classes such as electrical and electronic wastes. The future hydric needs will demand an increase in water reuse. It can lead to a higher occurrence and exposure to pharmacopollutant hazards (Jones et al. 2003). Figure 1 shows how close the pharmacopollution is from households when water reuse is adopted. Therefore, it is urgent to increase the patient's awareness and their apparent benefit to reduce generation and to improve the reverse logistics system. A low awareness about HWM results in few returns rate to the pharmacy (the reverse logistics recoil station), resulting in environmentally inadequate behaviors such as discard in the trash, sink, or toilet (Tong et al. 2011). Take-back

campaigns (secondary pathway) are easier and cheaper than excretion (primary) programs to reduce pharmacopollution environmental impacts (Vollmer 2010).

Conclusions

The household waste medicine (HWM) phenomenon brings many environmental, public health, and social challenges. The studies present few comprehensive and systematic monitoring data on pharmacopollution so far. The data is a real challenge to assessing potential human health risks and API concentrations. Therefore, the hazard of long-term exposure to low concentrations of pharmacopollutants and the combined effects of API mixtures is still uncertain. As this article presents, the HWM phenomenon is real as well as its potential consequences.

HWM is strongly related to pharmacopollution. Population growth tends to increase API excretion and HWM discard. As a result, more exposition to pharmacopollution is expected in the future. The Matthew effect is a challenge when considering a universe of 4000 existing APIs for medical and veterinary use, and few were assessed for environmental risk. Pharmacopollution is quite a sensitive topic since there are pharmaceutical industry pressure and insufficient environmental and socioeconomic studies about it. Generalizations about pharmacopollution are quite hard, once there are many methodologies, approaches, and conclusions about its environmental impact, animal, and human health risk assessment. New studies must settle the risks of antibiotics, estrogen, and other API according to the different volumes of pharmacopollution.

The Brazilian HWM case is remarkable because there is a wide number of private pharmacies and drugstores, a public medicine program, judicialization of health, self-medication habits, and no national take-back program running. There are only local take-back programs run by companies or institutions. A national reverse logistics for HWM is not just important to recoil and diminish pharmacopollution effects, but also can be used as a strategy to understand why and how is the generation of waste. When the public medicines (provided directly by SUS or through judicialization of health) become HWM, taxes are literally "littered". When the medicines bought by population become HWM, part of their income is also littered. Reverse logistics, the rational use of medicines, better regulations, and management can save taxes by reducing the public medicines waste; and for sure, it can save the money that would become HWM, considering the consumers who buy their medicines. The sector agreement for HWM is urgent to reduce the amount sent to rubbish dumps, too. The articles reviewed do not mention the risks to waste pickers who live in the rubbish dumps.

Authors recommend more systematic studies about the occurrence and fate of pharmacopollutants in the environment, standardization of protocols for sampling, health risk assessment, and analytical determination to the data comparison. It is necessary to conduct medium and long-term studies about API risks to human health since there is plenty of evidence of pharmacopollution effects on animals. Finally, other classes of household pollutants must also be a focus of further studies.

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