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REVIEW

Pharmaceuticals and personal care products in waters: occurrence, toxicity, and risk

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Abstract Pharmaceuticals and personal care products (PPCP) are compounds with special physical and chemical properties that address the care of animal and human health. PPCP have been detected in surface water and wastewater in the ng/L to μg/L concentration range worldwide. PPCP ecotoxicity has been studied in a variety of organisms, and multiple methods have been used to assess the risk of PPCP in the environment to ecological health. Here we review the occurrence, effects, and risk assessment of PPCP in aquatic systems, as well as the sustainability of current methods for managing PPCP contamination in aquatic systems. The major points are the following: (1) a number of PPCP present potential concerns at environmentally relevant concentrations. PPCP mixtures may produce synergistic toxicity. (2) Various methods have been used for the ecological risk assessment of PPCP in aquatic systems. There are similarities in these methods, but no consensus has emerged regarding best practices for the ecological risk assessment of these compounds. (3) Human health risk assessments of PPCP contamination in aquatic systems have generally indicated little cause for concern. However, there is a lack of information regarding whether antibiotic contamination in wastewater and aquatic systems could lead to an increase in clinically relevant antibiotic-resistant bacteria and antibiotic-resistant genes. (4) Over the next century, the combination of increasing global population size and potential droughts may result in reduced water availability, increased need for water reuse, and increasing concentrations of PPCP in wastewaters. The current wastewater treatment methods do not remove all PPCP effectively. This, coupled with the possibility that antibiotics may promote the development of antibiotic-resistant bacteria and antibiotic-resistant genes, leads to concerns about the sustainability of global water supplies.

Keywords Pharmaceuticals · Personal care products · Aquatic systems · Environment · Risk · Antibiotic resistance · Antibiotic-resistant genes · Antibiotic-resistant bacteria · Sustainability · Review

Introduction

Ever since pharmaceuticals and personal care products were given the collective term "PPCP" (Daughton and Ternes 1999), interest in these emerging contaminants as environmental pollutants has increased rapidly, leading to the publication of numerous articles detailing the scale and impacts of PPCP in the environment (Ribeiro et al. 2015a, b; Richardson and Ternes 2014; Vasudevan and Oturan 2014). A number of pharmaceuticals have been detected in the environment (Fig. 1). PPCP include prescription and non-prescription human drugs, illegal drugs, and veterinary drugs, as well as their subsequent metabolites and conjugates, including antibiotics, hormones, anticonvulsants, antidepressants, lipid regulators, antihypertensives, and nonsteroidal anti-inflammatory drugs (NSAIDS; Fig. 1). Many chiral pharmaceuticals have been analyzed in the environment (Ribeiro et al. 2012, 2014). PPCP also include sunscreen, soaps, moisturizers, lipsticks, fragrances, insect repellent, and shampoo (Daughton and Ternes 1999; Loraine and Pettigrove 2006; Olkowska et al. 2014; Ramos et al.

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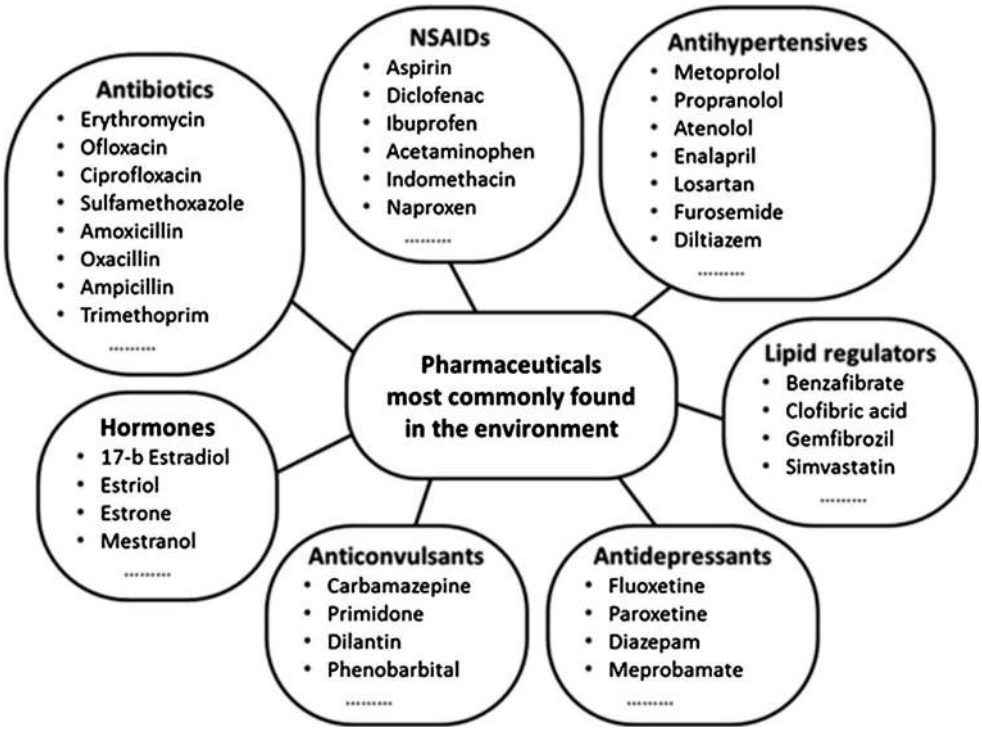

Fig. 1 Pharmaceuticals frequently detected in the environment (adapted from Magureanu et al. (2015) with the permission of Elsevier Inc.)

2015; Sharma et al. 2009b; Teo et al. 2015). The United States Environmental Protection Agency (US EPA) defines PPCP as "any product used by individuals for personal health or cosmetic reasons or used by agribusiness to enhance growth or health of livestock" (U.S. Environmental Protection Agency 2012). This encompasses thousands of different chemicals (U.S. Environmental Protection Agency 2012).

Globally, several thousands of PPCP are produced per year, and the release of PPCP in the environment remains an unavoidable by-product of a modernized lifestyle (Caldwell et al. 2014; Fatta-Kassinos et al. 2011; Khetan and Collins 2007; Tran et al. 2015). PPCP may enter the environment as components of human or animal waste, after incomplete absorption and excretion from the body, or may result from emissions of medical, industrial, agricultural, or household wastes (Li 2014; Michael et al. 2013; Sharma et al. 2009a; Taylor and Senac 2014). The exact amount introduced into aquatic systems is not well characterized (Schwarzenbach et al. 2006). However, multiple studies have identified trace amounts of PPCP-related compounds in waste, aquatic ecosystems, or finished drinking water (Anquandah et al. 2013; Kuzmanovic et al. 2015; Michael et al. 2013; Petrovic et al. 2014; Qin et al. 2015; Sharma et al. 2009b, 2013; Tölgyesi et al. 2010; Verlicchi et al. 2010), suggesting that contamination may be widespread. Below are some of the examples of measurement of PPCP in various aquatic environments of the world.

A study of 36 PPCP in urban rivers in Beijing, Changzhou, and Shenzhen, China, detected 28 compounds from five therapeutic classes (Wang et al. 2015). In this study, antibiotics accounted for approximately half of the total contaminant levels; the compounds with the highest median concentrations included sulfadimethoxine, sulpiride, and atenolol (164, 77.3, and 52.9 ng/L, respectively; Wang et al. 2015). Another study used solid-phase microextraction to analyze phthalates in drinking water samples from Leipzig, Germany, and Katowice, Poland (Luks-Betlej et al. 2001). Four of the investigated phthalates, diethyl phthalate, di-*n*-butyl phthalate, butylbenzyl phthalate, and di(2-ethylhexyl) phthalate, were all found in concentrations ranging from 0.02 to 0.6 μg/1 (Luks-Betlej et al. 2001). A separate study conducted in Lausanne, Switzerland, screened wastewater treatment plant influent and effluent, and raw drinking water samples, for 37 pharmaceuticals, four hormones, and a number of other micropollutants (Morasch et al. 2010; Perazzolo et al. 2010). All the pharmaceuticals and hormones except 17α-ethinylestradiol were detected in at least one sample of influent or effluent from the wastewater treatment plant. In addition, 22 pharmaceuticals were detected in the raw drinking water (Morasch et al. 2010). The concentrations of paracetamol, ciprofloxacin, and sulfamethoxazole were equal to or greater in raw drinking water than the predicted no-effect concentrations, which could present a risk of ecotoxicity (Morasch et al. 2010). In a recent study of rivers in the

Iberian Peninsula that were sampled in 2010 and 2011, pharmaceuticals and personal care products were identified in all four rivers, with the category of pharmaceuticals and hormones present in higher concentrations in the water than personal care products (Kuzmanovic et al. 2015). These results are consistent with the findings of other researchers, who have also identified PPCP in drinking and wastewaters in many distinct regions of the world, such as South Korea, China, and the USA (Kim et al. 2007; Loraine and Pettigrove 2006; Oliveira et al. 2015; Qiao et al. 2011).

The research to date on human and animal exposures to PPCP has linked them to an array of carcinogenic, mutagenic, and reproductive toxicity risks (Khan and Nicell 2015; Leung et al. 2013; Vasquez et al. 2014). A number of PPCP act as endocrine disruptors, which interfere with the functions of hormonal systems in both humans and animals (Catanese et al. 2015; Kiyama and Wada-Kiyama 2015; Petrie et al. 2014). Associations have been identified between endocrine disruptors and recent trends of increased incidences of breast and prostate cancers (Boberg et al. 2015; Prins 2008; Rochester 2013). Reproductive disorders have been found to occur following prenatal exposure to compounds such as diethylstilbestrol (Birnbaum 1994; Falconer et al. 2006; Inadera 2006; Maeda et al. 2014; Maranghi and Mantovani 2012; Wise et al. 2015). A number of studies have also been conducted to examine other responses to pharmaceuticals in ecological receptors. For example, Corcoran et al. (2010) reviewed studies in fish which examined a wide range of endpoints, including histological and cytological changes, inhibition of enzymes or hormones, behavioral effects, and oxidative stress, which can occur at concentrations that are orders of magnitude lower than those at which acute toxicity typically manifests (Corcoran et al. 2010). Alteration of key behaviors is an important endpoint. For example, the psychiatric drug oxazepam at environmentally relevant concentrations has been found to cause an increased feeding rate, reduction in sociability, and heightened activity in wild European perch (*Perca fluviatilis*; Brodin et al. 2013).

There is currently no established consensus on the best method for risk-based prioritization of PPCP within aquatic environments. The objective of this review is to summarize the toxicity of PPCP to ecological health, discuss the risk assessments of PPCP performed in the last decade, examine emerging concerns about antibiotic-resistant bacteria and antibiotic-resistant genes, and consider issues relating to the sustainability of current practices for managing PPCP in the environment.

Toxicity

A comprehensive review of the acute and chronic toxicities of PPCP compounds in aquatic organisms has been conducted (Brausch et al. 2012). Of the compounds investigated, dextropropoxyphene, sertraline, thioridazine, and diphenhydramine were highlighted as having the greatest potential for acute toxicity to the studied algal, invertebrate, and fish populations. Bacteria, fish, and amphibians were found to be relatively insensitive to the acute toxicity of analgesic drugs, while phytoplankton and invertebrates were most sensitive to the acute toxicity of these compounds. Overall, the antiarrhythmic, antidepressant, antidiabetic, antiandrogenic, and synthetic estrogen compounds were not anticipated to pose acute risks at the expected environmental concentrations (Brausch et al. 2012). With respect to chronic toxicity, estrogens (i.e., 17α-ethinylestradiol, DES, and 17β-estradiol) and selective serotonin reuptake inhibitors (fluoxetine and sertraline), as well as sulfadimethoxine, carbamazepine, fadrozole, levonorgestrel, and clofibrate, displayed high levels of chronic toxicity to the aquatic organisms under study (Brausch et al. 2012). Additional research is needed to assess the risks posed by Selective Serotonin Reuptake Inhibitors (SSRI) (Brausch et al. 2012).

Another study employed two widely used Life Cycle Impact Assessment (LCIA) models, the Danish method for Environmental Design of Industrial Products (EDIP97) and the Uniform System for the Evaluation of Substances adapted for LCA purposes (USES-LCA; Muñoz et al. 2008). These were used to characterize the potential environmental impact of 98 pollutants, including 57 PPCP and PPCP metabolites, as well as priority pollutants, polycylic aromatic hydrocarbons, and heavy metals in samples of wastewater influent and effluent from a wastewater treatment plant in Spain. The potential effects of these substances in marine water, freshwater, and soil were assessed. The predictions of both models provided several important results regarding PPCP toxicity. First, if the wastewaters under study discharged directly into freshwater systems, the USES-LCA model predicted that ciprofloxacin, triclosan, and fluoxetine would produce the major share of toxic impacts within the aquatic environment (Fig. 2). Second, according to both models, ciprofloxacin held the greatest potential for terrestrial impacts via wastewater used in irrigation. Third, according to the EDIP97 model, nicotine and gemfibrozil were ranked as having among the highest human toxicity potential of any contaminant if they were present in wastewater used to irrigate crops. Finally, of the 98 emerging or priority pollutants that were assessed, 16 compounds were considered

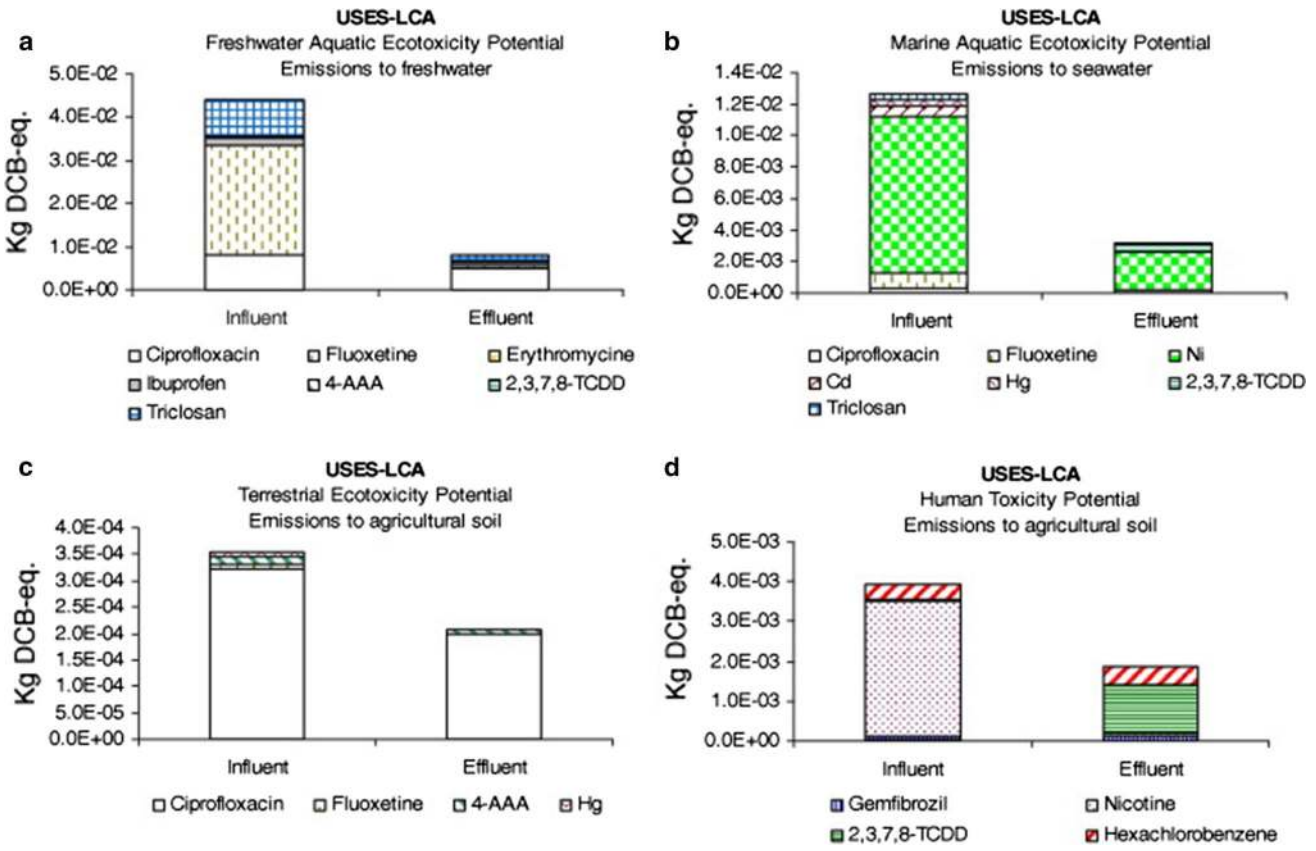

Fig. 2 Eco- and human toxicity scores obtained for El Ejido wastewater treatment plant influent and effluent, per L wastewater, with the USES-LCA model (adapted from Muñoz et al. (2008) with the permission from Elsevier Inc.)

to present the most significant potential impact, and 10 of these 16 were PPCP (Muñoz et al. 2008).

A separate study ranked the cytogenetic effects of five specific PPCP, triclosan, trimethoprim, diclofenac, ibuprofen, and paracetamol (Parolini et al. 2013). This was accomplished by exposing the freshwater bivalve *Dreissena polymorpha* to environmentally relevant concentrations (290, 290, 318, 200, and 154 ng/L, respectively) over a 96-h period. The biological responses of eight biomarkers were then integrated into a simple biomarker response index (BRI). The results indicated that triclosan produced notable acute effects; for example, it induced primary lesions to hemocyte DNA following only 24 h of exposure ($p < 0.01$) with a significant time-dependent relationship (Parolini et al. 2013). In contrast, 96 h of exposure to trimethoprim, diclofenac, ibuprofen, or paracetamol produced only minor effects on cellular and genetic endpoints. The application of the BRI enabled the researchers to clearly differentiate between the relative toxicities of each compound, resulting in the following order: triclosan > trimethoprim > ibuprofen > diclofenac = paracetamol (Parolini et al. 2013).

Another study examined the sublethal and cytotoxic effects of PPCP, individually and in mixtures, using the RTG-2 rainbow trout cell line to assess cell viability, oxidative stress, cellular senescence, and induction of CYP1A (Fernández et al. 2013). The effects of individual compounds were largely heterogeneous: atenolol, caffeine, and diphenylhydantoin, for instance, showed no measurable cytotoxicity even at the highest concentrations (500 μM), whereas eight other compounds (e.g., fluoxetine, cashmeran, galaxolide, ethinyl estradiol, and bisphenol A) produced decreases in cell viability. In terms of interactivity, however, the cytotoxicity of a number of the mixtures with chemicals from the same and different classes was much greater than expected, suggesting a synergistic effect. For instance, only cashmeran and galaxolide exhibited EC_{50} values for the β-galactosidase assay below 40 μg/L, and most of the tested individual compounds had EC_{50} values of 150 μg/L or higher. In contrast, the mixture of pharmaceuticals and endocrine-disrupting compounds had a predicted β-galactosidase EC_{50} of 489.21 μg/L, and an experimentally observed EC_{50} value in this assay of 32.23 μg/L (95 % CI 17.89–164.36; Fernández et al. 2013).

A separate study exposed zebrafish (*Danio rerio*) to a complex pharmaceutical cocktail (MIX) containing acetaminophen (also called paracetamol), carbamazepine, gemfibrozil, and venlafaxine or to diluted wastewater

effluent over a 6-week period (Galus et al. 2013a, b). After sufficient exposure time, researchers collected blood and histological samples, as well as embryos from control and treated specimens. The embryos were examined for hatching, mortality, and common developmental abnormalities including pericardial edema, spinal cord deformations, stunted growth, and yolk sac edema. The treated populations of fish showed pervasive kidney tubule regression following exposure to either the pharmaceutical cocktail or wastewater effluent, and a reduced average cumulative number of viable embryos produced by each female, relative to the control groups. Further, direct exposure of treated embryos to 10 µg/L pharmaceutical cocktail produced a 25 % increase in mortality relative to controls. An unexpected result was that exposure to wastewater effluent (5 and 25 % dilutions) significantly decreased mortality by 33 and 23 %, respectively, compared to controls. Exposure of the zebrafish embryos to 25 % wastewater effluent and 10 µg/L pharmaceutical cocktail, however, exhibited a 1.8- and 24-fold increase in developmental abnormalities, respectively, relative to controls (Galus et al. 2013a).

The interactions of ten prescription drugs or their metabolites (clofibrinic acid, carbamazepine, propranolol, metoprolol, ibuprofen, diclofenac, naproxen, captopril, and metformin) in diverse aquatic organisms (*Daphnia magna*, *Desmodesmus subspicatus*, and *Lemna minor*) were examined (Cleuvers 2003). Bioassays that use immobilization and growth rate inhibition as relevant endpoints were employed. The results of these tests indicated that, for most substances, individual toxicities were moderate, with most EC_{50} values ranging from 10 to 100 mg/L or above. Propranolol, metoprolol, and diclofenac were the only compounds with EC_{50} values below 10 mg/L. However, upon combination, several mixtures revealed much stronger effects than would be expected based on their individual components. The mixture toxicity of ibuprofen and diclofenac in the *Daphnia* test, for example, exceeded both the independent action of each compound as well as the predicted concentration addition effects, indicating a notable synergistic effect (Fig. 3; Cleuvers 2003). In a separate study, the influence of temperature on the chronic toxicity of the veterinary antibiotic florfenicol to *D. magna* was assessed by conducting a 21-day laboratory assay at 20 and 25 °C (Martins et al. 2013). The toxicity of the florfenicol was modified by the increase in temperature (Martins et al. 2013). However, more investigations on the combined effect of temperature variation and pharmaceutical contamination are required to comprehend the alteration in toxicity due to variation in temperature.

A study was conducted to assess the effects of exposing male fish, of the freshwater species *Hoplias malabaricus,* to prey species containing diclofenac or dexamethasone.

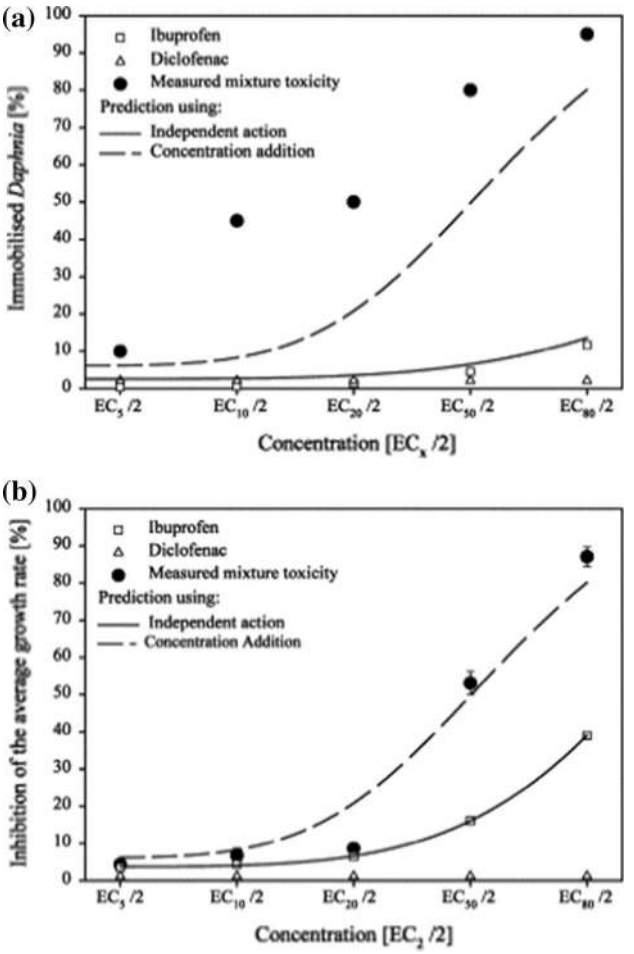

Fig. 3 **a** Measured mixture toxicity of diclofenac and ibuprofen as obtained in the acute *Daphnia* test in comparison with the singly measured toxicities and the mixture toxicity predicted by the concepts of concentration addition and independent action. For the assessment of mixture toxicities, half the calculated effect concentrations (EC_5/2, EC_{10}/2, EC_{20}/2, EC_{50}/2 and EC_{80}/2) were used. **b** Measured mixture toxicity of diclofenac and ibuprofen as obtained in the algal test in comparison with the singly measured toxicities and the mixture toxicity predicted by the concepts of concentration addition and independent action. For the assessment of mixture toxicities, half the calculated effect concentrations (EC_5/2, EC_{10}/2, EC_{20}/2, EC_{50}/2 and EC_{80}/2) were used (adapted from Cleuvers (2003) with the permission of Elsevier Inc.)

Twice per week, the fish were fed *Astyanax* sp. that had been given intraperitoneal injections of either diclofenac (0, 0.2, 2.0, or 20.0 µg/kg) or dexamethasone (0, 0.03, 0.3, or 3.0 µg/kg; Guiloski et al. 2015). This exposure to diclofenac decreased the glutathione-*s*-transferase (GST) activity in the liver, while decreased levels of testosterone were seen with both the diclofenac and dexamethasone exposures (Guiloski et al. 2015).

A toxicity study was conducted using mixtures of 13 pharmaceuticals (bezafibrate, ciprofloxacin, furosemide, atenolol, cyclophosphamide, hydrochlorothiazide, ibuprofen, ranitidine, salbutamol, lincomycin, ofloxacin, carbamazepine,

and sulfamethoxazole) at environmentally relevant concentrations (Pomati et al. 2006). The human embryonic kidney cell line HEK293 was selected to examine the mechanism of cytotoxicity at the molecular level (Fig. 4; Pomati et al. 2006). The studied mixture of chosen pharmaceuticals inhibited the proliferation of HEK293 cells at concentrations equal to or greater than environmental levels. After 48 h, cell proliferation was decreased by 30–40 % compared with negative control values (Fig. 4a, d). The positive control representing the effects of the cytotoxic chemical cisplatin on HEK293 is shown in Fig. 4a. The study also performed the treatment of cells for 72 h. The maximum growth inhibition was attained after 48-h exposure when no change of the pharmaceuticals in the culture media was made during the exposure time period (Fig. 4b). Significantly, when the culture media was changed and a fresh mixture of pharmaceuticals was added every 24 h, the decrease in cell proliferation with time was continuous, except at the lowest dose (Fig. 4c). It appears that physical or biological degradation processes may have occurred under the experimental conditions, or that the pharmaceuticals may have accumulated in the cells (Pomati et al. 2006). Another experiment was conducted to determine whether cyclophosphamide, the strongest cytotoxic agent of the 13 selected pharmaceuticals, was responsible for all the inhibition of cell proliferation that was observed with the mixture (Fig. 4d). Interestingly, at all concentrations except the highest dose, the cyclophosphamide treatment produced greater cell proliferation than the untreated control, and growth inhibition only occurred at the highest dose (Fig. 4d; Pomati et al. 2006). Overall, mixtures of pharmaceuticals may have unanticipated effects on aquatic life. Fundamental approaches for assessing the toxicity of pharmaceutical mixtures have recently been reviewed (Backhaus 2014).

Interactions between PPCP and drinking water disinfectants in water treatment plants are also a potential concern. Nitrosamine formation potential tests were conducted to determine whether a group of 20 PPCP containing amine groups could serve as *N*-nitrosodimethylamine (NDMA) or *N*-nitrosodiethylamine (NDEA) precursors during chloramine disinfection (Shen and Andrews 2011). Of the tested compounds, eight pharmaceuticals produced molar yields greater than 1 %. Of these, ranitidine produced the highest level of conversion (89.9–94.2 %), and conversion was also seen with sumatriptan (6.1 %), doxylamine (8.0–9.7 %),

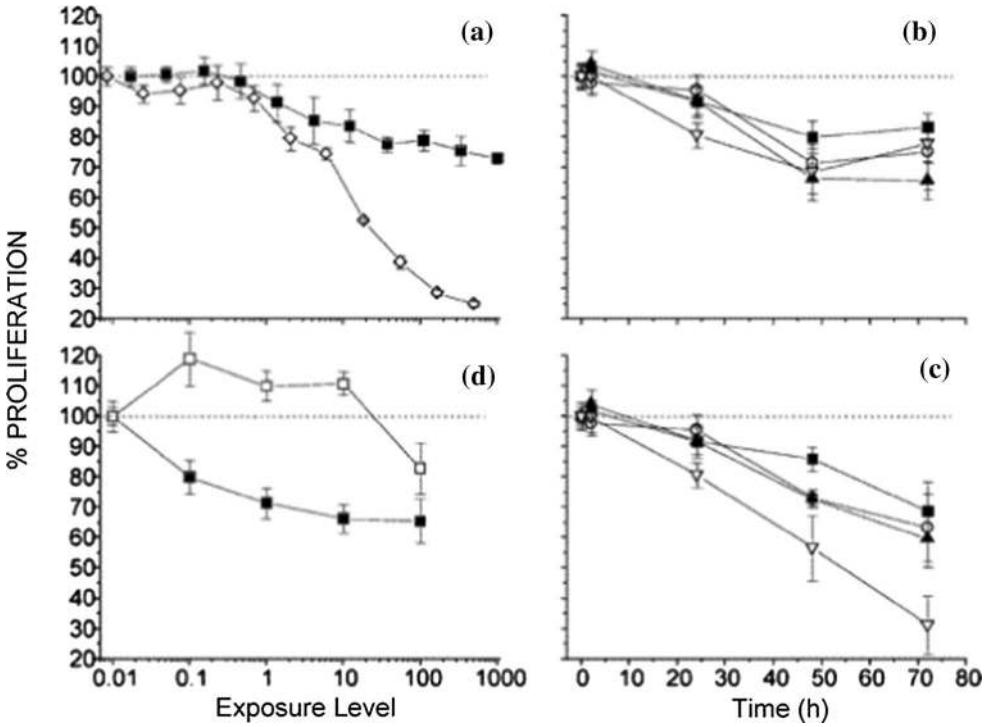

Fig. 4 Effects of pharmaceuticals on HEK293 cell proliferation. Values are reported as % proliferation compared to untreated controls (100 %) and expressed as average ± SE ($N = 3$). **a** 48-h dose–response plot of serial dilutions of the therapeutic drug mixture (*filled square*) compared to different concentrations of cisplatin as reference for cytotoxicity (μM, *open diamond*); DMSO control for cisplatin was not shown. **b** Cytotoxicity of pharmaceutical dilutions over time. **c** Cytotoxicity of pharmaceuticals over time, changing culture media added with fresh drug mixture every 24 h. Exposure: *filled square* is level 0.1; *open circle* is level 1; *filled triangle* is level 10; *open inverted triangle* is level 100. **d** Comparison between the complete drug mixture (*filled square*) and corresponding concentrations of cyclophosphamide (*open square*) after 48-h exposure without replacing the drug mixture [reprinted (adapted) with permission from Pomati et al. (2006), copyright 2006 American Chemical Society]

chlorphenamine (5.2–5.5 %), diltiazem (2.1–2.6 %), nizatidine (4.5–4.8 %), tetracycline (0.8–1.2 %), and carbinoxamine (1.0–1.4 %). Although the majority of these 20 PPCP yielded less than the compounds listed above, all were able to form nitrosamines during chloramine disinfection, and, taken together, still contributed significantly to overall nitrosamine formation in treated waters (Shen and Andrews 2011). The presence of pharmaceuticals in water has also led to the formation of potentially carcinogenic disinfection byproducts during treatment processes such as chlorination, chloramination, ozonation, and UV/hydrogen peroxide (Postigo and Richardson 2014).

Risk assessment

Several approaches have been used to rank PPCP, based on their environmental risks, in order to set up monitoring programs and develop regulatory and policy responses (Ågerstrand et al. 2015; Besse and Garric 2008). Approaches that have been proposed include the adverse outcome pathway approach, quantitative risk-based ranking, integrated, spatially explicit (or location-specific) ranking, calculation of the risk quotient (RQ), and use of structure–activity relationships (Caldwell et al. 2014; De Voogt et al. 2009; Di Nica et al. 2015; Dong et al. 2013; Oldenkamp et al. 2013, 2014; Ortiz de Garcia et al. 2014; Sanderson et al. 2004).

In the quantitative risk-based approach, the potential ecological and human health impacts of pharmaceuticals were assessed by combining (1) production estimate, (2) attenuation, and (3) toxicity thresholds for multiple endpoints (Dong et al. 2013). The authors of this study claimed that their approach is simple and environmentally relevant. In a recent study, a ranking method called RANKVET was developed for comparing and prioritizing the environmental risk of veterinary pharmaceuticals (VAT) to aquatic and terrestrial organisms (Di Nica et al. 2015). The RANKVET method calculated a risk quotient (RQ), which is the ratio of predicted environmental concentration (PEC) to predicted no-effect concentration (PNEC). According to this method, if the RQ $\geq$ 1, a risk mitigation measure must be proposed for reducing the risk to a level that is acceptable. If the RQ continues to be $\geq$1, the environmental risk remains (Di Nica et al. 2015).

Risk quotients have been used in Europe as a screening tool for the location-specific assessment of the risk of pharmaceuticals to human and environmental health (Oldenkamp et al. 2013). Risk quotients of a set of 11 human antibiotics and seven antineoplastics in the aquatic environment were highest for ciprofloxacin, levofloxacin, and doxycycline in densely populated areas in Europe, e.g., London, the Ruhr area, Krakow, and the Milan region. The risk quotient values were influenced by the aquatic toxicities of the compounds, their removal rates in the environment and sewage treatment plants, use location, and consumption pattern. The predicted and measured concentrations of the pharmaceuticals in this study were within approximately one order of magnitude (Oldenkamp et al. 2013). Recently, predicted and measured concentrations of pharmaceutically active compounds were also applied to evaluate the human health risk associated with exposure to pharmaceutically active compounds in Canadian drinking water (Khan and Nicell 2015).

Sanderson et al. (2004) ranked the ecotoxicological risk of 2986 compounds using quantitative structure–activity relationship (QSAR) models. Using the EPIWIN program, these compounds were ranked based on several factors including their hazard to fish, daphnids, and algae, and the chemical octanol–water partition coefficient (log K_{ow}). For compounds with molecular weight <1000 that are small enough to be absorbed through membranes, log K_{ow} can be used to characterize a compound's affinity for cell membranes and thereby its tendency to bioaccumulate (Sanderson et al. 2004). The STPWIN program with EPIWIN was also used to predict removal of the compounds in the sludge fraction of sewage treatment plants. The estimated relative order of susceptibility of the different test organisms was daphnids > fish > algae. Table 1 gives a summary of their findings obtained from the QSAR analysis (Sanderson et al. 2004). The hazard quotient (HQ) was defined as predicted environmental concentration divided by predicted no-effect concentration. The predicted no-effect concentration was determined by dividing the EC_{50} (the concentration at which 50 % of the organisms exhibited a specific adverse effect) by an uncertainty factor which was typically set equal to 1000 (Sanderson et al. 2004). The calculation of the hazard quotient was obtained by assuming the worst-case scenario with the predicted environmental concentration in the water equal to 1 μg/L, which is the value in the USA that triggers additional risk assessment. The authors acknowledge that the actual environmental concentration of most pharmaceuticals is below their assumed predicted environmental concentration (Sanderson et al. 2004). They determined the predicted percent of compounds in each class that had HQ > 1 as a frequency estimate. They then calculated an overall estimate of predicted hazard for each class, based on frequency and toxicity. A final ranking was developed for use in prioritizing the classes for additional risk assessment. This ranking considered all parameters. In 12 % of the classes, more than 50 % of the compounds had HQ > 1, and in the paraffin class, 92 % of the modifying additive compounds had HQ > 1. Overall, in the aquatic environment, cardiovascular and gastrointestinal pharmaceuticals were the most hazardous therapeutic classes based on predicted hazard, potential to bioaccumulate, and frequency (Sanderson et al. 2004).

Table 1 Ranking of the five predicted highest ranked classes based on all parameters

Rank	Algae	Daphnids	Fish	log K_{ow}	Removal	Total
1	Paraffin	Paraffin	Paraffin	Paraffin	A-surfactant	Paraffin
2	A-surfactant	A-surfactant	Cardiovascular	N-surfactant	Paraffin	A-surfactant
3	Pesticides	Pesticides	Gastrointestinal	A-surfactant	Sex hormone	Pesticides
4	Vitamins	A-sedatives	A-surfactant	Sex hormone	Pesticides	Cardiovascular
5	Cardiovascular	Cardiovascular	A-sedatives	Sunscreen	Sunscreen	A-sedatives

Using the EPIWIN program, a total of 2986 pharmaceuticals in 51 classes were ranked based on hazard to algae, daphnids, and fish (adapted from Sanderson et al. (2004) with the permission of Elsevier Inc)

A-surfactant, anionic surfactant; N-surfactant, nonionic surfactant; A-sedatives, anxiolytic sedatives hypnotics, and antipsychotics

Recently, a comprehensive environmental risk assessment of 26 PPCP that were relevant in the aquatic environment of Spain was conducted (Ortiz de Garcia et al. 2014). The researchers conducted Microtox acute ecotoxicity tests and activated sludge respirometry assays. The US EPA Ecological Structure–Activity Relationships (ECOSAR^{TM}) QSAR program was used to predict the estimated ecotoxicological effects of these compounds. The results demonstrated that, based on at least two ecotoxicity values, approximately 65 % of the PPCP in this study ranked as "highly toxic" or "harmful to aquatic organisms" (Ortiz de Garcia et al. 2014). Of these, the most toxic chemicals were 1,4-benzoquinone, omeprazole, triclosan, and propylparaben (see Fig. 5; Ortiz de Garcia et al. 2014).

One approach that has been proposed is an integrated assessment that includes the adverse outcome pathway (AOP) approach and exposure assessment (Caldwell et al. 2014). The AOP approach provides a framework for following the steps that lead to toxicity, first at the molecular level, which leads to cellular effects, followed by tissue or organ effects, leading to impacts on the whole organism, followed by population-level effects (Caldwell et al. 2014). The large amount of data available on pharmaceuticals would assist with this approach. This should be combined with exposure assessment that evaluates not only chemical concentrations, but also lipophilicity across environmentally relevant pH ranges and ionization potential, which influence bioavailability (Caldwell et al. 2014). In addition to examining total environmental concentration, the exposure assessment component of risk assessments should examine the fraction of chemicals that are available for uptake by organisms (Caldwell et al. 2014). In addition, data on absorption, distribution, metabolism, and excretion (ADME) by organisms can be used to better understand the internal doses inside the organisms (Caldwell et al. 2014). Finally, the sales data for the pharmaceutical and the amount metabolized or removed by wastewater treatment should be considered (Caldwell et al. 2014). Several studies have proposed using sales data, environmental concentrations, and toxicity benchmarks to assess risk (Caldwell et al. 2014; Diamond et al. 2011; Kostich and Lazorchak 2008; Roos et al. 2012). These can be used with the physicochemical characteristics of the compounds, which can be used to assess environmental degradation or persistence (Caldwell et al. 2014).

The tendency of PPCP to accumulate in the bodies of aquatic organisms is also an important factor in assessing exposures. A study of 23 human pharmaceuticals in a river in central Texas, USA, found that accumulation of pharmaceuticals occurred at higher concentrations in invertebrates than in fish (Du et al. 2014). In addition, elevated concentrations of sertraline occurred in the Asian clam (*Corbicula fluminea*) the pondhorn mussel (*Uniomerus tetralasmus*) and the paper pondshell mussel (*Utterbackia imbecillis*; Du et al. 2014). The pH of the water is also important for evaluating the potential bioaccumulation of pharmaceuticals that are weak acids or weak bases. For example, diphenhydramine, a weak base with pK_a close to 9.0, is more likely to accumulate in fish when the water has an elevated, environmentally relevant pH value, which would favor the formation the neutral species of this compound (Nichols et al. 2015).

Another important consideration is whether there is a transfer of contaminants between trophic levels in aquatic ecosystems. This could lead to high concentrations of the contaminant in the bodies of animals with higher trophic positions (e.g., predators at the top of the food chain). A study that examined the trophic transfer of diphenhydramine and carbamazepine in a stream in central Texas, USA, found that neither compound underwent trophic magnification, suggesting that inhalation rather than dietary exposure was a primary route of exposure to these compounds (Du et al. 2014).

Risk assessments of the human health effects of pharmaceuticals in drinking water have been conducted and have found that overall, individual pharmaceuticals are expected to pose a negligible risk to human health (Bercu

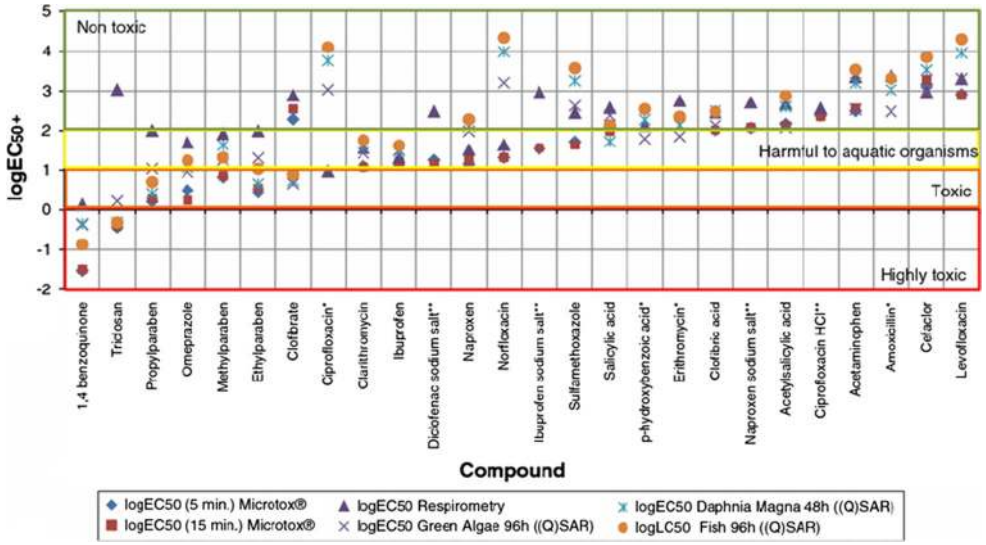

Fig. 5 Ecotoxicity results from (Q)SAR (fish, crustaceans and algae), bioluminescence (*Vibrio fischeri*) and respirometry (activated sludge) assays and from the GHS classification $^{+}EC_{50}$ and LC_{50} units: mg/L. *Asterisks*: for these compounds, the EC_{50} values of bioluminescence were not determined; however, the highest effect was provided (at a 95 % CI): amoxicillin $EC_{33\pm2}$ (2019 mg/L) at 5 min and $EC_{33\pm4}$ (2019 mg/L) at 15 min, ciprofloxacin $EC_{13\pm4}$ (63 mg/L) at 5 and 15 min; erythromycin $EC_{31\pm4}$ (900 mg/L) at 5 min and $EC_{45\pm7}$ (900 mg/L) at 15 min, *p*-hydroxybenzoic acid $EC_{27\pm2}$ (391.18 mg/L) at 5 min and $EC_{29\pm8}$ (391.18 mg/L) at 15 min. *Double asterisks*: for these compounds, the predicted ecotoxicity values were not estimated because ECOSAR™ has been primarily developed for the evaluation of neutral organic molecules (adapted from Ortiz de Garcia et al. (2014) with kind permission from Springer Science and Business Media)

et al. 2008; de Jesus Gaffney et al. 2015; de Jongh et al. 2012; Leung et al. 2013; Schwab et al. 2005; World Health Organization 2012). However, there is concern about antibiotics in the environment. The occurrence of antibiotic-resistant bacteria (ARB) has emerged as a major global concern because of increasing rates of morbidity and mortality, and greater healthcare costs (Meredith et al. 2015).

Antibiotic resistance

The possible production of antibiotic-resistant bacteria (ARB) and antibiotic-resistant genes (ARG) due to the presence of antibiotics has not been a major consideration in the risk assessments that have focused on PPCP in aquatic systems. However, the World Health Organization (WHO) has defined antibiotic resistance as one of the major public health issues of the twenty-first century (World Health Organization 2014). Prescriptions of antibiotics amount to more than 250 million in the USA each year, and a widespread use of antibiotics results in their release to human waste (Rosi-Marshall and Kelly 2015; Wu et al. 2015). Wastewater treatment plants (WWTP) receive effluent not only from communities, but also from hospitals and animal-feeding operations (Devarajan et al. 2015). WWTP are an important source of ARB and ARG in aquatic systems as well as a hot spot for horizontal gene transfer (Devarajan et al. 2015; Martinez 2008). In addition, sediments with a high clay and silt content can protect DNA from degradation, thereby potentially assisting the movement of biologically active DNA in water-saturated soil and groundwater (Devarajan et al. 2015; Pote et al. 2003).

The potential for the development of antibiotic resistance due to antibiotic contamination in the environment has been identified as a priority focus area (Boxall et al. 2012). Key questions include whether environmental exposure to PPCP residues results in the selection of microbes that are resistant to antimicrobials, and whether this has an important human health impact (Boxall et al. 2012). One study in Austria found there were similarities in the antibiotic resistance patterns in *Escherichia coli* isolated from sewage sludge and patients under medical treatment in 2000 and 2009, but there was not a correlation between fluoroquinolone resistance in humans and sewage sludge in either year (Reinthaler et al. 2013). There is increasing evidence that the development and spread of antibiotic resistance in the environment promotes antibiotic resistance in urban and medical settings; however, there is a lack of standardized methods for reliably comparing environmental samples and clinical data (Berendonk et al. 2015). Data collection and analysis procedures should be standardized so that data from environmental media can be directly compared with clinical data on antibiotic resistance (Berendonk et al. 2015). These guidelines should specify

the number of isolates, diversity of bacterial species or strains included, the conditions for DNA extraction or bacterial cultivation, and the resistance genotypes and phenotypes or primer sets of interest (Berendonk et al. 2015). The data that are currently available are insufficient to evaluate the abundance and distribution of ARB and ARG in the environment, which is important for determining the risk of transmission of resistance to clinically relevant bacteria (Berendonk et al. 2015). The reasons for this lack of data include (1) lack of standardized procedures for data collection, (2) lack of an established system for organizing and publishing the data that are collected, and (3) insufficient surveillance of ARB and ARG in the environment (Berendonk et al. 2015). There is a critical need for data collection and management systems that permit joint analysis of data from environmental and clinical settings (Berendonk et al. 2015).

Population growth, climate change, and sustainable water sources

Droughts have the potential to increase human and ecosystem exposure to PPCP by reducing the amount of available freshwater, and concentrating PPCP in the remaining water. A study of Lake Mead, USA, during 2003–2007 showed a statistically significant decrease in the water volume of this lake, and at the same time, a statistically significant increase in the concentrations of pharmaceuticals and endocrine-disrupting compounds (Benotti et al. 2010). Water reuse is being promoted as a means of responding to drought conditions (Association of California Water Agencies 2015; Oklahoma Water Resources Board 2015), and is seen as a valuable means of meeting current and future water needs (Alan Plummer Associates 2015; US Environmental Protection Agency 2012). In the USA, the volume of water being reused is increasing approximately 15 % per year, and is expected to play a growing role during this century, possibly in all 50 states (Miller 2006). As the human population grows, if PPCP and water consumption per capita remains the same, total PPCP and water use will increase. This could lead to increasing PPCP concentrations in aquatic systems unless wastewater treatment plants are able to remove PPCP effectively. A review of PPCP removal during wastewater treatment in 14 countries/regions found the percent removal of these compounds was highly variable and depended on PPCP properties and the operating conditions of the wastewater treatment plant (Luo et al. 2014). In addition, little is currently understood about effective methods for removal of ARB and ARG from wastewater (Pruden 2014), leading to concerns about the sustainability of global water supplies.

Conclusion

In prioritizing the risk of PPCP to aquatic organisms, three overarching factors have typically been considered, including location-specific environmental concentration (preferably taking into account bioavailability), ecotoxicity [often expressed as the predicted no-effect concentration (PNEC)], and potential for bioaccumulation (assessed for example using log K_{ow} for nonionized compounds). Toxicity screening in the studies reviewed above was conducted using a variety of organisms including algae, duckweed, bacteria, daphnids, freshwater bivalves, and fish (Cleuvers 2003; Galus et al. 2013a, b; Ortiz de Garcia et al. 2014; Parolini et al. 2013). In vitro assays were also used (Fernández et al. 2013; Pomati et al. 2006; Pomati et al. 2008). The use of multiple species and toxicity endpoints is important because the most sensitive species and the most relevant toxic endpoint may vary between compounds. Mechanistic and pharmacokinetic mammalian datasets are prepared during the development of human drugs, and these also provide useful information for assessing interactions between drugs, dose–response for adverse effects, and no adverse effect levels or lowest observed adverse effect levels (Caldwell et al. 2014).

Computer models are an essential component for screening the large number of PPCP that are currently in use. A number of modeling programs have been developed. PhATE (USA) and GREAT-ER are two exposure models (Banjac et al. 2015; Caldwell et al. 2014). In addition, the US EPA ECOSAR^{TM} model estimates the short-term and long-term toxicities of chemicals to freshwater and saltwater organisms. This is one of the models in the EPI Suite^{TM} set of models, which also contain models for estimating certain physicochemical parameters (e.g., water solubility or log K_{ow}) and chemical fate in the environment (e.g., aerobic and anaerobic biodegradation, partitioning of chemicals among water, sediment and air, or removal of a chemical in an activated sludge-based sewage treatment plant) (USEPA 2013). These models can be used with sales data to estimate environmental concentrations. Modeling makes it feasible to compile and analyze data on the environmental fate and toxicity of large numbers of compounds, to identify PPCP that are likely to pose the greatest risk in a given location.

In addition to examining the toxicity of compounds individually, it is necessary to evaluate the health effects of PPCP mixtures. Synergistic effects have been seen with PPCP mixtures, for example with ibuprofen and diclofenac in the *Daphnia* test (Cleuvers 2003), but these synergistic effects may not be the same across all organisms. Martins et al. (2013) also noted that the toxicity of florfenicol was modified by increasing temperature, an important environmental parameter. Bioaccumulation and trophic transfer are also

important considerations and should be further examined for PPCP. The mechanistic information in the existing pharmaceutical datasets should assist with identifying specific compounds that could produce synergistic interactions.

Antibiotic resistance is a major human health concern, and risk assessments of PPCP in aquatic systems should incorporate strategies to monitor ARB and ARG. Wastewater treatment plant procedures should be upgraded to improve the removal of ARB and ARG from effluents (Berendonk et al. 2015; Devarajan et al. 2015; Reinthaler et al. 2013). In addition, risk assessments of antibiotics in the environment should include not only toxicity assessment, but also an evaluation of the range of concentrations at which antibiotics promote the development of ARB (Berendonk et al. 2015).

In the USA, water reuse may increase in the coming decades due in part to population growth and droughts. This, along with growing PPCP and water needs due to the increasing population size, could result in greater concentrations of PPCP, ARB, and ARG in wastewaters. This suggests that additional research and improvements in water treatment technology may be needed to maintain healthy aquatic ecosystems and improve the sustainability of global water supplies. In addition, standardized methods are needed for assessing and monitoring the risks associated with these contaminants.

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